Appendices

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

R Knowles, I Griebsch, C Dezateux, J Brown, C Bull and C Wren

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Appendix I

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$).ti,ab,kw.
25. (switch adj operation).ti,ab,kw.
27. senning.ti,ab,kw.
28. (univentric$ 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
<table>
<thead>
<tr>
<th>Study</th>
<th>Year of publication</th>
<th>Congenital heart defect</th>
<th>Study type</th>
<th>Country; sample size (n); age range; controls</th>
<th>Follow-up period</th>
<th>Outcomes</th>
<th>Method</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abu-Harb14</td>
<td>1994</td>
<td>All congenital heart defects</td>
<td>Retrospective cohort study</td>
<td>UK ( n = 1074 ) Age: &lt;1 year old</td>
<td>1 year</td>
<td>Causes of death</td>
<td>All births, infant deaths, and surviving babies with congenital heart defects in one health region in 1985 to 1990 were identified</td>
<td>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</td>
</tr>
<tr>
<td>Abu-Harb(^{18})</td>
<td>1994</td>
<td>HLH, IAA, COA, AS</td>
<td>Retrospective cohort study</td>
<td>UK ( n = 120 ) Age: &lt;1 year old</td>
<td>1 year</td>
<td>Causes of death</td>
<td>All cases of obstructive left heart malformations presenting in infancy in one health region from 1987 to 1991 were analysed retrospectively</td>
<td>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</td>
</tr>
<tr>
<td>Aharon(^{428})</td>
<td>1994</td>
<td>Mitral valve defects</td>
<td>Case series</td>
<td>US ( n = 79 ) Mean age at surgery: 5 years (range 2 months–17 years)</td>
<td>Mean 4 years (1–10 years)</td>
<td>Actuarial survival</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Alden(^{182})</td>
<td>1998</td>
<td>TGA</td>
<td>Qualitative study: uncontrolled</td>
<td>Sweden ( n = 31 ) Mean age at follow-up: 13 years</td>
<td>Mean 11 years</td>
<td>Cognitive outcome; behaviour</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Alexiou(^{124})</td>
<td>2000</td>
<td>AS and other aortic valve defects (some not congenital)</td>
<td>Case series</td>
<td>UK ( n = 56 ) (including 33 congenital AS) Mean 11 years (range 1–16 years)</td>
<td>Mean 7 years (range 0–26 years)</td>
<td>Actuarial survival; exercise capacity</td>
<td>Patients undergoing aortic valve replacement in a single centre from 1972 to 1999 were evaluated at follow-up. Deaths and exercise capacity were reported</td>
<td>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</td>
</tr>
</tbody>
</table>

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<th>Follow-up period</th>
<th>Outcomes</th>
<th>Method</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alexiou</td>
<td>2001</td>
<td>TOF</td>
<td>Case series</td>
<td>USA n = 89, Median age at operation: 6 months</td>
<td>Mean 13 years (1–25 years)</td>
<td>Actuarial survival; exercise capacity</td>
<td>Children undergoing surgical repair from 1974 to 2000 were retrospectively reviewed for operative deaths, reoperation, cardiac function and exercise capacity</td>
<td>98% survival at 20 years; 85% freedom from reoperation. Few late complications, such as arrhythmia. 86 of 88 survivors in NYHA Class I</td>
</tr>
<tr>
<td>Al Halees</td>
<td>2002</td>
<td>Congenital aortic valve disease: AS (18), mixed stenosis/regurgitation (32), aortic regurgitation (3)</td>
<td>Case series</td>
<td>Saudi Arabia n = 260 (including 53 congenital AS), Mean age at surgery: 8 years</td>
<td>Mean 4 years (up to 10 years)</td>
<td>Actuarial survival</td>
<td>All children/young adults who underwent a Ross operation for aortic valve disease in a single centre from 1990 to 2000</td>
<td>94% survival at 10 years. All patients but one were NYHA Class I or II</td>
</tr>
<tr>
<td>Amaral</td>
<td>1997</td>
<td>COA</td>
<td>Case series</td>
<td>Brazil/UK n = 104</td>
<td>Not reported</td>
<td>Exercise capacity</td>
<td>Patients were grouped according to age at operation and outcomes compared: resting hypertension, exercise hypertension, limitation in activities and abilities</td>
<td>Older age at surgery (&gt;10 years) was associated with resting hypertension. Limitation in function was not common and 94% could undertake normal activity</td>
</tr>
<tr>
<td>Ashraf</td>
<td>1993</td>
<td>CAVSD</td>
<td>Case series</td>
<td>USA n = 104, Mean age at surgery: 1 year (primary repair), 2 years (second operation)</td>
<td>1–13 years (for 90% survivors)</td>
<td>Actuarial survival; exercise capacity</td>
<td>Children receiving a specific operation from 1978 to 1991 at a single centre were followed up for deaths and exercise capacity</td>
<td>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</td>
</tr>
<tr>
<td>Bacha</td>
<td>2001</td>
<td>TOF</td>
<td>Case series</td>
<td>USA n = 57, Median age at surgery: 8 months</td>
<td>Median 23 years</td>
<td>Actuarial survival; exercise capacity</td>
<td>Children who underwent surgery from 1972 to 1977 were followed up and survival and freedom from reintervention were determined</td>
<td>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</td>
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<tr>
<td>Balderston\textsuperscript{129} 1992</td>
<td>COA</td>
<td>Case–control</td>
<td>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</td>
<td>Mean 8 years</td>
<td>Exercise capacity</td>
<td>Children who had surgery for COA and controls underwent bicycle exercise tests and ventilatory gas measurement</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Bando\textsuperscript{160} 1995</td>
<td>CAVSD</td>
<td>Case series</td>
<td>USA $n = 203$ Mean 5 years after surgery</td>
<td>Actuarial survival; exercise capacity</td>
<td>Children undergoing surgical repair from 1974 to 1995 were retrospectively reviewed for operative deaths, reoperation, valve function and exercise capacity</td>
<td>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</td>
<td></td>
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</tr>
<tr>
<td>Bauer\textsuperscript{229} 1992</td>
<td>Congenital AS</td>
<td>Case series</td>
<td>Germany $n = 86$ Mean age at surgery: 7 years Up to 20 years after surgery</td>
<td>Actuarial survival</td>
<td>Follow-up of children who underwent surgery for AS in a single centre</td>
<td>There were 7/86 (8.1%) early deaths and 6/67 (9.4%) 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</td>
<td></td>
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<tr>
<td>Beitzke\textsuperscript{155} 1990</td>
<td>TOF</td>
<td>Case series</td>
<td>Austria $n = 127$ Mean age at surgery: 4 years (1–18 years) Mean 5 years (0–15 years) after surgery</td>
<td>Exercise capacity</td>
<td>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</td>
<td>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</td>
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<td>Bell430 1998</td>
<td>Double-outlet right ventricle</td>
<td>Case series</td>
<td>France</td>
<td>Median 52 months after surgery</td>
<td>Actuarial survival</td>
<td>Children who underwent surgery for double-outlet right ventricle from 1985 to 1996 at a single centre</td>
<td>86% survival at 10 years</td>
<td></td>
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<tr>
<td>Bellinger180 1995</td>
<td>TGA</td>
<td>Randomised trial</td>
<td>USA</td>
<td>1 year after surgery</td>
<td>Neurodevelopment; predictive factors</td>
<td>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</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Bellinger165 1999</td>
<td>TGA</td>
<td>Long-term follow-up of randomised trial</td>
<td>USA</td>
<td>4 years</td>
<td>Neurodevelopment; cognitive outcome</td>
<td>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%)</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Benatar431 1995</td>
<td>Complex congenital heart defects</td>
<td>Case series</td>
<td>The Netherlands</td>
<td>Mean 3 years (10 months–7 years)</td>
<td>Actuarial survival</td>
<td>Children who underwent a specific procedure in a single centre were followed for deaths and complications</td>
<td>Early surgical mortality was 16%. Median hospital stay was 26 days. The 1-year and 5-year actuarial survival was 69%</td>
<td></td>
</tr>
<tr>
<td>Boening208 2002</td>
<td>Atrioventricular septal defect</td>
<td>Case series</td>
<td>Germany</td>
<td>Mean 7 years</td>
<td>Actuarial survival</td>
<td>Children who underwent surgery at a single centre from 1975–1995 were followed up</td>
<td>Actuarial survival after 1 year was 80%, after 10 years was 78% and after 20 years was 65%</td>
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<tr>
<td>Boger126</td>
<td>1999</td>
<td>TAPVC</td>
<td>Case series</td>
<td>USA; ( n = 44 ); Age range: 0–16 years</td>
<td>Mean 12 years (range 0–24 years) after surgery</td>
<td>Actuarial survival; exercise capacity</td>
<td>Case series of children who underwent cardiac surgery. Deaths, reoperation, exercise capacity and medication recorded</td>
<td>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</td>
</tr>
<tr>
<td>Bove80</td>
<td>1983</td>
<td>All congenital heart defects</td>
<td>Case series</td>
<td>UK; ( n = 212 ); Mean age at surgery: &lt;1 year</td>
<td>3–8 years</td>
<td>Predictive factors</td>
