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Appendices

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

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Appendix 1

Search strategy for outcomes

Concept 1: congenital heart defects (80,477 hits)

1. exp Heart Defects, Congenital/
2. (congenital$ adj3 cardi$).ti,ab,kw.
3. (congenital adj3 heart$).ti,ab,kw.
4. coarct$.ti,ab,kw.
5. (double adj outlet adj right adj ventricle).ti,ab,kw.
6. DORV.ti,ab,kw.
7. (double adj outlet adj2 ventricle).ti,ab,kw.
8. (endocardial adj cushion adj defect).ti,ab,kw.
9. (hypoplastic adj left adj heart).ti,ab,kw.
10. HLH$.ti,ab,kw.
11. Norwood.ti,ab,kw.
12. Fontan.ti,ab,kw.
13. (interrupt$ adj3 aort$ adj arch).ti,ab,kw.
14. IAA.ti,ab,kw.
15. LVOT$.ti,ab,kw.
16. (left adj ventric$ adj outflow adj2 obstruct$).ti,ab,kw.
17. (mitral adj atresia).ti,ab,kw.
18. (aort$ adj atresia).ti,ab,kw.
19. (mitral adj stenosis).ti,ab,kw.
20. (aortic adj stenosis).ti,ab,kw.
21. PVOD.ti,ab,kw.
22. (Eisenmenger$ adj syndrome).ti,ab,kw.
23. TGA.ti,ab,kw.
24. (transposition adj3 great adj arter$).ti,ab,kw.
25. (switch adj operation).ti,ab,kw.
26. (switch adj surg$).ti,ab,kw.
27. senning.ti,ab,kw.
28. (univentric$ adj heart).ti,ab,kw.
29. (Mustard adj surg$).ti,ab,kw.
30. (Mustard adj operat$).ti,ab,kw.
31. (Mustard adj procedure$).ti,ab,kw.
32. (switch adj procedure$).ti,ab,kw.
33. Rastelli.ti,ab,kw.
34. (single adj ventric$).ti,ab,kw.
35. UVH.ti,ab,kw.
36. (anomalous adj pulmonary adj2 drainage).ti,ab,kw.
37. (anomalous adj pulmonary adj venous adj return).ti,ab,kw.
38. (anomalous adj pulmonary adj venous adj connection).ti,ab,kw
39. TAPVD.ti,ab,kw.
40. TAPVR.ti,ab,kw.
41. TAPVC.ti,ab,kw
42. PAPVD.ti,ab,kw.
43. PAPVR.ti,ab,kw.
44. (ventricular adj septal adj defect).ti,ab,kw.
45. VSD.ti,ab,kw.
46. (atrioventricular adj septal adj defect).ti,ab,kw.
47. AVSD.ti,ab,kw.
48. (pulmonary adj2 atresia).ti,ab,kw.
49. (pulmonary adj2 stenosis).ti,ab,kw.
50. (tricuspid adj2 stenosis).ti,ab,kw.
51. (pulmonary adj2 atresia).ti,ab,kw.

Concept 2a: long-term mortality and morbidity outcomes (593,483 hits)

52. (natural adj history).ti,ab,kw.
53. (adult adj congenital adj heart).ti,ab,kw.
54. death.ti,ab,kw.
55. surviv$.ti,ab,kw.
56. (long-term adj surviv$).ti,ab,kw.
57. mortality.ti,ab,kw.

AND

58. (long-term.ti,ab,kw. OR follow-up.ti,ab,kw.)

Concept 2b: full mortality and morbidity outcomes (1,292,653 hits)

52. (natural adj history).ti,ab,kw.
53. (adult adj congenital adj heart).ti,ab,kw.
54. death.ti,ab,kw.
55. surviv$.ti,ab,kw.
56. (long-term adj surviv$).ti,ab,kw.
57. mortality.ti,ab,kw.
58. morbidity.ti,ab,kw.
59. follow-up$.ti,ab,kw.
60. exercise.ti,ab,kw.
61. neuro$.ti,ab,kw.
62. (cardiac adj function).ti,ab,kw.
63. cogniti$.ti,ab,kw.
64. (actuarial adj survival).ti,ab,kw
65. (long-term adj survival).ti,ab,kw
66. NYHA.ti,ab,kw.

Concept 3: screening (208,309 hits)

67. exp Mass Screening/ all subheadings
68. screen$.ti,ab,kw

Limits applied

Children and younger adults: limit to (infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescent <13 to 18 years> or adult <19 to 44 years>)
Human: limit to human
Publication date: limit to 1988–2003
Papers with abstracts: limit to abstracts

Search 1: long-term outcomes

Concept 1 AND Concept 2a with limits: 2143 abstracts
Actuarial survival
[Search 1] AND (actuarial survival).ab
Exercise capacity
[Search 1] AND (exercise$.ab,ti,kw. OR NYHA.ab,ti,kw)
Neurological outcomes
[Search 1] AND neuro$.ti,ab,kw

Search 2: outcomes after screening

Concept 1 AND Concept 2b AND Concept 3 with limits: 167 abstracts [0 eligible]
(an extended version of the outcomes concept was used to widen the search)

Appendix 2

Literature table for childhood outcomes

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Abu-Harb[14]	1994	All congenital heart defects	Retrospective cohort study	UK *n* = 1074 Age: <1 year old	1 year	Causes of death	All births, infant deaths, and surviving babies with congenital heart defects in one health region in 1985 to 1990 were identified	Of the 1074 infants diagnosed in infancy, 185 died and 56 of these (30%) died undiagnosed. Severe extra-cardiac malformations were present in 29 of the 56 infants
Abu-Harb[18]	1994	HLH, IAA, COA, AS	Retrospective cohort study	UK *n* = 120 Age: <1 year old	1 year	Causes of death	All cases of obstructive left heart malformations presenting in infancy in one health region from 1987 to 1991 were analysed retrospectively	Of 120 infants presenting with obstructive left heart malformations, 12 symptomatic or died within 24 hours. 94 babies went home, 51 developed heart failure and another seven died without diagnosis. The neonatal and 6-week examinations performed poorly as screening tests
Aharon[428]	1994	Mitral valve defects	Case series	US *n* = 79 Mean age at surgery: 5 years (range 2 months–17 years)	Mean 4 years (1–10 years)	Actuarial survival	Five patients with mitral stenosis and 74 patients with mitral regurgitation underwent mitral valve repair from 1982 to 1993 in a single centre. 68 had additional heart defects	Actuarial survival was 94% at 1 year, 84% at 2 years and 82% at 5 years, and actuarial freedom from reoperation was 89% at 8 years
Alden[182]	1998	TGA	Qualitative study: uncontrolled	Sweden *n* = 31 Mean age at follow-up: 13 years	Mean 11 years	Cognitive outcome; behaviour	The psychological consequences of a single congenital heart defect were assessed through tests of intellectual function, self-perception, 'body image', psychiatric symptoms and family climate	IQ was slightly lower than in the general population. Six children (19%) had clinically significant psychiatric symptoms: they were more likely to have poorer cardiac function and more disturbed family life. Overall, children and families functioned well
Alexiou[124]	2000	AS and other aortic valve defects (some not congenital)	Case series	UK *n* = 56 (including 33 congenital AS) Mean 11 years (range 1–16 years)	Mean 7 years (range 0–26 years)	Actuarial survival; exercise capacity	Patients undergoing aortic valve replacement in a single centre from 1972 to 1999 were evaluated at follow-up. Deaths and exercise capacity were reported	93% survival at 10 years and 20 years for 33 children with congenital AS. Of all 50 survivors in study, 44 were in NYHA Class I and 6 in Class II at follow-up

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Alexiou[154]	2001	TOF	Case series	USA *n* = 89 Median age at operation: 6 months	Mean 13 years (1–25 years)	Actuarial survival exercise capacity	Children undergoing surgical repair from 1974 to 2000 were retrospectively reviewed for operative deaths, reoperation, cardiac function and exercise capacity	98% survival at 20 years; 85% freedom from reoperation. Few late complications, such as arrhythmia. 86 of 88 survivors in NYHA Class I
Al Halees[429]	2002	Congenital aortic valve disease: AS (18), mixed stenosis/regurgitation (32), aortic regurgitation (3)	Case series	Saudi Arabia *n* = 260 (including 53 congenital AS) Mean age at surgery: 8 years	Mean 4 years (up to 10 years)	Actuarial survival	All children/young adults who underwent a Ross operation for aortic valve disease in a single centre from 1990 to 2000	94% survival at 10 years. All patients but one were NYHA Class I or II
Amaral[131]	1997	COA	Case series	Brazil/UK *n* = 104	Not reported	Exercise capacity	Patients were grouped according to age at operation and outcomes compared: resting hypertension, exercise hypertension, limitation in activities and abilities	Older age at surgery (>10 years) was associated with resting hypertension. Limitation in function was not common and 94% could undertake normal activity
Ashraf[159]	1993	CAVSD	Case series	USA *n* = 104 Mean age at surgery: 1 year (primary repair), 2 years (second operation)	1–13 years (for 90% survivors)	Actuarial survival; exercise capacity	Children receiving a specific operation from 1978 to 1991 at a single centre were followed up for deaths and exercise capacity	11 patients died within 30 days of operation and 4 died later. Actuarial survival at 13 years is 81% and 76 (95%) survivors were in NYHA Class I
Bacha[153]	2001	TOF	Case series	USA *n* = 57 Median age at surgery: 8 months	Median 23 years	Actuarial survival; exercise capacity	Children who underwent surgery from 1972 to 1977 were followed up and survival and freedom from reintervention were determined	There were 8 early surgical deaths and 1 late death. 45 (92%) survivors were followed up. Actuarial survival was 86% at 20 years and 41 (91%) survivors were in NYHA Class I

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Balderston[129]	1992	COA	Case–control	USA *n* = 31 Mean age at surgery: 3 years Mean age at follow-up: 11 years 22 age/gender matched controls without congenital heart defects	Mean 8 years	Exercise capacity	Children who had surgery for COA and controls underwent bicycle exercise tests and ventilatory gas measurement	Normal exercise capacity in children with COA, but mean power was reduced relative to controls and maximal oxygen consumption was 89% of predicted. No significant difference in blood pressure on exercise between children with and without heart defects was noted
Bando[160]	1995	CAVSD	Case series	USA *n* = 203	Mean 5 years after surgery	Actuarial survival; exercise capacity	Children undergoing surgical repair from 1974 to 1995 were retrospectively reviewed for operative deaths, reoperation, valve function and exercise capacity	91% survival at 10 years. All survivors in NYHA Class I or II. 8 reoperations with 5 survivors. Only 6% had significant valve problems currently. Preoperative factors associated with worse outcome were pulmonary hypertension and valve failure
Bauer[229]	1992	Congenital AS	Case series	Germany *n* = 86 Mean age at surgery: 7 years	Up to 20 years after surgery	Actuarial survival	Follow-up of children who underwent surgery for AS in a single centre	There were 7/86 (8.1%) early deaths and 6/67 (7.7%) late deaths. Age and duration of cardiopulmonary bypass were significant prognostic factors for early death. 97% survival at 5 years, 94% at 10 years, 90% at 15 years and 87% at 20 years
Beitzke[155]	1990	TOF	Case series	Austria *n* = 127 Mean age at surgery: 4 years (1–18 years)	Mean 5 years (0–15 years) after surgery	Exercise capacity	Case series of children operated from 1975 to 1989 with 118 survivors reinvestigated at follow-up. Clinical tests including echocardiography and cardiac catheterisation at follow-up. Exercise capacity recorded	97% in NYHA Class I and 3% in Class II at follow-up. 38% survivors had an enlarged heart and 95% had abnormal conduction. 8% reoperated

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Belli[430]	1998	Double-outlet right ventricle	Case series	France *n* = 154 Mean age at surgery: 10 months	Median 52 months after surgery	Actuarial survival	Children who underwent surgery for double-outlet right ventricle from 1985 to 1996 at a single centre	86% survival at 10 years
Bellinger[180]	1995	TGA	Randomised trial	USA *n* = 171 Mean age at surgery: <3 months	1 year after surgery	Neuro-development; predictive factors	Randomised study comparing low-flow cardiopulmonary bypass with circulatory arrest during arterial Switch operation. Developmental and neurological evaluations and magnetic resonance imaging (MRI) were performed at 1 year old	Of 171 children enrolled, 155 were evaluated. Heart surgery performed with circulatory arrest is associated with a higher risk of delayed motor development and neurological abnormalities at the age of 1 year than is low-flow cardiopulmonary bypass
Bellinger[165]	1999	TGA	Long-term follow-up of randomised trial	USA *n* = 163 Age at surgery: <3 months	4 years	Neuro-development; cognitive outcome	Randomised study comparing low-flow cardiopulmonary bypass with circulatory arrest during arterial Switch operation. Developmental and neurological status evaluated at 4 years of age in 158 of 163 eligible children (97%)	The performance of the full cohort was below expectations in IQ, expressive language, visual–motor integration, motor function and oromotor control. Circulatory arrest during surgery was associated with worse motor coordination and planning but not with lower IQ or worse overall neurological status. Seizures in the perioperative period were associated with increased risk of neurological abnormalities
Benatar[431]	1995	Complex congenital heart defects	Case series	The Netherlands *n* = 31	Mean 3 years (10 months–7 years)	Actuarial survival	Children who underwent a specific procedure in a single centre were followed for deaths and complications	Early surgical mortality was 16%. Median hospital stay was 26 days. The 1-year and 5-year actuarial survival was 69%
Boening[208]	2002	Atrioventricular septal defect	Case series	Germany *n* = 121 Median age at surgery: 1 year	Mean 7 years	Actuarial survival	Children who underwent surgery at a single centre from 1975–1995 were followed up	Actuarial survival after 1 year was 80%, after 10 years was 78% and after 20 years was 65%

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Boger[126]	1999	TAPVC	Case series	USA *n* = 44 Age range: 0–16 years	Mean 12 years (range 0–24 years) after surgery	Actuarial survival; exercise capacity	Case series of children who underwent cardiac surgery. Deaths, reoperation, exercise capacity and medication recorded	84% survival at 15 years; 74% reoperation-free survival at 15 years. Perioperative factors influencing survival explored. All survivors were using no cardiac medication and reported normal exercise capacity, school attendance or employment
Bove[80]	1983	All congenital heart defects	Case series	UK *n* = 212 Mean age at surgery: <1 year	3–8 years	Predictive factors	All 212 neonates who underwent cardiac surgery at a single centre from 1976 to 1980 were reviewed	Metabolic acidosis and the need for preoperative respiratory support were appreciably greater in non-surviving patients. 40 required open-heart surgery with 23 (57%) deaths. 44 (25%) of the neonates undergoing non-bypass procedures died
Bove[78]	1998	HLH	Case series	USA *n* = 253 Mean age at surgery: less than 1 year	Up to 4 years	Actuarial survival	Children who underwent the Norwood operation for classic HLH syndrome from 1990 to 1997 were followed up	Hospital survival was 76% for the first stage (all children), 97% for the second stage and 88% for the third stage (94 children)
Bowyer[109]	1990	TGA	Case–control	UK *n* = 12 Age range: 7–13 years 20-age and size-matched controls	6–12 years after surgery	Exercise capacity	Children who underwent Mustard operation before 1 year old. Exercise capacity tested by self-report questionnaire adapted for children, and treadmill test, oxygen saturation and consumption, echocardiography and cardiac catheterisation	Compared with controls, 7 children with transposition had normal exercise tolerance, 10 had a moderate reduction and 3 a severe reduction in exercise capacity
Bradley[432]	2002	UVH	Case series	USA *n* = 22 Median age at surgery: 8 days	Up to 5 years	Actuarial survival	Follow-up of infants receiving surgery for UVH at a single centre from 1996 to 2001	Actuarial survival beyond 30 months was 90%

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Braun[125]	1998	AS, IAA and other defects obstructing blood flow from the left ventricle	Case series	The Netherlands *n* = 41 Mean age at surgery: 10 years (35 days to 19 years)	Mean 2 years (range 44 days–4 years)	Exercise capacity	Case series of children operated from 1994 to 1998 in a single centre. Deaths, reoperation and exercise capacity recorded at follow-up	2 patients died postoperatively after repair of interrupted aortic arch. No later deaths. 3 reoperations. 97% children in NYHA Class I and one in Class II
Breymann[433]	1999	HLH and complex defects with aortic hypoplasia	Case series	Germany Typical HLH: *n* = 48, median age at surgery: 15 days Complex lesions: *n* = 12, median age at surgery: 59 days	Mean 7 years	Actuarial survival	Children who underwent Norwood procedure (stage I) at a single centre from 1989 to 1998 were reviewed for deaths and risk factors. Typical HLH syndrome and complex lesions were compared	Stage I hospital survival was 73% for typical HLH compared with 83% for complex defects. Improvements in actuarial survival at 4 years were noted for the HLH group from 28% in 1989–94 to 58% in 1994–97. No late deaths in complex group
Brizard[434]	1997	Truncus	Case series	Australia *n* = 82 Age at surgery: <3 months	Mean 6 years	Actuarial survival	Follow-up of children who underwent surgery in a single centre from 1979 to 1995	Actuarial survival at 7 years was 81%
Brown[83]	2001	TGA	Case series	USA *n* = 201 Mean age at surgery: 10 days	Not reported	Actuarial survival; predictive factors	Follow-up of consecutive children who underwent a Switch operation in a single centre from 1986 to 1999	Actuarial survival was 90.4% at 1 month, 87.9% at 1 year and 87.9% at 5 years. In the analysis by period, the operative mortality declined from 28% to 6%
Brown[218]	2003	All congenital heart defects	Case series	UK *n* = 355	1 year	Predictive factors	A retrospective review was performed of pre-, intra- and postoperative factors for children undergoing open heart surgery in a single centre from 1999 to 2000. All factors were evaluated for strength of association with length of intensive care unit (ICU) stay (LOS)	Children above the 95th percentile for LOS had a three-fold greater mortality. Preoperative mechanical ventilation, neonatal status, major medical problems, operative complexity, cardiopulmonary bypass time and a postoperative complication score were independently associated with LOS

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Cabezuelo[435]	1990	TAPVC	Case series	Spain *n* = 36 (26 received operation) Mean age at surgery: 2 months	Not reported	Actuarial survival	Follow-up of infants attending a single centre from 1971 to 1988	Operative mortality rate of 57.7%. Actuarial survival rate was 34.4% in the total group and 42.3% in the operated group
Carano[139]	1999	COA	Case series	Italy *n* = 28	Not reported	Exercise capacity	Patients who had undergone successful COA repair were evaluated during exercise	Age at surgery did not predict hypertension on exercise. Increased narrowing of the aorta was related to a higher rise in blood pressure during exercise
Casey[188]	1994	Complex congenital heart defects	Case–control	UK Cases: *n* = 26 children with complex congenital heart defects Control group: *n* = 26 children with innocent murmur	Up to school age	Behaviour	Examined the behavioural adjustment at school age of 26 children with surgically treated complex congenital heart disease compared with that of 26 children who had been diagnosed as having an innocent murmur	Children with complex heart defects were rated by parents as more withdrawn, having more social problems and engaging in fewer activities, and by their teachers as more withdrawn. This was associated more strongly with family adjustment than physical disability
Chang[223]	1991	HLH, AS and left heart outflow obstruction	Case series	USA *n* = 21 Age at surgery: 2 days	Up to hospital discharge	Predictive factors	In 22 cases of fetal diagnosis of critical left heart obstruction, 21 were correct and 17 underwent surgery at a single centre	77% of infants survived surgery and were discharged. Transfer to a tertiary centre for delivery permitted surgery at a younger age and may be associated with better survival
Cho[206]	2002	TOF	Case series	USA *n* = 495 (160 palliative repair, 335 complete repair)	Mean 6 years (palliative repair) Mean 12 years (complete repair)	Actuarial survival	Records of children operated on from 1977 to 1999 were reviewed for deaths and factors affecting mortality. Two groups: children having palliative repair and those having complete repair	Actuarial survival of 86% at 10 years and 75% at 20 years

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Clancy[234]	2003	All congenital heart defects, except HLH	Case series	USA *n* = 164 Age at surgery: neonates	Early post-operative period (up to hospital discharge)	Predictive factors	To identify pre- and intraoperative risk factors associated with postoperative acute neurological events, including seizures, in newborn survivors of congenital heart surgery with circulatory arrest	Seizures or coma, which appeared in 19% of all survivors, were significantly associated with specific types of congenital heart disease, the presence of genetic conditions, and prolonged circulatory arrest time
Clapp[436]	1987	CAVSD	Case series	USA *n* = 121 Age at surgery: 1–9 months	Up to 10 years	Actuarial survival	Review of patients who presented to a single centre for surgery over a 10-year period. Follow-up of long-term management and overall outcome	Of 121 patients, 70 underwent corrective surgery, 21 (30%) of whom died perioperatively. Of 49 patients who survived surgery, 36 are in NYHA Class I
Cobanoglu[228]	2002	TOF	Case series	USA *n* = 63 Age at surgery: <1 year	Mean 12 years	Actuarial survival	A retrospective review of consecutive patients who underwent corrective surgery at <1 year of age in a single centre. Risk factors for operative mortality and functional status at follow-up were analysed. Follow-up through clinic appointments and telephone questionnaires	Actuarial survival was 89% at 20 years. 88% of survivors have good-to-excellent functional status over 15 years after surgery
Cohen[437]	1989	COA	Case series	USA *n* = 646	Median 20 years	Actuarial survival	Long-term follow-up of children and adults who underwent surgical repair at a single centre from 1946 to 1981	For children aged ≤ 14 year at surgery, actuarial survival was 91% at 20 years. Age at the time of initial repair is the most important predictor of long-term survival. Coronary artery disease is the most common cause of late death. 25% survivors developed hypertension

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Crepaz[138]	1993	COA	Case–control	Italy *n* = 35 Mean age at operation: 12 years Mean age at follow-up: 23 years (1–47 years) 20 controls without congenital heart defects	Mean 10 years	Exercise capacity	Cases and controls underwent echocardiography, blood pressure and exercise test	28% cases were hypertensive at rest and this was more likely if age at surgery was greater. Exercise-induced hypertension was seen in 80% of cases
Daebritz[438]	2000	TGA	Case series	USA *n* = 312 Mean age at surgery: 84 days	Mean 4 years	Actuarial survival	Risk factors for mortality and morbidity were analysed retrospectively in patients who underwent surgery at a single centre from 1982 to 1997	Actuarial survival was 92% at 5 and 10 years. Operative survival improved after 1990
Dajani[102]	1997	All congenital heart defects	Review	USA	Not applicable	Causes of death	Updated guidelines on prevention of infective endocarditis prepared for the American Heart Association	Major changes include: (1) emphasis that most cases of endocarditis are not attributable to an invasive procedure; (2) procedures for which prophylaxis is recommended are more clearly specified; (3) for oral or dental procedures the antibiotic prophylaxis is simplified and the dose reduced for some procedures
Dearani[204]	2003	Complex congenital heart defects	Case series	USA *n* = 1095 Mean age at surgery: 10 years	Mean 11 years	Actuarial survival; predictive factors	Late outcome of patients who underwent surgery at a single centre from 1964 to 1992	For early survivors, actuarial survival was 77% at 10 years and 59% at 20 years. Younger age at operation was associated with improved late survival
DeBoer[439]	1990	Congenital AS	Case series	USA *n* = 51 Mean age at surgery: 11 years	Mean 17 years	Actuarial survival	Follow-up of patients who underwent surgery at a single centre from 1956 to 1986	Actuarial survival was 94% at 10 and 15 years, 82% at 20 and 25 years and 71% at 28 years

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Delamater[105]	2001	All congenital heart defects	Review	UK	Not applicable	Exercise capacity; neurodevelopment; cognitive outcome; behaviour; predictive factors	Review of outcomes, including exercise capacity, in children with congenital heart defects	–
Delius[440]	1996	TAPVC	Case series	UK *n* = 232 Mean age at surgery: 2 months (range 1 day–46 months)	Not reported	Actuarial survival	Review of outcomes after surgery in a single centre from 1971 to 1994	Actuarial survival was 73% at 10 years
Delius[441]	1997	Atrioventricular septal defect with TOF	Case series	UK *n* = 35 Mean age at definitive surgery: 6 years (palliation) 4 years (primary repair)	Up to 8 years	Actuarial survival	Review of children who underwent definitive surgery (either as a primary repair or after a palliative procedure) at a single centre from 1980 to 1995. 77% had Down's syndrome	Operative mortality at definitive operation was 10%. Actuarial survival was 77% at 7 years for all patients (84% for primary repair and 65% if a palliative shunt procedure was included)
de Ruijter[442]	2002	TOF	Case series	The Netherlands *n* = 171 Mean age at surgery: 2 years	Mean 10 years	Actuarial survival	Review of all patients who underwent surgery in a single centre from 1977 to 2000	Actuarial survival was 91% at 20 years
Di Filippo[140]	1997	COA	Review	France	Not applicable	Complications after surgery; exercise capacity	Review of long-term results after surgery for COA in children	Mortality, stenosis and exercise hypertension influenced by surgical techniques and age at operation

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Ekman Joelsson[443]	2001	PA and IVS	Cohort study	Sweden *n* = 84	Median 6 years (14 days–20 years)	Actuarial survival	Follow-up of all children born with PA/IVS in Sweden from 1980 to 1999. Retrospective study of medical records and investigations	Incidence of 4.2 per 100,000 live births. Operations performed in 77 children with 75% survival at 1 year after surgery. At the end of follow-up, 52 children were alive. Significant risk factors for death were low birth weight, male sex, type of PA and type of intervention
Elgamal[444]	2002	COA	Case series	USA *n* = 65 Mean age at surgery: 13 days (range 1–43 days)	Not reported	Actuarial survival	Follow-up of early outcomes in infants who underwent surgery in a single centre from 1995 to 2000.	Actuarial survival was 91% at 5 years
Elkins[445]	1994	TGA	Case series	USA *n* = 53 Mean age at surgery: 2 months (range 1 day–36 months)	Median 23 months	Actuarial survival	Review of functional outcomes in consecutive patients who underwent surgery at a single centre from 1985 to 1993	Actuarial survival was 83% at 8 years. All survivors in NYHA Class I
Elkins[446]	2001	Congenital AS	Case series	USA *n* = 178 Mean age at surgery: 3 days–17 years	Up to 15 years	Actuarial survival	Retrospective review of children who underwent surgery at a single centre from 1986 to 2001	Operative mortality was 4.5%. Actuarial survival was 92% at 12 years

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Fallon[81]	1995	All congenital heart defects	Case notes review	UK *n* = 523	1–30 months after surgery	Neuro-development; predictive factors	Cardiac surgical discharge summaries were searched for recorded evidence of adverse neurological events occurring between operation and time of discharge	Neurological events were recorded in 31 cases and included seizures (*n* = 16), pyramidal signs (*n* = 11), extrapyramidal signs (*n* = 8), coma (*n* = 6) and neuro-ophthalmic deficits (*n* = 6). There were significantly more adverse neurological events after aortic arch surgery (16.6% of cases) and with longer intraoperative bypass duration. Long-term data on 19 of 23 survivors indicated that four were normal, nine had neurological problems beginning preoperatively and 6 had neurological problems beginning perioperatively
Ferrieri[98]	2002	All congenital heart defects	Review	USA	Not applicable	Causes of death	Review of infective endocarditis in childhood	
Forbess[447]	1995	HLH	Case series	USA *n* = 212 Mean age at surgery: neonatal	Up to 1 year (to second-stage surgery)	Actuarial survival	Review of outcomes after Stage 1 Norwood surgery at a single institution from 1983 to 1993	Operative mortality was 46.2%. Overall first-year survival was 59% after 1 year for infants with mitral or aortic stenosis subtypes and it was 33% for all others. Preoperative anatomic subtypes and physiological state are predictors of mortality
Forbess[181]	2001	Complex congenital heart defects	Case–control study	USA *n* = 27 Mean age at surgery: 2 years Age at follow-up: 5 years Control group: 133 children who underwent surgery in 1970–90 (mean age at surgery: 7 years)	Median 5 years	Cognitive outcome	Follow-up of children who underwent Fontan surgery to look at cognitive outcomes and changes over time. Standardised IQ tests were given to cases and compared with population means and with a historical cohort of controls	IQ scores in children after Fontan are within the normal range, but performance remains lower than the general population mean. Compared with a historical cohort, there was no evidence of worse IQ scores with Fontan at an earlier age