<td>All 212 neonates who underwent cardiac surgery at a single centre from 1976 to 1980 were reviewed</td>
<td>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</td>
</tr>
<tr>
<td>Bove78</td>
<td>1998</td>
<td>HLH</td>
<td>Case series</td>
<td>USA; ( n = 253 ); Mean age at surgery: less than 1 year</td>
<td>Up to 4 years</td>
<td>Actuarial survival</td>
<td>Children who underwent the Norwood operation for classic HLH syndrome from 1990 to 1997 were followed up</td>
<td>Hospital survival was 76% for the first stage (all children), 97% for the second stage and 88% for the third stage (94 children)</td>
</tr>
<tr>
<td>Bowyer109</td>
<td>1990</td>
<td>TGA</td>
<td>Case–control</td>
<td>UK; ( n = 12 ); Age range: 7–13 years; 20-age and size-matched controls</td>
<td>6–12 years after surgery</td>
<td>Exercise capacity</td>
<td>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</td>
<td>Compared with controls, 7 children with transposition had normal exercise tolerance, 10 had a moderate reduction and 3 a severe reduction in exercise capacity</td>
</tr>
<tr>
<td>Bradley432</td>
<td>2002</td>
<td>UVH</td>
<td>Case series</td>
<td>USA; ( n = 22 ); Median age at surgery: 8 days</td>
<td>Up to 5 years</td>
<td>Actuarial survival</td>
<td>Follow-up of infants receiving surgery for UVH at a single centre from 1996 to 2001</td>
<td>Actuarial survival beyond 30 months was 90%</td>
</tr>
</tbody>
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<tr>
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<tbody>
<tr>
<td>Braun</td>
<td>1998</td>
<td>AS, IAA and other defects obstructing blood flow from the left ventricle</td>
<td>Case series</td>
<td>The Netherlands n = 41 Mean age at surgery: 10 years (35 days to 19 years)</td>
<td>Mean 2 years (range 44 days–4 years)</td>
<td>Exercise capacity</td>
<td>Case series of children operated from 1994 to 1998 in a single centre. Deaths, reoperation and exercise capacity recorded at follow-up</td>
<td>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</td>
</tr>
<tr>
<td>Breymann</td>
<td>1999</td>
<td>HLH and complex defects with aortic hypoplasia</td>
<td>Case series</td>
<td>Germany Typical HLH: n = 48, median age at surgery: 15 days Complex lesions: n = 12, median age at surgery: 59 days</td>
<td>Mean 7 years</td>
<td>Actuarial survival</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Brizard</td>
<td>1997</td>
<td>Truncus</td>
<td>Case series</td>
<td>Australia n = 82 Age at surgery: &lt;3 months</td>
<td>Mean 6 years</td>
<td>Actuarial survival</td>
<td>Follow-up of children who underwent surgery in a single centre from 1979 to 1995</td>
<td>Actuarial survival at 7 years was 81%</td>
</tr>
<tr>
<td>Brown</td>
<td>2001</td>
<td>TGA</td>
<td>Case series</td>
<td>USA n = 201 Mean age at surgery: 10 days</td>
<td>Not reported</td>
<td>Actuarial survival; predictive factors</td>
<td>Follow-up of consecutive children who underwent a Switch operation in a single centre from 1986 to 1999</td>
<td>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%</td>
</tr>
<tr>
<td>Brown</td>
<td>2003</td>
<td>All congenital heart defects</td>
<td>Case series</td>
<td>UK n = 355</td>
<td>1 year</td>
<td>Predictive factors</td>
<td>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)</td>
<td>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</td>
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<thead>
<tr>
<th>Study</th>
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<tbody>
<tr>
<td>Cabezuelo⁴¹⁵</td>
<td>1990</td>
<td>TAPVC</td>
<td>Case series</td>
<td>Spain; n = 36 (26 received operation) Mean age at surgery: 2 months</td>
<td>Not reported</td>
<td>Actuarial survival</td>
<td>Follow-up of infants attending a single centre from 1971 to 1988</td>
<td>Operative mortality rate of 57.7%. Actuarial survival rate was 34.4% in the total group and 42.3% in the operated group</td>
</tr>
<tr>
<td>Carano¹³⁹</td>
<td>1999</td>
<td>COA</td>
<td>Case series</td>
<td>Italy; n = 28</td>
<td>Not reported</td>
<td>Exercise capacity</td>
<td>Patients who had undergone successful COA repair were evaluated during exercise</td>
<td>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</td>
</tr>
<tr>
<td>Casey¹⁸⁸</td>
<td>1994</td>
<td>Complex congenital heart defects</td>
<td>Case–control</td>
<td>UK; Cases: n = 26 children with complex congenital heart defects Control group: n = 26 children with innocent murmur</td>
<td>Up to school age</td>
<td>Behaviour</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Chang²²³</td>
<td>1991</td>
<td>HLH, AS and left heart outflow obstruction</td>
<td>Case series</td>
<td>USA; n = 21 Age at surgery: 2 days</td>
<td>Up to hospital discharge</td>
<td>Predictive factors</td>
<td>In 22 cases of fetal diagnosis of critical left heart obstruction, 21 were correct and 17 underwent surgery at a single centre</td>
<td>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</td>
</tr>
<tr>
<td>Cho²⁰⁶</td>
<td>2002</td>
<td>TOF</td>
<td>Case series</td>
<td>USA; n = 495 (160 palliative repair, 335 complete repair)</td>
<td>Mean 6 years (palliative repair) Mean 12 years (complete repair)</td>
<td>Actuarial survival</td>
<td>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</td>
<td>Actuarial survival of 86% at 10 years and 75% at 20 years</td>
</tr>
<tr>
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<tr>
<td>Clancy¹³⁴</td>
<td>2003</td>
<td>All congenital heart defects, except HLH</td>
<td>Case series</td>
<td>USA  ( n = 164 ) Age at surgery: neonates</td>
<td>Early post-operative period (up to hospital discharge)</td>
<td>Predictive factors</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Clapp¹³⁶</td>
<td>1987</td>
<td>CAVSD</td>
<td>Case series</td>
<td>USA  ( n = 121 ) Age at surgery: 1–9 months</td>
<td>Up to 10 years</td>
<td>Actuarial survival</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Cobanoglu¹³⁸</td>
<td>2002</td>
<td>TOF</td>
<td>Case series</td>
<td>USA  ( n = 63 ) Age at surgery: &lt;1 year</td>
<td>Mean 12 years</td>
<td>Actuarial survival</td>
<td>A retrospective review of consecutive patients who underwent corrective surgery at &lt;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</td>
<td>Actuarial survival was 89% at 20 years. 88% of survivors have good-to-excellent functional status over 15 years after surgery</td>
</tr>
<tr>
<td>Cohen¹³⁷</td>
<td>1989</td>
<td>COA</td>
<td>Case series</td>
<td>USA  ( n = 646 )</td>
<td>Median 20 years</td>
<td>Actuarial survival</td>
<td>Long-term follow-up of children and adults who underwent surgical repair at a single centre from 1946 to 1981</td>
<td>For children aged ( \leq 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</td>
</tr>
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<tr>
<td>Crepaz138</td>
<td>1993</td>
<td>COA</td>
<td>Case–control</td>
<td>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</td>
<td>Mean 10 years</td>
<td>Exercise capacity</td>
<td>Cases and controls underwent echocardiography, blood pressure and exercise test</td>
<td>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</td>
</tr>
<tr>
<td>Daebritz438</td>
<td>2000</td>
<td>TGA</td>
<td>Case series</td>
<td>USA, n = 312, Mean age at surgery: 84 days</td>
<td>Mean 4 years</td>
<td>Actuarial survival</td>
<td>Risk factors for mortality and morbidity were analysed retrospectively in patients who underwent surgery at a single centre from 1982 to 1997</td>
<td>Actuarial survival was 92% at 5 and 10 years. Operative survival improved after 1990</td>
</tr>
<tr>
<td>Dajani102</td>
<td>1997</td>
<td>All congenital heart defects</td>
<td>Review</td>
<td>USA, Not applicable</td>
<td>Causes of death</td>
<td>Updated guidelines on prevention of infective endocarditis prepared for the American Heart Association</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Dearani204</td>
<td>2003</td>
<td>Complex congenital heart defects</td>
<td>Case series</td>
<td>USA, n = 1095, Mean age at surgery: 10 years</td>
<td>Mean 11 years</td>
<td>Actuarial survival; predictive factors</td>
<td>Late outcome of patients who underwent surgery at a single centre from 1964 to 1992</td>
<td>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</td>
</tr>
<tr>
<td>DeBoer499</td>
<td>1990</td>
<td>Congenital AS</td>
<td>Case series</td>
<td>USA, n = 51, Mean age at surgery: 11 years</td>
<td>Mean 17 years</td>
<td>Actuarial survival</td>
<td>Follow-up of patients who underwent surgery at a single centre from 1956 to 1986</td>
<td>Actuarial survival was 94% at 10 and 15 years, 82% at 20 and 25 years and 71% at 28 years</td>
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<tr>
<td>Delamater(^{102}) 2001</td>
<td>All congenital heart defects</td>
<td>Review</td>
<td>UK</td>
<td>Not applicable</td>
<td>Exercise capacity; neurodevelopment; cognitive outcome; behaviour; predictive factors</td>
<td>Review of outcomes, including exercise capacity, in children with congenital heart defects</td>
<td></td>
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</tr>
<tr>
<td>Delius(^{40}) 1996</td>
<td>TAPVC</td>
<td>Case series</td>
<td>UK (n = 232) Mean age at surgery: 2 months (range 1 day–46 months)</td>
<td>Not reported</td>
<td>Actuarial survival</td>
<td>Review of outcomes after surgery in a single centre from 1971 to 1994</td>