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Forbess[185]	2002	All congenital heart defects	Cross-sectional study	USA *n* = 243 Median age at operation: 2 months Age at survey: 5 years	Median 5 years	Cognitive outcome; predictive factors	Survey of neurodevelopment of 5-year-old children following congenital heart surgery. Neuropsychological tests performed between 1998 and 2001	IQ scores were in the normal range. Lower socioeconomic status and Di George syndrome were associated with lower IQ scores. Trends toward worse outcomes were observed in single-ventricle patients, after long postoperative intensive care stays and after longer duration of circulatory arrest during surgery
Forbess[225]	2002	Various congenital heart defects (defined by operation)	Case series	USA *n* = 69 Median age at surgery: 3 months Age at follow-up: 5 years	Not reported	Cognitive outcome; predictive factors	Children who had undergone biventricular repair of congenital heart defects were assessed using standardised IQ test at age 5 years	IQ scores overall were within the normal range. Circulatory arrest for longer than 39 minutes was associated with deficits in visual–motor and fine motor skills and possibly in full-scale IQ, after adjustment for socioeconomic status
Franklin[448]	1991	Double-inlet ventricle	Case series	UK *n* = 191	2 years	Actuarial survival	Review of outcomes in complex defects and suitability for surgery at 2 years of age	Actuarial survival was better than for those deemed unsuitable for surgery (*n* = 55; 68% versus 28% at 1 year). Only 78 patients (57%) were alive and suitable candidates for surgery at 2 years of age
Franklin[449]	1993	TA	Case series	UK *n* = 237	Median 8 years	Actuarial survival	Outcomes of infants with TA diagnosed from 1972 to 1987 in a single centre were reviewed	Actuarial survival was 72% at 1 year, 53% at 5 years and 46% at 10 years
Frontera[450]	1990	UVH	Case series	Spain *n* = 90	Mean 9 years	Complications after surgery; causes of death	Retrospective review of patients found to have univentricular heart at catheterisation in a single centre from 1971 to 1988	Of 90 children, 43 died in the first year of life and 7 later, giving an overall survival rate of 38.5% at 5 years. Survival was marginally better for those given a palliative operation

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Fulton[451]	1999	IAA	Case series	Australia *n* = 72 Mean age at surgery: 3 days (range 1–180 days)	Mean 4 years	Actuarial survival	Review of immediate and long-term outcomes in infants who underwent operation in a single centre from 1985 to 1997	Actuarial survival for the whole cohort was 85% at 12 years. 28 patients have required at least one reoperation
Gabriel[145]	2002	VSD	Case series	Austria *n* = 229 Mean age at follow-up: 30 years	Mean 7 years	Exercise capacity	Adults with VSD which did not require repair in childhood were followed up and given a clinical examination and exercise test	97% of the original group underwent follow-up, 6% had spontaneous closure of defect, 2% had infective endocarditis, 95% had no death, endocarditis or surgery by 8 years of follow-up, 95% were symptom-free although 13% had arrhythmias at follow-up. Mean exercise capacity was 92% of expected for age and size
Garcia Hernandez[452]	1994	TOF	Case series	Spain *n* = 101 Mean age at surgery: 7 months (palliation only), 3 years (corrective surgery after palliation), 3 years (primary repair)	Mean 4 years	Actuarial survival	Review of children who underwent surgery in a single centre from 1979 to 1992. Before 1985, palliative surgery was used exclusively	Actuarial survival was 86% at 6 years. After 1985, mortality reduced from 6.7% to 2.3%
Garcia Hernandez[119]	1995	TGA	Case series	Spain *n* = 21 Mean age at surgery: 10 days Mean age at follow-up: 21 months	2 months to 5 years after surgery	Exercise capacity	Deaths and exercise capacity at follow-up reported for a case series of children receiving arterial Switch repair from 1988 to 1993 in a single centre	17 survivors are in NYHA Class I and one survivor is in Class II. Three early postoperative deaths occurred and no late deaths

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Gaynor[453]	1999	Complex congenital heart defects	Case series	USA *n* = 73 Median age at surgery: 5 days (range 1 day–2 years)	Not reported	Actuarial survival	Retrospective review of factors influencing the survival of infants who were admitted to a single centre from 1984 to 1997	12 patients died before the operation and 61 infants had surgery. Overall survival was 45% at 6 months of age, 37% at 1 year and 19% at 5 years. Survival for patients undergoing surgery was 54% at 6 months of age, 44% at 1 year, and 23% at 5 years
Gaynor[210]	2002	HLH and UVH with left outflow tract obstruction	Case series	USA *n* = 102 (hypoplastic left heart), 56 (other)	Up to 1 year old	Predictive factors	A retrospective study of risk factors for operative and 1-year mortality in infants undergoing the Norwood operation in a single centre from 1998 to 2001	Operative survival was 78% (HLH) and 75% (other). Survival at 1 year after surgery was 66% in both groups. Additional cardiac or extracardiac anomalies were predictors of poor outcome
Gaynor[209]	2002	Complex congenital heart defects	Case series	USA *n* = 332 Median age at surgery: 22 months	Not reported	Predictive factors	A study to evaluate factors contributing to decreasing early mortality and morbidity after the Fontan procedure from 1992 to 1999	Overall mortality was 6.6%. Patient characteristics may be predictive of outcome but anatomic variations are not. The decrease in mortality and morbidity in the current era is attributed to changes in management strategies
Genoni[454]	1996	TGA	Case series	Switzerland *n* = 342 Mean age at surgery: 69 months	Mean 13 years	Actuarial survival	Children operated from 1962 to 1994 at a single centre were reviewed	Actuarial survival for all patients was 88% after 10 years and 82% after 20 years. Most survivors were symptom free (66% NYHA Class I) or they had slight symptoms (29% NYHA Class II). Only 5% were NYHA Class III or IV

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Gewillig[115]	1991	TGA	Case series	UK *n* = 249 Mean age at definitive surgery: 2 years	Mean 12 years (up to 24 years) after surgery	Causes of death; actuarial survival; exercise capacity	Case series of children operated from 1965 to 1980 as infants using Mustard operation at a single centre. Deaths, cardiac function and exercise capacity measured at follow-up	Operative mortality of 9%. 50 late deaths, of which 7 were not cardiac and 37 were sudden cardiac deaths. Actuarial survival after 1, 10 and 20 years was 85, 75 and 67%. Risk of death highest around surgery and 8–15 years later. 87% in NYHA Class I at follow-up. Risk of arrhythmia increased over time after surgery at a constant rate
Gildein[147]	1994	VSD; tetralogy of Fallot; TGA; TA	Case series	Germany *n* = 35 Mean age at follow-up: 11 years	2–12 years	Exercise capacity	Children with mixed group of congenital heart defects tested after surgery. Oxygen uptake on exercise recorded	Children with a VSD repair, Fontan surgery or tetralogy of Fallot patching have reduced capacity for both intensive and endurance exercise
Gomelsky[227]	1998	TGA	Cohort study	USA *n* = 57 Mean age at follow-up: 8 years	8 years	Predictive factors	Evaluation of cognitive, functional, educational achievement and behavioural status related to birth and operative variables in participants who were initially enrolled in the Baltimore–Washington Infant Study and survived surgery for transposition	Non-verbal skills (short-term memory and visual–motor integration) appeared sensitive to variations in surgical strategies. Neurological events, such as seizures, were related to global deficits in intellectual functioning
Haas[455]	1999	TGA	Case series	Germany *n* = 285 Median age at surgery: < 1 month	1–15 years	Actuarial survival	Review of outcomes in patients who underwent surgery from 1983 to 1997 in a single centre	Cumulative survival for all patients at 5 and 10 years was 93% and at 15 years was 86%. 88% of the patients had no limitations with exercise
Hamada[226]	2002	TOF	Case series	Japan *n* = 167 Mean age at surgery: 6 years	Not reported	Actuarial survival; predictive factors	Review of patients who underwent surgery in a single centre from 1965 to 1975	Actuarial survival was 86% at 29 years. 7 deaths were sudden cardiac deaths. Older age at surgery and longer cardiac arrest duration during surgery were associated with late mortality. 89% of survivors in NYHA Class I

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Haneda[149]	1990	TOF	Case series	Japan *n* = 166	Mean 9 years (1–19 years) after surgery	Actuarial survival; exercise capacity	Case series of children with surgical correction since 1971 at a single centre. Deaths, exercise capacity and cardiac function recorded at follow-up	96% survival at 5 years and 90% at 13 years. 72% of survivors were in NYHA Class I, 26% in Class II and 2% in Class III. Some patients reported limitations in school and social life
Haneda[161]	1992	CAVSD	Case series	Japan *n* = 28 (including 10 with Down's syndrome)	Mean 7 years (1–17 years) after surgery	Actuarial survival; exercise capacity	Case series of children with surgical repair since 1972. Exercise capacity, cardiac function, reoperation and deaths recorded at follow-up	Actuarial survival rate 86% at 12 years. 14 patients (70%) of 20 evaluated were in NYHA Class I, 4 (20%) in Class II and 2 (10%) in Class III at follow-up
Hauser[135]	2000	COA	Case–control	UK *n* = 55 Mean age at surgery: 3 years (range 0–12 years) Mean age at follow-up: 11 years (range 6–21 years) 40 age-matched controls	Mean 8 years after surgery	Exercise capacity	Growth, blood pressure, echocardiography and physiological reactions to exercise treadmill test (Bruce protocol) recorded for 55 children with repaired COA and 40 age-matched controls	Children with repaired COA had normal exercise capacity and physiological reactions to exercise compared with controls. Resting hypertension was recorded in 45% of children with COA
Hawkins[456]	1998	Congenital AS	Case series	USA *n* = 37 Mean age at surgery: 26 days	5 years (range 3 months–11 years)	Actuarial survival	Review of infants who underwent surgery for critical AS in the first 3 months of life at a single centre from 1986 to 1996	Actuarial survival was 92% at 1 month, 78% at 1 year and 73% at 10 years
Heger[134]	1997	COA	Case series	Austria *n* = 41 Mean age at surgery: 12 years Mean age at follow-up: 28 years	Mean 16 years after surgery	Exercise capacity	Evaluation of outcomes after COA repair performed from 1945 to 1997. Physical examination, bicycle exercise test and cardiac function tests undertaken	Exercise-induced hypertension was found in 44% of patients. Patients who were >9 years old at surgery had a significantly higher risk of hypertension at rest but were also older at the time of follow-up

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Heying[174]	1999	All congenital heart defects	Cross-sectional survey	USA *n* = 11 Median age at surgery: 6 years (range 2–10 years)	Median 3 years (range 1–6 years)	Neuro-development	Evaluation of neurodevelopmental status in children who survived multiple system organ failure after cardiac operations for congenital cardiac defects. Clinical and laboratory examinations included cardiac, pulmonary, renal, hepatic, neurological and psychological function tests	All patients had adequate cardiac function. Lung function was abnormal in 3 children and renal function was abnormal in 2 children. Severe neurological sequelae such as diplegia (*n* = 1) and learning difficulties (*n* = 1), delayed motor, graphomotor and/or speech development (*n* = 5) and abnormal intelligence (*n* = 20) were also observed
Hisatomi[151]	1991	TOF	Case series	Japan *n* = 166	≥ 10 years after surgery	Exercise capacity	Survivors followed up 10 years after surgery. Cardiac function and exercise capacity recorded	85% in NYHA Class I, the rest had limitations to normal activity. Valve problems present in majority
Hokanson[457]	1999	TOF	Review	USA	Not applicable	Causes of death; complications after surgery	Review of long-term outcomes in adults with repaired TOF	–
Horstkotte[152]	1993	TOF	Case series	Germany *n* = 246 Mean age at follow-up: 12 years	Mean 20 years (18–29 years)	Exercise capacity	All children with surgical repair in a single institution from 1961 to 1972 were followed up after 20 years. Causes of death, cardiac complications and exercise capacity were recorded	46 operative deaths and 21 late deaths occurred. 18 late deaths were due to cardiac causes: arrhythmias (9), infective endocarditis (4), heart failure (5). Cumulative survival was 68% at 20 years after surgery. 59% were in NYHA Class I and 36% in Class II after 20 years
Hoshino[458]	1999	HLH	Case series	Japan *n* = 26	Up to 2 years	Actuarial survival	Retrospective study of outcomes and natural history in infants with unoperated HLH. Predictive factors associated with longer survival were sought	The mean duration of survival was 60 days. Long-term survival was significantly correlated with stable ductal blood flow without COA of the aorta, restriction of interatrial communication without hypoxemia, and no metabolic acidosis

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Hovels-Gurich[166]	1997	TGA	Case series	Germany *n* = 96 Mean age at surgery: 7 days (range 2–39 days) Mean age at follow-up: 5 years (range 3–9 years)	Mean 5 years	Neuro-development; predictive factors	Of 96 children who underwent open-heart surgery in a single centre from 1986 to 1992, 77 were followed up for clinical neurological status and examined using standardised tests of intelligence, acquired abilities and vocabulary, gross motor and fine motor functions. Results were related to preoperative, perioperative and postoperative status and management	Neurologic impairment was more frequent (9.1%) than in the normal population. Intelligence was within the normal range using standardised tests but motor function, vocabulary and acquired abilities were below normal. Reduced intelligence was found in 9.1%, fine motor dysfunction in 22.1% and gross motor dysfunction in 23.4% of the children. Intelligence was significantly inversely related to the duration of bypass and tended to be inversely related to the duration of circulatory arrest
Hovels-Gurich[167]	2001	TGA	Case–control study	Germany *n* = 33 Age at follow-up: 3–5 years Control group: 32 age-matched children with no congenital heart defects	Not applicable	Neuro-development; cognitive outcome; predictive factors	Children who underwent surgery as neonates and normal controls underwent evaluation of socio-economic and clinical neurological status and standardised tests of development. Results were related to the control group, to population norms and to perioperative risk factors	Clinical neurological status was normal in 26 patients (79%) and reduced in 7 (21%). Developmental scores for motor function, visual perception, learning and memory, cognitive function, language and socio-emotional functions were similar to population norms. The control group scored higher on tests of overall development, cognition and language, but also on socio-economic status. Both circulatory arrest and low-flow bypass during surgery are associated with neurological impairment

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Hovels-Gurich[176]	2002	TGA	Case series	Germany *n* = 60 Age at follow-up: 10 years (range 8–14 years)	Mean 5 years (since previous assessment), mean 10 years since surgery	Neuro-development; cognitive outcome; predictive factors	Within a longitudinal study, 60 unselected children operated on as neonates were re-evaluated for neurological status and using standardised tests for gross motor function, intelligence, acquired abilities, language, and speech. Results were related to perioperative status and neuro-developmental status at 5 years	Neurologic and speech impairments were more frequent (27% and 40%, respectively) than in the general population. Intelligence and socio-economic status were not different, whereas motor function, acquired abilities and language were reduced. Overall developmental impairment in one or more domains was greater than at 5 years. Preoperative acidosis and hypoxia predicted reduced motor function, whereas longer bypass duration predicted both neurological and speech dysfunction
Hovels-Gurich[190]	2002	TGA	Case series	Germany *n* = 60 Age at follow-up: 10 years (range 8–14 years)	Mean 5 years (since previous assessment), mean 10 years since surgery	Behaviour	60 children operated as neonates were assessed using the Child Behaviour Checklist (CBCL) and the Inventory for the Assessment of Quality of Life in Children and Adolescents (IQCL)	Parent-reported behavioural outcome was worse, whereas quality of life on self-reported IQCL scores was not reduced compared with the normal population
Hraska[116]	1999	TGA	Case series	Slovakia Group 1 (Senning repair) *n* = 21 Group 2 (Switch repair) *n* = 90 Mean age at surgery: Group 1 = 135 days Group 2 = 15 days	Mean 3 years (range 0–6 years)	Actuarial survival; exercise capacity	Follow-up of children operated in a single centre with comparison of mortality and exercise outcomes after two surgical techniques	94% survival at 5 years for combined group. All children receiving arterial Switch repair were in NYHA Class I at follow-up

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Hucin[114]	2000	TGA	Case series	Czech Republic *n* = 177 Age at surgery: <1 year	12–18 years	Exercise capacity; neuro-development	Case series of children who underwent Mustard operation at single centre from 1979 to 1984. Cardiac function and exercise test recorded at follow-up	61% of survivors had normal heart rhythm. 10 sudden cardiac deaths occurred. Valve problems treated with medication in 16%. Neurological sequelae in 13% (10% present preoperatively) and severe neurological damage in 4%. 96% had reasonable exercise ability on oxygen consumption testing and 84% were in NYHA Class I
Huysmans[133]	1989	COA	Case series	The Netherlands *n* = 30 Age at surgery: <3 years	Mean 22 years (range 15–34 years)	Exercise capacity	30 children of 121 who underwent surgical repair at a single centre attended for follow-up, including cardiac imaging and exercise tests	Valve stenosis was found in 23 adults. 18 also had exercise-induced hypertension, which was not related to age at surgery or degree of valve narrowing
Isomatsu[459]	2001	COA	Case series	Japan *n* = 79 Median age at surgery: 28 days (range 4–90 days)	Mean 9 years (range 2–18 years)	Actuarial survival	Review of outcomes after two-stage surgery at a single centre from 1984 to 1998	Actuarial survival was 92% at 10 years
Jonas[221]	1994	HLH	Case series	USA *n* = 78	Not reported	Predictive factors	Retrospective study of patients who underwent palliative surgery in a single centre from 1983 to 1991 to identify predictors of mortality	Actuarial survival estimate among hospital survivors only was 34% at 3 years and 25% at 5 years. Aortic or mitral atresia or perioperative acidosis had a higher mortality risk
Kappetein[132]	1993	COA	Case–control	The Netherlands *n* = 30 Mean age at surgery: 11 months Control group: 30 age- and sex-matched students without congenital heart defects	Mean 22 years (14–33 years)	Exercise capacity	Clinical imaging investigation and bicycle exercise testing at follow-up in patients who underwent COA repair and a control group	Narrowing at the site of COA surgery on digital imaging (but not MRI) correlated significantly with exercise hypertension

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Karl[460]	1992	TOF	Case series	Australia *n* = 366 Mean age at surgery: 15 months	Mean 3 years	Actuarial survival	Review of outcomes in children who underwent surgery in a single centre from 1980 to 1991	Actuarial survival was 97% at 3 years
Kawashima[150]	1990	TOF	Case series	Japan *n* = 380	Up to 30 years after surgery	Actuarial survival; exercise capacity	Long-term survivors of surgery from 1956 to 1988. Late deaths, reoperation, arrhythmias and exercise capacity recorded	94% survival at 10 years, 90% at 20 years and 85% at 30 years. 287 followed up: 80% in NYHA Class I, 17% in Class II, 3% in Class III, none in Class IV. Ventricular arrhythmias more common in survivors >10 years after surgery
Keane[99]	1993	AS	Case series	USA *n* = 462 Age at surgery: 25 children aged <2 years; mean age 10 years for remaining 432 children	>16 years	Complications after surgery; actuarial survival; exercise capacity	Children and adults with AS diagnosed on cardiac catheterisation from 1958 to 1969 followed up at least 15 years later. Children aged <2 years at operation were excluded from further analysis. Deaths, operations, infective endocarditis, cardiac function and exercise capacity measured at follow-up in 371 survivors contacted	85% survival at 20 years overall. Children aged >2 years at surgery had 90% survival at 20 years. Children aged <2 years at surgery had 64% survival at 1 year. 92% survivors in NYHA Class I. Higher than normal risk of arrhythmias. Almost half had valve problems at follow-up. Reported clinical status excellent in 30% and poor in 19% at follow-up
Kerdaniel-Ariche[141]	1999	COA	Case series	France *n* = 75 Age at surgery: <6 months	Up to 19 years	Exercise capacity	Children operated at a young age for COA in a single centre from 1980 to 1996 were reviewed. Deaths and reoperation for the whole group and exercise tests in 19 children were reported	2 early postoperative deaths and 2 later deaths occurred. 6 children had reoperations. In 8 of 19 children studied, exercise-induced hypertension was found

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Kirjavainen[461]	1999	TGA	Case series	Finland *n* = 100	Mean 13 years	Actuarial survival	Retrospective review of outcomes in children operated in a single centre	Actuarial survival was 90% (simple transposition) and 78% (complex transposition)
Kirkham[168]	1998	All congenital heart defects	Review	UK	Not applicable	Neuro-development	Review of neurodevelopmental outcomes after open-heart surgery and predictive factors	There is a high incidence of acute neurological events in the immediate postoperative period and cognitive and motor deficits at long-term follow-up in some survivors. Some children may be at higher risk owing to anatomic or genetic predisposition, or incidence may vary with surgical technique
Kirshbom[205]	2002	TAPVC	Case series	USA *n* = 100 Median age at surgery: 15 days (range 1 day–2 years)	Median 6 years	Actuarial survival; cognitive outcome	Medical records of children who underwent surgery from 1983 to 2001 were reviewed and a standardised questionnaire was administered to guardians of survivors	Actuarial survival was 84% at 15 years. Carers described their child's health as excellent, 27% good, 9% fair and 0% poor. On school performance, 40% of children were described as above average, 29% average, 4% below average and 27% were in special education classes
Konstantinides[88]	1991	ASDs	Review	USA	Not applicable	Causes of death; complications after surgery	Review of natural history of children with ASDs	Some survive unoperated to 80 years old but average age at death does not exceed 50 years. Complications included arrhythmia, PVOD or congestive heart failure
Kramer[183]	1989	All congenital heart defects	Case–control	Germany *n* = 128 Age at follow-up: 4–15 years Control group: 89 children without congenital heart defects	Not applicable	Cognitive outcome	Cases and controls were evaluated for development of personality and intelligence. Children with congenital heart defects were divided into two groups: those with physical handicap due to heart defects (*n* = 77) and those without disability but with heart defects (*n* = 51)	Children with disability have lower IQ scores than control children. Parents found no difference in behaviour. They also had feelings of inferiority and anxiety and more impulsive behaviour. None of these observations could be detected in children without disability or controls

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Laane[195]	1997	All congenital heart defects	Cohort study	Sweden *n* = 200 Age at follow-up: 6 years Control group: 400 geographical- and age-matched	Not applicable	Behaviour	Quality of life was measured in children with congenital heart defects from a total population of infants born live in the period from 1982 to 1991	164 (82%) of the families answered a questionnaire. There were no statistically significant differences between the cases and controls for overall quality of life but there was a trend to better quality of life in cases, which may reflect coping mechanisms
Limperopoulos[175]	1999	All congenital heart defects	Case series	Canada *n* = 56 Age at assessment: newborn	Not applicable	Neuro-development	Prospective study to determine extent of neurobehavioral abnormalities in newborns with congenital heart defects before surgery	Neurobehavioral abnormalities were found in 50%, including hypotonia, motor asymmetry and feeding difficulties. Three infants had seizures and 20 were microcephalic
Limperopoulos[164]	2001	All congenital heart defects	Case series	Canada *n* = 131 Age at assessment: preoperative, postoperative and 12–18 months after surgery	Not applicable	Neuro-development; behaviour; predictive factors	Prospective study of infants undergoing first open-heart surgery in a single centre. Functional assessments using standardised instruments and assessment of burden of care	Only 21% of the cohort was functioning within their expected age range. Moderate disability was noted in 37% and 6% had severe disability. Over half had socialisation difficulties
McCarthy[462]	1996	Congenital mitral valve anomalies	Case series	USA *n* = 23 Mean age at surgery: 3 years (range 2 months–11 years)	Mean 4 years	Actuarial survival	Retrospective review of outcomes for children operated in a single centre from 1983 to 1994	Actuarial survival was 82% at 1 year and 77% at 7 years. 17 (94%) survivors are in NYHA Class I or II
McElhinney[463]	1997	Complex congenital heart defects	Case series	USA *n* = 36	Mean 2 years	Actuarial survival	Review of outcomes for children operated in a single centre from 1990 to 1995	Actuarial survival was 87% at 1 year and 81% at 3 years
Mahle[464]	2000	HLH	Case series	USA *n* = 840 Median age at surgery: 6 days (range 0–218 days)	0–15 years	Actuarial survival	Review of infants who underwent first stage operation from 1984 to 1999 at a single centre	Actuarial survival for the entire cohort was 51% at 1 year, 43% at 2 years, 40% at 5 years, 39% at 10 years and 39% at 15 years. Three-year survival rose from 28% (1984–88) to 66% (1995–98)

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Mahle[172]	2000	HLH	Cross-sectional	USA *n* = 138 Mean age at follow-up: 9 years	Not applicable	Neuro-development; predictive factors	Review at school-age of survivors of palliative surgery at a single centre. Postal questionnaire to assess quality of life, school performance and medical complications in whole cohort. A subgroup of local patients underwent standardised testing of cognitive function and neurological examination. Potential predictors of outcome were analysed	Response rate to questionnaire was 83%. Of 34 children invited for testing 28 attended. Most parents described their child's health as good (34%) or excellent (45%) and academic performance as average (42%) or above average (42%). One-third of the children were receiving special education. Median IQ score for the group was below normal average and predicted by perioperative seizures
Mahle[173]	2001	Complex congenital heart defects	Review	USA	Not applicable	Neuro-development	Review of perioperative factors that led to later neurodevelopmental abnormalities	–
Mahle[215]	2002	All congenital heart defects	Case series	USA *n* = 24	Up to 1 year after surgery	Predictive factors	Study of serial MRI studies of the brain in a cohort of neonates undergoing open-heart surgery to assess neurological damage	Mild ischaemic lesions occur before surgery and in >50% after surgery. Resolution is common by 6 months
Mahle[158]	2002	TOF	Case series	USA *n* = 193 Mean age at surgery: 11 months Mean age at follow-up: 12 years	Not reported	Exercise capacity	Review of bicycle exercise test results in children who had primary surgical repair at a single centre. Bicycle exercise test results compared for children who had surgery before and after 1 year old	Of 193 children who had surgery, 30% underwent exercise testing, and results were available for 50 children (88%). There was no significant difference in exercise capacity between those operated before or after 1 year old

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Mair[143]	1997	PA with IVS	Case series	USA *n* = 40 Median age at surgery 6 years (2–21 years) Median age at follow-up: 13 years (range 4–30 years)	Median 6 years (6 months–13 years)	Exercise capacity	Children who survived infancy and were operated from 1979 to 1995 with Fontan repair at a single centre. Follow-up either with clinical examination, questionnaire or telephone interview	There were 3 operative deaths and 3 late deaths. 33 of 34 survivors in NYHA Class I or II. Majority of survivors were either full-time students or working full time
Majnemer[169]	1999	All congenital heart defects	Review	Canada	Not applicable	Neuro-development; behaviour	Review of outcomes of open heart surgery in infants	Severe neurological sequelae are uncommon; however, mild to moderate developmental disabilities are prevalent
Malan[142]	1991	COA	Case–control	South Africa *n* = 119 Age at surgery: 4 days–13 years 11 controls without congenital heart defects	Mean 6 years	Exercise capacity	Case series of children operated in a single centre. Graded exercise testing, blood pressure undertaken in 15 children and 11 controls	7 late deaths and 17 losses to follow-up from original case series. Of those in follow-up, 17% of cases and no controls were hypertensive. Significantly higher blood pressure on exercise in cases compared with controls
Malec[216]	1999	All congenital heart defects	Case series	Poland *n* = 100 Mean age at surgery: 3 years	Mean 3 years (7 months–6 years)	Actuarial survival; predictive factors	Review of outcomes in children with Down's syndrome who underwent heart surgery in a single centre from 1990 to 1997	The total death rate was 6%. Survivors were in NYHA Class I or II
Malec[127]	2000	HLH	Case series	Poland *n* = 30 Age at 1st operation: 5–39 days Age at 2nd operation (18 children): 7 months Age at 3rd operation (16 children): 18 months	Not reported	Exercise capacity	Consecutive case series of children undergoing Norwood operation in 1997–98 at a single centre. Operative factors recorded. Outcomes included deaths and exercise capacity	Early surgical mortality was 37%. Survivors had significantly higher birth weight, older age at operation, lower preoperative bilirubin and lower circulatory arrest time during operation. All survivors of 2nd and 3rd stage operations were in NYHA Class I or II at follow-up

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Mandelik[163]	1994	ASD	Case series	USA *n* = 127 Age: 9 years (range 4 months–20 years) at surgery	~12–35 years after surgery	Exercise capacity	Children who underwent atrial septal defect repair from 1957 to 1980 were followed up and survival and exercise capacity recorded	74% in NYHA Class I before surgery and 94% in NYHA Class I at follow-up. Age at repair did not influence outcomes. Presence of pulmonary hypertension at surgery increased risk of poor outcome
Masi[189]	1996	All congenital heart defects	Review	Italy	Not applicable	Behaviour	Review of psychological implications of chronic disease in children and adolescents and their families	–
Masi[192]	1999	All congenital heart defects	Review	Italy	Not applicable	Behaviour	Review of the emotional development of adolescents with congenital heart defects, including impact on interactions with family and body image	–
Masuda[465]	1999	Complex congenital heart defects	Case series	Japan *n* = 27 Mean age at surgery: 5 months (range 10 days–5 years)	Not reported	Actuarial survival	Review of outcomes in patients who underwent surgery from 1986 to 1997 at a single centre	Actuarial survival rate was 83% at 9 years
Masuda[466]	2001	All congenital heart defects	Case series	Japan *n* = 856	Not reported	Actuarial survival	Review of longer term outcomes in all patients receiving cardiac surgery at a single centre over 24 years	Actuarial survival was 98% in TOF, 86% in atrioventricular canal defect and 90% in TGA at 15 years