<td>Actuarial survival was 73% at 10 years</td>
<td></td>
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<tr>
<td>Delius(^{41}) 1997</td>
<td>Atrioventricular septal defect with TOF</td>
<td>Case series</td>
<td>UK (n = 35) Mean age at definitive surgery: 6 years (palliation) 4 years (primary repair)</td>
<td>Up to 8 years</td>
<td>Actuarial survival</td>
<td>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</td>
<td>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)</td>
<td></td>
</tr>
<tr>
<td>de Ruijter(^{42}) 2002</td>
<td>TOF</td>
<td>Case series</td>
<td>The Netherlands (n = 171) Mean age at surgery: 2 years</td>
<td>Mean 10 years</td>
<td>Actuarial survival</td>
<td>Review of all patients who underwent surgery in a single centre from 1977 to 2000</td>
<td>Actuarial survival was 91% at 20 years</td>
<td></td>
</tr>
<tr>
<td>Di Filippo(^{40}) 1997</td>
<td>COA</td>
<td>Review</td>
<td>France</td>
<td>Not applicable</td>
<td>Complications after surgery; exercise capacity</td>
<td>Review of long-term results after surgery for COA in children</td>
<td>Mortality, stenosis and exercise hypertension influenced by surgical techniques and age at operation</td>
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<tr>
<td>Ekman Joelsson⁴⁴³</td>
<td>2001</td>
<td>PA and IVS</td>
<td>Cohort study</td>
<td>Sweden</td>
<td>Median 6 years (14 days–20 years)</td>
<td>Actuarial survival</td>
<td>Follow-up of all children born with PA/IVS in Sweden from 1980 to 1999. Retrospective study of medical records and investigations</td>
<td>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</td>
</tr>
<tr>
<td>Elgamal⁴⁴⁴</td>
<td>2002</td>
<td>COA</td>
<td>Case series</td>
<td>USA</td>
<td>Not reported</td>
<td>Actuarial survival</td>
<td>Follow-up of early outcomes in infants who underwent surgery in a single centre from 1995 to 2000.</td>
<td>Actuarial survival was 91% at 5 years</td>
</tr>
<tr>
<td>Elkins⁴⁴⁵</td>
<td>1994</td>
<td>TGA</td>
<td>Case series</td>
<td>USA</td>
<td>Median 23 months</td>
<td>Actuarial survival</td>
<td>Review of functional outcomes in consecutive patients who underwent surgery at a single centre from 1985 to 1993</td>
<td>Actuarial survival was 83% at 8 years. All survivors in NYHA Class I</td>
</tr>
<tr>
<td>Elkins⁴⁴⁶</td>
<td>2001</td>
<td>Congenital AS</td>
<td>Case series</td>
<td>USA</td>
<td>Up to 15 years</td>
<td>Actuarial survival</td>
<td>Retrospective review of children who underwent surgery at a single centre from 1986 to 2001</td>
<td>Operative mortality was 4.5%. Actuarial survival was 92% at 12 years</td>
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<tr>
<td>Fallon(^8^1) 1995</td>
<td>All congenital heart defects</td>
<td>Case notes review</td>
<td>UK</td>
<td>n = 523</td>
<td>1–30 months after surgery</td>
<td>Neurodevelopment; predictive factors</td>
<td>Cardiac surgical discharge summaries were searched for recorded evidence of adverse neurological events occurring between operation and time of discharge</td>
<td>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</td>
</tr>
<tr>
<td>Ferrieri(^9^6) 2002</td>
<td>All congenital heart defects</td>
<td>Review USA Not applicable Causes of death</td>
<td>Review of infective endocarditis in childhood</td>
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<tr>
<td>Forbes(^4^7^1) 1995</td>
<td>HLH</td>
<td>Case series USA</td>
<td>n = 212 Mean age at surgery: neonatal</td>
<td>Up to 1 year (to second-stage surgery)</td>
<td>Actuarial survival</td>
<td>Review of outcomes after Stage 1 Norwood surgery at a single institution from 1983 to 1993</td>
<td>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</td>
<td></td>
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<tr>
<td>Forbes(^1^8^1) 2001</td>
<td>Complex congenital heart defects</td>
<td>Case–control study USA</td>
<td>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)</td>
<td>Median 5 years Cognitive outcome</td>
<td>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</td>
<td>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</td>
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<tr>
<td>Forbes</td>
<td>2002</td>
<td>All congenital heart defects</td>
<td>Cross-sectional study</td>
<td>USA n = 243 Median age at operation: 2 months Age at survey: 5 years</td>
<td>Median 5 years</td>
<td>Cognitive outcome; predictive factors</td>
<td>Survey of neurodevelopment of 5-year-old children following congenital heart surgery. Neuropsychological tests performed between 1998 and 2001</td>
<td>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</td>
</tr>
<tr>
<td>Forbes</td>
<td>2002</td>
<td>Various congenital heart defects (defined by operation)</td>
<td>Case series</td>
<td>USA n = 69 Median age at surgery: 3 months Age at follow-up: 5 years</td>
<td>Not reported</td>
<td>Cognitive outcome; predictive factors</td>
<td>Children who had undergone biventricular repair of congenital heart defects were assessed using standardised IQ test at age 5 years</td>
<td>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</td>
</tr>
<tr>
<td>Franklin</td>
<td>1991</td>
<td>Double-inlet ventricle</td>
<td>Case series</td>
<td>UK n = 191</td>
<td>2 years</td>
<td>Actuarial survival</td>
<td>Review of outcomes in complex defects and suitability for surgery at 2 years of age</td>
<td>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</td>
</tr>
<tr>
<td>Franklin</td>
<td>1993</td>
<td>TA</td>
<td>Case series</td>
<td>UK n = 237</td>
<td>Median 8 years</td>
<td>Actuarial survival</td>
<td>Outcomes of infants with TA diagnosed from 1972 to 1987 in a single centre were reviewed</td>
<td>Actuarial survival was 72% at 1 year, 53% at 5 years and 46% at 10 years</td>
</tr>
<tr>
<td>Frontera</td>
<td>1990</td>
<td>UVH</td>
<td>Case series</td>
<td>Spain n = 90</td>
<td>Mean 9 years</td>
<td>Complications after surgery; causes of death</td>
<td>Retrospective review of patients found to have univentricular heart at catheterisation in a single centre from 1971 to 1988</td>
<td>Of 90 children, 43 died in the first year of life and 7 later, giving an overall survival rate of 38.3% at 5 years. Survival was marginally better for those given a palliative operation</td>
</tr>
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<tr>
<td>Fulton451</td>
<td>1999</td>
<td>IAA</td>
<td>Case series</td>
<td>Australia n = 72 Mean age at surgery: 3 days (range 1–180 days)</td>
<td>Mean 4 years</td>
<td>Actuarial survival</td>
<td>Review of immediate and long-term outcomes in infants who underwent operation in a single centre from 1985 to 1997</td>
<td>Actuarial survival for the whole cohort was 85% at 12 years. 28 patients have required at least one reoperation</td>
</tr>
<tr>
<td>Gabriel146</td>
<td>2002</td>
<td>VSD</td>
<td>Case series</td>
<td>Austria n = 229 Mean age at follow-up: 30 years</td>
<td>Mean 7 years</td>
<td>Exercise capacity</td>
<td>Adults with VSD which did not require repair in childhood were followed up and given a clinical examination and exercise test</td>
<td>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</td>
</tr>
<tr>
<td>Garcia Hernandez452</td>
<td>1994</td>
<td>TOF</td>
<td>Case series</td>
<td>Spain n = 101 Mean age at surgery: 7 months (palliation only), 3 years (corrective surgery after palliation), 3 years (primary repair)</td>
<td>Mean 4 years</td>
<td>Actuarial survival</td>
<td>Review of children who underwent surgery in a single centre from 1979 to 1992. Before 1985, palliative surgery was used exclusively</td>
<td>Actuarial survival was 86% at 6 years. After 1985, mortality reduced from 6.7% to 2.3%</td>
</tr>
<tr>
<td>Garcia Hernandez19</td>
<td>1995</td>
<td>TGA</td>
<td>Case series</td>
<td>Spain n = 21 Mean age at surgery: 10 days Mean age at follow-up: 21 months</td>
<td>2 months to 5 years after surgery</td>
<td>Exercise capacity</td>
<td>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</td>
<td>17 survivors are in NYHA Class I and one survivor is in Class II. Three early postoperative deaths occurred and no late deaths</td>
</tr>
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</table>
| Gaynor  | 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  | 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  | 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  | 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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<tr>
<td>Gewillig</td>
<td>1991</td>
<td>TGA</td>
<td>Case series</td>
<td>UK: n = 249; Mean age at definitive surgery: 2 years</td>
<td>Mean 12 years (up to 24 years) after surgery</td>
<td>Causes of death; actuarial survival; exercise capacity</td>
<td>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</td>
<td>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</td>
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<td>Gildein</td>
<td>1994</td>
<td>VSD; tetralogy of Fallot; TGA; TA</td>
<td>Case series</td>
<td>Germany: n = 35; Mean age at follow-up: 11 years</td>
<td>2–12 years</td>
<td>Exercise capacity</td>
<td>Children with mixed group of congenital heart defects tested after surgery. Oxygen uptake on exercise recorded</td>