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Matthys[148]	1990	VSD and ASD	Case–control	Belgium *n* = 134 Age at follow-up: 5–14 years Control group of children with tetralogy of Fallot or without congenital heart defects	1–10 years after surgery	Exercise capacity	Maximal exercise testing using modified Bruce protocol and treadmill for all subjects and controls	No difference in blood pressure of cases and controls at rest. Statistically significant rise in blood pressure in response to exercise for cases compared to control group
Mehta[467]	2000	VSD	Review	USA *n* = 124	Up to 5 years old	Natural history	Prospective study to evaluate natural history of VSD in the first 5 years of life in Tennessee and Virginia regions	Spontaneous closure was 34% at 1 year and 67% at 5 years. However, 17% remained open at 5 years of age and needed long-term follow-up
Meijboom[146]	1994	VSD	Case series	The Netherlands *n* = 176 Age at surgery: up to 16 years	Mean 14 years after surgery	Exercise capacity	Children operated consecutively at a single centre from 1968 to 1980. Interview, physical examination, echocardiography, ECG undertaken	78% of original case series were followed up. 84% reported own health as good and 89% were free of medication or further intervention since surgery. Normal exercise capacity reported by 84%. 6% had residual defects
Merlo[468]	1991	TGA	Case series	Italy *n* = 104	Mean 12 years	Actuarial survival	Review of outcomes of surgery in a single centre from 1971 to 1978	Actuarial survival was 84% for simple and 94% for complex transposition at 18 years
Messmer[469]	1991	Congenital AS	Case series	Germany *n* = 28 Mean age at surgery: 1 month	Mean 5 years	Actuarial survival	Review of outcomes of surgery in a single centre	Actuarial survival was 78% at 10 years

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Miller[230]	1995	All congenital heart defects	Case series	USA *n* = 91 Age at surgery: neonates	Until hospital discharge	Predictive factors	Prospective analysis of mortality and neurological morbidity before hospital discharge, related to potential predictive factors, in children who underwent surgery in a single centre from 1989 to 1992	Mortality and neurological morbidity may be due to type of lesion, pre-existing brain abnormalities, duration of deep hypothermia and strokes
Miller[171]	1996	All congenital heart defects	Case series	USA *n* = 104 Age at surgery: neonates	2 years	Neuro-develop-ment; predictive factors	Study of neurodevelopmental outcomes in children who underwent surgery from 1987 to 1989. Survivors had formal neurological and psychometric examinations after 2 years of age	Mean IQ was 90, and 78% had scores above 70. Cerebral palsy occurred in 22%. Neurological morbidity was related to type of lesion, duration of hypothermia, preoperative congenital and acquired lesions and possible perioperative cerebrovascular events
Miller[214]	1999	All congenital heart defects	Review	USA	Not applicable	Predictive factors	Review of causes of neurological deficit and methods of measuring	Neurodevelopmental deficits are common in children with congenital heart defects and due to multiple factors. MRI is useful to display congenital and acquired lesions, and should be performed preoperatively in addition to genetic studies
Morris[103]	1991	TOF, VSD, ASD, COA, AS, PS, TGA, PDA	Case series	USA *n* = 94 Age at surgery: <18 years	Up to 25 years	Actuarial survival	Children operated for 8 types of congenital heart defects from 1958 to 1989 in a single centre	Late cardiac mortality at 25 years after surgery was 5% for TOF and isolated VSD, 10% for COA, 17% for AS, 5% for PS and <1% for PDA. There were no late deaths after ASD repair. Late cardiac mortality for TGA was 15% at 15 years (Mustard surgery) and 2% at 10 years (Senning surgery)

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Mosca[470]	1997	Complex congenital heart defects	Case series	USA *n* = 38 Mean age at surgery: 15 days	Mean 3 years	Actuarial survival	Review of outcomes in patients who underwent a modified Norwood procedure from 1987 to 1996 at a single centre	Actuarial survival was 89% at 1 month, 82% at 1 year and 71% at 5 years
Mukherjee[194]	2000	Not applicable	Cross-sectional study	USA *n* (pupils) = 33, *n* (parents) = 58, *n* (teachers) = 34	Not applicable	Behaviour	Qualitative study investigating the support needs of pupils with chronic illness or disability in mainstream school. Data were collected from pupils, parents and teachers	Young people identified a need for support for dealing with school absence, taking part in school activities, peer relationships and health-related worries. Staff need help with communicating health information, providing and coordinating care
Murphy[471]	1990	ASD	Case series	USA *n* = 123 Age at surgery: all Control group: age- and sex-matched	27–32 years after surgery	Actuarial survival	Follow-up of all children who underwent surgery at a single centre from 1956 to 1960. Clinical status was determined by written questionnaires and telephone interviews. Hospital records and death certificates were obtained	Overall actuarial survival rate among survivors of the perioperative period was 74% compared with 85% for controls. When repair was performed in patients >25 years, late cardiac failure, stroke and atrial fibrillation were significantly more frequent
Myridakis[472]	1994	TGA	Case series	USA *n* = 85 (63 simple transposition, 22 complex transposition) Age at surgery: 2 days–17 years	10–20 years	Actuarial survival	Follow-up of children who underwent Mustard operation at a single centre from 1971 to 1981	Actuarial survival rate was 86% at 15 years for simple and 64% for complex TGA
Najm[473]	1997	PA with IVS	Case series	Canada *n* = 22 Mean age at surgery: 6 years	Mean 4 years (range 1–12 years)	Actuarial survival	Review of children who underwent surgery at a single centre from 1980 to 1994	Actuarial survival was 80% at 10 years

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Najm[474]	1997	CAVSD	Case series	Canada *n* = 363 Median age at surgery: 8 months	10 years	Actuarial survival	Review of outcomes in children who underwent surgery at a single centre from 1982 to 1995	Actuarial survival was 83% at 10 years. Operative mortality was 10%
Najm[475]	1998	ASD	Case series	Canada *n* = 180 Mean age at surgery: 5 years (range 1 month–16 years)	Mean 6 years (range 2 months–14 years)	Actuarial survival	Review of outcomes of children who underwent surgery in a single centre from 1982 to 1996. One-fifth of children presented with severe symptoms or heart failure	Actuarial survival was 98% at 10 years
Newburger[232]	2003	TGA	Case series	USA *n* = 160 Age at surgery: <1 year	Mean follow-up: 8 years	Cognitive outcome; predictive factors	Children who underwent surgery in infancy were evaluated for cognitive outcome at 8 years old	Longer ICU stay after surgery was associated with lower IQ scores (and lower verbal, performance and maths subscores) even after adjustment for socio-economic status and perioperative events
Niederhuser[144]	1992	PA with IVS	Case series	Switzerland *n* = 26 Mean age at surgery: 10 days	Mean 11 years after surgery	Actuarial survival; exercise capacity	Case series of children who underwent palliative surgery from 1970 to 1989 at a single centre. Three groups with mild, moderate or severe right heart hypoplasia defined. Mortality and exercise capacity recorded at follow-up	10 children died perioperatively and 4 children died later. 44% survival at 5 and 10 years after surgery. 12 survivors mostly in NYHA Class I. Severity of right heart hypoplasia predictive of postoperative outcome
Nieminen[77]	2003	All congenital heart defects	Cohort study	Finland *n* = 6336 (of 6461 operations)	Mean 22 years (range 9–45 years)	Actuarial survival	All operations for congenital heart defects performed from 1953 to 1989 were followed up in 1998 and 96% patients traced. Data relating to operations (e.g. number of operations) and patients' status were collected from national statistics and hospital records	Actuarial survival was 78% for patients at 45 years compared with 93% for the general population. Survival and the number of operations varied with defect

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Nollert[220]	1997	TOF	Case series	Germany *n* = 658 Mean age at surgery: 12 years (range 2–67 years)	20–36 years after surgery	Actuarial survival; predictive factors	Patients who underwent surgery at a single centre from 1958 to 1977 were followed up to evaluate long-term survival and outcomes	Actuarial survival was 97% at 10 years, 94% at 20 years, 89% at 30 years and 85% at 36 years. Mortality risk increased 25 years after surgery. The most common cause of death was sudden cardiac death, followed by heart failure
Norgaard[156]	1999	TOF	Case series	Denmark *n* = 185 Median age at operation: 13 years	Mean 25.5 years (range 20–38 years)	Exercise capacity	185 children operated from 1960 to 1977 were traced in 1997 and deaths recorded. Survivors (97) were asked to complete postal questionnaire concerning medication, employment, family life and exercise capacity	No losses to follow-up recorded. 60 hospital deaths and 16 late cardiac deaths were reported. 16% of survivors took cardiac medication, 89% were employed, 64% of women had given birth and 51% played sports regularly
Oechslin[476]	1999	TOF	Case series	Canada *n* = 60 Mean age at surgery: 9 years Mean age at reoperation: 33 years	Mean 5 years after reoperation	Actuarial survival	Review of outcomes in consecutive adults referred for reoperation from 1975 to 1997 at a single centre	Actuarial survival is 92% at 10 years. At most recent follow-up, 93% of patients were in NYHA Class I or II
Oechslin[123]	2000	TGA	Case series	Switzerland/ Canada *n* = 342 (Zurich) Mean age at surgery: 6 years (7 days–8.5 years) *n* = 478 (Toronto) Mean age at surgery not given	Not given	Causes of death; actuarial survival; exercise capacity	Follow-up of the first children to have the arterial Switch operation in Zurich and Mustard operation in Toronto. Deaths and exercise capacity reported	Actuarial survival was 75% after 25 years and better in those with simple TGA compared with complex TGA. Congestive heart failure and sudden death were the principal modes of death. Most of the survivors had no or mild limitations in daily activities

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Oechslin[92]	2000	All congenital heart defects	Cross-sectional study	Canada *n* = 2609 Mean age at death: 37 years	Not applicable	Causes of death	Study of 2609 consecutive adults attending a single clinic, focusing on modes of death in 199 deceased patients	Data were available for 197 of 199 deceased patients. Mortality was highest for congenitally corrected TGA (26%), TA (25%), and UVH (23%). Most common causes of death were sudden death (26%), heart failure (21%) and perioperative death (18%)
Onat[477]	1998	VSD	Case series	Turkey *n* = 106 Mean ages for assessment: 9 and 17 years	Mean 13 years (range 7–19 years)	Natural history	Children with unoperated VSD were followed up through adolescence	Deaths/operation occurred in 4%. Defect closed spontaneously in 23% and decreased on average in all patients during puberty. Mild aortic valve regurgitation developed in 9%. PVOD occurred in 2 patients – one was stable and one died. No infective endocarditis
Ong[137]	1992	COA	Case–control	USA *n* = 15 Age at surgery: <15 years 15 age- and sex-matched controls without congenital heart defects	Not given	Exercise capacity	Cases and controls with normal resting blood pressure underwent bicycle exercise testing	Resting and exercise blood pressure were significantly increased in cases compared with controls
Otterstad[478]	1985	VSD	Case series	Sweden *n* = 125 Age at diagnosis: ≥ 10 years	Mean 15 years (4–21 years)	Complications after surgery	Patients with septal defect diagnosed after 10 years old were followed until death or until 30 years old. Group 1 was 40 patients who were operated, Group 2 was 70 patients not thought to need surgery, and Group 3 was inoperable	Long-term mortality was 5% in Group 1, 9% in Group 2 and 71% in Group 3. Group 2 had higher valve incompetence and infective endocarditis rates than Group 1. Differences between groups were small but favoured surgical treatment

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Parks[479]	1995	COA of the aorta	Case series	USA *n* = 39 Mean age at surgery: 6 years (range 10 days–14 years)	Mean 8 years (range 1–12 years)	Complications after surgery	Review of outcomes in children who underwent surgery in a single centre from 1976 to 1987. MRI was used to determine development of aneurysm size	6 patients died after aortic aneurysm rupture at a mean of 8 years after surgical repair. Survivors were followed up with MRI, which was accurate in detecting complications
Pawade[480]	1993	PA with IVS	Case series	Australia *n* = 48 Mean age at surgery: 3 years	10 years	Actuarial survival	Review of outcomes in infants admitted to a single centre for further management from 1976 to 1987	Actuarial survival was 93% at 8 years. It was better in patients able to undergo biventricular repair than patients able to tolerate only palliative surgery
Pearson[219]	2001	All congenital heart defects	Validation study of intensive care scoring system	UK *n* = 7258	Not applicable	Predictive factors	Children admitted to paediatric intensive care were scored using the paediatric index of mortality (PIM) and the predictive value was assessed	The PIM score was predictive of actual mortality and not affected by standard or type of care
Pigula[481]	1999	TOF	Case series	USA *n* = 99 Age at surgery: 0–90 days	Not reported	Actuarial survival	Review of outcomes in infants who underwent surgery in a single centre	Actuarial survival was 94% at 1 year and 92% at 5 years
Planche[482]	1993	TGA	Case series	France *n* = 40 Mean age at surgery: Group 1: 19 days (first operation); 95 days (second operation) Group 2: 10 days (single operation)	Mean 5 years (Group 1) and 2 years (Group 2)	Actuarial survival	Review of outcomes in infants who underwent surgery in a single centre from 1982 to 1992. Group 1 (two-stage operation) and Group 2 (single operation) compared	Actuarial survival was 58% at 5 years (Group 1) and 78% at 3 years (Group 2). Majority of survivors in both groups were in NYHA Class I at follow-up

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Pridjian[483]	1993	HLH, PA with IVS, TA, complex congenital heart defects	Case series	USA *n* = 50 Mean age at surgery: 12 months (range 1 month–5 years)	Mean 1 year	Actuarial survival	Review of outcomes in infants who underwent surgery in a single centre from 1989 to 1992	Actuarial survival for whole group was 92% at 1 month
Reddy[117]	1996	TGA	Case series	USA *n* = 54 Age at first operation: <1 month	Mean 6 years (6 months–12 years)	Exercise capacity	Case series that underwent Senning operation at a single centre since 1982	9% early surgical mortality. No late deaths. Of 49 survivors, 94% were in NYHA Class I and all had normal heart rhythm
Reddy[484]	2000	PA with VSD	Case series	USA *n* = 85 Mean age at surgery: 7 months	1 month–6 years	Actuarial survival	Review of outcomes in infants who underwent surgery in a single centre from 1992 to 2000	Actuarial survival was 80% at 3 years
Reller[485]	1998	Congenital heart defects with Down's syndrome	Case series	USA *n* = 3965 Age at operation: <18 years	Up to 20 years	Actuarial survival	Review of outcomes in infants with Down's syndrome who underwent surgery for congenital heart defects in one US state from 1958 to 1998	Complete atrioventricular septal defect is associated with higher mortality in children with Down's syndrome compared with those without. For all other heart defects mortality is similar for children with and without Down's syndrome
Reybrouck[107]	1995	VSD, AS, PS, TOF and complex congenital heart defects	Case–control	Belgium *n* = 79 Age: not given 234 age- and gender-matched controls	Up to 5 years after surgery	Exercise capacity	Aerobic capacity and daily activity recorded in 79 patients with different congenital heart defects, including small VSD (14), AS (12), PS (12), TOF (16), large VSD (13) and Fontan operation (12). Comparison with control group	Aerobic capacity in all groups was below normal and decreased over time in children whose exercise was restricted by the heart defect (TOF, Fontan)

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Reybrouck[121]	2001	TGA	Case series	Belgium *n* = 22 Age at surgery: <1 year	5–17 years after surgery	Exercise capacity	Children undergoing arterial Switch repair evaluated for cardiac function and exercise capacity at follow-up. Serial testing over 3.5 years using gas-exchange measurements and echocardiography	All children in NYHA Class I at follow-up. Ventilatory anaerobic threshold 78% of normal mean value. Increase in oxygen uptake during exercise was below normal in 10 patients at latest follow-up. Echocardiography in 17 children
Robinson[207]	2000	Congenital AS	Case series	USA *n* = 95 Median age at surgery: 5 days (0–191 days)	Mean 2 years (range 0–9 years)	Actuarial survival	Review of outcomes in infants who underwent surgery in a single centre from 1988 to 1999	Actuarial survival 76% at 3 years
Rogers[170]	1995	HLH	Case series	USA *n* = 11	Not reported	Neuro-development	All survivors of staged surgical repair at one children's hospital received standardised neurodevelopmental assessments	Of theses survivors, 64% had major developmental disabilities that affected quality of life
Ross[486]	1991	ASD	Case series	Canada *n* = 37 Mean age at surgery: 2 years	Not reported	Actuarial survival	Review of outcomes in infants who underwent surgery in a single centre from 1986 to 1990	Actuarial survival was 88% at 3 years. All survivors in NYHA Class I or II
Rubay[487]	1992	COA	Case series	Belgium *n* = 146 Median age at surgery: 1 month (2 days–11 months)	Not reported	Actuarial survival	Review of outcomes in infants who underwent surgery in a single centre from 1976 to 1991	Actuarial survival was 100% at 10 years (isolated COA), 94% at 10 years (COA with VSD) and 62% at 10 years (complex anomalies)

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Rubay[488]	1999	Congenital AS	Case series	Belgium *n* = 80 (of which 57 congenital defects and 27 children) Mean age at surgery: 31 years (adults and children)	Not reported	Actuarial survival	Review of outcomes in infants who underwent surgery in a single centre from 1991 to 1997	Actuarial survival was 98% at 5 years. All survivors in NYHA Class I
Ruttenberg[130]	1999	COA	Review	USA	Not applicable	Exercise capacity	Review of exercise studies in children with COA of the aorta	Oxygen consumption/exercise tests normal in children after surgery
Samanek[76]	1999	All congenital heart defects	Cohort study	Czech Republic *n* = 5030 Age at death: 0–15 years old	Up to 15 years	Causes of death; actuarial survival	Prospective study of children with confirmed congenital heart defects born 1980–90 and dying before the age of 15 years	Actuarial survival for operated and unoperated cases calculated for different defects
Samango-Sprouse[233]	1997	All congenital heart defects	Review	USA	Not applicable	Predictive factors	Review of behaviour and neurological sequelae following surgery for congenital heart defects	Length of circulatory arrest and pH management during surgery are associated with IQ
Sano[489]	1995	Congenitally corrected TGA	Case series	Australia *n* = 28	Median 5 years	Actuarial survival	Review of children who underwent surgery at a single centre	Actuarial survival was 89% at 1 year, 83% at 5 years and 83% at 10 years. All survivors in NYHA Class I or II

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Schmid[128]	1999	HLH	Case series	Germany *n* = 39 Age at surgery: <1 year Mean age at 1st operation (26 infants): 9.1 days Mean age at 2nd operation (16 infants): 7.6 months Mean age at 3rd operation (3 infants): 2 years	Mean 28 months (14 days–5 years)	Causes of deaths; exercise capacity	Neonates referred to a single centre from 1994 to 1998. Infants receiving Norwood repair were followed up for deaths, exercise and neurodevelopmental outcomes	The hospital mortality in the first stage of the Norwood procedure was 23%. No late deaths occurred. In 18 out of the 20 survivors neurodevelopmental outcome and exercise performance were within the normal range. Two children had global neurological difficulties
Seirafi[490]	1998	COA	Case series	France *n* = 16 Age at operation: <2 years old	Median 7 years	Complications after surgery	Review of risk factors and complications after surgery for COA	Overall mortality 7%. Hypertension identified in 17% of survivors at 5 years. Hypertension more likely if operated at >1 year of age (27% compared with 4%)
Serraf[491]	1991	TGA	Case series	France *n* = 118 Mean age at surgery: 3 months (range 4 days–4 years)	Mean 3 years	Actuarial survival	Review of children who underwent surgery at a single centre from 1983 to 1991	Actuarial survival was 84% at 5 years
Serraf[492]	1991	Complex congenital heart defects (Taussig–Bing)	Case series	France *n* = 27 Mean age at surgery: 1 year	Mean 3 years	Actuarial survival	Review of children who underwent surgery at a single centre from 1978 to 1990	Actuarial survival was 73% at 5 years. All survivors were in NYHA Class I
Serraf[493]	1999	Complex congenital heart defects (subaortic stenosis)	Case series	France *n* = 160 Mean age at surgery: 10 years	Median 13 years	Actuarial survival	Review of children who underwent surgery at a single centre	Actuarial survival was 94% at 15 years

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Shinoka[494]	1993	TGA	Case series	Japan *n* = 137 Mean age at surgery: 2 years (1 month–15 years)	Mean 7 years (Senning operation), 11 years (Mustard operation)	Actuarial survival	Review of outcomes in children who underwent a switch operation from 1970 to 1992 at a single centre, with a comparison of two groups (previous Senning operation and previous Mustard operation)	Actuarial survival was 90% at 12 years (Senning group) and 64% at 12 and 22 years (Mustard group). Most deaths were sudden cardiac deaths and arrhythmias were more common in the Mustard operation group
Sohn[495]	2000	TOF	Case series	Korea *n* = 48 Age at surgery: >15 years	Median 5 years (range (3 months–11 years)	Actuarial survival	Review of outcomes after surgery at a single centre	Actuarial survival was 97% at 10 years. Of survivors, 81% were in NYHA Class I
Sousa[118]	1993	TGA	Case series	France *n* = 105 Age at surgery: 10 days (arterial Switch repair), 4 months (Senning repair)	Mean 6 years (Switch), 9 years (Senning)	Actuarial survival; exercise capacity	Survivors of the first 30 days after surgery were followed up and deaths, reoperation, cardiac function and exercise capacity recorded	100% survival at 5 years in arterial Switch group and 86% survival in Senning group. 101 children in NYHA Class I at follow-up
Stellin[496]	2000	Congenital mitral valve problems	Case series	Italy *n* = 34 Mean age at surgery: 6 years (range 45 days–18 years)	Mean 6 years (4 months–12 years)	Actuarial survival	Review of outcomes in children who underwent surgery at a single centre from 1987 to 1999	Actuarial survival 97% at 12 years. All survivors were asymptomatic at follow-up
Suominen[224]	2001	All congenital heart defects	Case–control study	Finland *n* = 82 Control groups: 65 children operated with circulatory arrest and 278 children operated without circulatory arrest	Not applicable	Predictive factors	The survival of children who had cardiopulmonary arrest in ICU after heart surgery was compared with children who had circulatory arrest as a supportive measure during heart surgery and those who had heart surgery but no circulatory arrest	Survival rate after cardiopulmonary arrest in ICU was 56% immediately after and 19% at 1 year. Cardiopulmonary arrest is associated with surgery requiring circulatory arrest, complex congenital heart defects, preoperative instability and postoperative complications

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Tchervenkov[497]	1998	IAA	Case series	Canada *n* = 40 Median age at surgery: 17 days	Mean 3 years	Actuarial survival	Review of outcomes in children who underwent surgery at a single centre from 1988 to 1997	Actuarial survival was 89% at 8 years
Thies[162]	1991	Atrio-ventricular septal defect	Case series	Germany *N* = 40 Age at surgery: 4 months (1–12 months)	Mean 22 months (3–46 months)	Exercise capacity	Outcomes after surgical repair during first year of life in a single centre. Surgical complications, deaths, exercise capacity and growth recorded	Four early postoperative deaths and no later deaths. 83% survivors in NYHA Class I, 11% in Class II and 6% in Class III. Mild/moderate valve problems in 47% postoperatively. Normal growth
Thompson[498]	2001	Truncus	Case series	USA *n* = 65 Median age at surgery: 10 days	Median 3 years	Actuarial survival	Review of outcomes in children who underwent surgery at a single centre from 1992 to 1999	Actuarial survival was 92% at 1 year
Thu[136]	1999	COA of the aorta	Case series	Norway *n* = 102	Range 1–21 years	Exercise capacity	Survivors of surgical repair from 1975 to 1995 were sent a postal questionnaire asking about symptoms and exercise capacity	Six early postoperative deaths and 12 later deaths occurred. 98% of survivors returned a questionnaire. Of these, 35 no longer had cardiology follow-up, 29% reported reduced exercise capacity and 62% reported symptoms including fatigue, headache and leg pain
Tlaskal[82]	1998	IAA	Case series	Czech Republic *n* = 40 Age at operation: <1 year	Mean 5 years	Exercise capacity; predictive factors	Mortality and clinical status for two groups – primary surgical repair (*n* = 19) or two-stage repair (*n* = 21) – were compared	Early surgical mortality was 62% for the two-stage operation and 37% for primary repair. Perioperative risk factors for death were poor clinical status, acidosis and complications. Of 8 survivors of two-stage repair, 5 were in NYHA Class I and 3 were in NYHA Class III–IV (poor). All 12 survivors of primary repair were in NYHA Class I or II

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Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Trinquet[211]	1988	COA	Case series	France *n* = 178 Age at surgery: <3 months	Mean 3 years	Actuarial survival; predictive factors	Review of outcomes in infants who underwent surgery at a single centre. Simple COA was present in 63 infants (Group 1), 47 infants had additional VSDs in 47 infants (Group 2), and complex heart disease in 68 infants (Group 3)	Actuarial survival at 5 years was 90% for the first group, 84% for the second group, and 40% for the third group. Mortality was not influenced by type of COA repair but was determined by clinical status at operation and associated major cardiac anomalies
Turner[499]	1999	VSD	Cohort study	UK *n* = 68	Mean 6 years	Natural history	Follow-up of a cohort of children with VSDs to correlate size and position with closure rate	Of all defects, 35 closed spontaneously. After more than 6 years one-third of perimembranous and two thirds of muscular defects closed spontaneously
Tweddell[500]	1996	CAVSD	Case series	USA *n* = 115 Mean age at surgery: 2 years (>1 year old before 1982 and <1 year old after 1982)	Up to 11 years after surgery	Actuarial survival	Retrospective review of pre-, intra- and postoperative factors and outcomes in patients who underwent surgery at a single centre from 1974 to 1993	Actuarial survival was 81% at 10 years. Early mortality was predicted by the era of surgical repair. Down's syndrome was present in 82% of patients
Tworetzky[22]	2001	HLH	Case series	USA *n* = 88	Not reported	Predictive factors	Review of patients diagnosed pre- or postnatally from 1992 to 1999 to evaluate the influence of prenatal diagnosis on preoperative clinical status, outcomes of surgery, and parental decisions about care	Of 88 patients, 33 were diagnosed prenatally and 55 after birth. Of 33 prenatally diagnosed, 22 were live born, and pregnancy terminated in 11. Of 22 prenatally diagnosed live-born infants, 14 underwent surgery, and parents elected for no treatment in 8. Of 55 patients diagnosed postnatally, 38 underwent surgery. Survival was 75% (39/52) for those having surgery. Prenatal diagnosis was associated with improved preoperative clinical status and survival after surgery

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Urban[501]	1998	Truncus	Case series	Germany *n* = 46 Mean age at surgery: 2 months (21 days–7 years)	Mean 3 years (3 months–10 years)	Actuarial survival	Review of outcomes in consecutive patients who underwent surgery from 1987 to 1997	Actuarial survival was 93% at 4 months and at 10 years. Survival until hospital discharge in all patients was 95% and in uncomplicated truncus was 100%
Utens[187]	1993	All congenital heart defects	Cross-sectional survey	The Netherlands *n* = 144 parents, 179 adolescents Age at follow-up: 10–17 years	>9 years after surgery	Behaviour	Behavioural/emotional problems were assessed after surgical correction in childhood. Parents completed the Child Behavior Checklist (CBCL) and adolescents completed the Youth Self-Report (YSL)	Children with congenital heart defects obtained significantly higher problem scores than same-aged peers from normal reference groups. Lower IQ scores in children with heart defects were associated with higher CBCL total problem scores
Utens[196]	1994	All congenital heart defects	Cross-sectional survey	The Netherlands *n* = 288	Mean 16 years after surgery	Behaviour	Study investigating long-term psychosocial outcomes: emotional, intellectual and social functioning of young adults assessed with standardised tests, and compared with that of reference groups	Patients reported significantly fewer emotional problems and had better self-esteem than reference subjects. Outcomes for daily and leisure-time activities were within normal ranges
Utens[191]	1998	All congenital heart defects	Cross-sectional survey	The Netherlands *n* = 125 Age at follow-up: 10–15 years	Not applicable	Behaviour	Study to investigate behavioural/emotional problems in children using parent-reported Child Behavior Checklist (CBCL)	Higher CBCL total problem scores were associated with a greater number of operations and circulatory arrest during surgery
Utens[197]	2000	All congenital heart defects	Cross-sectional survey	The Netherlands *n* = 75	Not applicable	Behaviour	Study to assess the psychological distress and coping styles of parents of children with congenital heart defects. Standardised questionnaires completed 4 weeks before surgery	Higher levels of psychological distress, and poor styles of coping, were found in study parents, especially mothers, compared with reference groups

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Van Arsdell[157]	2000	TOF	Case series	USA *n* = 227 Age at operation: Group 1 = 17 months, Group 2 = 8 months	Up to 9 years after surgery	Exercise capacity	Two groups of children undergoing surgical repair from 1993 to 1998 were compared. Group 1 (operated before 1995–96) received a palliative operation followed by a later definitive operation, whilst Group 2 (operated after 1995–96) received primary repair at <6 months of age	Lower mortality, shorter ventilation time and length of hospital stay were associated with primary repair between 3 and 11 months of age compared with definitive surgery at an older age
Veldtman[193]	2000	All congenital heart defects	Qualitative survey	UK *n* = 69 Age at assessment: 7–18 years	Not applicable	Behaviour	Prospective study to evaluate illness knowledge and understanding in children with heart disease, related to age, sex or complexity of the heart disease	Only 30% of patients had a good understanding of their illness; 77% did not know the medical name and 33% had a poor understanding of their condition. Understanding was unrelated to age, sex or type of heart disease
Verheijen[222]	2001	All congenital heart defects	Case series	The Netherlands *n* = 408 Age at surgery: <31 days	Until hospital discharge	Predictive factors	Retrospective study compared the occurrence of preoperative metabolic acidosis in patients with and without prenatal diagnosis of congenital heart defects	Prenatal diagnosis of congenital heart disease minimises metabolic acidosis in patients with congenital heart defects and may be associated with improved long-term neurological outcome
von Bernuth[122]	2000	TGA	Case series	Germany *n* = 188 Age at surgery: 6 days (simple transposition), 9 days (complex)	Mean 6 years after surgery	Actuarial survival; exercise capacity; neuro-develop-ment	Follow-up of case series of children receiving surgery in neonatal period, including deaths, neurodevelopmental outcome and exercise tests	Early surgical mortality of 6% overall. 5 later deaths. 91% survival at 5 and 10 years after surgery. Parents and physicians reported good health for 98% at 8 years after surgery. 96% reported no physical limitation at 5-year follow-up. Of 50 who underwent exercise treadmill test, 94% were normal at 4–9 years after surgery. 74% had normal neurodevelopment at follow-up. 4 had microcephaly

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Visconti[184]	1999	ASD	Case–control study	USA *n* = 26 (surgery), 19 (transcatheter) Mean age at surgery: 6 years Mean age at follow-up: 10 years (surgery), 12 years (transcatheter)	4–6 years after intervention	Cognitive outcome	Standardised neuropsychological testing was performed on children after closure of ASD through surgery or transcatheter device	IQ and achievement scores were in the normal range for both groups. Some differences noted on subscores but inconclusive
Wernovsky[502]	2003	All congenital heart defects	Review	USA	Not applicable	Neuro-development	Editorial review of neurodevelopmental outcomes in children with complex congenital heart defects	–
Wetter[120]	2001	TGA	Case series	Germany *n* = 105 Median age at surgery: 24 days	Median 6 years after surgery	Actuarial survival; exercise capacity	Risk factors at the time of surgery were related to later follow-up. Outcomes reported were deaths, reoperation and exercise capacity	92% survival at 6 years after surgery. 5 postoperative deaths in hospital and 4 later deaths occurred. There were reoperations in 14 children. 87% survivors in NYHA Class I and 13% in NYHA Class II or requiring cardiac medication
Williams[178]	1980	COA	Case series	USA *n* = 191 Age at surgery: <1 year	Not reported	Actuarial survival; neurode-velopment	Follow-up of infants who underwent surgery during a 14-year period in a single centre	The 5-year mortality rate was 25%. Hypertension developed in 27% of the children followed more than 5 years after repair
Williams[179]	2000	HLH	Case series and cross-sectional survey	USA *n* = 106 (stage I = 106; stage II = 49; stage III = 25; 4 transplantations)	Not reported	Actuarial survival; neurode-velopment	A review of survival, developmental status, quality of life and direct medical costs of children who have undergone Stage I, II and III Norwood surgery at a single centre from 1990 to 99. Parents assessed quality of life and development on standardised questionnaires	Actuarial survival was 58% at 1 year and 54% at 5 years. Developmental progress was better in those who survived to Stage II and III surgery. A need for preoperative inotropic support predicted worse survival

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Wilson[503]	1998	TGA	Case series	USA *n* = 113	Up to 28 years	Actuarial survival	Review of late outcome in patients after Mustard surgery from 1964 to 1982, including quality of life of adult survivors assessed by medical review and a lifestyle questionnaire	Actuarial survival was 90% at 10 years, 80% at 20 years and 80% at 28 years. 76% of survivors in NYHA Class I. 75% of survivors lead a normal life, 20% have some lifestyle modification and 5% are unable to work
Wray[186]	2001	All congenital heart defects	Case–control study	UK *n* = 47 Age at assessment: 3–17 years. Two control groups: healthy children (*n* = 51) and children awaiting bone marrow transplantation (*n* = 51)	1 year after surgery	Cognitive outcome	Prospective study in which children were assessed immediately before surgery and 12 months later to evaluate changes in cognitive functioning	Children with cyanosis had cognitive deficits pre- and postoperatively compared with those without. Bone marrow transplant and cyanotic heart defect children showed continued impairment of cognitive function even after treatment
Wray[177]	1999	All congenital heart defects	Case–control study	UK *n* = 25 Age at assessment: 0–3 years. Two control groups: healthy children (*n* = 15) and children awaiting bone marrow transplantation (*n* = 15)	1 year after surgery	Neuro-development; cognitive outcome	Three groups of children <3.5 years old were assessed immediately before treatment and 12 months later: a group with congenital heart disease awaiting surgery, a group awaiting bone marrow transplantation, and a healthy comparison group	Neurodevelopmental means in all groups were in normal range, but preoperatively cardiac and transplant groups showed deficits compared with healthy controls. Postoperatively, developmental deficits were significant only in the children with cyanotic lesions. Preschool children improve more than older children

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Wren[86]	2000	All congenital heart defects	Review of deaths	UK *n* = 2523 deaths Age at death: 1–20 years	Not applicable	Causes of death	A review of all sudden deaths at age 1–20 years in one English health region from 1985 to 1994	In a population of 806,500 children and adolescents aged 1–20 years there were 2523 deaths in 10 years. Half of all sudden deaths in children or adolescents were attributed to an already diagnosed condition, including epilepsy, asthma and cardiac causes
Wren[12]	2001	All congenital heart defects	Cohort study	UK *n* = 1942 Age at diagnosis: <1 year old	15 years	Actuarial survival	All confirmed cardiovascular malformations diagnosed from 1985 to 1999 in children born 1985–94 were followed to calculate survival, underascertainment and to predict need for long-term follow-up. Actuarial survival for different defects was obtained from literature review and applied to local population	1942 cases were diagnosed in infancy (incidence = 5.2/1000). 1588 (82%) survived to 1 year and 1514 were predicted to survive to age 16. 605 further diagnoses were made in childhood (678 if adjusted for under-ascertainment). Thus, 2192 children were predicted to reach age 16, with 784 requiring long-term adult follow-up. The predicted need for adult follow-up is 200 extra cases per 100,000 live births each year or 1600 extra cases per year every year in the UK
Wren[93]	2002	All congenital heart defects	Review	UK	Not applicable	Causes of death	Review of literature concerning causes of sudden death in childhood	–
Zafra[504]	1993	Congenital AS	Case series	Spain *n* = 107 Mean age at surgery: 6 years (range 14 days–15 years)	Mean 5 years	Actuarial survival	Follow-up of children who underwent surgery in a single centre from 1969 to 1989	Actuarial survival of 95% at the age of 15 years

continued

Study	Year of publication	Congenital heart defect	Study type	Country; sample size (*n*); age range; controls	Follow-up period	Outcomes	Method	Main results
Zehr[505]	1995	COA	Case series	USA *n* = 179 Age at surgery: <1 year (majority <3 months)	Not reported	Actuarial survival	Follow-up of infants who underwent surgery at a single centre from 1962 to 1991. Comparison of time periods: group I (1962 to 1971), group II (1972 to 1981) and group III (1982 to 1991)	Actuarial survival was 58% at 27 years in group I, 66% at 20 years in group II and 77 % at 9 years in group III
Zobel[231]	1993	All congenital heart defects	Case series	Austria *n* = 441 (128 developed cardiopulmonary insufficiency and were followed up)	Until hospital discharge	Predictive factors	Prospective study undertaken in a single paediatric ICU from 1989 to 1992, to evaluate the predictive value of clinical scoring systems [Acute Physiologic Score for Children (APSC), Pediatric Risk of Mortality (PRISM), Therapeutic Intervention Scoring System (TISS) and Organ System Failure (OSF)] in children with cardiopulmonary insufficiency after cardiac surgery	Overall hospital mortality rate was 9.9%, and for patients with cardiopulmonary insufficiency was 34%. APSC, PRISM and TISS describe accurately the severity of illness in children with cardiopulmonary insufficiency after cardiac surgery and all scores identify those patients at increased risk for mortality

Appendix 3

Actuarial survival and causes of death for different malformations

Malformation	Actuarial survival	Main complications and causes of death	Comments
TGA	78–90% 5 years[83,438,445,455,482,491] 65–67% 15 years[12,77] 90% 10–15 years[122,438,455,461,466,472,494] 84% 18 years[468] 82% 20 years[454] 80% 20 years[503] 75% 25 years[123] 49% 30 years[77] *Worse if*: Mustard operation[123] 78% 3 years[461,482] 64% 10 years[472,494] 67% 20 years[115]	Sudden cardiac death[86,92,93] Congestive heart failure[92] Reoperation PVOD	
AS	76% 3 years[207] 95–98% 5 years[488,504] 73% 10 years[456] 90% 10 years[12,124,429,446] 90% 15 years[229,439] 85–87% 20 years[124,229] *Worse if*: Critical AS 70–80% 10 years[469] 37% 15 years[12]	Sudden cardiac death[86,92,93] Infective endocarditis[98,99,102] Reoperation in 20%[99]	Studies vary in the severity of cases included. Only a few studies report the proportion of critical (severe) cases. This difference in case mix between studies is likely to give rise to the wide variation in survival rates
TAPVC	23% 5 years (operated)[453] 42% 10 years (operated)[435] 73% 10 years[440] 70% 15 years[12] 84% 15 years[126,205] *Worse if*: Obstructed TAPVC, associated cardiac lesions, preoperative collapse	Congestive heart failure	Studies vary in the severity of cases included. A few studies report the proportion of obstructed (severe) cases. This difference in case mix between studies is likely to give rise to the wide variation in survival rates

continued

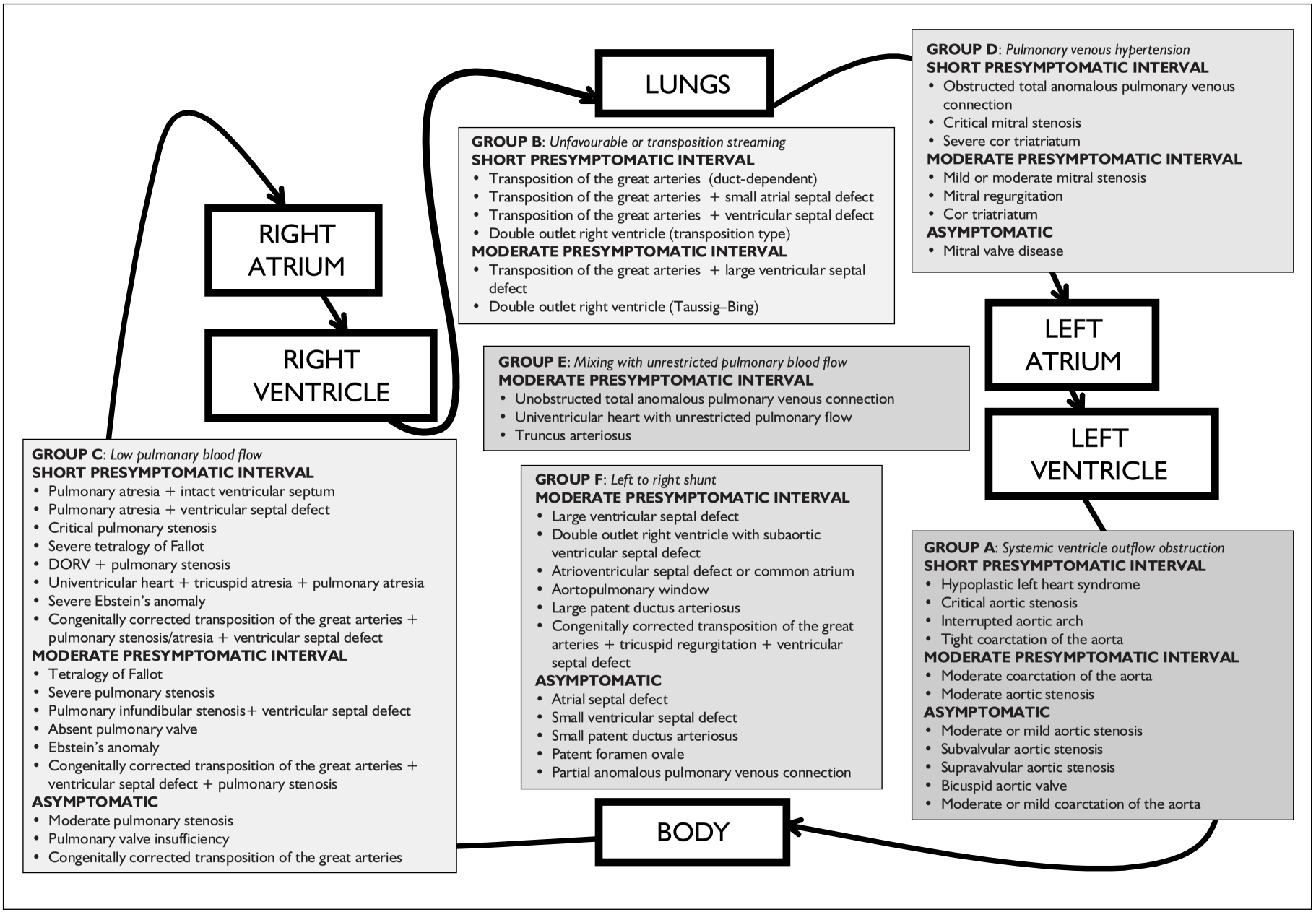
Malformation	Actuarial survival	Main complications and causes of death	Comments
HLH	33–59% 1 year[447] 58% survival to school age[178,179,433] 0% 15 years[12] 40% 15 years[78,464] *Worse if:* Unoperated (60 days)[458]		Other studies agree with survival 40–60% after operation[19,21,79,128] Few long-term studies as 'new' operation; Antenatal diagnosis affects choice of palliative care and termination[22]
MA (MA is often classified as a univentricular heart, complex heart defect or severe HLH)	32% 15 years[12] 45% 15 years (for all univentricular hearts)[77]		
COA	90% 5 years[211,444] 90–100% 10 years[103 437 459 479,487] 86% 15 years[12] 92% 15 years[77] 58% 27 years[505] 40–60% 5–10 years (complex)[211,487] *Worse if:* COA presenting in newborn	Sudden cardiac death[86,92,93] Reoperation for recurrent COA in 14–54%[140] Systemic hypertension in 17–27%[135,140,490]	
IAA	89% 8 years[497] 85% 12 years[451]	Sudden cardiac death[86,92,93]	
PA/IVS and PA/VSD	PA/IVS: 75% 1 year[443] 77% 8 years[144,473,480] 31% 15 years[12] PA/VSD: 80% 3 years[484] 48% 15 years[12]	Sudden cardiac death[86,92,93] Reoperation	Severity is dependent on associated cardiac defects
VSD	64% 15 years[12] 83% 15 years[77] 94% 20 years[466]	PVOD Infective endocarditis[98,102,450] Valve lesions occur if unoperated[478]	40–67% spontaneous closure by years of age[450,467,499] 19–25% require surgical closure by 5 years of age[467,499] 22% require follow-up after 5 years of age[467] 20% close during adolescence (up to 19 years of age)[477]

continued

Malformation	Actuarial survival	Main complications and causes of death	Comments
TOF	97% 3 years[460] 92% 5 years[481] 86% 6 years[452] 85–97% 10 years[70,149,206,476,495] 84% 15 years[12] 98% 15 years[466] 94–98% 20 years[154,438] 91% 20 years[442] 86% 20 years[153] 75% 20 years[206] 86–89% 30 year[220,226,228]	Sudden cardiac death[86,92,93,156,457] Reoperation[154,457,476]	
Atrioventricular septal defect (AVSD)	88% 3 years[486] 78–91% 10 years[159,160,208,474,500] 86% 15 years[466] 54–72% 15 years[12] 65% 20 years[208] *Worse if*: Down's syndrome[161,485]	Congestive heart failure[216] PVOD[216,436] Atrioventricular valve incompetency (10–15%)	Down's syndrome is associated with 30% of AVSD
ASD	98% 10 years[475] 84% 15 years[12] 74% 30 years[471] 94% 45 years[77] *Worse if*: Older age at repair (>25 years)[475]	Congestive heart failure[88] PVOD Atrial arrhythmias[88]	Unoperated life expectancy of 50 years[88]
UVH	77–87% 1 year (complex UVH)[463,506] 81% 3 years[463] 38% 5 years (includes operated and unoperated)[450] 66% 5 years (operated)[506] 46–49% 10 years[449,506] 45% 15 years[77]	Congestive heart failure	Actuarial survival rates vary between series depending on case mix and type of defect
Truncus arteriosus	80–90% <1 year[434,501] 92% 1 year[498] 31% 15 years[12]	Sudden cardiac death[86,92,93]	
Congenitally corrected TGA	83% 10 years[489] 96% 15 years[12]		
Miscellaneous and rare defects	Double outlet right ventricle[430,465] Subaortic stenosis[493] Congenital mitral valve defects[428,462,496] Complex heart defects[204,431,432,441,448,470,483,492]		This is a mixed group for which overall survival rates cannot be given

Appendix 4

Screening classification for congenital heart defects


LUNGS
RIGHT ATRIUM
RIGHT VENTRICLE
LEFT ATRIUM
LEFT VENTRICLE
BODY
GROUP B: Unfavourable or transposition streaming
SHORT PRESYMPTOMATIC INTERVAL
• 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)
MODERATE PRESYMPTOMATIC INTERVAL
• Transposition of the great arteries + large ventricular septal defect
• Double outlet right ventricle (Taussig–Bing)
GROUP D: Pulmonary venous hypertension
SHORT PRESYMPTOMATIC INTERVAL
• Obstructed total anomalous pulmonary venous connection
• Critical mitral stenosis
• Severe cor triatriatum
MODERATE PRESYMPTOMATIC INTERVAL
• Mild or moderate mitral stenosis
• Mitral regurgitation
• Cor triatriatum
ASYMPTOMATIC
• Mitral valve disease
GROUP E: Mixing with unrestricted pulmonary blood flow
MODERATE PRESYMPTOMATIC INTERVAL
• Unobstructed total anomalous pulmonary venous connection
• Univentricular heart with unrestricted pulmonary flow
• Truncus arteriosus
GROUP C: Low pulmonary blood flow
SHORT PRESYMPTOMATIC INTERVAL
• 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
MODERATE PRESYMPTOMATIC INTERVAL
• 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
ASYMPTOMATIC
• Moderate pulmonary stenosis
• Pulmonary valve insufficiency
• Congenitally corrected transposition of the great arteries
GROUP F: Left to right shunt
MODERATE PRESYMPTOMATIC INTERVAL
• 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
ASYMPTOMATIC
• Atrial septal defect
• Small ventricular septal defect
• Small patent ductus arteriosus
• Patent foramen ovale
• Partial anomalous pulmonary venous connection
GROUP A: Systemic ventricle outflow obstruction
SHORT PRESYMPTOMATIC INTERVAL
• Hypoplastic left heart syndrome
• Critical aortic stenosis
• Interrupted aortic arch
• Tight coarctation of the aorta
MODERATE PRESYMPTOMATIC INTERVAL
• Moderate coarctation of the aorta
• Moderate aortic stenosis
ASYMPTOMATIC
• Moderate or mild aortic stenosis
• Subvalvular aortic stenosis
• Supravalvular aortic stenosis
• Bicuspid aortic valve
• Moderate or mild coarctation of the aorta

Congenital heart disease classification system

Short presymptomatic interval

	Group A	Group B	Group C	Group D
Physiology	Duct-dependent systemic blood flow	Unfavourable streaming (transposition-streaming)	Duct-dependent pulmonary blood flow	Pulmonary venous hypertension
Description	Progressively impaired systemic perfusion; breathlessness, collapse	Critical cyanosis (hypoxia) – worse if little intracardiac mixing; high pulmonary flow	Right ventricular outflow obstruction, right ventricular hypertrophy and right heart failure, oligaemic lungs, cyanosed body	Obstructed pulmonary venous return; pulmonary oedema
Congenital heart defects included	HLH syndrome Critical AS IAA Tight COA	TGA (duct-dependent) TGA + small ASD TGA + VSD Double-outlet right ventricle (transposition type)	PA + IVS PA + VSD Critical PS Severe TOF Double-outlet right ventricle + PS UVH + TA + PA Severe Ebstein's anomaly Congenitally corrected TGA + PS/PA + VSD	Obstructed TAPVC Critical mitral stenosis Severe cor triatriatum
ICD 10 codes/OPCS4 codes	Q23.0/Q23.4 Q25.1/Q25.4 K26 K30.2 K31.2 K32.2 K35.2 L12.1 L20.1/L20.2 L23.1/L23.2/L23.3	Q20.1/Q20.3 Q21.0/Q21.1 K05 K06 K11 K10 K20.1	Q20.1/Q20.4/Q20.5 Q21.0/Q21.3 Q22.0/Q22.1/Q22.5 K06 K11 K04 K28 K30.4 K31.4 K32.4 K35.4 K27.5	Q23.2 Q24.2 Q26.2 K07 K25 K30.1 K31.1 K32.1 K35.1
Common symptoms and signs at presentation	Poor feeding Breathless Poor (femoral) pulses[a] Cyanosis Shock Congestive heart failure	Cyanosis Poor feeding Shock Critical hypoxia	Cyanosis Murmur Shock Critical hypoxia	Poor feeding Breathless Cyanosis Murmur Respiratory distress (pulmonary oedema)

[a] COA = poor femoral pulses/good upper limb pulses; IAA = poor femoral pulses and left upper limb pulses/good right upper limb pulses; HLH/critical AS = all pulses poor.

Moderate presymptomatic interval

	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
Description	Left ventricular outflow tract obstruction	Cyanosis	Right ventricular outflow tract obstruction	High left atrial pressure	Progressive breathlessness as pulmonary vascular resistance falls; mild cyanosis	Progressive breathlessness as pulmonary vascular resistance falls; no cyanosis
Congenital heart defects included	COA Moderate AS	TGA with large VSD Double-outlet right ventricle (Taussig–Bing type)	TOF Severe PS Pulmonary infundibular stenosis+ VSD Absent pulmonary valve Ebstein's anomaly Congenitally corrected TGA + VSD + PS	Mild/moderate mitral stenosis Mitral regurgitation Cor triatriatum	Unobstructed TAPVC UVH with unrestricted pulmonary flow Truncus	Large VSD Double-outlet right ventricle with subaortic VSD Atrioventricular septal defect or common atrium Aortopulmonary window Large PDA Congenitally corrected TGA + tricuspid regurgitation + VSD
ICD 10 codes/ OPCS4 codes	Q23.0 Q25.1/Q25.4 K26 K30.2 K31.2 K32.2 K35.2 K37/K37.4 L12.1 L20.1/L20.2/L20.3 L23.1/L23.2/L23.3	Q20.1/Q20.3 Q21.0 K05 K06 K11	Q20.5 Q21.0/Q21.3 Q22.1/Q22.5 Q24.3/Q24.8 K04 K11 K27.5 K28 K30.4 K31.4 K32.4 K35.4 K37.2	Q23.2/Q23.3 Q24.2 K25 K30.1 K31.1 K32.1 K35.1	Q20.0/Q20.4 Q26.2 K07 L01.1	Q20.1/Q20.5 Q21.0/Q21.2/Q21.4 Q22.8 Q25.0 K09 K11 K27 L01.4 L02

continued

	Group A	Group B	Group C	Group D	Group E	Group F
Common symptoms and signs of presentation	Poor feeding Poor pulses Breathlessness Congestive heart failure Arrhythmias Sudden death	Poor feeding Cyanosis Murmur PVOD	Murmur Mild cyanosis (spells) Progressive cyanosis	Breathless Poor feeding Murmur PVOD	Poor feeding Sweaty Breathless Failure to thrive Cyanosis Congestive heart failure PVOD	Poor feeding Murmur Chest infections Failure to thrive Congestive heart failure PVOD

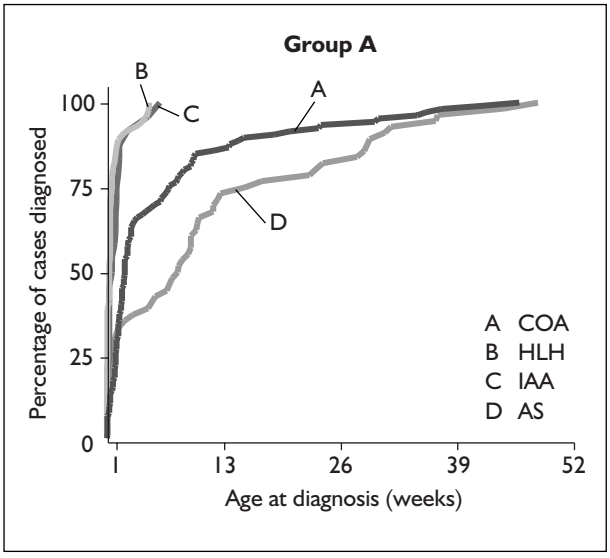
Asymptomatic in early childhood

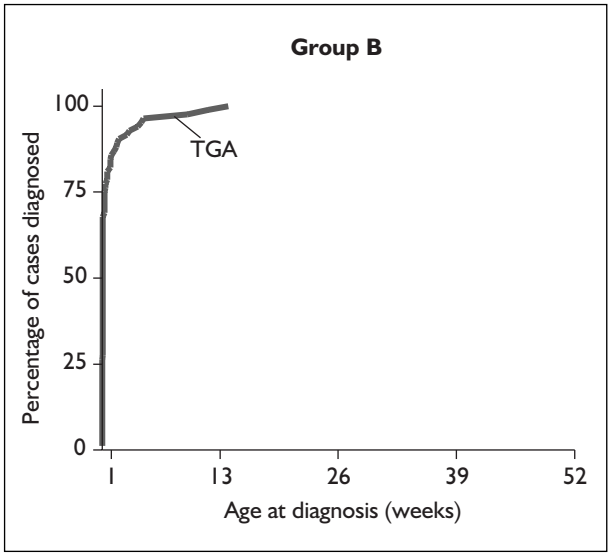
	Group A	Group B	Group C	Group D	Group E	Group F
Physiology	Systemic ventricle outflow obstruction	Unfavourable streaming (transposition-streaming)	Low pulmonary blood flow	Pulmonary venous hypertension	Mixing with unrestricted pulmonary blood flow	Shunt left to right
Description	Left ventricular outflow obstruction		Right ventricular outflow obstruction	High left atrial pressure		No cyanosis as mixing
Congenital heart defects included	Moderate or mild AS Subvalvular AS Supravalvular AS Bicuspid aortic valve Moderate or mild COA		Moderate PS Pulmonary valve insufficiency Congenitally corrected TGA	Mitral valve disease		ASD Small VSD Small PDA PFO Partial anomalous pulmonary venous connection
ICD 10 codes/ OPCS4 codes	Q23.0/Q23.1 Q24.4 Q25.1 Q25.3 K26 K30.2 K31.2 K32.2 K35.2 K37/K37.4 L23.1/20.2/20.3 L20.1/20.2 L12.1	Unlikely to present during this time period	Q20.5 Q22.1/Q22.2 K28 K30.4 K31.4 K32.4 K35.4	Q23.2/Q23.3 K25 K30.1 K31.1 K32.1 K35.1	Unlikely to present during this time period	Q21.0/Q21.1/Q21.2 Q25.0 Q26.3 K09.4 K11 K10 K20.1/K20.2 L02
Symptoms and signs at presentation	Murmur Sudden death Arrhythmias Infective endocarditis		Increased right ventricular workload Murmur Right ventricular failure	Arrhythmia PVOD		Murmur PVOD Infective endocarditis

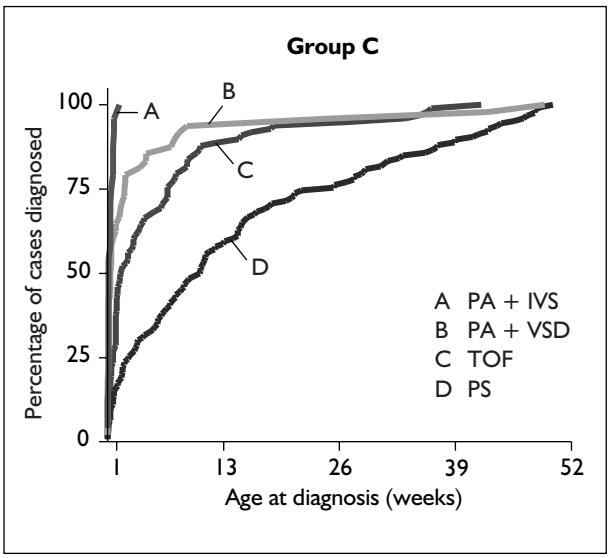
Appendix 5

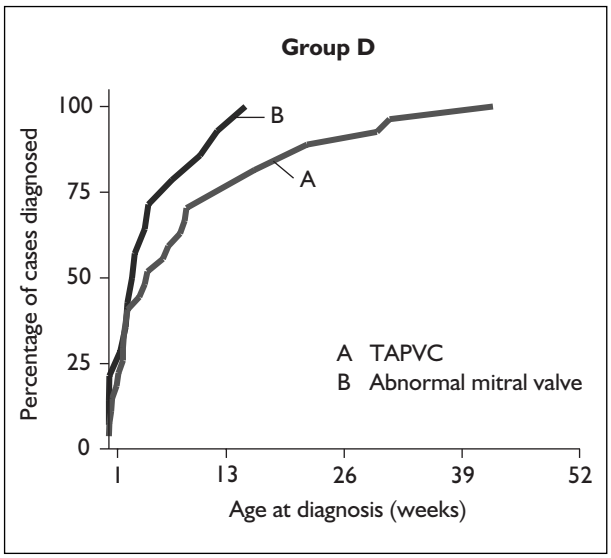
Proportion of each diagnostic group with a confirmed diagnosis by age at diagnosis during the first year of life

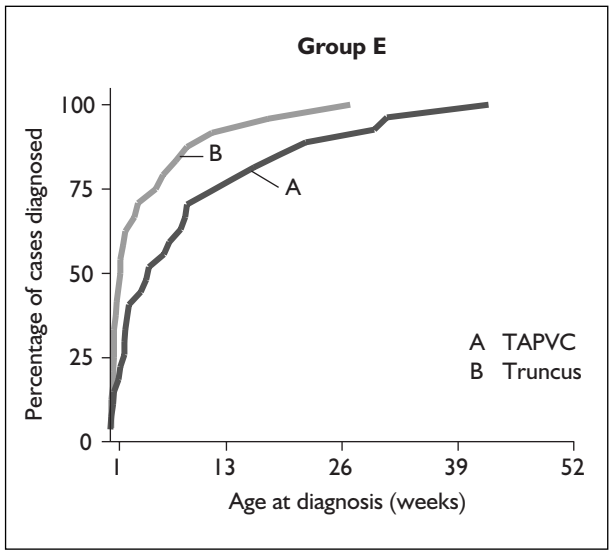
TAPVC appears in the graphs for Groups D and E as it cannot be attributed to a single group using the Northern Region diagnostic categories.