<td>Children with a VSD repair, Fontan surgery or tetralogy of Fallot patching have reduced capacity for both intensive and endurance exercise 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</td>
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<tr>
<td>Gomelsky</td>
<td>1998</td>
<td>TGA</td>
<td>Cohort study</td>
<td>USA: n = 57; Mean age at follow-up: 8 years</td>
<td>8 years</td>
<td>Predictive factors</td>
<td>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</td>
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<tr>
<td>Haas</td>
<td>1999</td>
<td>TGA</td>
<td>Case series</td>
<td>Germany: n = 285; Median age at surgery: &lt; 1 month</td>
<td>1–15 years</td>
<td>Actuarial survival</td>
<td>Review of outcomes in patients who underwent surgery from 1983 to 1997 in a single centre</td>
<td>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</td>
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<td>Hamada</td>
<td>2002</td>
<td>TOF</td>
<td>Case series</td>
<td>Japan: n = 167; Mean age at surgery: 6 years</td>
<td>Not reported</td>
<td>Actuarial survival; predictive factors</td>
<td>Review of patients who underwent surgery in a single centre from 1965 to 1975</td>
<td>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</td>
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<td>Haneda149</td>
<td>1990</td>
<td>TOF</td>
<td>Case series</td>
<td>Japan; n = 166; Mean 9 years (1–19 years) after surgery</td>
<td>Actuarial survival; exercise capacity</td>
<td>Case series of children with surgical correction since 1971 at a single centre. Deaths, exercise capacity and cardiac function recorded at follow-up</td>
<td>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</td>
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<td>Haneda161</td>
<td>1992</td>
<td>CAVSD</td>
<td>Case series</td>
<td>Japan; n = 28 (including 10 with Down’s syndrome); Mean 7 years (1–17 years) after surgery</td>
<td>Actuarial survival; exercise capacity</td>
<td>Case series of children with surgical repair since 1972. Exercise capacity, cardiac function, reoperation and deaths recorded at follow-up</td>
<td>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</td>
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<tr>
<td>Hauser135</td>
<td>2000</td>
<td>COA</td>
<td>Case–control</td>
<td>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</td>
<td>Exercise capacity</td>
<td>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</td>
<td>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</td>
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<td>Hawkins156</td>
<td>1998</td>
<td>Congenital AS</td>
<td>Case series</td>
<td>USA; n = 37; Mean age at surgery: 26 days; 5 years (range 3 months–11 years)</td>
<td>Actuarial survival</td>
<td>Review of infants who underwent surgery for critical AS in the first 3 months of life at a single centre from 1986 to 1996</td>
<td>Actuarial survival was 92% at 1 month, 78% at 1 year and 73% at 10 years</td>
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<tr>
<td>Heger134</td>
<td>1997</td>
<td>COA</td>
<td>Case series</td>
<td>Austria; n = 41; Mean age at surgery: 12 years; Mean age at follow-up: 28 years</td>
<td>Exercise capacity</td>
<td>Evaluation of outcomes after COA repair performed from 1945 to 1997. Physical examination, bicycle exercise test and cardiac function tests undertaken</td>
<td>Exercise-induced hypertension was found in 44% of patients. Patients who were &gt;9 years old at surgery had a significantly higher risk of hypertension at rest but were also older at the time of follow-up</td>
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<tr>
<td>Heying</td>
<td>1999</td>
<td>All congenital heart defects</td>
<td>Cross-sectional survey</td>
<td>USA (n = 11) Median age at surgery: 6 years (range 2–10 years)</td>
<td>Median 3 years (range 1–6 years)</td>
<td>Neurodevelopment</td>
<td>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.</td>
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<tr>
<td>Hisatomi</td>
<td>1991</td>
<td>TOF</td>
<td>Case series</td>
<td>Japan (n = 166) (\geq 10) years after surgery</td>
<td>Exercise capacity</td>
<td>Causes of death; complications after surgery</td>
<td>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.</td>
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<tr>
<td>Hokanson</td>
<td>1999</td>
<td>TOF</td>
<td>Review</td>
<td>USA</td>
<td>Not applicable</td>
<td>Exercise capacity</td>
<td>Review of long-term outcomes in adults with repaired TOF</td>
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<tr>
<td>Horstkotte</td>
<td>1993</td>
<td>TOF</td>
<td>Case series</td>
<td>Germany (n = 246) Mean age at follow-up: 12 years</td>
<td>Mean 20 years (18–29 years)</td>
<td>Exercise capacity</td>
<td>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.</td>
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<tr>
<td>Hoshino</td>
<td>1999</td>
<td>HLH</td>
<td>Case series</td>
<td>Japan (n = 26)</td>
<td>Up to 2 years</td>
<td>Actuarial survival</td>
<td>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.</td>
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| Hovels-    | 1997                | TGA                     | Case series                     | Germany n = 96 Mean age at surgery: 7 days   | 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.
| Gurich     |                     |                         |                                 | (range 2–39 days) Mean age at follow-up: 5   |                 |                 | years (range 3–9 years)                                                                                                                                                                                                                                           |
|            |                     |                         |                                 | years)                                         |                 |                 |                                                                                                                                                                                                               |
| Hovels-    | 2001                | TGA                     | Case–control study              | Germany n = 33 Age at follow-up: 3–5 years   | 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. |
| Gurich     |                     |                         |                                 | Control group: 32 age-matched children with  |                 |                 |                                                                                                                                                                                                               |
|            |                     |                         |                                 | no congenital heart defects                       |                 |                 |                                                                                                                                                                                                               |

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<tr>
<td>Hovels-Gurich</td>
<td>2002</td>
<td>TGA</td>
<td>Case series</td>
<td>Germany n = 60 Age at follow-up: 10 years (range 8–14 years)</td>
<td>Mean 5 years (since previous assessment), mean 10 years since surgery</td>
<td>Neurodevelopment; cognitive outcome; predictive factors</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Hovels-Gurich</td>
<td>2002</td>
<td>TGA</td>
<td>Case series</td>
<td>Germany n = 60 Age at follow-up: 10 years (range 8–14 years)</td>
<td>Mean 5 years (since previous assessment), mean 10 years since surgery</td>
<td>Behaviour</td>
<td>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)</td>
<td>Parent-reported behavioural outcome was worse, whereas quality of life on self-reported IQCL scores was not reduced compared with the normal population</td>
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<td>Hraska</td>
<td>1999</td>
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<td>Case series</td>
<td>Slovakia Group 1 (Senning repair) n = 21 Group 2 (Switch repair) n = 20 Mean age at surgery: Group 1 = 135 days Group 2 = 15 days</td>
<td>Mean 3 years (range 0–6 years)</td>
<td>Actuarial survival; exercise capacity</td>
<td>Follow-up of children operated in a single centre with comparison of mortality and exercise outcomes after two surgical techniques</td>
<td>94% survival at 5 years for combined group. All children receiving arterial Switch repair were in NYHA Class I at follow-up</td>
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<td>Hucin114</td>
<td>2000</td>
<td>TGA</td>
<td>Case series</td>
<td>Czech Republic, n = 177, Age at surgery: &lt;1 year</td>
<td>12–18 years</td>
<td>Exercise capacity; neuro-development</td>
<td>Case series of children who underwent Mustard operation at single centre from 1979 to 1984. Cardiac function and exercise test recorded at follow-up</td>
<td>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</td>
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<tr>
<td>Huysmans133</td>
<td>1989</td>
<td>COA</td>
<td>Case series</td>
<td>The Netherlands, n = 30, Age at surgery: &lt;3 years</td>