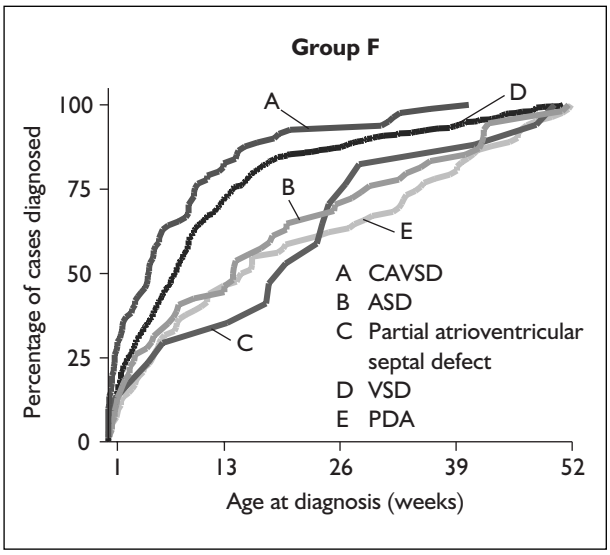









Group E
Percentage of cases diagnosed
100
75
50
25
0
1
13
26
39
52
Age at diagnosis (weeks)
A
B
A TAPVC
B Truncus


Group F
Percentage of cases diagnosed
100
75
50
25
0
1
13
26
39
52
Age at diagnosis (weeks)
A
B
C
D
E
A CAVSD
B ASD
C Partial atrioventricular septal defect
D VSD
E PDA

Appendix 6

Prevalence of congenital heart defects by group in the screening classification

	Group A	Group B	Group C	Group D	Group E	Group F
	Systemic ventricle outflow obstruction	Unfavourable streaming	Low pulmonary blood flow	Pulmonary venous hypertension	Mixing with unrestricted pulmonary blood flow	Left to right shunt
Merseyside 1979–88 Total LB = 203,880 Total CHD = 1543 (7.6/1000) Classifiable = 1420 Unclassifiable = 123 (Jackson[264])	**Numbers**	**Numbers**	**Numbers**	**Numbers**	**Numbers**	**Numbers**
	COA = 72 HLH = 39 IAA = 11 AS = 77 Bicuspid = 19	TGA = 61	PA = 34 PS = 142 TOF = 66 UVH = 23 Tricuspid atresia = 30	TAPVC = 32 Mitral valve = 8	Truncus = 13	VSD = 416 (*excluding spontaneous closure = 42*) PDA = 138 ASD = 76 AVSD = 63
	Total = 1/1000 (16%)	Total = 0.3/1000 (5%)	Total = 1.4/1000 (22%)	Total = 0.2/1000 (3%)	Total = 0.06/1000 (1%)	Total = 3.4/1000 (53%)
Baltimore–Washington Infant Study 1981–82 Total LB = 179,697 Total CHD = 664 (3.7/1000) Classifiable = 3.3 Unclassifiable = 0.4 (Ferencz[265])	**Prevalence per 1000 live births**					
	COA = 0.2 HLH = 0.3 AS = 0.1	TGA = 0.2	PA = 0.1 PS = 0.2 TOF = 0.3 Tricuspid atresia = 0.04	TAPVC = 0.1	Truncus = 0.06	AVSD = 0.4 VSD = 0.9 ASD = 0.3 PDA = 0.1
	Total = 0.6/1000 (18%)	Total = 0.2/1000 (6%)	Total = 0.64/1000 (19%)	Total = 0.1/1000 (3%)	Total = 0.06/1000 (2%)	Total = 1.7/1000 (51%)
Northern Region 1985–97 Total LB = 477,960 Total CHD = 2671 (5.6/1000) Classifiable = 5.4 Unclassifiable = 0.2 (Wren[4])	**Prevalence per 1000 live births**					
	COA = 0.24 HLH = 0.14 AS = 0.20	TGA = 0.30	PA = 0.16 PS = 0.57 TOF = 0.31 DIV = 0.07 Tricuspid atresia = 0.05 Mitral atresia = 0.03	TAPVC = 0.09	Truncus = 0.09	AVSD = 0.35 VSD = 2.38 ASD = 0.28 PDA = 0.23
	Total = 0.58/1000 (10%)	Total = 0.30/1000 (5%)	Total = 1.19/1000 (21%)	Total = 0.09/1000 (2%)	Total = 0.09/1000 (2%)	Total = 3.24/1000 (58%)

AS, aortic stenosis; ASD, atrial septal defect; Bicuspid, bicuspid aortic valve; CAVSD, complete atrioventricular septal defect; CHD, congenital heart defects; COA, coarctation of the aorta; DIV, double inlet ventricle; HLH, hypoplastic left heart; IAA, interrupted aortic arch; LB, live births; PA + IVS, pulmonary atresia with intact ventricular septum; PA + VSD, pulmonary atresia with ventricular septal defect; PDA, persistent ductus arteriosus; PS, pulmonary stenosis; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; Truncus, truncus arteriosus; UVH, univentricular heart; VSD, ventricular septal defect.

Appendix 7

Search strategy and abstract review for prevalence and probability parameters

Search strategy

Search strategy using Ovid MEDLINE to determine the prevalence of congenital heart defects and the probability values within the decision model.

Concept 1: congenital heart defects (total references = 147,679)

1. Explode "CARDIOVASCULAR ABNORMALITIES" /all subheadings
2. Explode "HEART DEFECTS, CONGENITAL"/all subheadings
3. Explode "HEART VALVE DISEASES" /all subheadings
4. (congenital$ adj3 cardi$).ti,ab,kw.
5. (congenital adj3 heart$).ti,ab,kw.
6. coarct$.ti,ab,kw.
7. (double adj outlet adj right adj ventricle).ti,ab,kw.
8. DORV.ti,ab,kw.
9. (double adj outlet adj2 ventricle).ti,ab,kw.
10. (endocardial adj cushion adj defect).ti,ab,kw.
11. (hypoplastic adj left adj heart).ti,ab,kw.
12. HLH$.ti,ab,kw.
13. Norwood.ti,ab,kw.
14. Fontan.ti,ab,kw.
15. (interrupt$ adj3 aort$ adj arch).ti,ab,kw.
16. IAA.ti,ab,kw.
17. LVOT$.ti,ab,kw.
18. (left adj ventric$ adj outflow adj2 obstruct$).ti,ab,kw.
19. (mitral adj atresia).ti,ab,kw.
20. (aort$ adj atresia).ti,ab,kw.
21. (mitral adj stenosis).ti,ab,kw.
22. (aortic adj stenosis).ti,ab,kw.
23. PVOD.ti,ab,kw.
24. (Eisenmenger$ adj syndrome).ti,ab,kw.
25. TGA.ti,ab,kw.
26. (transposition adj3 great adj arter$).ti,ab,kw.
27. (switch adj operation).ti,ab,kw.
28. (switch adj surg$).ti,ab,kw.
29. (switch adj procedure$).ti,ab,kw.
30. senning.ti,ab,kw.
31. (univentric$ adj heart).ti,ab,kw.
32. UVH.ti,ab,kw.
33. (single adj ventric$).ti,ab,kw.
34. (Mustard adj surg$).ti,ab,kw.
35. (Mustard adj operat$).ti,ab,kw.
36. (Mustard adj procedure$).ti,ab,kw.
37. Rastelli.ti,ab,kw.
38. (anomalous adj pulmonary adj2 drainage).ti,ab,kw.
39. (anomalous adj pulmonary adj venous adj return).ti,ab,kw.
40. TAPVD.ti,ab,kw.
41. TAPVR.ti,ab,kw.
42. PAPVD.ti,ab,kw.
43. PAPVR.ti,ab,kw.
44. (ventricular adj septal adj defect).ti,ab,kw.
45. VSD.ti,ab,kw.
46. (atrioventricular adj septal adj defect).ti,ab,kw.
47. AVSD.ti,ab,kw.
48. Explode "CONGENITAL, HEREDITARY, AND NEONATAL DISEASES AND ABNORMALITIES" /all subheadings
49. cardi$.ti,ab,kw.
50. heart$.ti,ab,kw.
51. 49 or 50
52. 48 and 51
53. 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 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 52

Concept 2: age group (total references = 1,278,534)

54. "CHILD"/all subheadings
55. Explode "INFANT, NEWBORN, DISEASES"/all subheadings
56. child$.ti,ab,kw.
57. neonat$.ti,ab,kw.
58. infan$.ti,ab,kw.
59. newborn$.ti,ab,kw.
60. 54 or 55 or 56 or 57 or 58 or 59

Concept 3: screening and diagnostic accuracy (total references = 802,445)

61. Explode "SENSITIVITY AND SPECIFICITY"/all subheadings
62. Explode "MASS SCREENING"/ all subheadings
63. Explode "PREDICTIVE VALUE OF TESTS"/all subheadings

64. Explode "ROC Curve"/all subheadings
65. Explode "MORBIDITY"/all subheadings
66. specificit$.ti,ab,kw.
67. (false adj negative).ti,ab,kw.
68. accuracy.ti,ab,kw.
69. screening.ti,ab,kw.
70. sensitivit$.ti,ab,kw.
71. (predictive adj value).ti,ab,kw.
72. (likelihood adj ratio).ti,ab,kw.
73. (false adj positive).ti,ab,kw.
74. reproducibility.ti,ab,kw.
75. (logistic adj regression).ti,ab,kw.
76. 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75

Concept 4: diagnostic tests for newborn screening (total references = 7165)

77. auscultat$.ti,ab,kw.
78. (newborn adj exam$).ti,ab,kw.
79. (clinical adj exam$).ti,ab,kw.
80. (neonatal adj exam$).ti,ab,kw.
81. (cardiac adj5 murmur$).ti,ab,kw.
82. (heart$ adj5 murmur$).ti,ab,kw.
83. 77 or 78 or 79 or 80 or 81 or 82
84. 76 and 83
85. (pulse adj oximet$).ti,ab,kw.
86. (neonatal adj echo$).ti,ab,kw.
87. 84 or 85 or 86

Combine all concepts (total references = 167)

88. 53 and 60 and 76 and 87

Remove papers without abstracts (remove 4 papers)

89. limit 88 to abstracts

Remove papers with antenatal screening only (remove 14 papers)

90. limit 89 to all child <0 to 18 years>

Outcome of abstract review

Outcome of abstract review of papers identified using Ovid MEDLINE to determine the prevalence of congenital heart defects and the probability values within the decision model.

The 20 papers where there was disagreement on eligibility were reviewed again jointly and a joint decision made to include a further five papers in the data extraction process. The inclusion of 34 papers was then reviewed and agreed by the third reviewer (CB). Two of three reviewers extracted data from each paper to value the model inputs.

TABLE 34 *Papers deemed eligible for inclusion after the initial abstract review*[a]

	Reviewer 2			
Reviewer 1	**Eligible**	**Not eligible**	**Background**[b]	**Total**
Eligible	*29*	0	**15**	44
Not eligible	**1**	*191*	39	231
Background	**4**	9	*129*	142
Total	34	200	183	417

[a] Numbers in italics represent concordance between reviewers 1 and 2; numbers in bold represent disagreement on eligibility (n = 20).
[b] Some papers were also identified as providing useful background material, but no input data for the model.

TABLE 35 *Papers deemed eligible for inclusion after the final abstract review*[a]

	Reviewer 2			
Reviewer 1	**Eligible**	**Not eligible**	**Background**	**Total**
Eligible	*34*	0	0	34
Not eligible	0	*192*	39	231
Background	0	9	*143*	152
Total	34	201	182	417

[a] See *Table 34*.

Appendix 8

Prevalence figures

TABLE 36 *Prevalence table*

	CHD combined	TGA	AS	TAPVC	HLH and MA	COA and IAA	PA	VSD (no echo)	Clinically significant CHD excluding VSD (no echo)	No. of infants excluded from routine newborn screening	Clinically non-significant VSDs (total VSD with echo)[273]	Clinically non-significant CHD (PDA, PS, ASD with echo)[11]
NORTHERN REGION												
Total live births[6] (*excludes stillbirths*)[a]	300,102											
Total number of affected children born in the Northern Region 1987–94 with a confirmed diagnosis by 12 months of age	1590	84	67	27	45	132	74	590	571[1]		173	
Exclusions (1): number with major extracardiac abnormality, surgery or trisomy[6]	73	2	1	3	2	0	3	24	42			
Exclusions (2): number with lethal trisomies 13 and 18[6]	21	0	0	0	0	2	0	12	7			
Exclusions (3): number with Down's syndrome[6]	107								107			
Total exclusions (1–3) from routine newborn screening as proportion of condition-specific live births with congenital heart defects[6]	**0.126**	**0.024**	**0.015**	**0.111**	**0.044**	**0.015**	**0.041**	**0.061**	**0.273**			
No. of exclusions for antenatal diagnosis[6]	58	2	5	0	9	8	5	10	19			
Total exclusions due to antenatal diagnosis as proportion of condition-specific live-births with congenital heart defects[6]	**0.036**	**0.024**	**0.075**	**0.000**	**0.200**	**0.061**	**0.068**	**0.017**	**0.033**			

continued

TABLE 36 *Prevalence table (cont'd)*

	CHD combined	TGA	AS	TAPVC	HLH and MA	COA and IAA	PA	VSD (no echo)	Clinically significant CHD excluding VSD (no echo)	No. of infants excluded from routine newborn screening	Clinically non-significant VSDs (total VSD with echo)[273]	Clinically non-significant CHD (PDA, PS, ASD with echo)[11]
NATIONAL ANTENATAL DETECTION DATA												
No. of exclusions for antenatal diagnosis as proportion of condition-specific live births with congenital heart defects (national figures[8])	0.117	0.025	0.075	0.074	0.244	0.061	0.218	0.117	0.117			
BASE CASE FOR 100,000 LIVE BIRTHS												
Total number of infants with congenital heart defects per 100,000 live births diagnosed by 1 year old[6]	530	28	22	9	15	44	25	197	180			
Number of exclusions per 100,000 live births (extracardiac defects, Down's syndrome, lethal trisomy) with no congenital heart defects[275]										128		
Number of exclusions per 100,000 live births (1–3)[6]	67.0	0.3	1.0	0.7	0.7	1.0	0.7	12.0	49.2		4159	94
Number of exclusions per 100,000 live births (due to antenatal diagnosis)[6] BASE-CASE	19.3	1.6	0.0	3.0	2.7	1.7	0.7	3.3	6.0			
SCREENING TIME SCENARIOS												
Exclusions if screened at birth	86.3	1.3	2.0	1.0	3.7	3.3	2.7	15.4	55.9			
Number left after exclusions per 100,000 LB if screened at birth = A1	444	27	20	8	11	41	22	182	125		4159	59
Exclusions if screen at 24 hours	107	12	4	1	3	5	7	48	27	319.5		235

continued

TABLE 36 *Prevalence table (cont'd)*

	CHD combined	TGA	AS	TAPVC	HLH and MA	COA and IAA	PA	VSD (no echo)	Clinically significant CHD excluding VSD (no echo)	No. of infants excluded from routine newborn screening	Clinically non-significant VSDs (total VSD with echo)[273]	Clinically non-significant CHD (PDA, PS, ASD with echo)[11]
Number left after exclusions per 100,000 LB if screen at 24 hours = A2	337	15	16	7	8	36	15	134	98		4159	59
Exclusions if screen at 48 hours	209	20	8	4	8	15	14	69	71	421.5		337
Number left after exclusions per 100,000 LB if screen at 48 hours = A3	235	7	12	4	3	26	8	113	54		4159	59
NORTHERN REGION CASES DETECTED BETWEEN 1 AND 16 YEARS												
Number per 100,000 live births 1–16 = B[12] *(adjusted for deaths under 1[14])*	180	0	11.7	0.53	0.8	10.6	0	54.7	101.7			
A + B (total cases 0–16)	710	28	33.7	9.53	15.8	54.6	25	251.7	281.7			
A1 + B (total cases minus exclusions)	0.00624	0.00027	0.00032	0.00009	0.00012	0.00051	0.00022	0.00236	0.00226		0.99193	0.00214
A2 + B (cases left after 24 hours and exclusions)	0.00517	0.00015	0.00028	0.00008	0.00009	0.00046	0.00015	0.00188	0.00199		0.99273	0.00235
A3 + B (cases left after 48 hours and exclusions)	0.00415	0.00007	0.00024	0.00005	0.00004	0.00036	0.00008	0.00167	0.00155		0.99266	0.00337
BASE CASE PREVALENCE RATES												
Prevalence at point of screening – clinical examination alone	0.00517	0.00015	0.00028	0.00008	0.00009	0.00046		0.00188	0.00223		0.99249	0.00235
Prevalence at point of screening – pulse oximetry with clinical examination	0.00517	0.00015	0.00028	0.00008	0.00009	0.00046		0.00188	0.00223		0.99249	0.00235
Prevalence at point of screening – echocardiography with clinical examination	0.00517	0.00015	0.00028	0.00008	0.00009	0.00046		0.00188	0.00223			0.00235

[a] Atrial septal defects (71), persistent ductus arteriosus (81), pulmonary stenosis (135) = 287; tetralogy of Fallot (99), complete atrioventricular septal defects (81), truncus arteriousus (24), miscellaneous (80) = 284.

TABLE 37 *Prevalence figures from Eurocat surveillance data*

	Eurocat prevalence (1996–99) per 100,000 live-births
Down's syndrome	106.2
Lethal trisomy 18	8.1
Lethal trisomy 13	5.4
Gastroschisis	29.3
Omphalocoele	12.5
Anorectal atresia	31.7
Tracheo-oesophageal atresia	21.1

Source: European Surveillance of Congenital Anomalies (Eurocat). Eurocat Surveillance
Data: Table B3, 1996–1999, UK. URL: http://www.eurocat.ulster.ac.uk/pubdata/tables.html. Accessed 2001.

Appendix 9

Values and ranges of probabilities

Values and ranges of probabilities used in the base case and probabilistic cost-effectiveness analysis by specific defect

TABLE 38 *Transposition of the great arteries (TGA)*

Probability depicted in *Figure 25*	Base-case value	Range of subjective probabilities[a]	Probability distribution	Source
Detection rate: clinical examination alone [B]	0.389	N/A	Beta (7.0, 11.0)	Ref. 6
Detection rate: pulse oximetry with clinical examination [B]	0.950	0.900–1	Beta (17.1, 0.9)	Expert
Detection rate: screening echocardiography with clinical examination [B]	0.900	0.850–0.950	Beta (31.5, 3.5)	Expert
Probability of collapse before diagnosis given negative screening test or no screening [C]	0.200	0.150–0.250	Beta (12.6, 50.4)	Expert
Probability of collapse given positive screen and no diagnostic echocardiography [D]	0.125	0.085–0.165	Beta (8.4, 58.9)	Expert
Probability of death before diagnosis given negative screening test or no screening [E]	0.020	0.010–0.030	Beta (3.9, 191.1)	Expert
Probability of diagnosis without collapse given negative screen or no screening [F]	1.0	N/A	No distribution assigned as always diagnosed in first year	Ref. 6
Probability of death given collapse after positive screen [G]	0.005	0.003–0.007	Beta (6.2, 1236.5)	Expert

[a] The range of subjective probabilities are only relevant where data were derived from expert opinion.

TABLE 39 *Aortic stenosis (AS)*

Probability depicted in *Figure 25*	Base-case value	Range of subjective probabilities[a]	Probability distribution	Source
Detection rate: clinical examination alone [B]	0.544	N/A	Beta (31.0, 26.0)	Ref. 6
Detection rate: pulse oximetry with clinical examination [B]	0.596	N/A	Beta (34.0, 23.0)	Expert
Detection rate: screening echocardiography with clinical examination [B]	0.821	0.750–0.890	Beta (23.9, 5.2)	Expert
Probability of collapse given negative screening test or no screening [C]	0.050	0.030–0.070	Beta (5.9, 111.9)	Expert
Probability of collapse given positive screen and no diagnostic echocardiography [D]	0.100	0.050–0.150	Beta (3.5, 31.5)	Expert
Probability of death given negative screening test or no screening [E]	0.020	0.005–0.035	Beta (1.7, 84.4)	Expert
Probability of diagnosis without collapse given negative screen or no screening [F]	0.653	N/A	Beta (22.0, 11.7)	Ref. 6
Probability of death given collapse after positive screen [G]	0.020	0.005–0.035	Beta (1.7, 84.4)	Expert

[a] The range of subjective probabilities are only relevant where data were derived from expert opinion.

TABLE 40 *Total anomalous pulmonary venous connection (TAPVC)*

Probability depicted in *Figure 25*	Base-case value	Range of subjective probabilities[a]	Probability distribution	Source
Detection rate: clinical examination alone [B]	0.035	N/A	Beta (5.2, 143.9)	Ref. 6
Detection rate: pulse oximetry with clinical examination [B]	0.950	0.900–1	Beta (17.1, 0.9)	Expert
Detection rate: screening echocardiography with clinical examination [B]	0.600	0.400–0.800	Beta (3.0, 2.0)	Expert
Probability of collapse given negative screening test or no screening [C]	0.050	0.030–0.070	Beta (5.9, 111.9)	Expert
Probability of collapse given positive screen and no diagnostic echocardiography [D]	0.100	0.050–0.150	Beta (3.5, 31.5)	Expert
Probability of death given negative screening test or no screening [E]	0.050	0.030–0.070	Beta (5.9, 111.9)	Expert
Probability of diagnosis without collapse given negative screen or no screening [F]	0.944	N/A	Beta (9.0,0.5)	Ref. 6
Probability of death given collapse after positive screen [G]	0.050	0.030–0.070	Beta (5.9, 111.9)	Expert

[a] The range of subjective probabilities are only relevant where data were derived from expert opinion.

TABLE 41 *Hypoplastic left heart/mitral atresia (HLH/MA)*

Probability depicted in *Figure 25*	**Base-case value**	**Range of subjective probabilities[a]**	**Probability distribution**	**Source**
Detection rate: clinical examination alone [B]	0.375	N/A	Beta (6.0, 10.0)	Ref. 6
Detection rate: pulse oximetry with clinical examination [B]	0.950	0.900–1	Beta (17.1, 0.9)	Expert
Detection rate: screening echocardiography with clinical examination [B]	0.990	0.980–1	Beta (97.0, 1.0)	Expert
Probability of collapse given negative screening test or no screening [C]	0.900	0.800–1	Beta (7.2, 0.8)	Expert
Probability of collapse given positive screen and no diagnostic echocardiography [D]	0.350	0.300–0.400	Beta (31.5, 58.5)	Expert
Probability of death given negative screening test or no screening [E]	0.125	0.050–0.020	Beta (2.3, 16.1)	Expert
Probability of diagnosis without collapse given negative screen or no screening [F]	1.0	N/A	–	Ref. 6
Probability of death given collapse after positive screen [G]	0.020	0.010–0.030	Beta (3.9, 191.1)	Expert

[a] The range of subjective probabilities are only relevant where data were derived from expert opinion.

TABLE 42 *Coarctation of aorta/interruption of aortic arch (COA/IAA)*

Probability depicted in *Figure 25*	**Base-case value**	**Range of subjective probabilities[a]**	**Probability distribution**	**Source**
Detection rate: clinical examination alone [B]	0.221	N/A	Beta (21.0, 74.0)	Ref. 6
Detection rate: pulse oximetry with clinical examination [B]	0.600	0.300–0.900	Beta (1.0, 0.7)	Expert
Detection rate: screening echocardiography with clinical examination [B]	0.600	0.400–0.800	Beta (3.0, 2.0)	Expert
Probability of collapse given negative screening test or no screening [C]	0.150	0.100–0.200	Beta (7.5, 42.5)	Expert
Probability of collapse given positive screen and no diagnostic echocardiography [D]	0.150	0.100–0.200	Beta (7.5, 42.5)	Expert
Probability of death given negative screening test or no screening [E]	0.050	0.030–0.070	Beta (5.9, 111.9)	Expert
Probability of diagnosis without collapse given negative screen or no screening [F]	0.806	N/A	Beta (44.0,10.6)	Ref. 6
Probability of death given collapse after positive screen [G]	0.005	0.003–0.007	Beta (6.2, 1236.5)	Expert

[a] The range of subjective probabilities are only relevant where data were derived from expert opinion.

TABLE 43 *Pulmonary atresia (PA)*

Probability depicted in *Figure 25*	Base-case value	Range of subjective probabilities[a]	Probability distribution	Source
Detection rate: clinical examination alone [B]	0.469	N/A	Beta (15.0, 17.0)	Ref. 6
Detection rate: pulse oximetry with clinical examination [B]	0.940	0.900–0.980	Beta (32.2, 2.1)	Expert
Detection rate: screening echocardiography with clinical examination [B]	0.900	0.850–0.950	Beta (31.5, 3.5)	Expert
Probability of collapse given negative screening test or no screening [C]	0.500	0.400–0.800	Beta (12.0, 12.0)	Expert
Probability of collapse given positive screen and no diagnostic echocardiography [D]	0.075	0.050–0.100	Beta (8.3, 101.8)	Expert
Probability of death given negative screening test or no screening [E]	0.125	0.100–0.150	Beta (21.8, 152.3)	Expert
Probability of diagnosis without collapse given negative screen or no screening [F]	1.0	N/A	–	Ref. 6
Probability of death given collapse after positive screen [G]	0.015	0.010–0.020	Beta (8.9, 581.2)	Expert

[a] The range of subjective probabilities are only relevant where data were derived from expert opinion.

TABLE 44 *Ventricular septal defect (VSD)*

Probability depicted in *Figure 25*	Base-case value	Range of subjective probabilities[a]	Probability distribution	Source
Detection rate: clinical examination alone [B]	0.493	N/A	Beta (237.0, 244.0)	Ref. 6
Detection rate: pulse oximetry with clinical examination [B]	0.714	N/A	Beta (15.0, 6.0)	Ref. 253
Detection rate: screening echocardiography with clinical examination [B]	0.950	0.850–0.950	Beta (17.1, 0.9)	Expert
Probability of collapse given negative screening test or no screening [C]	0.005	0–0.010	Beta (1.0, 197.0)	Expert
Probability of collapse given positive screen and no diagnostic echocardiography [D]	0.005	0–0.010	Beta (1.0, 197.0)	Expert
Probability of death given negative screening test or no screening [E]	0.005	0–0.010	Beta (1.0, 197.0)	Expert
Probability of diagnosis without collapse given negative screen or no screening [F]	0.783	N/A	Beta (197.0, 54.7)	Ref. 6
Probability of death given collapse after positive screen [G]	0.005	0–0.010	Beta (1.0, 197.0)	Expert

[a] The range of subjective probabilities are only relevant where data were derived from expert opinion.

TABLE 45 *Other clinically significant non-life-threatening defects*

Probability depicted in *Figure 25*	Base-case value	Range of subjective probabilities[a]	Probability distribution	Source
Detection rate: clinical examination alone [B]	0.465	N/A	Beta (174.0, 200.0)	Ref. 6
Detection rate: pulse oximetry with clinical examination [B]	0.667	N/A	Beta (8.0, 4.0)	Ref. 253
Detection rate: screening echocardiography with clinical examination [B]	0.900	0.85–0.95	Beta (31.5, 3.5)	Expert
Probability of collapse given negative screening test or no screening [C]	0.005	0–0.010	Beta (1.0, 197.0)	Expert
Probability of collapse given positive screen and no diagnostic echocardiography [D]	0.005	0–0.010	Beta (1.0, 197.0)	Expert
Probability of death given negative screening test or no screening [E]	0.005	0–0.010	Beta (1.0, 197.0)	Expert
Probability of diagnosis without collapse given negative screen or no screening [F]	0.679	N/A	Beta (215.0, 101.7)	Ref. 6
Probability of death given collapse after positive screen [G]	0.005	0–0.010	Beta (1.0, 197.0)	Expert

[a] The range of subjective probabilities are only relevant where data were derived from expert opinion.