<td>Mean 22 years (range 15–34 years)</td>
<td>Exercise capacity</td>
<td>30 children of 121 who underwent surgical repair at a single centre attended for follow-up, including cardiac imaging and exercise tests</td>
<td>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</td>
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<td>Isomatsu459</td>
<td>2001</td>
<td>COA</td>
<td>Case series</td>
<td>Japan, n = 79, Median age at surgery: 28 days (range 4–90 days)</td>
<td>Mean 9 years (range 2–18 years)</td>
<td>Actuarial survival</td>
<td>Review of outcomes after two-stage surgery at a single centre from 1984 to 1998</td>
<td>Actuarial survival was 92% at 10 years</td>
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<td>Jonas221</td>
<td>1994</td>
<td>HLH</td>
<td>Case series</td>
<td>USA, n = 78</td>
<td>Not reported</td>
<td>Predictive factors</td>
<td>Retrospective study of patients who underwent palliative surgery in a single centre from 1983 to 1991 to identify predictors of mortality</td>
<td>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</td>
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<td>Kappetein132</td>
<td>1993</td>
<td>COA</td>
<td>Case–control</td>
<td>The Netherlands, n = 30, Mean age at surgery: 11 months Control group: 30 age- and sex-matched students without congenital heart defects</td>
<td>Mean 22 years (14–33 years)</td>
<td>Exercise capacity</td>
<td>Clinical imaging investigation and bicycle exercise testing at follow-up in patients who underwent COA repair and a control group</td>
<td>Narrowing at the site of COA surgery on digital imaging (but not MRI) correlated significantly with exercise hypertension</td>
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<td>Karl460</td>
<td>1992</td>
<td>TOF</td>
<td>Case series</td>
<td>Australia ( n = 366 ) Mean age at surgery: 15 months</td>
<td>Mean 3 years</td>
<td>Actuarial survival</td>
<td>Review of outcomes in children who underwent surgery in a single centre from 1980 to 1991</td>
<td>Actuarial survival was 97% at 3 years</td>
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<tr>
<td>Kawashima150</td>
<td>1990</td>
<td>TOF</td>
<td>Case series</td>
<td>Japan ( n = 380 ) Up to 30 years after surgery</td>
<td>Up to 30 years</td>
<td>Actuarial survival; exercise capacity</td>
<td>Long-term survivors of surgery from 1956 to 1988. Late deaths, reoperation, arrhythmias and exercise capacity recorded</td>
<td>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 &gt;10 years after surgery</td>
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<tr>
<td>Keane99</td>
<td>1993</td>
<td>AS</td>
<td>Case series</td>
<td>USA ( n = 462 ) Age at surgery: 25 children aged &lt;2 years; mean age 10 years for remaining 432 children</td>
<td>&gt;16 years</td>
<td>Complications after surgery; actuarial survival; exercise capacity</td>
<td>Children and adults with AS diagnosed on cardiac catheterisation from 1958 to 1969 followed up at least 15 years later. Children aged &lt;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</td>
<td>85% survival at 20 years overall. Children aged &gt;2 years at surgery had 90% survival at 20 years. Children aged &lt;2 years at surgery had 64% survival at 1 year. 92% survivors in NYHA Class I. Higher than normal risk of arrhythmias. Most half had valve problems at follow-up. Reported clinical status excellent in 30% and poor in 19% at follow-up</td>
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<tr>
<td>Kerdaniel-Aricè41</td>
<td>1999</td>
<td>COA</td>
<td>Case series</td>
<td>France ( n = 75 ) Age at surgery: &lt;6 months</td>
<td>Up to 19 years</td>
<td>Exercise capacity</td>
<td>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</td>
<td>2 early postoperative deaths and 2 late deaths occurred. 6 children had reoperations. In 8 of 19 children studied, exercise-induced hypertension was found</td>
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<tr>
<td>Kirjavainen (^{461})</td>
<td>1999</td>
<td>TGA</td>
<td>Finland n = 100</td>
<td>Mean 13 years</td>
<td>Actuarial survival</td>
<td>Retrospective review of outcomes in children operated in a single centre</td>
<td>Actuarial survival was 90% (simple transposition) and 78% (complex transposition)</td>
</tr>
<tr>
<td>Kirkham (^{68})</td>
<td>1998</td>
<td>All congenital heart defects</td>
<td>UK</td>
<td>Not applicable</td>
<td>Neurodevelopment</td>
<td>Review of neurodevelopment outcomes after open-heart surgery and predictive factors</td>
<td>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</td>
</tr>
<tr>
<td>Kirshbom (^{205})</td>
<td>2002</td>
<td>TAPVC</td>
<td>USA n = 100</td>
<td>Median 6 years</td>
<td>Actuarial survival; cognitive outcome</td>
<td>Medical records of children who underwent surgery from 1983 to 2001 were reviewed and a standardised questionnaire was administered to guardians of survivors</td>
<td>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</td>
</tr>
<tr>
<td>Konstantinides (^{88})</td>
<td>1991</td>
<td>ASDs</td>
<td>USA</td>
<td>Not applicable</td>
<td>Causes of death; complications after surgery</td>
<td>Review of natural history of children with ASDs</td>
<td>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</td>
</tr>
<tr>
<td>Kramer (^{183})</td>
<td>1989</td>
<td>All congenital heart defects</td>
<td>Germany n = 128</td>
<td>Not applicable</td>
<td>Cognitive outcome</td>
<td>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)</td>
<td>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</td>
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<th>Outcomes</th>
<th>Method</th>
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<tbody>
<tr>
<td>Laane</td>
<td>1997</td>
<td>All congenital heart defects</td>
<td>Sweden; $n = 200$ Age at follow-up: 6 years Control group: 400 geographical-and age-matched</td>
<td>Not applicable</td>
<td>Behaviour</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Limperopoulos</td>
<td>1999</td>
<td>All congenital heart defects</td>
<td>Canada; $n = 56$ Age at assessment: newborn</td>
<td>Not applicable</td>
<td>Neurodevelopment</td>
<td>Prospective study to determine extent of neurobehavioral abnormalities in newborns with congenital heart defects before surgery</td>
<td></td>
</tr>
<tr>
<td>Limperopoulos</td>
<td>2001</td>
<td>All congenital heart defects</td>
<td>Canada; $n = 131$ Age at assessment: preoperative, postoperative and 12–18 months after surgery</td>
<td>Not applicable</td>
<td>Neurodevelopment; 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</td>
<td></td>
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</tr>
<tr>
<td>McCarthy</td>
<td>1996</td>
<td>Congenital mitral valve anomalies</td>
<td>USA; $n = 23$ Mean age at surgery: 3 years (range 2 months–11 years)</td>
<td>Mean 4 years</td>
<td>Actuarial survival</td>
<td>Retrospective review of outcomes for children operated in a single centre from 1983 to 1994</td>
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<tr>
<td>McElhinney</td>
<td>1997</td>
<td>Complex congenital heart defects</td>
<td>USA; $n = 36$ Mean 2 years</td>
<td>Actuarial survival</td>
<td>Review of outcomes for children operated in a single centre from 1990 to 1995</td>
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<tr>
<td>Mahle</td>
<td>2000</td>
<td>HLH</td>
<td>USA; $n = 840$ Median age at surgery: 6 days (range 0–218 days)</td>
<td>Actuarial survival</td>
<td>Review of infants who underwent first stage operation from 1984 to 1999 at a single centre</td>
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<tr>
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<tr>
<td>Mahle 172</td>
<td>2000</td>
<td>HLH</td>
<td>Cross-sectional</td>
<td>USA</td>
<td>( n = 138 ) Mean age at follow-up: 9 years</td>
<td>Not applicable</td>
<td>Neurodevelopment; predictive factors</td>
<td>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</td>
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<tr>
<td>Mahle 173</td>
<td>2001</td>
<td>Complex congenital heart defects</td>
<td>Review</td>
<td>USA</td>
<td>Not applicable</td>
<td>Neurodevelopment</td>
<td>Review of perioperative factors that led to later neurodevelopmental abnormalities</td>
<td>–</td>
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<tr>
<td>Mahle 215</td>
<td>2002</td>
<td>All congenital heart defects</td>
<td>Case series</td>
<td>USA</td>
<td>( n = 24 ) Up to 1 year after surgery</td>
<td>Predictive factors</td>
<td>Study of serial MRI studies of the brain in a cohort of neonates undergoing open-heart surgery to assess neurological damage</td>
<td>Mild ischaemic lesions occur before surgery and in &gt;50% after surgery. Resolution is common by 6 months</td>
</tr>
<tr>
<td>Mahle 158</td>
<td>2002</td>
<td>TOF</td>
<td>Case series</td>
<td>USA</td>
<td>( n = 193 ) Mean age at surgery: 11 months Mean age at follow-up: 12 years</td>
<td>Not reported</td>
<td>Exercise capacity</td>
<td>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</td>
</tr>
<tr>
<td>Study</td>
<td>Year of publication</td>
<td>Congenital heart defect</td>
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<tr>
<td>Mair143</td>
<td>1997</td>
<td>PA with IVS</td>
<td>Case series</td>
<td>USA</td>
<td>Median 6 years</td>
<td>Exercise capacity</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Majnemer140</td>
<td>1999</td>
<td>All congenital heart defects</td>
<td>Review</td>
<td>Canada</td>
<td>Not applicable</td>
<td>Neurodevelopment; behaviour</td>
<td>Review of outcomes of open heart surgery in infants</td>
<td>Severe neurological sequelae are uncommon; however, mild to moderate developmental disabilities are prevalent</td>
</tr>
<tr>
<td>Malan142</td>
<td>1991</td>
<td>COA</td>
<td>Case–control</td>
<td>South Africa</td>
<td>Mean 6 years</td>
<td>Exercise capacity</td>
<td>Case series of children operated in a single centre. Graded exercise testing, blood pressure undertaken in 15 children and 11 controls</td>
<td>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</td>
</tr>
<tr>
<td>Malec216</td>
<td>1999</td>
<td>All congenital heart defects</td>
<td>Case series</td>
<td>Poland</td>
<td>Mean 3 years</td>
<td>Actuarial survival; predictive factors</td>
<td>Review of outcomes in children with Down’s syndrome who underwent heart surgery in a single centre from 1990 to 1997</td>
<td>The total death rate was 6%. Survivors were in NYHA Class I or II</td>
</tr>
<tr>
<td>Malec127</td>
<td>2000</td>
<td>HLH</td>
<td>Case series</td>
<td>Poland</td>
<td>Not reported</td>
<td>Exercise capacity</td>
<td>Consecutive case series of children undergoing Norwood operation in 1997–98 at a single centre. Operative factors recorded. Outcomes included deaths and exercise capacity</td>
<td>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</td>
</tr>
<tr>
<td>Study</td>
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<tr>
<td>Mandelik&lt;sup&gt;163&lt;/sup&gt; 1994</td>
<td>ASD</td>
<td>Case series</td>
<td>USA</td>
<td>( n = 127 ) &lt;br&gt; Age: 9 years &lt;br&gt;(range 4 months–20 years) at surgery</td>
<td>(-12\text{–}35) years after surgery</td>
<td>Exercise capacity</td>
<td>Children who underwent atrial septal defect repair from 1957 to 1980 were followed up and survival and exercise capacity recorded &lt;br&gt;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</td>
<td></td>
</tr>
<tr>
<td>Masi&lt;sup&gt;189&lt;/sup&gt; 1996</td>
<td>All congenital heart defects</td>
<td>Review</td>
<td>Italy</td>
<td>Not applicable</td>
<td>Behaviour</td>
<td>Review of psychological implications of chronic disease in children and adolescents and their families</td>
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<tr>
<td>Masi&lt;sup&gt;192&lt;/sup&gt; 1999</td>
<td>All congenital heart defects</td>
<td>Review</td>
<td>Italy</td>
<td>Not applicable</td>
<td>Behaviour</td>
<td>Review of the emotional development of adolescents with congenital heart defects, including impact on interactions with family and body image</td>
<td></td>
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</tr>
<tr>
<td>Masuda&lt;sup&gt;465&lt;/sup&gt; 1999</td>
<td>Complex congenital heart defects</td>
<td>Case series</td>
<td>Japan</td>
<td>( n = 27 ) &lt;br&gt;Mean age at surgery: 5 months &lt;br&gt;(range 10 days–5 years)</td>
<td>Not reported</td>
<td>Actuarial survival</td>
<td>Review of outcomes in patients who underwent surgery from 1986 to 1997 at a single centre &lt;br&gt;Actuarial survival rate was 83% at 9 years</td>
<td></td>
</tr>
<tr>
<td>Masuda&lt;sup&gt;466&lt;/sup&gt; 2001</td>
<td>All congenital heart defects</td>
<td>Case series</td>
<td>Japan</td>
<td>( n = 856 )</td>
<td>Not reported</td>
<td>Actuarial survival</td>
<td>Review of longer term outcomes in all patients receiving cardiac surgery at a single centre over 24 years &lt;br&gt;Actuarial survival was 98% in TOF; 86% in atrioventricular canal defect and 90% in TGA at 15 years</td>
<td></td>
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</tbody>
</table>
| Matthys148 | 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 |
| Mehta67    | 2000                | VSD                     | Review     | USA 
  n = 124  
  Up to 5 years old | Natural history | 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 |
| Meijboom146 | 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 |
| Merlo68    | 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 |
| Messmer69  | 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 |

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<tr>
<td>Miller(^{230}) 1995</td>
<td>All congenital heart defects</td>
<td>Case series</td>
<td>USA (n = 91)</td>
<td>Age at surgery: neonates</td>
<td>Until hospital discharge</td>
<td>Predictive factors</td>
<td>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</td>
<td>Mortality and neurological morbidity may be due to type of lesion, pre-existing brain abnormalities, duration of deep hypothermia and strokes</td>
</tr>
<tr>
<td>Miller(^{171}) 1996</td>
<td>All congenital heart defects</td>
<td>Case series</td>
<td>USA (n = 104)</td>
<td>Age at surgery: neonates</td>
<td>2 years</td>
<td>Neurodevelopment; predictive factors</td>
<td>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</td>
<td>Mean IQ was 90, and 78% had scores above 70. Neurological morbidity was related to type of lesion, duration of hypothermia, preoperative congenital and acquired lesions and possible perioperative cerebrovascular events</td>
</tr>
<tr>
<td>Miller(^{214}) 1999</td>
<td>All congenital heart defects</td>
<td>Review</td>
<td>USA</td>
<td>Not applicable</td>
<td>Predictive factors</td>
<td>Review of causes of neurological deficit and methods of measuring</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Morris(^{103}) 1991</td>
<td>TOF, VSD, ASD, COA, AS, PS, TGA, PDA</td>
<td>Case series</td>
<td>USA (n = 94)</td>
<td>Age at surgery: (&lt;18) years</td>
<td>Up to 25 years</td>
<td>Actuarial survival</td>
<td>Children operated for 8 types of congenital heart defects from 1958 to 1989 in a single centre</td>
<td>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 &lt;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)</td>
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<tr>
<td>Mosca470</td>
<td>1997</td>
<td>Complex congenital heart defects</td>
<td>Case series</td>
<td>USA $n = 38$ Mean age at surgery: 15 days</td>
<td>Mean 3 years</td>
<td>Actuarial survival</td>
<td>Review of outcomes in patients who underwent a modified Norwood procedure from 1987 to 1996 at a single centre</td>
<td>Actuarial survival was 89% at 1 month, 82% at 1 year and 71% at 5 years</td>
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<tr>
<td>Mukherjee194</td>
<td>2000</td>
<td>Not applicable</td>
<td>Cross-sectional study</td>
<td>USA $n$ (pupils) = 33, $n$ (parents) = 58, $n$ (teachers) = 34</td>
<td>Not applicable</td>
<td>Behaviour</td>
<td>Qualitative study investigating the support needs of pupils with chronic illness or disability in mainstream school. Data were collected from pupils, parents and teachers</td>
<td>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</td>
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<tr>
<td>Murphy471</td>
<td>1990</td>
<td>ASD</td>
<td>Case series</td>
<td>USA $n = 123$ Age at surgery: all Control group: age- and sex-matched</td>
<td>27–32 years after surgery</td>
<td>Actuarial survival</td>
<td>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</td>
<td>Overall actuarial survival rate among survivors of the perioperative period was 74% compared with 85% for controls. When repair was performed in patients &gt;25 years, late cardiac failure, stroke and atrial fibrillation were significantly more frequent</td>
</tr>
<tr>
<td>Myridakis472</td>
<td>1994</td>
<td>TGA</td>
<td>Case series</td>
<td>USA $n = 85$ (63 simple transposition, 22 complex transposition) Age at surgery: 2 days–17 years</td>
<td>10–20 years</td>
<td>Actuarial survival</td>
<td>Follow-up of children who underwent Mustard operation at a single centre from 1971 to 1981</td>
<td>Actuarial survival rate was 86% at 15 years for simple and 64% for complex TGA</td>
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<td>Najm473</td>
<td>1997</td>
<td>PA with IVS</td>
<td>Case series</td>
<td>Canada $n = 22$ Mean age at surgery: 6 years</td>
<td>Mean 4 years (range 1–12 years)</td>
<td>Actuarial survival</td>
<td>Review of children who underwent surgery at a single centre from 1980 to 1994</td>
<td>Actuarial survival was 80% at 10 years</td>
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<tr>
<td>Najm</td>
<td>1997</td>
<td>CAVSD</td>
<td>Case series</td>
<td>Canada n = 363; Median age at surgery: 8 months</td>
<td>10 years</td>
<td>Actuarial survival</td>
<td>Review of outcomes in children who underwent surgery at a single centre from 1982 to 1995</td>
<td>Actuarial survival was 83% at 10 years. Operative mortality was 10%</td>
</tr>
<tr>
<td>Najm</td>
<td>1998</td>
<td>ASD</td>
<td>Case series</td>
<td>Canada n = 180; Mean age at surgery: 5 years (range 1 month–16 years)</td>
<td>Mean 6 years (range 2 months–14 years)</td>
<td>Actuarial survival</td>
<td>Review of outcomes in children who underwent surgery at a single centre from 1982 to 1996. One-fifth of children presented with severe symptoms or heart failure</td>
<td>Actuarial survival was 98% at 10 years</td>
</tr>
<tr>
<td>Newburger</td>
<td>2003</td>
<td>TGA</td>
<td>Case series</td>