Probability distributions used in the base case

Table 46 summarises the choice of probability distributions for different types of model parameters.

The pathway probabilities were assigned beta distributions. The rationale is given in *Table 46*. Where the data are binomial and r is the total number of events (e.g. the number of affected infants with a positive test result) and the total sample size is n (e.g. number of affected infants who are screened) then the parameters for the beta distribution (α, β) are simply $\alpha = r$ and $\beta = n - r$.

Where probability ranges were elicited by expert opinion we used the method described by Spiegelhalter and colleagues to derive the

TABLE 46 *The choice of probability distribution for model parameters*

Parameter type	Distribution type	Rationale
Pathway probabilities	Beta	Beta distributions are bounded by 0 and 1. The distribution's parameters (α, β) represent the number of two possible complementary events such as success/failure, positive/negative test result, collapse/no collapse or life/death[276,277]
Prevalence data	Dirichlet	Generalisation of the beta distribution to more than two categories[507]
Staff time to perform screening test and diagnostic echocardiography	Gamma	Gamma distributions are bounded by zero and approximate the normal distribution for large samples.[508] They are often used to model the time to complete a task rather than normal distributions because of the non-negligible probability that the latter could take values <0 for smaller samples[507,509]
Unit costs, e.g. equipment for screening, management of collapsed infants, ambulance transport, post-mortem examination of collapsed infants	Uniform	With little information on the unit cost distribution, the uniform distribution reflects an equal chance of the unit cost estimated falling within the specified range.[509]

parameters (α, β) for the beta distribution such that $\alpha + \beta = n$ for all probability ranges elicited.[279] This method translates ranges into implicit fractions of patients and a more precise assessment of a range is reflected in a larger implicit sample size. Assuming that the elicited range reflects approximately the mean $\pm$ W standard deviations of a beta distribution (α, β), then it can be shown that

$$\alpha + \beta + 1 = g(1 - g)(W/h)^2$$

and

$$\alpha/(\alpha + \beta) = g$$

where g is the midpoint of the interval and h is half its range. For example, if the expert opinion is that the probability falls between 80 and 90%, then $g = 85\%$ and $h = 5\%$. Assuming a value for W, such as $W = 1$, both equations simultaneously will give α and β. For more detail, see Spiegelhalter and colleagues (1994)[279] and for a formal overview of different methods used to elicit prior distributions see Spiegelhalter and colleagues (2000).[510]

The Dirichlet distribution was used to model prevalence data. The Dirichlet distribution generalises the beta distribution to more than two categories and is the appropriate distribution to model multinomial data, that is, data that occur naturally across more than two categories.[507] For example, newborn infants with congenital heart disease can have one of several congenital heart defects. Therefore, the total sample of newborn babies with congenital heart defects is not split between two categories, but between eight possible categories (TGA, AS, TAPVC, HLH/MA, COA/IAA, PA, VSD and clinically non-significant congenital heart defects). The overall probability of having a congenital heart defect was modelled using the beta distribution.

Where no information was available on the variance of mean estimates (e.g. additional cases with congenital heart disease occurring between age 1 and 16 years), we assumed that the standard error was half of the value of the mean. This corresponds to a coefficient of variation of 0.5 and represents large uncertainty in the estimation of these data points.

For the cost estimates, staff time for the screening tests and diagnostic echocardiography were assigned gamma distributions. The rationale is given in *Table 46*. The method of moments was used to define the gamma distribution which only requires that the mean and variance are known. Values for the observed mean and variance were expressed in terms of α and β and both equations solved simultaneously:

$$\text{mean} = \frac{\alpha}{\beta}; \text{ variance} = \frac{\alpha}{\beta^2}$$

In the absence of data on the variance of the time taken to perform the pulse oximetry or echocardiography, the coefficient of variation (i.e. the standard deviation divided by the sample mean) was assumed to be equivalent to that for screening by clinical examination (0.28). The coefficient of variation and data on the sample mean was then used to derive the variance for pulse oximetry and echocardiography.[507]

A uniform distribution was assigned to the unit costs estimates. The rationale is given in *Table 46*. The lower and upper values of the conceivable range for the relevant unit cost (e.g. equipment cost per screen) were used to define the distribution.

Appendix 10

Expected value of information analysis

The EVPI for the population of current and future patient populations (here newborns) over the effective lifetime of the technology (T) can be estimated from the EVPI, that is, the mean opportunity cost associated with the wrong decision, the number of newborns (I) in each time period (t) discounted at rate r:[276,285,289]

$$\text{Population EVPI} = \text{EVPI} \times \sum_{t=1}^{T} \frac{I^t}{(1 + r)^t}$$

A more thorough explanation of this approach and technical detail on how to calculate the EVPI can be found in the HTA report by Chilcott and colleagues.[285]

Appendix 11

Outcome tables

TABLE 47 *Estimated screening performance of alternative screening strategies by condition (base case)*

	Life-threatening congenital heart defects								
	Transposition of the great arteries			Aortic stenosis			Total anomalous pulmonary venous connection		
	Screening strategy			Screening strategy			Screening strategy		
	CE	PO	SE	CE	PO	SE	CE	PO	SE
Expected number affected at birth	28.0	28.0	28.0	34.0	34.0	34.0	9.5	9.5	9.5
Number recognised before newborn screen (number antenatally)	13.7 (0.7)	13.7 (0.7)	13.7 (0.7)	5.3 (1.6)	5.3 (1.6)	5.3 (1.6)	1.9 (0)	1.9 (0)	1.9 (0)
Expected number affected at screen	14.3	14.3	14.3	28.7	28.7	28.7	7.6	7.6	7.6
Number screened[a]	13.3	13.3	13.0	26.7	26.7	26.1	7.1	7.1	7.0
Proportion of all affected and screened who are detected by newborn screen (*n*)	38.9% (5.2)	95.0% (12.7)	90.0% (11.7)	54.4% (14.5)	59.6% (15.9)	82.1% (21.4)	3.5% (0.2)	95.0% (6.7)	60.0% (4.2)
Proportion of all affected who are detected by newborn screen	18.5%	45.2%	42.8%	42.7%	46.8%	64.4%	2.6%	70.8%	43.8%
Number affected with positive screen[b] who collapse or die before definitive diagnosis (*n*) (failures of initial management)	0.6	1.6	1.5	1.5	1.6	2.1	0.0	0.7	0.4
Number of timely diagnoses (*n*) (receiving a definitive diagnosis after screen and without collapse or death)	4.5	11.1	10.3	13.1	14.3	19.3	0.2	6.1	3.8

continued

TABLE 47 *Estimated screening performance of alternative screening strategies by condition (base case) (cont'd)*

	Life-threatening congenital heart defects								
	Hypoplastic left heart/mitral atresia			Coarctation of the aorta/interrupted aortic arch			Pulmonary atresia		
	Screening strategy			Screening strategy			Screening strategy		
	CE	PO	SE	CE	PO	SE	CE	PO	SE
Expected number affected at birth	15.8	15.8	15.8	54.6	54.6	54.6	24.7	24.7	24.7
Number recognised before newborn screen (number antenatally)	7.0 (3.0)	7.0 (3.0)	7.0 (3.0)	8.0 (2.7)	8.0 (2.7)	8.0 (2.7)	10.0 (1.7)	10.0 (1.7)	10.0 (1.7)
Expected number affected at screen	8.8	8.8	8.8	46.6	46.6	46.6	14.7	14.7	14.7
Number screened[a]	8.2	8.2	8.0	43.3	43.3	42.4	13.6	13.6	13.3
Proportion of all affected and screened who are detected by newborn screen (*n*)	37.5% (3.1)	95.0% (7.8)	99.0% (7.9)	22.1% (9.6)	60.0% (26.0)	60.0% (25.4)	46.9% (6.4)	94.0% (12.8)	90.0% (12.0)
Proportion of all affected who are detected by newborn screen	19.4%	49.2%	50.2%	17.5%	47.6%	46.6%	25.9%	52.0%	48.7%
Number affected with positive screen[b] who collapse or die before definitive diagnosis (*n*) (failures of initial management)	1.1	2.7	2.8	1.4	3.9	3.8	0.5	1.0	0.9
Number of timely diagnoses (*n*) (receiving a definitive diagnosis after screen and without collapse or death)	2.0	5.1	5.2	8.1	22.1	21.6	5.9	11.9	11.1

continued

TABLE 47 *Estimated screening performance of alternative screening strategies by condition (base case) (cont'd)*

	Clinically significant congenital heart defects					
	Ventricular septal defects			Other congenital heart defects		
	Screening strategy			Screening strategy		
	CE	PO	SE[c]	CE	PO	SE[c]
Expected number affected at birth	251.3	251.3	251.3	292.0	292.0	292.0
Number recognised before newborn screen (number antenatally)	33.3 (3.3)	33.3 (3.3)	33.3 (3.3)	85.0 (6.0)	85.0 (6.0)	85.0 (6.0)
Expected number affected at screen	218.0	218.0	218.0	207.0	207.0	207.0
Number screened[a]	202.7	202.7	198.4	192.5	192.5	188.4
Proportion of all affected and screened who are detected by newborn screen (*n*)	49.3% (99.9)	71.4% (144.8)	95.0% (188.4)	46.5% (89.6)	66.7% (128.3)	90.0% (169.5)
Proportion of all affected who are detected by newborn screen	39.7%	57.6%	75.0%	30.7%	44.0%	58.1%
Number affected with positive screen[b] who collapse or die before definitive diagnosis (*n*) (failures of initial management)	–	–		–	–	
Number of timely diagnoses (*n*) (receiving a definitive diagnosis after screen and without collapse or death)	–	–		–	–	

CE, clinical examination alone; PO, pulse oximetry with clinical examination; SE, screening echocardiography with clinical examination.
[a] Coverage: CE 93%, PO 93% and SE 91%.
[b] Excludes those whose congenital heart defects are diagnosed as a result of antenatal screening or clinical symptoms before screen or other abnormalities at birth.
[c] Excluding all non-clinically significant cases that will be detected by echocardiography.

TABLE 48 *Estimated performance of alternative screening strategies: screening at birth (numbers per 100,000 live births, rounded to nearest whole number, unless stated otherwise)*

	Strategy		
	Clinical examination (CE) alone	**Pulse oximetry with clinical examination (PO)**	**Screening echocardiography with clinical examination (SE)**
Expected number of life-threatening congenital heart defects at birth (*n*)	167	167	167
Expected number of other congenital heart defects at birth (*n*):	543	543	543
Congenital heart defects only detected by echo (n)	*N/A*	*N/A*	*4218*
Number screened[a]	92799	92799	90804
Expected prevalence of life-threatening congenital heart defects at screen	153	153	153
Positive screening result:			
n (as % of number screened)	530 (0.6%)	1304 (1.4%)	5002 (5.5%)
True positives	*50*	*107*	*107*
False positives	*480*	*1197*	*4895*
Negative screening result	92269	91495	85802
False negatives	*91*	*35*	*32*
True negatives	*92178*	*91461*	*85770*
Number of cases with timely diagnosis due to newborn screen[b]	44	92	92
Detection rate (%)	33.1%	70.4%	70.4%
Positive predictive value	9.5%	8.2%	2.1%
False-positive rate	0.5%	1.3%	5.4%

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

[b] Timely diagnosis = diagnosed before collapse or death occurs.

TABLE 49 *Estimated performance of alternative screening strategies: screening at 48 hours after birth (numbers per 100,000 live births, rounded to nearest whole number, unless stated otherwise)*

	Strategy		
	Clinical examination (CE) alone	**Pulse oximetry with clinical examination (PO)**	**Screening echocardiography with clinical examination (SE)**
Expected number of life-threatening congenital heart defects at birth (*n*)	167	167	167
Expected number of other congenital heart defects at birth (*n*):	543	543	543
Congenital heart defects only detected by echo (n)	*N/A*	*N/A*	*4218*
Number screened[a]	92606	92606	90614
Expected prevalence of life-threatening congenital heart defects at screen	84	84	84
Positive screening result: *n* (as % of number screened)	444 (0.5%)	1161 (1.3%)	4833 (5.3%)
True positives	*27*	*55*	*56*
False positives	*417*	*1106*	*4777*
Negative screening result	92161	91445	85781
False negatives	*51*	*24*	*20*
True negatives	*92110*	*91421*	*85761*
Number of cases with timely diagnosis due to newborn screen[b]	24	47	49
Detection rate (%)	32.2%	64.9%	66.9%
Positive predictive value	6.1%	4.7%	1.2%
False positive rate	0.5%	1.2%	5.3%

[a,b] See *Table 48*.

TABLE 50 *Estimated screening performance of alternative screening strategies by condition (birth)*

	Life-threatening congenital heart defects								
	Transposition of the great arteries			Aortic stenosis			Total anomalous pulmonary venous connection		
	Screening strategy			Screening strategy			Screening strategy		
	CE	PO	SE	CE	PO	SE	CE	PO	SE
Expected number affected at birth	28.0	28.0	28.0	34.0	34.0	34.0	9.5	9.5	9.5
Number recognised before newborn screen (number antenatally)	1.3 (0.7)	1.3 (0.7)	1.3 (0.7)	2.0 (1.6)	2.0 (1.6)	2.0 (1.6)	1.0 (0)	1.0 (0)	1.0 (0)
Expected number affected at screen	26.7	26.7	26.7	32.0	32.0	32.0	8.5	8.5	8.5
Number screened[a]	24.8	24.8	24.3	29.8	29.8	29.1	7.9	7.9	7.8
Proportion of all affected and screened who are detected by newborn screen (*n*)	38.9% (9.6)	95.0% (23.6)	90.0% (21.8)	54.4% (16.2)	59.6% (17.8)	82.1% (23.9)	3.0% (0.3)	95.0% (7.5)	60.0% (4.7)
Proportion of all affected who are detected by newborn screen	34.4%	84.1%	79.7%	47.6%	52.2%	71.9%	2.9%	79.1%	48.9%
Number affected with positive screen[b] who collapse or die before definitive diagnosis (*n*) (failures of initial management)	1.2	2.9	2.7	1.6	1.8	2.4	0.0	0.8	0.5
Number of timely diagnoses (*n*) (receiving a definitive diagnosis after screen and without collapse or death)	8.4	20.6	19.1	14.6	16.0	21.5	0.2	6.8	4.2

continued

TABLE 50 *Estimated screening performance of alternative screening strategies by condition (birth) (cont'd)*

	Life-threatening congenital heart defects								
	Hypoplastic left heart/mitral atresia			Coarctation of the aorta/interrupted aortic arch			Pulmonary atresia		
	Screening strategy			Screening strategy			Screening strategy		
	CE	PO	SE	CE	PO	SE	CE	PO	SE
Expected number affected at birth	15.8	15.8	15.8	54.6	54.6	54.6	24.7	24.7	24.7
Number recognised before newborn screen (number antenatally)	3.7 (3.0)	3.7 (3.0)	3.7 (3.0)	3.3 (2.7)	3.3 (2.7)	3.3 (2.7)	2.7 (1.7)	2.7 (1.7)	2.7 (1.7)
Expected number affected at screen	12.1	12.1	12.1	51.3	51.3	51.3	22.0	22.0	22.0
Number screened[a]	11.3	11.3	11.0	47.7	47.7	46.6	20.5	20.5	20.0
Proportion of all affected and screened who are detected by newborn screen (*n*)	37.5% (4.2)	95.0% (10.7)	99.0% (10.9)	22.1% (10.5)	60.0% (28.6)	60.0% (28.0)	46.9% (9.6)	94.0% (19.2)	90.0% (18.0)
Proportion of all affected who are detected by newborn screen	26.8%	67.8%	69.2%	19.3%	52.4%	51.3%	38.9%	78.0%	73.0%
Number affected with positive screen[b] who collapse or die before definitive diagnosis (*n*) (failures of initial management)	1.5	3.8	3.8	1.6	4.3	4.2	0.7	1.4	1.4
Number of timely diagnoses (*n*) (receiving a definitive diagnosis after screen and without collapse or death)	2.7	7.0	7.1	9.0	24.3	23.8	8.9	17.8	16.7

continued

TABLE 50 *Estimated screening performance of alternative screening strategies by condition (birth) (cont'd)*

	Clinically significant congenital heart defects					
	Ventricular septal defects			Other congenital heart defects		
	Screening strategy			Screening strategy		
	CE	PO	SE[c]	CE	PO	SE[c]
Expected number affected at birth	251.3	251.3	251.3	292.0	292.0	292.0
Number recognised before newborn screen (number antenatally)	15.4 (3.3)	15.4 (3.3)	15.4 (3.3)	55.2 (6)	55.2 (6)	55.2 (6)
Expected number affected at screen	236.0	236.0	236.0	233.7	233.7	233.7
Number screened[a]	219.5	219.5	214.7	217.3	217.3	212.6
Proportion of all affected and screened who are detected by newborn screen (*n*)	49.3% (108.1)	71.4% (156.8)	95.0% (204.0)	46.5% (101.1)	66.7% (144.9)	90.0% (191.4)
Proportion of all affected who are detected by newborn screen	43.0%	62.4%	81.2%	34.6 %	49.6%	65.5%
Number affected with positive screen[b] who collapse or die before definitive diagnosis (*n*) (failures of initial management)	–	–	–	–	–	–
Number of timely diagnoses (*n*) (receiving a definitive diagnosis after screen and without collapse or death)	–	–	–	–	–	–

CE, Clinical examination alone; PO, pulse oximetry with clinical examination; SE, screening echo with clinical examination.
[a] Coverage: CE 93%, PO 93% and SE 91%.
[b] I.e. excludes those whose congenital heart defects are diagnosed as a result of antenatal screening or clinical symptoms before screen or other abnormalities at birth.
[c] Excluding all non-clinically significant cases that will be detected by echocardiography.

TABLE 51 *Estimated screening performance of alternative screening strategies by condition (48 hours)*

	Life-threatening congenital heart defects								
	Transposition of the great arteries			Aortic stenosis			Total anomalous pulmonary venous connection		
	Screening strategy			Screening strategy			Screening strategy		
	CE	PO	SE	CE	PO	SE	CE	PO	SE
Expected number affected at birth	28.0	28.0	28.0	34.0	34.0	34.0	9.5	9.5	9.5
Number recognised before newborn screen (number antenatally)	21.7 (0.7)	21.7 (0.7)	21.7 (0.7)	10.3 (1.6)	10.3 (1.6)	10.3 (1.6)	4.6 (0)	4.6 (0)	4.6 (0)
Expected number affected at screen	6.3	6.3	6.3	23.7	23.7	23.7	5.0	5.0	5.0
Number screened[a]	5.9	5.9	5.8	22.0	22.0	21.6	4.6	4.6	4.5
Proportion of all affected and screened who are detected by newborn screen (*n*)	38.9% (2.3)	95.0% (5.6)	90.0% (5.2)	54.4% (12.0)	59.6% (13.1)	82.1% (17.7)	0% (0.2)	95.0% (4.4)	60.0% (2.7)
Proportion of all affected who are detected by newborn screen	8.2%	20.0%	18.6%	35.2%	38.6%	53.2%	1.7%	46.1%	28.5%
Number affected with positive screen[b] who collapse or die before definitive diagnosis (*n*) (failures of initial management)	0.3	0.7	0.6	1.2	1.3	1.8	0	0.4	0.3
Number of timely diagnoses (*n*) (receiving a definitive diagnosis after screen and without collapse or death)	2.0	4.9	4.5	10.8	11.8	15.9	0.1	4.0	2.4

continued

TABLE 51 *Estimated screening performance of alternative screening strategies by condition (48 hours) (cont'd)*

	Life-threatening congenital heart defects								
	Hypoplastic left heart/mitral atresia			Coarctation of the aorta/interrupted aortic arch			Pulmonary atresia		
	Screening strategy			Screening strategy			Screening strategy		
	CE	PO	SE	CE	PO	SE	CE	PO	SE
Expected number affected at birth	15.8	15.8	15.8	54.6	54.6	54.6	24.7	24.7	24.7
Number recognised before newborn screen (number antenatally)	11.3 (3.0)	11.3 (3.0)	11.3 (3.0)	18.3 (2.7)	18.3 (2.7)	18.3 (2.7)	16.3 (1.7)	16.3 (1.7)	16.3 (1.7)
Expected number affected at screen	4.5	4.5	4.5	36.3	36.3	36.3	8.3	8.3	8.3
Number screened[a]	4.2	4.2	4.2	33.7	33.7	33.0	7.7	7.7	7.6
Proportion of all affected and screened who are detected by newborn screen (*n*)	37.5% (1.6)	95.0% (3.9)	99.0% (4.0)	22.1% (7.5)	60.0% (20.2)	60.0% (19.8)	46.9% (3.6)	94.0% (7.3)	90.0% (6.8)
Proportion of all affected who are detected by newborn screen	9.9%	25.0%	25.5%	13.7%	37.1%	36.3%	14.7%	29.5%	27.7%
Number affected with positive screen[b] who collapse or die before definitive diagnosis (*n*) (failures of initial management)	0.5	1.4	1.4	1.1	3.0	3.0	0.3	0.5	0.5
Number of timely diagnoses (*n*) (receiving a definitive diagnosis after screen and without collapse or death)	1.0	2.6	2.6	6.3	17.2	16.8	3.4	6.7	6.3

continued

TABLE 51 *Estimated screening performance of alternative screening strategies by condition (48 hours) (cont'd)*

	Clinically significant congenital heart defects					
	Ventricular septal defects			Other congenital heart defects		
	Screening strategy			Screening strategy		
	CE	PO	SE[c]	CE	PO	SE[c]
Expected number affected at birth	251.3	251.3	251.3	292.0	292.0	292.0
Number recognised before newborn screen (number antenatally)	84.4 (3.3)	84.4 (3.3)	84.4 (3.3)	129.3 (6.0)	129.3 (6.0)	129.3 (6.0)
Expected number affected at screen	167.0	167.0	167.0	162.7	162.7	162.7
Number screened[a]	155.3	155.3	152.0	151.3	151.3	148.0
Proportion of all affected and screened who are detected by newborn screen (*n*)	49.3% (76.5)	71.4% (110.9)	95.0% (144.4)	46.5% (70.4)	66.7% (100.9)	90.0% (133.2)
Proportion of all affected who are detected by newborn screen	30.5%	44.1%	57.4%	24.1 %	34.5%	45.6%
Number affected with positive screen[b] who collapse or die before definitive diagnosis (*n*) (failures of initial management)	–	–	–	–	–	–
Number of timely diagnoses (*n*) (receiving a definitive diagnosis after screen and without collapse or death)	–	–	–	–	–	–

CE, Clinical examination alone; PO, pulse oximetry with clinical examination; SE, screening echocardiography with clinical examination.
[a] Coverage: CE 93%, PO 93% and SE 91%.
[b] I.e. excludes those whose congenital heart defects are diagnosed as a result of antenatal screening or clinical symptoms before screen or other abnormalities at birth.
[c] Excluding all non-clinically significant cases that will be detected by echocardiography.

TABLE 52 *Scenarios investigated within the economic analysis using the primary outcome*

	Clinical examination alone			Pulse oximetry with clinical examination			Screening echocardiography with clinical examination		
	Costs (£)	**Timely diagnoses**	**ICER (£)**	**Costs (£)**	**Timely diagnoses**	**ICER (£)**	**Costs (£)**	**Timely diagnoses**	**ICER (£)**
Base-case analysis using primary outcome	296,891	34.0	–	476,193	70.6	4,894	3,540,388	71.3	4,496,666
Scenarios using primary outcome:									
National antenatal detection rate	289,803	33.0	–	470,212	68.2	5,115	3,537,014	69.3	2,800,813
National antenatal detection rate doubled	269,937	30.0	–	455,956	61.9	5,867	3,514,038	62.8	3,456,666
Screening at birth	340,909	43.9	–	506,290	92.4	3,406	3,578,532	92.4	Dominated
Screening at 48 hours	243,986	23.7	–	436,249	47.1	8,195	3,513,094	48.7	1,928,151
Probability of collapse after a positive screen is zero	267,902	38.9	–	418,529	81.8	3,516	3,394,034	82.8	2,965,836
Coverage for screening echocardiography with clinical examination is 93%	298,060	34.0	–	476,282	70.4	4,890	3,612,467	72.9	1,245,211
Sensitivities of screening echocardiography with clinical examination are 100%	297,942	33.8	–	476,544	70.6	4,855	3,548,403	94.9	126,606
Best case for screening echocardiography (Northern Region antenatal detection rate, screening at birth, probability of collapse after positive screen is zero, coverage for screening echocardiography is 93%, sensitivities of screening echocardiography are 100%)	306,039	50.5	–	433,638	107.9	2,224	3,445,783	142.1	88,103

ICER, incremental cost-effectiveness ratio.

TABLE 53 *Scenarios investigated within the economic analysis using the secondary outcome*

	Clinical examination alone			Pulse oximetry with clinical examination			Screening echocardiography with clinical examination		
	Costs (£)	**Timely diagnoses**	**ICER (£)**	**Costs (£)**	**Timely diagnoses**	**ICER (£)**	**Costs (£)**	**Timely diagnoses**	**ICER (£)**
Base-case analysis using secondary outcome	297,627	222.4	–	476.016	342.2	1,489	3,457,233	427.4	36,013
Scenarios using secondary outcome:									
National antenatal detection rate	289,427	210.2	–	470,864	323.5	1,601	3,543,476	404.1	38,126
National antenatal detection rate doubled	269,265	192.5	–	456,329	296.5	1,799	3,527,724	370.0	41,781
Screening at birth	341,236	252.2	–	506,226	392.4	1,176	3,565,572	485.7	32,789
Screening at 48 hours	243,377	170.0	–	435,640	258.0	2,183	3,506,168	324.9	46,010
Probability of collapse after a positive screen is zero	268,541	228.2	–	419,221	355.1	1,187	3,407,392	440.3	35,089
Coverage for screening echocardiography with clinical examination is 93%	297,643	222.4	–	477,000	342.2	1,497	3,603,169	436.7	33,093
Sensitivities of screening echocardiography with clinical examination are 100%	296,990	222.4	–	475,616	343.3	1,490	3,538,335	479.7	22,291
Best case for screening echocardiography (Northern Region antenatal detection rate, screening at birth, probability of collapse after positive screen is zero, coverage for screening echocardiography is 93%, sensitivities of screening echocardiography are 100%)	305,169	259.8	–	433,541	408.5	863	3,456,218	578.7	17,755

ICER, incremental cost-effectiveness ratio.

Appendix 12

Additional sensitivity analysis concerning the effect of differing rates of antenatal detection on newborn screening

Introduction

As described in the section 'Antenatal diagnosis of congenital heart defects' (p. 69), our original screening model 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 were 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 with the Antenatal and Child Health sub-groups of the National Screening Committee at a workshop on 23 January 2004, we undertook this further analysis and calculated the outcomes, costs and incremental cost-effectiveness ratios for the primary and secondary outcome measures across a wider range of antenatal detection rates from 0 to 100% (assumed to be constant across all congenital heart defects). Newborn screening was assumed to take place at 24 hours of age.

Primary outcome

As antenatal detection of cases, as a percentage of the total number of cases of congenital heart defects known to be present at birth, increases, then the number of cases that can potentially be detected through newborn screening is lower. In addition, each of the three screening strategies will have a different ability to detect cases amongst those that remain undetected by birth.

Figure 40 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.

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 and 10 further cases of life-threatening congenital heart defects would be detected by newborn screening. This suggests 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.

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 41*).

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).

The ICER for pulse oximetry, compared with the baseline newborn screening strategy of clinical examination alone, rises sharply if more than 70% of cases are detected antenatally (*Figure 31* in Chapter 7). The ICER for each additional case detected by pulse oximetry, once an antenatal detection rate of 80% is reached, is ~£30,000, and with an antenatal detection rate of 90% the ICER is ~£50,000.

Similarly, for additional cases detected by screening echocardiography, the cost per timely diagnosis rises sharply after a 70% antenatal detection rate is reached (*Figure 32* in Chapter 7).

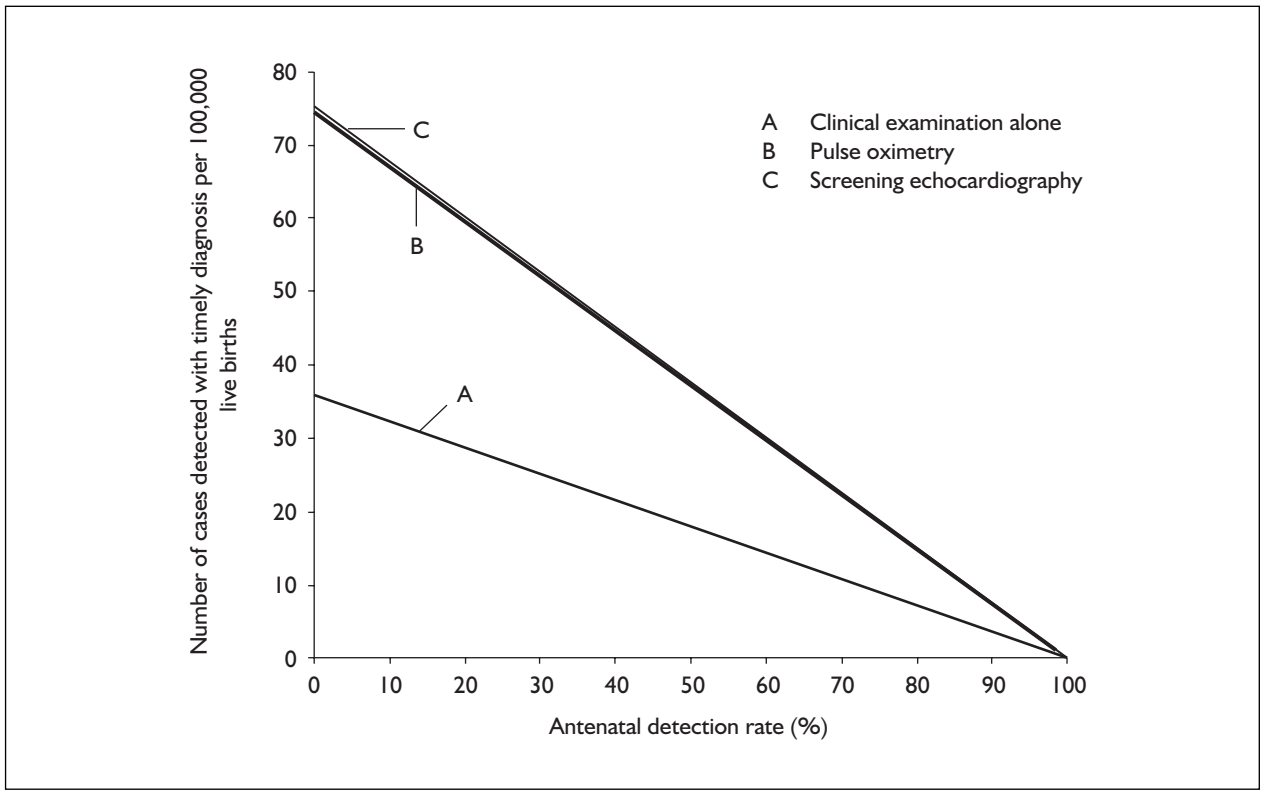


FIGURE 40 *Number of cases detected with timely diagnosis and antenatal detection rate (per 100,000 live births)*

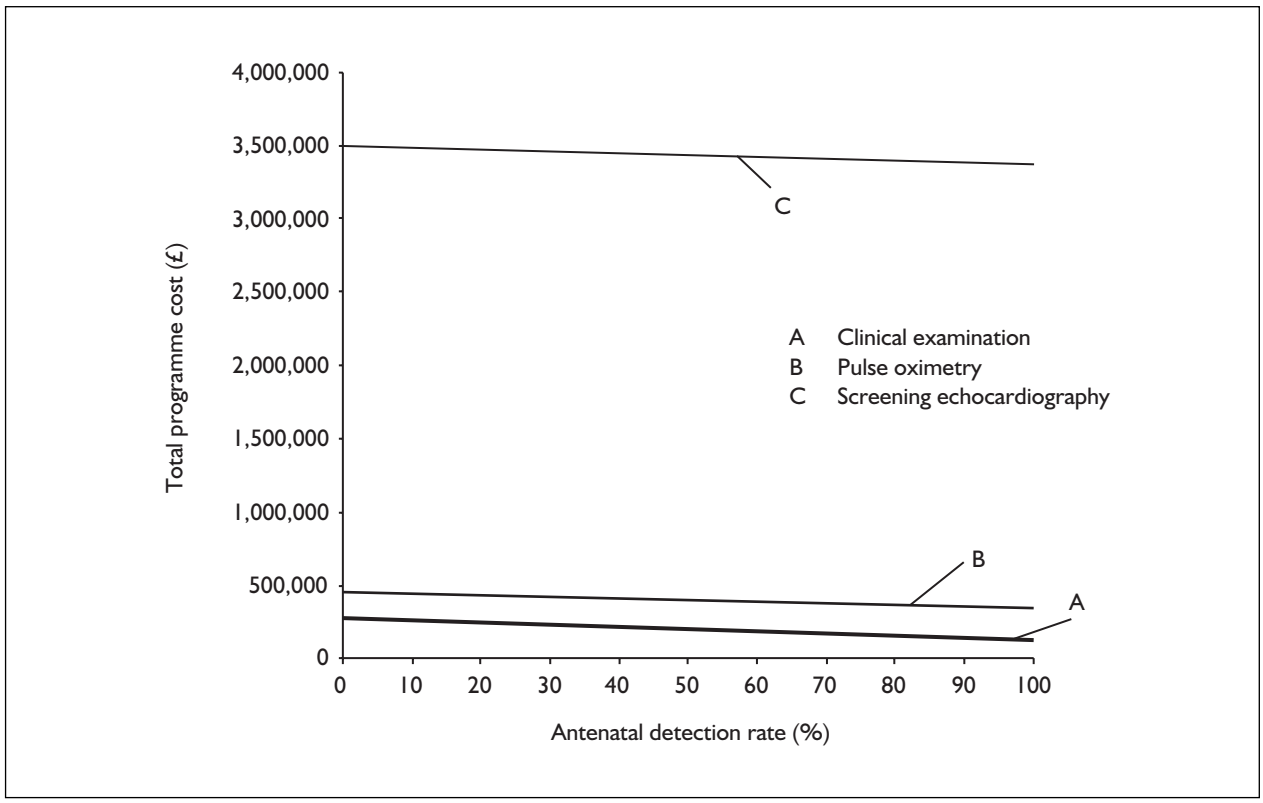


FIGURE 41 *Total programme costs and antenatal detection rate (per 100,000 live births)*

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

Secondary outcome

If the secondary outcome of the model, detection of all clinically significant and life-threatening congenital heart defects, is considered for a population of 100,000 live births, then the number of cases remaining to be detected by newborn screening using pulse oximetry or screening echocardiography is ~100 with an 80% antenatal detection rate and 50 with a 90% antenatal detection rate (*Figure 42*). Therefore, even with high antenatal detection rates, the number of cases of congenital heart defects that would still be detected by newborn screening is significant.

The total programme costs for the newborn screening programme still decrease very little with increased antenatal detection when the secondary outcome is used.

The cost of detecting additional cases of clinically significant or life-threatening congenital heart defects rises steeply after an antenatal detection rate of 80–90% is reached. For pulse oximetry compared with clinical examination alone, the ICER rises from £10,000 to £30,000 per additional case (*Figure 43*), and for screening echocardiography compared to pulse oximetry, the ICER rises from £200,000 to £700,000 per additional case detected (*Figure 44*).

Summary

As antenatal detection of congenital heart defects 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) could be detected by employing pulse oximetry or screening echocardiography as newborn screening strategies in addition to clinical examination.

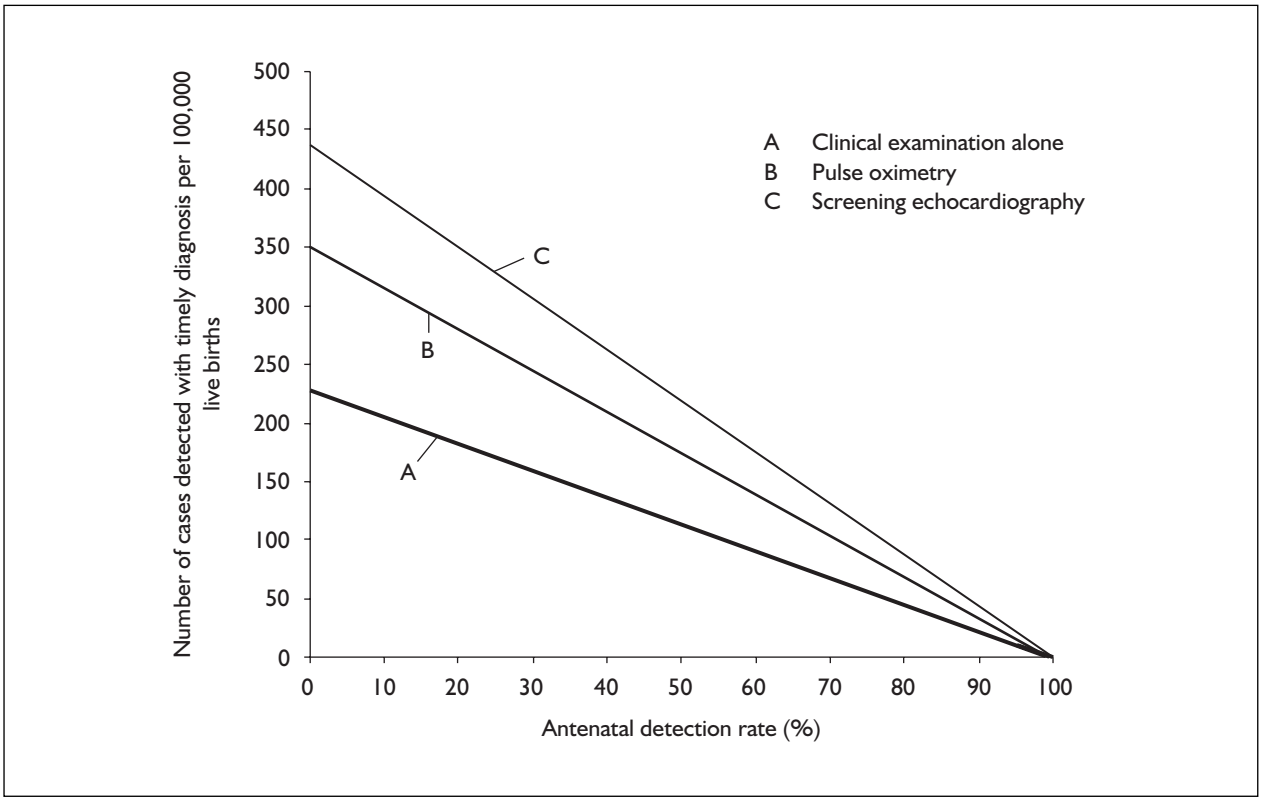


FIGURE 42 *Number of cases detected and antenatal detection rate: secondary outcome (per 100,000 live births)*

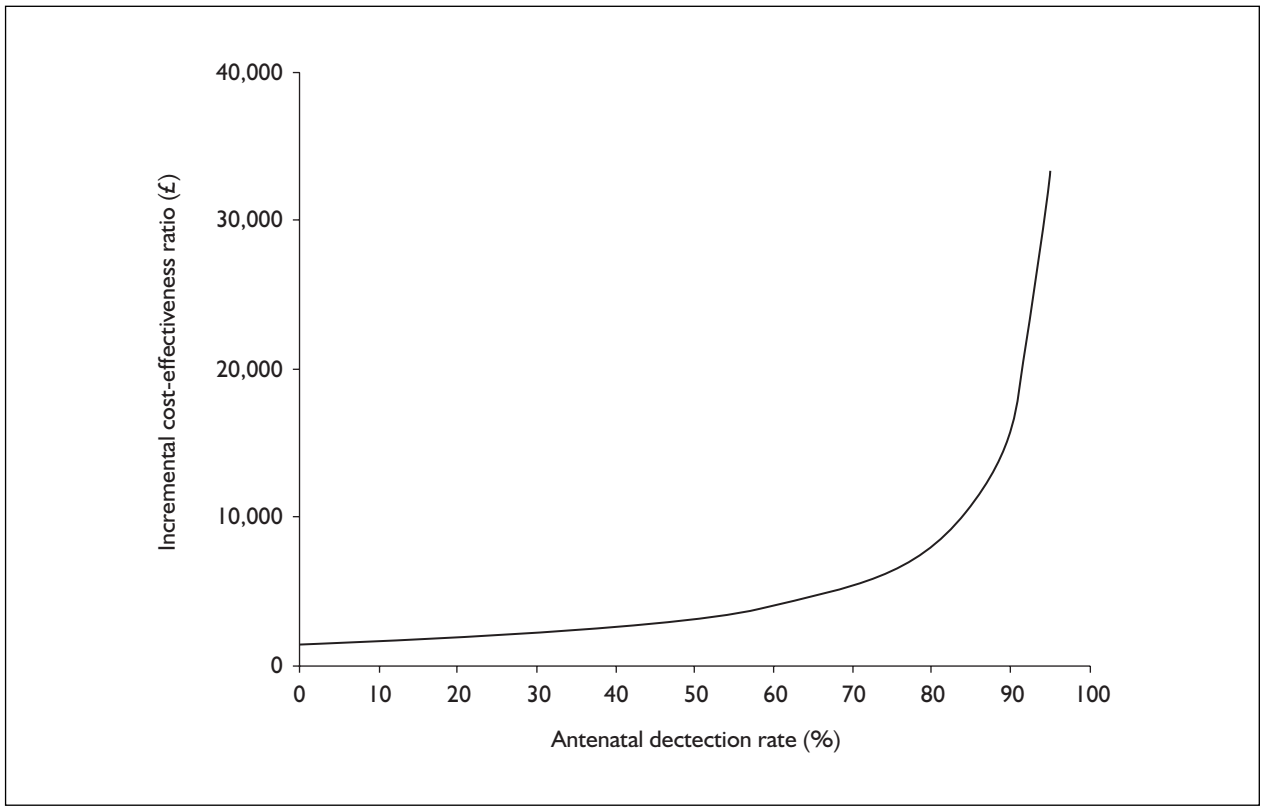


FIGURE 43 *Incremental cost-effectiveness ratio for pulse oximetry (pulse oximetry relative to clinical examination alone) and antenatal detection rate – secondary outcome*

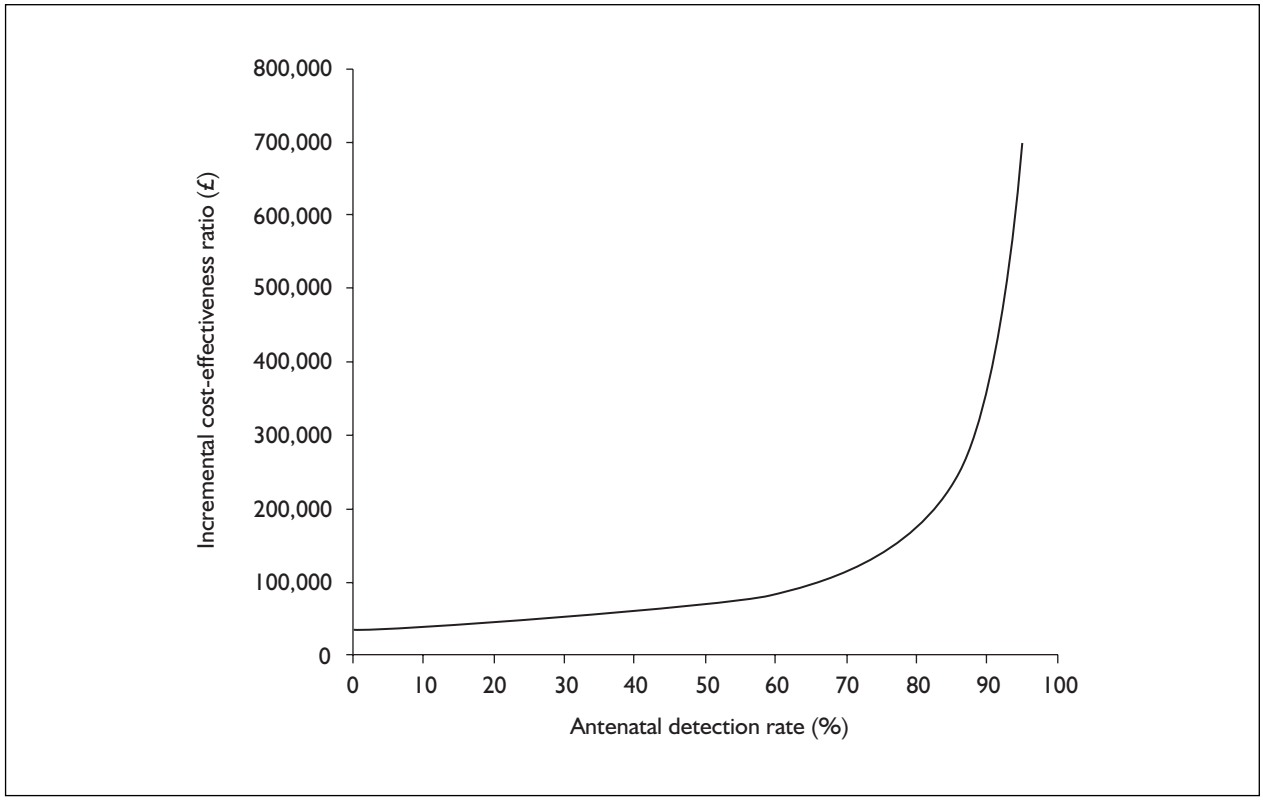


FIGURE 44 *Incremental cost-effectiveness ratio for screening echocardiography (screening echocardiography relative to pulse oximetry) and antenatal detection rate – secondary outcome*

The cost of detecting additional cases of life-threatening and clinically significant congenital heart defects 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 influence the thresholds used to determine 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.

Appendix 13

Health state descriptions

Health state: pink
- Has always eaten well
- Development as a toddler has been as fast as other children
- Walks and runs as well as other children of the same age
- Rarely tired before end of the day
- Sees and hears normally
- Eats, baths, dresses and goes to toilet independently
- Joins in as well as other children in the classroom
- Learns normally for age
- Speech and communication are normal for age
- Generally happy and free from worry
- Visits hospital regularly once or twice a year; takes medication only very rarely

Health state: green
- Eating has always been a struggle; needs extra feeds by stomach tube
- Development as a toddler has been much slower than other children
- Sits in a special chair; walks with help; uses buggy or wheelchair if outdoors
- Tires quite easily
- Poor vision; hears normally
- Needs help to eat, bath and dress and go to toilet; uses nappies at night
- Recognises carers and classmates
- Learns very slowly; attends special school
- Some words and some sign language; communicates own needs with difficulty
- Generally settled but also periods when angry or frustrated; becomes anxious when breathless
- Visits hospital regularly once or twice a year; takes some courses of medication

Health state: orange
- Has always eaten well
- Development as a toddler has been slower than other children
- Walks and runs but a bit clumsy
- Rarely tired before end of the day
- Sees and hears normally
- Eats, baths, dresses and goes to toilet independently but with some difficulty; occasional bedwetting
- Joins in with some difficulty in the classroom
- Learns a little more slowly than normal for age; gets special help at school
- Speech can still be difficult to understand; usually manages to communicate own needs
- Generally happy but can be angry or upset and difficult to handle
- Visits hospital regularly twice a year; takes medication only very rarely

Health state: purple
- Eats well now but some problems as a younger child
- Development as a toddler has been as fast as other children
- Walks normally but a bit breathless if runs
- Tires more easily than other children
- Sees and hears normally
- Eats, baths, dresses and goes to toilet independently
- Joins in as well as other children in the classroom
- Learns normally for age
- Speech and communication are normal for age
- Generally happy but can get upset and worried; aware of own limitations and can be anxious about own health
- Visits hospital and doctor quite frequently; takes medication every day

Health state: turquoise
- Eats well now but some problems as a younger child
- Development as a toddler has been slower than other children
- Walks and runs but a bit clumsy and breathless
- Tires more easily than other children of same age
- Sees and hears normally
- Eats, baths, dresses and goes to toilet independently with some difficulty; occasional bedwetting
- Joins in with some difficulty in the classroom
- Learns more slowly than normal for age; gets special help
- Speech can still be difficult to understand; usually manages to communicate own needs
- Generally happy but can be angry or upset and difficult to handle; can be anxious about own health
- Visits hospital and doctor quite frequently; takes medication every day

Health state: red
- Eating is still a struggle; still has some mashed and puréed food
- Development as a toddler has been slower than other children
- Walks and runs but becomes quickly breathless; uses buggy or wheelchair if outdoors
- Often tired
- Sees and hears normally
- Eats, baths, dresses and goes to toilet independently with some difficulty; occasional bedwetting
- Joins in with some difficulty in the classroom
- Learns more slowly than normal for age; gets special help
- Speech can still be difficult to understand; usually manages to communicate own needs
- Generally happy but can be angry or upset and difficult to handle; can be anxious about own health
- Frequent hospital visits; takes medication every day

Health state: yellow
- Eating is still slow but more problems as a younger child
- Development as a toddler has been slower than other children
- Walks but becomes breathless if runs; sometimes uses buggy or wheelchair if outdoors
- Often tired
- Sees and hears normally
- Eats, baths, dresses and goes to toilet independently
- Joins in with other children in the classroom but limited by physical effort
- Learns normally for age considering school absences due to health problems
- Speech and communication are normal for age
- Generally happy but can get upset and worried; often anxious about own health
- Visits hospital and doctor frequently; takes medication every day

Health state: blue
- Eating is still a struggle; needs extra feeds by stomach tube
- Development as a toddler has been slower than other children
- Sits in special chair; stands and walks with help; uses buggy or wheelchair if outdoors
- Often tired
- Poor vision; hears normally
- Needs help to eat, bath and dress and go to toilet; uses nappies at night
- Recognises carers and classmates
- Learns very slowly; attends special school
- Some words and some sign language; communicates own needs with difficulty
- Generally settled but also periods when angry or frustrated; becomes anxious when breathless
- Frequent hospital visits; takes medication every day

Appendix 14

Search strategy for parent views

Search strategy using Ovid MEDLINE for published literature relating to parents' views of newborn screening.

Concept A: Age at screening (total references = 118,531)

1. neonatal$
2. newborn$
3. infan$
4. exp NEONATAL SCREENING/
5. INFANT, NEWBORN/
6. baby

Concept B: Population screening (total references = 105,052)

1. screen$
2. check$
3. exp MASS SCREENING/

Concept C: Outcomes of screening (total references = 430,234)

1. expectation$
2. satisfaction$
3. acceptab$
4. belief$
5. attitude$
6. emotion$
7. stress$
8. anxi$
9. behavio$
10. wellbeing
11. psycho$
12. social
13. counsel$
14. awareness
15. knowledge
16. exp COMMUNICATION/
17. exp FALSE POSITIVE REACTIONS/
18. exp FALSE NEGATIVE REACTIONS/
19. exp ANXIETY/
20. exp FAMILY RELATIONS/px [Psychology]
21. exp PHYSICIAN-PATIENT RELATIONS/
22. exp NURSE-PATIENT RELATIONS/
23. exp PARENT-CHILD RELATIONS/

Concept D: People affected (total references = 73,403)

1. exp PARENTS/px [Psychology]
2. parent$
3. mother$
4. father$

Concept E: Cardiac-related (total references = 196,019)

1. cardi$
2. heart$
3. congenital heart disease

Combining concepts A–D with AND yielded 529 references, and all abstracts were reviewed. Adding concept E using AND yielded 26 references specifically related to cardiac disease.

Appendix 15

Literature tables of parents' views of newborn screening

TABLE 54 *Anxiety and uncertainty related to screening*

Study	Year	Setting: country; participants; sample size	Methods	Results (relevant to screening for congenital heart defects)
Bekker[351]	1994	UK; general practice; 441 adults (18–45 years)	Adults were given test for cystic fibrosis gene mutations; 14 carriers identified; questionnaire before test and on receipt of results and 3 months later; asked about anxiety, knowledge, perception of health and risk for future children	Positive carrier result associated with transient increased anxiety (<3 months); negative carrier status believed no risk to future children; results had no effect on perceptions of own health
Jarvinen[352]	1999	Finland; hospital genetics clinic; 46 women relatives of males with genetic disorders	Women tested as children with parents' consent, followed up 10–15 years later with postal questionnaire; asked about knowledge of carrier status and HRQoL	7 carriers, 17 non-carriers, 22 uncertain; normal HRQoL scores (standardised instrument); transient psychological effects (anxiety) as children
Sorenson[356]	1984	USA; hospital clinic; 60 infants and their parents	Parents of infants, being re-tested after an abnormal newborn blood test for metabolic disorders, were asked to complete a standardised questionnaire of anxiety and depression (MAACL)	No increased anxiety due to false-positive result. 36% were concerned about infant's health because they felt they were given too little information
Gibson[422]	1997	UK; hospital maternity unit; 83 mothers of screen-positive infants and 54 control mothers	Mothers of infants referred for further investigation of possible spina bifida occulta on newborn clinical examination; survey after further investigation including standardised anxiety instrument (Spielberger STAI)	No differences in maternal adjustment or anxiety; a few anxious mothers remained anxious after a normal result
Watkin[357]	1998	UK; audiology clinic; 288 mother–infant pairs; control group of mothers	Mothers given survey when baby received hearing test at 0–3 days (n = 288), retests at 6 weeks (n = 56), and postal survey at 6–9 months old (n = 150); 61 control (untested) mothers replied to postal survey at 6 weeks; attitudes to screen, standardised anxiety instrument (Spielberger STAI)	Anxiety increased at 6-week retest but still not significantly different compared with control mothers
Parsons[359]	2002	UK; Duchenne muscular dystrophy pilot screening study; 42 families in pilot and 43 control families	Involved 20 families of affected boys detected by screening, 18 families with false-positive results; 16 families of affected boys detected clinically and 48 control families. Families asked to complete questionnaires and interviews about attitude to newborn screening, anxiety, impact on relationship with child and on reproductive choices	Parents were in favour of newborn screening because it gave them time to prepare; no long-term disruption to mother–baby interaction; screening-related anxiety was temporary; reproductive choice was affected (chose terminations of four affected pregnancies)

continued

TABLE 54 *Anxiety and uncertainty related to screening (cont'd)*

Study	Year	Setting: country; participants; sample size	Methods	Results (relevant to screening for congenital heart defects)
Yu[511]	1999	US; clinic; 8 mothers	Children tested for gene related to future diabetes risk: comparison between high- and low-risk results; Measured change in parenting stress and total stress scores (TSS) before and after test result	No difference in changes in parenting stress and TSS between the two groups
Bell[368]	1994	UK research screening programme for neuroblastoma; parents of 7 infants	Parents of infants given a false-positive result interviewed 13 months after normal test	5 parents worried or very worried by result; 2 with concerns lasting over 1 year; 1 mother very worried because she felt there was too little information
Dobrovoljski[369]	2003	Austrian neuroblastoma screening programme; 32 parents of 16 infants	Included infants with false-positive results from programme involving 270,000 infants; telephone interviews about psychological responses	31 parents still supported screening; anxiety low at screen but high during hospital admission for investigation (severe anxiety in 19 parents)
Stuart[360]	2000	USA; audiology clinic; 40 mothers	20 mothers of infants who passed newborn hearing test and 20 mothers of infants who failed; given standardised parenting stress index (PSI) in telephone interview at 1 month after test (4–5 weeks old) before retest	No significant differences in PSI scores between the two groups; initial hearing retest does not increase parenting stress
Owen[361]	2001	UK; local health clinics; parents of 683 infants	Short written survey of anxiety; given after newborn hearing test	Mean anxiety score increased with successive repeat tests; parents liked tests as simple, quick, could be done on young infants and no discomfort
Vohr[362]	2001	USA; audiology clinic; 307 mothers at initial screen, 40 mothers at rescreen	Questionnaire asked mothers about worry, knowledge and demographic data in 1997 and 1999	Maternal worry significantly greater at rescreen. Maternal knowledge increased between 1997 and 1999
Clemens[363]	2000	USA; 2% of parents of 5010 screened infants	Parents of infants given false-positive results on newborn hearing screening included in telephone survey of anxiety and satisfaction with test; hospital data on false-positive rates	80% of screen-positive infants passed retest; 9% survey parents reported treating child differently before retest and 14% had lasting anxiety, especially after 2 failed tests; 90% supported screening
Magnuson[358]	1999	Sweden; 49 parents of 26 children	Parents of infants given newborn hearing screening were interviewed about anxiety and attitudes to test	Positive attitudes to screening overall but less if infant retested; more anxiety if retested but this resolved after a definitive diagnosis or normal retest