<td>USA n = 160; Age at surgery: &lt;1 year</td>
<td>Mean follow-up: 8 years</td>
<td>Cognitive outcome; predictive factors</td>
<td>Children who underwent surgery in infancy were evaluated for cognitive outcome at 8 years old</td>
<td>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</td>
</tr>
<tr>
<td>Niederhuser</td>
<td>1992</td>
<td>PA with IVS</td>
<td>Case series</td>
<td>Switzerland n = 26; Mean age at surgery: 10 days</td>
<td>Mean 11 years after surgery</td>
<td>Actuarial survival; exercise capacity</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Nieminen</td>
<td>2003</td>
<td>All congenital heart defects</td>
<td>Cohort study</td>
<td>Finland n = 6336 (of 6461 operations)</td>
<td>Mean 22 years (range 9–45 years)</td>
<td>Actuarial survival</td>
<td>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</td>
<td>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</td>
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<tr>
<td>Nollert</td>
<td>1997</td>
<td>TOF</td>
<td>Case series</td>
<td>Germany&lt;br&gt; n = 658&lt;br&gt; Mean age at surgery: 12 years (&lt;br&gt;range 2–67 years)</td>
<td>20–36 years after surgery</td>
<td>Actuarial survival; predictive factors</td>
<td>Patients who underwent surgery at a single centre from 1958 to 1977 were followed up to evaluate long-term survival and outcomes</td>
<td>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</td>
</tr>
<tr>
<td>Norgaard</td>
<td>1999</td>
<td>TOF</td>
<td>Case series</td>
<td>Denmark&lt;br&gt; n = 185&lt;br&gt; Median age at operation: 13 years (&lt;br&gt;range 20–38 years)</td>
<td>25.5 years after surgery</td>
<td>Exercise capacity</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Oechslin</td>
<td>1999</td>
<td>TOF</td>
<td>Case series</td>
<td>Canada&lt;br&gt; n = 60&lt;br&gt; Mean age at surgery: 9 years&lt;br&gt; Mean age at reoperation: 33 years</td>
<td>Mean 5 years after reoperation</td>
<td>Actuarial survival</td>
<td>Review of outcomes in consecutive adults referred for reoperation from 1975 to 1997 at a single centre</td>
<td>Actuarial survival is 92% at 10 years. At most recent follow-up, 93% of patients were in NYHA Class I or II</td>
</tr>
<tr>
<td>Oechslin</td>
<td>2000</td>
<td>TGA</td>
<td>Case series</td>
<td>Switzerland/Canada&lt;br&gt; n = 342 (Zurich)&lt;br&gt; Mean age at surgery: 6 years (&lt;br&gt;7 days–8.5 years)&lt;br&gt; n = 478 (Toronto)&lt;br&gt; Mean age at surgery not given</td>
<td>Not given</td>
<td>Causes of death; actuarial survival; exercise capacity</td>
<td>Follow-up of the first children to have the arterial Switch operation in Zurich and Mustard operation in Toronto. Deaths and exercise capacity reported</td>
<td>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</td>
</tr>
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<tr>
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</thead>
</table>
| Oechslin92 | 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%) |
| Onat477 | 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 |
| Ong137 | 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 |
| Otterstad76 | 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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<tbody>
<tr>
<td>Parks479</td>
<td>1995</td>
<td>COA of the aorta</td>
<td>Case series</td>
<td>USA n = 39 Mean age at surgery: 6 years (range 10 days–14 years)</td>
<td>Mean 8 years (range 1–12 years)</td>
<td>Complications after surgery</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Pawade480</td>
<td>1993</td>
<td>PA with IVS</td>
<td>Case series</td>
<td>Australia n = 48 Mean age at surgery: 3 years</td>
<td>10 years</td>
<td>Actuarial survival</td>
<td>Review of outcomes in infants admitted to a single centre for further management from 1976 to 1987</td>
<td>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</td>
</tr>
<tr>
<td>Pearson219</td>
<td>2001</td>
<td>All congenital heart defects</td>
<td>Validation study of intensive care scoring system</td>
<td>UK n = 7258 Not applicable</td>
<td>Predictive factors</td>
<td>Children admitted to paediatric intensive care were scored using the paediatric index of mortality (PIM) and the predictive value was assessed</td>
<td>The PIM score was predictive of actual mortality and not affected by standard or type of care</td>
<td></td>
</tr>
<tr>
<td>Pigula481</td>
<td>1999</td>
<td>TOF</td>
<td>Case series</td>
<td>USA n = 99 Age at surgery: 0–90 days</td>
<td>Not reported</td>
<td>Actuarial survival</td>
<td>Review of outcomes in infants who underwent surgery in a single centre</td>
<td>Actuarial survival was 94% at 1 year and 92% at 5 years</td>
</tr>
<tr>
<td>Planche482</td>
<td>1993</td>
<td>TGA</td>
<td>Case series</td>
<td>France n = 40 Mean age at surgery: Group 1: 19 days (first operation); 95 days (second operation) Group 2: 10 days (single operation)</td>
<td>Mean 5 years (Group 1) and 2 years (Group 2)</td>
<td>Actuarial survival</td>
<td>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</td>
<td>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</td>
</tr>
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<tr>
<td>Pridjian</td>
<td>1993</td>
<td>HLH, PA with IVS, TA,</td>
<td>Case series</td>
<td>USA n = 50 Mean age at surgery: 12 months</td>
<td>Mean 1 year</td>
<td>Actuarial survival</td>
<td>Review of outcomes in infants who underwent surgery in a single centre from 1989 to 1992</td>
<td>Actuarial survival for whole group was 92% at 1 month</td>
</tr>
<tr>
<td>Reddy</td>
<td>1996</td>
<td>TGA</td>
<td>Case series</td>
<td>USA n = 54 Age at first operation: &lt; 1 month</td>
<td>Mean 6 years</td>
<td>Exercise capacity</td>
<td>Case series that underwent Senning operation at a single centre since 1982</td>
<td>9% early surgical mortality. No late deaths. Of 49 survivors, 94% were in NYHA Class I and all had normal heart rhythm</td>
</tr>
<tr>
<td>Reddy</td>
<td>2000</td>
<td>PA with VSD</td>
<td>Case series</td>
<td>USA n = 85 Mean age at surgery: 7 months</td>
<td>1 month–6 years</td>
<td>Actuarial survival</td>
<td>Review of outcomes in infants who underwent surgery in a single centre from 1992 to 2000</td>
<td>Actuarial survival was 80% at 3 years</td>
</tr>
<tr>
<td>Reller</td>
<td>1998</td>
<td>Congenital heart defects with Down's syndrome</td>
<td>Case series</td>
<td>USA n = 3965 Age at operation: &lt; 18 years</td>
<td>Up to 20 years</td>
<td>Actuarial survival</td>
<td>Review of outcomes in infants with Down's syndrome who underwent surgery for congenital heart defects in one US state from 1958 to 1998</td>
<td>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</td>
</tr>
<tr>
<td>Reybrouck</td>
<td>1995</td>
<td>VSD, AS, PS, TOF and</td>
<td>Case–control</td>
<td>Belgium n = 79 Age: not given</td>
<td>Up to 5 years</td>
<td>Exercise capacity</td>
<td>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</td>
<td>Aerobic capacity in all groups was below normal and decreased over time in children whose exercise was restricted by the heart defect (TOF, Fontan)</td>
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<tr>
<td>Reybrouck</td>
<td>2001</td>
<td>TGA</td>
<td>Case series</td>
<td>Belgium; n = 22; Age at surgery: &lt;1 year</td>
<td>5–17 years after surgery</td>
<td>Exercise capacity</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Robinson</td>
<td>2000</td>
<td>Congenital AS</td>
<td>Case series</td>
<td>USA; n = 95; Median age at surgery: 5 days (0–191 days)</td>
<td>Mean 2 years (range 0–9 years)</td>
<td>Actuarial survival</td>
<td>Review of outcomes in infants who underwent surgery in a single centre from 1988 to 1999</td>
<td>Actuarial survival 76% at 3 years</td>
</tr>
<tr>
<td>Rogers</td>
<td>1995</td>
<td>HLH</td>
<td>Case series</td>
<td>USA; n = 11</td>
<td>Not reported</td>
<td>Neurodevelopment</td>
<td>All survivors of staged surgical repair at one children’s hospital received standardised neurodevelopmental assessments</td>
<td>Of these survivors, 64% had major developmental disabilities that affected quality of life</td>
</tr>
<tr>
<td>Ross</td>
<td>1991</td>
<td>ASD</td>
<td>Case series</td>
<td>Canada; n = 37; Mean age at surgery: 2 years</td>
<td>Not reported</td>
<td>Actuarial survival</td>
<td>Review of outcomes in infants who underwent surgery in a single centre from 1986 to 1990</td>
<td>Actuarial survival was 88% at 3 years. All survivors in NYHA Class I or II</td>
</tr>
<tr>
<td>Rubay</td>
<td>1992</td>
<td>COA</td>
<td>Case series</td>
<td>Belgium; n = 146; Median age at surgery: 1 month (2 days–11 months)</td>
<td>Not reported</td>
<td>Actuarial survival</td>
<td>Review of outcomes in infants who underwent surgery in a single centre from 1976 to 1991</td>
<td>Actuarial survival was 100% at 10 years (isolated COA), 94% at 10 years (COA with VSD) and 62% at 10 years (complex anomalies)</td>
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<tr>
<td>Rubay</td>
<td>1999</td>
<td>Congenital AS</td>
<td>Case series</td>
<td>Belgium n = 80 (of which 57 congenital defects and 27 children) Mean age at surgery: 31 years (adults and children)</td>
<td>Not reported</td>
<td>Actuarial survival</td>
<td>Review of outcomes in infants who underwent surgery in a single centre from 1991 to 1997</td>