TABLE 55 *Communication of newborn screening results*

Study	Year	Setting: country; participants; sample size	Methods	Results (relevant to screening for congenital heart defects)
Thelin[374]	1985	Sweden; primary care; parents of 61 children (59 mothers, 48 fathers)	Parents of children identified with alpha 1-antitrypsin disorder on newborn screening were interviewed for attitudes to follow-up and future screening recommendations	Parents were positive towards knowledgeable and emotionally supportive clinicians but negative towards repeated blood tests; parents recommended that they should find out early about child's condition and both parents informed together at a special appointment
Holtzman[376]	1983	USA; newborn screening for phenylketonuria (PKU); 418 study mothers, 210 control mothers	Stratified randomised samples; study mothers asked to give informed consent to screen, control mothers given basic information only; test of knowledge and satisfaction after test	Knowledge greater in mothers given more information before consenting
Bell[378]	1994	UK research screening programme for neuroblastoma; parents of 85 infants	Parents of recently screened infants interviewed about knowledge of the test and disorder and anxiety	Knowledge was poor and 13% did not know infant was tested; one-third were anxious, increasing if retested; information provided was often inadequate
Weichbold[375]	2001	Austria; maternity unit; 90 mothers	Mothers of infants given newborn hearing screening were given a knowledge and attitude questionnaire by interview on the postnatal unit	84% of mothers supported newborn screening despite knowledge of false-positive rates; women supporting screening were better informed overall
Young[373]	2001	UK; critical review of literature about newborn hearing screening	Review of studies reporting the effects on parents of screening, especially where parent experiences directly assessed	Implications for universal newborn hearing screening in the UK outlined
Luterman[379]	1999	USA; postal survey of 75 parents of hearing-impaired children aged 3 months–24 years	Retrospective survey of parents	83% of parents would like to know about child's deafness at birth; parents thought ideal management of diagnosis should include time to understand information, counselling from a skilled audiologist and contact with other parents of hearing impaired children

continued

TABLE 55 *Communication of newborn screening results (cont'd)*

Study	Year	Setting: country; participants; sample size	Methods	Results (relevant to screening for congenital heart defects)
Oliver[377]	1996	UK; hospital maternity unit; 26 pregnant women, 14 midwives, ultrasonographers	New leaflets on antenatal ultrasound introduced with more detail on safety and informed choice; first questionnaire to 26 women (booking scan), second questionnaire to 13 women (detailed scan); survey of midwives' and ultrasonographers' views	No increased anxiety in women with increased information; resistance to new leaflet from ultrasonographers; welcomed by midwives
Sorenson[356]			See *Table 54*	
Bell[368]			See *Table 54*	
Parsons[359]			See *Table 54*	
Clemens[363]			See *Table 54*	

TABLE 56 *Parents' support for screening*

Study	Year	Setting: country; participants; sample size	Methods	Results (relevant to screening for congenital heart defects)
Cystic fibrosis screening				
Al-Jader[385]	1990	UK; screening programme; families of 18 screened and 11 unscreened infants	Pilot newborn screening programme for cystic fibrosis; parents of infants diagnosed early (screened) and late (clinically) interviewed (40 questions)	Over 80% support screening; 50% would abort an affected fetus; most anxiety if there is a delay between screen and confirming diagnosis – temporary rejection of 4 infants occurred in this period
Cobb[390]	1991	UK; school; 216 pupils (14–16 years)	Pupils given information about screening then tested on knowledge retained and attitudes to cystic fibrosis screening	Good increase in knowledge; over 80% supported carrier and antenatal screening
Mischler[398]	1998	USA; Wisconsin cystic fibrosis screening project	Several questionnaires to families with cystic fibrosis children diagnosed clinically or on screening, control families, and families receiving false-positive results	Only one-quarter of affected families used antenatal diagnosis in future pregnancies; up to 10% of false positive families think about the results often; some confusion about meaning of carrier results
Duchenne muscular dystrophy screening				
Bradley[370]	1993	UK; pilot screening programme; 9 families	Screening uptake and false-positive rates assessed and families of boys with Duchenne muscular dystrophy detected through screening interviewed at 6 months, including a satisfaction questionnaire	One family very distressed, affected bonding with child and local uptake rates; 8 families supported screening programme and valued knowing the diagnosis early in life
Smith[393]	1990	UK; hospital maternity unit; 201 mothers	Structured questionnaire with interview to assess attitudes towards the newborn screening for Duchenne muscular dystrophy	68% aware screening was carried out; majority would like screening, would like to know of disability at birth and would probably terminate affected pregnancies
Firth[394]	1983	UK; 53 families of boys with Duchenne muscular dystrophy nationally	Boys aged 4 years to adulthood. Families interviewed about diagnosis, family impact and newborn screening	Parents complained about delay in diagnosis and lack of information; siblings and marriages were affected; 75% supported newborn screening
Parsons[359]			See *Table 54*	
Newborn hearing screening				
Moulin[386]	2001	France; mothers of 124 screened infants	Anonymous questionnaire to mothers whose newborn infants received hearing screening test	95% supported screening; 35% experienced low anxiety; knowledge about hearing loss was low

continued

TABLE 56 *Parents' support for screening (cont'd)*

Study	Year	Setting: country; participants; sample size	Methods	Results (relevant to screening for congenital heart defects)
Hergils[387]	2000	Sweden; audiology clinic; parents of 87 infants (6 months old)	Parents of screened children given a written questionnaire about attitudes to screening, knowledge and anxiety	95% positive towards screening; 4% against newborn screening; 77% had sufficient information; repeat testing increased anxiety
Weichbold[375]			See *Table 55*	
Young[373]			See *Table 55*	
Clemens[363]			See *Table 54*	
Magnuson[358]			See *Table 54*	
Metabolic and other screening programmes				
Warren[392]	1982	USA; State screening programme for haemoglobinopathy; 18 parents	Parents interviewed about child's health, their knowledge of sickle cell disease and views on newborn screening	Parents had fair knowledge of sickle cell disorder; many felt isolated and some felt anxious or depressed; majority supported newborn screening for earlier detection
Read[397]	2002	USA; six-State regional survey; 230 parents	Parents of children with metabolic disorders participated in telephone interviews using standardised questionnaires for health behaviour, parenting stress and adaptive behaviour	56% were receptive to future antenatal testing; 10% would terminate an affected pregnancy and 41% had taken steps to prevent an affected pregnancy; very few saw a genetic counsellor
Sveger[512]	1999	Sweden; primary care; parents of 85 children with ATD and 89 matched controls	Parents of 22–23 year-old children identified with alpha 1-antitrypsin disorder (ATD) on newborn screening were interviewed for attitudes to follow-up study, physical and psychosomatic problems compared with controls	88% parents considered newborn period best for screening; most thought awareness of ATD had affected their lives and ATD mothers had more anxiety than controls; no difference in views about child's future, physical or mental health
Thelin[374]			See *Table 55*	
Dobrovoljski[369]			See *Table 54*	
Bell[368]			See *Table 54*	

TABLE 57 *Technologies used in screening for congenital heart defects*

Study	Year	Setting: country; participants; sample size	Methods	Results (relevant to screening for congenital heart defects)
Clinical examination in newborn infants				
Owen[361]	2001	UK; local health clinics; parents of 683 infants	Short written survey of anxiety; given after newborn hearing test	Mean anxiety score increased with successive repeat tests; parents liked tests as simple, quick, could be done on young infants and no discomfort
Wolke[382]	2002	UK; district general hospital maternity unit; 826 mother–infant pairs	RCT assigning infants to newborn examination by midwife or SHO; excluded 47% of all births (higher risk); maternal satisfaction questionnaire	No difference in referral rates; no difference in satisfaction related to examiner type; increased satisfaction if wider health care issues discussed and continuity of care
McCrindle[381]	1995	Canada; hospital paediatric cardiology department; parents of 182 children (1 day–18 years)	Parents surveyed before cardiology appointment to investigate child's heart murmur and at 1-month follow-up; completed questionnaire about knowledge of heart murmurs and heart defects, expectations and concerns for child, perceived vulnerability of child	Parents often did not understand concept of heart murmur; 10% believed a heart malformation was present even after reassurance that the heart was normal
McDonald[383]	1996	UK; hospital cardiology outpatients; 40 consecutive patients	30 adults referred for investigation of a heart murmur, 10 for symptoms; medical consultations and semistructured interviews with patients tape-recorded; cardiologists completed questionnaire; patient knowledge and anxiety explored	28 murmurs associated with normal heart, but 20 anxious short term and 11 anxious longer term
Ultrasound (and echocardiography) of infants				
Garcia[384]	2002	UK; structured review of women's views of antenatal ultrasound screening	Review of research directly reporting women's views of antenatal ultrasound screening, including early and late (detailed, including heart) scans	Women have minimal fear of ultrasound technology; prefer to have some explanation during the scan

TABLE 58 *'Early' screening diagnosis compared with 'late' clinical diagnosis*

Study	Year	Setting: country; participants; sample size	Methods	Results (relevant to screening for congenital heart defects)
Pollitt[342]	1997	UK; systematic review of the psychosocial effects of newborn screening for inborn errors of metabolism	Review of literature; comparing screening and clinical diagnosis, the acceptability of screening and management of the screening process	Psychological benefits of screening outweigh the costs; particular problem areas are repeat testing and information provision
Merelle[400]	2003	The Netherlands; cystic fibrosis regional centre; parents of 45 children with cystic fibrosis	Parents were asked about experience of the prediagnostic period, contact with the medical profession, coping, future perspective and attitudes towards newborn screening in structured interview	Groups with early (<3 months old) versus later diagnosis were compared; early diagnosis was associated with less negative feelings and more confidence in the medical profession
Baroni[401]	1997	USA; hospital outpatients; 51 parents of children with cystic fibrosis and 47 control parents	14 false-positive results at newborn screen; 20 true-positive screening diagnoses and 17 clinical diagnoses; postal questionnaire with parenting stress index (PSI)	Parents of children diagnosed clinically did not have higher parenting stress scores than those diagnosed through screening; lowest stress scores reported by false-positive parents
Al-Jader[385]			See *Table 56*	
Firth[402]	1983	UK; community setting; 69 parents of boys with Duchenne muscular dystrophy	Interview survey of parent views about newborn screening for Duchenne muscular dystrophy and their experiences of diagnosis	Most parents favoured newborn screening and expressed dissatisfaction with current delays, methods of disclosure and support
Firth[394]			See *Table 56*	
Smith[393]			See *Table 54*	
Parsons[359]			See *Table 54*	
Warren[392]			See *Table 56*	
Bradley[370]			See *Table 56*	
Magnuson[403]	2000	Sweden; audiology clinic; 10 parents of 8 children with hearing impairment	Interviews with parents whose children were diagnosed late with hearing impairment	Parents describe 4 phases: unawareness, suspicion, confirmation, habilitation; diagnosis results in relief and sorrow; all parents supported newborn hearing screening
Green[404]	1996	UK; parents of 158 boys with Duchenne muscular dystrophy	Postal questionnaire to parents asking about experiences of diagnosis	Parents satisfied if they are given the information that they want and feel they have understood it; length of time between suspecting problem and diagnosis is important
Watkin[405]	1995	UK; audiology clinic; 208 parents of children with hearing impairment	Parents were asked about their satisfaction with the way in which the diagnosis was made	Only 58 were satisfied that the diagnosis was made at an early enough age; the majority would want a newborn screening test if it was available, equally for unilateral or mild problem

TABLE 59 *Results of screening tests*

Study	Year	Setting: country; participants; sample size	Methods	Results (relevant to screening for congenital heart defects)
Diagnosis of congenital heart defects: true positive results				
Pelchat[416]	1999	Canada; 144 parents (72 couples)	Parents of 18 infants with congenital heart defects, 19 with cleft palate, 16 with Down's syndrome and 19 non-disabled; self-administered questionnaire at 6 months old; parenting stress, psychological distress measured	Parents of infants with congenital heart defects and Down's syndrome reported higher levels of parenting stress and psychological distress; mothers report more stress and distress
Rona[406]	1998	UK; fetal and paediatric cardiology outpatients; 108 mothers	Comparing anxiety and depression in pregnant mothers referred to cardiology (true positives and false positives) and infants with clinically detected congenital heart defects; psychological status using HAD	Higher levels of anxiety in mothers whose infants had a confirmed heart malformation than for false positives; depression scores highest in mothers of clinically diagnosed infants; mothers who had a termination for abnormality were depressed 6–10 months after
Clark[372]	1999	USA; hospital ward; 8 fathers	Fathers of children hospitalised with a congenital heart defect interviewed about experiences	Fathers experience conflicting emotions: joy at fatherhood, sadness at illness, attachment and fear, loss of control, and the need to remain strong for partners
Luterman[379]			See *Table 55*	
Kaden[380]	1985	USA; Baltimore–Washington Infant Study; 285 mothers	Interview including questionnaire about information gained from cardiology consultation	One-third of mothers demonstrated poor understanding of the heart malformation; parents in biomedical occupations answered better
False-negative results				
Petticrew[348]	2000	UK	Review of the impact of false negative results in screening programmes	Discusses relevant psychosocial issues
Hall[417]	2000	UK; home interviews with parents of 179 children with Down's syndrome	Children aged 2–6 years old; parents asked about anxiety, depression, parenting stress, attitudes towards child, attributions of blame for the birth	Parents adjusted well; higher parenting stress if child born after false-negative screening result; mothers more negative towards children if false negative, poorer adjustment and more likely to blame others
Rona[406]			See above	
True-negative results				
Bekker[351]			See *Table 54*	

continued

TABLE 59 *Results of screening tests (cont'd)*

Study	Year	Setting: country; participants; sample size	Methods	Results (relevant to screening for congenital heart defects)
Murray[345]	1999	UK	Expert review; single chapter in wider review	Review of psychosocial issues of Down's syndrome screening
Hergils[387]			See *Table 56*	
False-positive results				
Statham[419]	1993	UK; 20 women	Of 20 women who had had serum screening for Down's syndrome and amniocentesis, 8 were false positives; telephone interviews	All women were anxious after screening result; medical staff were often unclear about risk and did not recognise women's concerns; many remained anxious after normal amniocentesis
Bodegard[420]	1983	USA; congenital hypothyroid screening; 102 families	Interviews about anxiety and psychological distress 6 months after a false-positive result	78 families had strong initial reactions but 18 remained anxious at 6 months after test; possible effects on parenting adjustment
Fyro[421]	1987	USA; congenital hypothyroid screening; 32 families	Interviews about anxiety and psychological distress four years after a false-positive result	19 families anxious at 4 years after test; 8 children with behaviour problems
Rona[406]			See above	
McCrindle[381]			See *Table 57*	
Bekker[351]			See *Table 54*	
Bell[368]			See *Table 54*	
Dobrovoljski[369]			See *Table 54*	
Pollitt[342]			See *Table 58*	
Detection of 'non-disease'				
Laane[424]	1997	Sweden; 51 children born 1986–91 and 83 matched controls	Children with VSDs diagnosed neonatally and closing within first 24 months of life; quality of life questionnaires administered to cases and control group	No significant differences in quality of life experienced by cases and controls; cases more likely to have lower satisfaction with family networks suggesting some minor social effect

continued

TABLE 59 *Results of screening tests (cont'd)*

Study	Year	Setting: country; participants; sample size	Methods	Results (relevant to screening for congenital heart defects)
Harding[425]	1999	UK; 70 parents of affected children, 52 controls	Parents of infants with abnormal urinary tracts on fetal scans sent postal questionnaire about follow-up, problems and concerns	Follow-up is unselective and too intense for the majority who have spontaneously resolving or insignificant lesions; high levels of concern generated
Axworthy[427]	1996	UK; six cystic fibrosis screening centres; 280 carriers and 466 controls	Postal survey of cystic fibrosis gene carriers and controls	Uncertainty for some about meaning of carrier status; no difference in anxiety; carriers had poorer perception of own health; no difference in reproductive intentions
Henneman[513]	2002	The Netherlands; 9 cystic fibrosis carrier couples	Seven couples were interviewed and 2 completed a questionnaire; 2–8 years after receiving result	Difficulties with reproductive decisions and in disclosing carrier result to wider family; antenatal diagnosis in pregnancies resulted in terminations of affected pregnancies (6); no regrets about testing
Luterman[379]			See *Table 55*	

TABLE 60 *Genetic testing*

Study	Year	Setting: country; participants; sample size	Methods	Results (relevant to screening for congenital heart defects)
Marteau[391]	1998	Expert review of psychological responses to genetic testing	–	Considers impact on individuals, society and families of different genetic tests
Michie[514]	2001	UK and Australia; 8 regional genetics centres; 148 adults, 60 children	Adults and children at risk of familial adenomatous polyposis (FAP) were tested for the gene, then given standardised tests for anxiety (SSTAI), depression (HAD), situational stress, behaviour (children), perceptions of illness and coping	125 negative and 23 positive adults; 29 negative and 31 positive children; children were not clinically significantly distressed in the year after genetic test, whatever the result; adults with positive results tended to be clinically anxious particularly if poorer coping skills
Umans-Eckenhausen[515]	2002	The Netherlands; familial hypercholesterolaemia (FH) screening programme; 35 couples	Parents with FH gene offered genetic testing for their children; telephone survey of parents' attitudes to FH screening	61 parents wanted testing (7 couples disagreed with each other); information, experience and expectation do not influence this decision but emotion is the main influencing factor
Whitelaw[516]	1996	UK; hospital outpatients; 62 adults with familial adenomatous polyposis	62 adults asked about attitudes to antenatal, newborn and childhood genetic testing for familial adenomatous polyposis in a semi-structured interview	64% would request antenatal genetic testing if it was available, of which 24% would proceed to termination of an affected fetus; over 90% believed that the best time for testing children was as newborns
Bassett[389]	2001	Australia; hospital antenatal clinic; 135 women and partners	Women given information and offered newborn genetic testing for hereditary haemochromatosis	Test accepted in over 90%; low level of anxiety about the test
Senior[371]	1999	UK; newborn screening programme for familial hypercholesterolaemia; parents of 24 children	Interviews with parents after positive screening test result received for their children; asked about response to screening and knowledge	Parents were more anxious if they saw the risk as genetic and uncontrollable as opposed to dietary and controllable; genetic testing might induce fatalism

Appendix 16

Questions asked within focus group

What made you want to come here today?

What experiences have you had of screening your child for heart disease?

When you/your partners were pregnant did any of you have a scan that detected heart disease in your child?

What was good about getting a diagnosis/possible diagnosis before your child's birth/What was not good, about getting this information in pregnancy?

What other experiences have you had of screening on your child for heart disease?

What kind of information did you receive before the scan/test examination was carried out?

Additional questions:
Was the purpose/reason for the scan explained?

Was it explained how it would be carried out, type of equipment used, etc.?

Were you given information about what would happen when the scan was completed?

Who carried out the scan?

Were you asked for your consent for this procedure?

What was the best thing about having this scan/test/examination and what was the worst thing about having this test?

Additional questions:
What were the good things about the way the scan/test was carried out?

Could you view the screen?

Was the procedure explained to you as it was being carried out?

Did you feel able to ask questions?

Did the person carrying out the scan/test make you feel at ease?

If you had a magic wand and could describe how screening could be provided in the future, what things would you like to see provided? How would they differ from existing services?

Now getting back to the screening you experienced

Did you get a clear explanation of the scan/test results?

Additional questions:
Did you feel an equal partner in your child's care when information was given to you about the scan?

If the scan/test needed repeating: did you feel the reasons for this were explained fully to you? Did you feel you got the results quickly enough?

If the scan/test identified areas of concern, did you feel listened to, were your views/concerns valued?

Did you feel you were given enough information about living with a child with this heart condition?

Additional questions:
Did you feel well enough informed to share in the decision making process? Were you given enough information about his/her future care?

What impact did those experiences have on you and your family?

How could the negative effects of screening be improved?

Scenarios Minutes allowed (10)

(The following scenarios were distributed and discussed within the group.)

1. (False-negative) **James is sent home after normal check up but becomes unwell at home and needs to be rushed back to hospital**.

   Additional questions:
   If you were a parent in this situation how do think you would feel?

   What would you like to see improved in this child's care?

2. (False-negative antenatal test) **Donna has routine scans during her pregnancy; these are normal. But after Alfie is born he develops breathing difficulties and feeding problems whilst still in hospital**.

   Additional questions:
   What would you like to see improved in this child's care?

   How would you feel if this happened to you?

   Has it changed your opinion of antenatal scans?

3. **Ferdushi was born in hospital by normal delivery. A few hours after delivery she is examined by the doctor, who is concerned that Ferdushi is not well. The doctor feels that there may be a problem with her heart. She is examined by a more senior doctor and is observed on the ward. Ferdushi is sent home and asked to return four days later for a scan (echo). The echo shows everything to be normal, no further investigations are needed**.

   Additional questions:
   If this happened to you/your child, how would you feel?

   Would you feel reassured or would you want to see changes in screening?

Final question
How acceptable do you feel it is to ask all parents of newborn infants to return to hospital (within 7 days) for a heart scan (echocardiogram)?

Additional question:
Do you think it would be more beneficial or more harmful to do this given a higher level of false results?

I would like to thank you for coming here today.

Appendix 17

The National Screening Committee Criteria

The criteria for appraising the viability, effectiveness and appropriateness of a screening programme

The condition

1.1. The condition should be an important health problem.

a. *Congenital heart defects affect 7–8 per 1000 live-born infants, three-quarters of whom will be diagnosed by 1 year of age.*
b. *This prevalence estimate increases at least 10-fold if small muscular ventricular septal defects and other functionally unimportant anatomical abnormalities, detectable largely only by echocardiography, are included.*
c. *Overall 18–25% of affected infants die in the first year of life, with a further 4% of those surviving infancy dying by 16 years of age. Congenital heart defects account for 3% of all infant deaths. Not all congenital heart defects may be diagnosed before or at death.*
d. *Specific defects with a high first-year mortality include hypoplastic left heart, interrupted aortic arch, transposition of the great arteries, total anomalous pulmonary venous connection, aortic stenosis and pulmonary atresia. Although individually rare, taken together these defects contribute significantly to death in infancy from congenital heart defects.*

1.2. 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, or disease marker and a latent period or early symptomatic stage.

a. *The rationale for screening for congenital heart defects lies in its potential to influence natural history by early presymptomatic detection and intervention.*
b. *Antenatal screening gives parents an opportunity for information and counselling with options for a planned delivery and intervention or termination of pregnancy.*
c. *Newborn screening allows the presymptomatic identification of life-threatening congenital heart defects. This may lead to better postoperative and longer term outcomes.*
d. *Newborn screening also allows other clinically important defects with later onset to be detected, that are associated with heart failure in infancy or pulmonary vascular disease in later life.*
e. *Congenital heart defects can be classified by presymptomatic interval and natural history, allowing identification of defects with the greatest potential to benefit from newborn screening.*
f. *Life-threatening congenital heart defects are structural cardiac malformations in which collapse is likely and this group comprises: transposition of the great arteries, coarctation/interrupted aortic arch, aortic stenosis, pulmonary atresia and hypoplastic left heart/mitral atresia.*
g. *Clinically significant congenital heart defects are structural cardiac malformations which have effects on heart function but collapse is unlikely or the prevention of collapse is unlikely to be feasible. The most common defects in this group are ventricular septal defect, complete atrioventricular septal defect, atrial septal defect and tetralogy of Fallot.*
h. *Clinically non-significant defects are anatomically defined cardiac malformations which have no functional clinical significance and include the ventricular septal defects which are only detectable using echocardiography. These require no treatment.*
i. *From this we propose the detection of life-threatening congenital heart defects with a view to preventing death and avoiding preoperative collapse as the primary objective of newborn screening for congenital heart defects.*
j. *A secondary objective of newborn screening is the detection of clinically significant congenital heart defects.*

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

There are no primary preventive strategies available as yet.

The test

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

The heterogeneity of congenital heart defects presents particular problems for newborn screening as screening

tests vary widely in their capacity to detect specific defects and no test can detect all defects equally well.

There are three possible candidate tests for newborn screening: clinical examination (current practice), pulse oximetry and screening echocardiography. These are described below.

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.*
- *Usually carried out by a junior doctor responsible for the routine examination of all newborn infants before discharge from the maternity unit, although, increasingly in some areas, midwives are taking on this role. We defined a presumptive positive result in this strategy as the finding of cyanosis or murmurs or weak pulses in the groin.*

Pulse oximetry

- *Is a simple non-invasive method of monitoring the percentage of haemoglobin which is saturated with oxygen.*
- *Consists of a probe attached to the infant's finger, toe or edge of the foot, which is in turn linked to a computerised display of the percentage of haemoglobin saturated with oxygen as well as the heart rate. Light shines from the probe and is partly absorbed by haemoglobin. This information can be used to calculate the proportion of haemoglobin which is oxygenated.*
- *This examination can be performed by a junior doctor or midwife or other health professional.*
- *The equipment required is portable and can be used in the home as well as hospital.*
- *Normal values for pulse oximetry are generally assumed to be the same as those for arterial oxygen saturation in the newborn. These values may be influenced by altitude but in general levels below 95% are considered to be abnormal. The precision of oximeter readings varies with the absolute value and the readings are generally cited as ±2% above 70% and ±4% below 70%. The accuracy and precision of these monitors has been studied in a range of populations, including newborn infants. Low peripheral perfusion (blood flow to the skin and limbs) or skin temperature, skin pigmentation and movement may all interfere with precision or introduce biased estimates of arterial saturation.*
- *Although pulse oximetry may identify babies with congenital heart defects that result in cyanosis, it will not identify defects that are only associated with murmurs or delayed or absent pulses. So we assumed that screening with pulse oximetry would be carried out together with clinical examination.*
- *Finally, pulse oximetry may also identify babies who are cyanosed for other (non-cardiac) reasons, including lung disease, and therefore a baby with a positive screening test result may require other investigations. In principle, a hyperoxia test, which monitors changes in the degree of cyanosis whilst oxygen is being administered, can help distinguish lung disease from cyanotic heart defects.*

Screening echocardiography

- *An echocardiogram is a scan of the heart using sound waves. It allows the four chambers, large blood vessels and the heart valves to be visualised while the heart is beating. With Doppler technology, it can also be used to assess the direction of blood flow.*
- *The examiner uses a small hand-held probe with gel over the end and moves it gently over the chest to locate the heart and examine its structures. Visualisation of the main chambers of the heart by this method is usually referred to as a four-chamber view, 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. The examination may also reveal developmental structural abnormalities of the heart which are not considered clinically important and which may not have been recognised otherwise since they may not be associated with murmurs or other clinical signs or symptoms.*
- *An echocardiogram may be used as a screening test for congenital heart defects in newborn babies. Such screening examinations are usually carried out by a trained radiographer or echocardiographer. The equipment is not portable. A clinical examination is usually carried out as well.*

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

This is only really relevant to pulse oximetry. Four studies have reported use of pulse oximetry to screen newborns for congenital heart defects. Three of these have defined a value below 95% on initial reading as an indication for further assessment. In one paper it was specified that the reading be taken over 2 minutes and the probe be clipped to the border of the foot. In this study values in 5% of infants were initially low and this persisted in only 1%. The suitability of this as a cut-off is uncertain in relation to the false negative rate.

1.6. The test should be acceptable to the population.

All three strategies are acceptable.

1.7. 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.

Abnormalities in clinical examination warrant an echocardiogram and an expert cardiological opinion.

Abnormalities in pulse oximetry require further assessment for congenital heart defects. It is unclear whether the hyperoxia test can be used to determine whether the underlying problem is likely to be cardiac or non-cardiac in origin. An agreed policy is needed for non-cardiac causes.

Abnormalities on screening echocardiogram include the finding of small muscular ventricular septal defects and other clinically unimportant structural abnormalities.

The treatment

1.8. 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 irrespective of how the diagnosis has been made. However, earlier detection through newborn screening might improve outcomes by allowing definitive management to be commenced either before death or before the acute onset of clinical deterioration experienced by individuals with some types of congenital heart defects. Prevention of preoperative collapse, through the timely commencement of effective clinical management, could improve both short-term outcomes (mortality and length of stay in hospital) and longer term outcomes (neurological status and educational attainment).

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

See above.

1.10. Clinical management of the condition and patient outcomes should be optimised by all healthcare providers prior to participation in a screening programme.

There is evidence that timely management is not initiated in some infants with a positive screening result. Protocols for management will need to be developed and agreed.

The screening programme

1.11. There must be evidence from high-quality randomised controlled trials 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' (e.g. 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.

There is one randomised controlled trial of screening echocardiography compared with routine clinical examination. Two further randomised controlled trials report an evaluation of one versus two screening examinations per household. With these exceptions, evidence is from observational studies.

1.12. 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.

The parent focus group suggests that parents support screening and professional support is assumed. There is an ethical consideration regarding the high rate of false-positive screening results associated with screening echocardiography and public and professional attitudes to this require further exploration.

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

This depends on the screening test and benefits may not be considered to outweigh harms for screening echocardiography.

1.14. The opportunity cost of the screening programme (including testing, diagnosis, treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money).

The cost-effectiveness analysis suggests that the incremental cost-effectiveness ratio for pulse oximetry is within an acceptable range but that total programme costs and incremental cost-effectiveness ratio for screening echocardiography (in relation to timely diagnoses of life-threatening congenital heart defects) may not be.

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

This is lacking and needs to be established.

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

This needs to be explored in relation to paediatric cardiologists, echocardiographers and midwives, who are all in short supply. Telemedicine may provide an option for assisted diagnosis in remote areas but expertise in initial acute management is unlikely to be available at the maternity unit and for some defects this suggests that fetal diagnosis and planned delivery may be a more optimal strategy than newborn screening.

1.17. All other options for managing the condition should have been considered (e.g. 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 congenital heart defects have recently been reviewed by the Bristol Royal Infirmary Inquiry and recommendations made to improve services.

1.18. 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 lacking and needs to be established.

1.19. 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.

While professionals and parents are concerned to improve current practice in screening and to maximise effectiveness of antenatal screening, there is currently no public pressure for any particular newborn screening option. In the parent focus group parents expressed concern that clinical examination was 'old-fashioned'.

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.ncchta.org) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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