<td>Actuarial survival was 98% at 5 years. All survivors in NYHA Class I</td>
</tr>
<tr>
<td>Ruttenberg</td>
<td>1999</td>
<td>COA</td>
<td>Review</td>
<td>USA</td>
<td>Not applicable</td>
<td>Exercise capacity</td>
<td>Review of exercise studies in children with COA of the aorta</td>
<td>Oxygen consumption/exercise tests normal in children after surgery</td>
</tr>
<tr>
<td>Samanek</td>
<td>1999</td>
<td>All congenital heart defects</td>
<td>Cohort study</td>
<td>Czech Republic n = 5030 Age at death: 0–15 years old</td>
<td>Up to 15 years</td>
<td>Causes of death; actuarial survival</td>
<td>Prospective study of children with confirmed congenital heart defects born 1980–90 and dying before the age of 15 years</td>
<td>Actuarial survival for operated and unoperated cases calculated for different defects</td>
</tr>
<tr>
<td>Samango-Sprouse</td>
<td>1997</td>
<td>All congenital heart defects</td>
<td>Review</td>
<td>USA</td>
<td>Not applicable</td>
<td>Predictive factors</td>
<td>Review of behaviour and neurological sequelae following surgery for congenital heart defects</td>
<td>Length of circulatory arrest and pH management during surgery are associated with IQ</td>
</tr>
<tr>
<td>Sano</td>
<td>1995</td>
<td>Congenitally corrected TGA</td>
<td>Case series</td>
<td>Australia n = 28</td>
<td>Median 5 years</td>
<td>Actuarial survival</td>
<td>Review of children who underwent surgery at a single centre</td>
<td>Actuarial survival was 89% at 1 year; 83% at 5 years and 83% at 10 years. All survivors in NYHA Class I or II</td>
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</table>
| 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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| Shinoka494 | 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 |
| Sohn495 | 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 |
| Sousa118 | 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 |
| Stellin496 | 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 |
| Suominen224 | 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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<tr>
<td>Tchervenkov&lt;sup&gt;197&lt;/sup&gt; 1998</td>
<td>IAA</td>
<td>Case series</td>
<td>Canada</td>
<td>$n = 40$; Median age at surgery: 17 days</td>
<td>Mean 3 years</td>
<td>Actuarial survival</td>
<td>Review of outcomes in children who underwent surgery at a single centre from 1988 to 1997</td>
<td>Actuarial survival was 89% at 8 years</td>
</tr>
<tr>
<td>Thies&lt;sup&gt;162&lt;/sup&gt; 1991</td>
<td>Atrio-ventricular septal defect</td>
<td>Case series</td>
<td>Germany</td>
<td>$N = 40$; Age at surgery: 4 months (1–12 months)</td>
<td>Mean 22 months (3–46 months)</td>
<td>Exercise capacity</td>
<td>Outcomes after surgical repair during first year of life in a single centre. Surgical complications, deaths, exercise capacity and growth recorded</td>
<td>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</td>
</tr>
<tr>
<td>Thompson&lt;sup&gt;198&lt;/sup&gt; 2001</td>
<td>Tuncus</td>
<td>Case series</td>
<td>USA</td>
<td>$n = 65$; Median age at surgery: 10 days</td>
<td>Median 3 years</td>
<td>Actuarial survival</td>
<td>Review of outcomes in children who underwent surgery at a single centre from 1992 to 1999</td>
<td>Actuarial survival was 92% at 1 year</td>
</tr>
<tr>
<td>Thu&lt;sup&gt;136&lt;/sup&gt; 1999</td>
<td>COA of the aorta</td>
<td>Case series</td>
<td>Norway</td>
<td>$n = 102$; Range 1–21 years</td>
<td>Range 1–21 years</td>
<td>Exercise capacity</td>
<td>Survivors of surgical repair from 1975 to 1995 were sent a postal questionnaire asking about symptoms and exercise capacity</td>
<td>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</td>
</tr>
<tr>
<td>Tlaskal&lt;sup&gt;82&lt;/sup&gt; 1998</td>
<td>IAA</td>
<td>Case series</td>
<td>Czech Republic</td>
<td>$n = 40$; Age at operation: &lt;1 year</td>
<td>Mean 5 years</td>
<td>Exercise capacity; predictive factors</td>
<td>Mortality and clinical status for two groups – primary surgical repair ($n = 19$) or two-stage repair ($n = 21$) – were compared</td>
<td>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</td>
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<tr>
<td>Trinquet \cite{21}</td>
<td>1988</td>
<td>COA</td>
<td>Case series</td>
<td>France; ( n = 178 ); Age at surgery: &lt;3 months</td>
<td>Mean 3 years</td>
<td>Actuarial survival; predictive factors</td>
<td>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)</td>
<td>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</td>
</tr>
<tr>
<td>Turner \cite{1999}</td>
<td>1999</td>
<td>VSD</td>
<td>Cohort study</td>
<td>UK; ( n = 68 ); Mean 6 years</td>
<td>Natural history</td>
<td>Follow-up of a cohort of children with VSDs to correlate size and position with closure rate</td>
<td>Of all defects, 35 closed spontaneously. After more than 6 years one-third of perimembranous and two thirds of muscular defects closed spontaneously</td>
<td></td>
</tr>
<tr>
<td>Tweddell \cite{500}</td>
<td>1996</td>
<td>CAVSD</td>
<td>Case series</td>
<td>USA; ( n = 115 ); Mean age at surgery: 2 years (&gt;1 year old before 1982 and &lt;1 year old after 1982)</td>
<td>Up to 11 years after surgery</td>
<td>Actuarial survival</td>
<td>Retrospective review of pre-, intra- and postoperative factors and outcomes in patients who underwent surgery at a single centre from 1974 to 1993</td>
<td>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</td>
</tr>
<tr>
<td>Tworetzky \cite{22}</td>
<td>2001</td>
<td>HLH</td>
<td>Case series</td>
<td>USA; ( n = 88 ); Not reported</td>
<td>Predictive factors</td>
<td>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</td>
<td>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</td>
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<tr>
<td>Urban</td>
<td>1998</td>
<td>Truncus</td>
<td>Case series</td>
<td>Germany, n = 46; Mean age at surgery: 2 months (21 days–7 years)</td>
<td>Mean 3 years (3 months–10 years)</td>
<td>Actuarial survival</td>
<td>Review of outcomes in consecutive patients who underwent surgery from 1987 to 1997</td>
<td>Actuarial survival was 93% at 4 months and 10 years. Survival until hospital discharge in all patients was 95% and in uncomplicated truncus was 100%</td>
</tr>
<tr>
<td>Utens</td>
<td>1993</td>
<td>All congenital heart defects</td>
<td>Cross-sectional survey</td>
<td>The Netherlands, n = 144 parents, 179 adolescents; Age at follow-up: 10–17 years</td>
<td>&gt;9 years after surgery</td>
<td>Behaviour</td>
<td>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)</td>
<td>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</td>
</tr>
<tr>
<td>Utens</td>
<td>1994</td>
<td>All congenital heart defects</td>
<td>Cross-sectional survey</td>
<td>The Netherlands, n = 288; Age at follow-up: 10–17 years</td>
<td>Mean 16 years after surgery</td>
<td>Behaviour</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Utens</td>
<td>1998</td>
<td>All congenital heart defects</td>
<td>Cross-sectional survey</td>
<td>The Netherlands, n = 125; Age at follow-up: 10–15 years</td>
<td>Not applicable</td>
<td>Behaviour</td>
<td>Study to investigate behavioural/emotional problems in children using parent-reported Child Behavior Checklist (CBCL)</td>
<td>Higher CBCL total problem scores were associated with a greater number of operations and circulatory arrest during surgery</td>
</tr>
<tr>
<td>Utens</td>
<td>2000</td>
<td>All congenital heart defects</td>
<td>Cross-sectional survey</td>
<td>The Netherlands, n = 75</td>
<td>Not applicable</td>
<td>Behaviour</td>
<td>Study to assess the psychological distress and coping styles of parents of children with congenital heart defects. Standardised questionnaires completed 4 weeks before surgery</td>
<td>Higher levels of psychological distress, and poor styles of coping, were found in study parents, especially mothers, compared with reference groups</td>
</tr>
</tbody>
</table>

continued
<table>
<thead>
<tr>
<th>Study</th>
<th>Year of publication</th>
<th>Congenital heart defect</th>
<th>Study type</th>
<th>Country; sample size (n); age range; controls</th>
<th>Follow-up period</th>
<th>Outcomes</th>
<th>Method</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Arsdel[57]</td>
<td>2000</td>
<td>TOF</td>
<td>Case series</td>
<td>USA (n = 227) Age at operation: (\text{Group 1} = 17 \text{ months, Group 2} = 8 \text{ months})</td>
<td>Up to 9 years after surgery</td>
<td>Exercise capacity</td>
<td>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 &lt;6 months of age to 9 years after surgery</td>
<td>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</td>
</tr>
<tr>
<td>Veldman[93]</td>
<td>2000</td>
<td>All congenital heart defects</td>
<td>Qualitative survey</td>
<td>UK (n = 69) Age at assessment: 7–18 years</td>
<td>Not applicable</td>
<td>Behaviour</td>
<td>Prospective study to evaluate illness knowledge and understanding in children with heart disease, related to age, sex or complexity of the heart disease</td>
<td>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</td>
</tr>
<tr>
<td>Verheijen[22]</td>
<td>2001</td>
<td>All congenital heart defects</td>
<td>Case series</td>
<td>The Netherlands (n = 408) Age at surgery: &lt;31 days</td>
<td>Until hospital discharge</td>
<td>Predictive factors</td>
<td>Retrospective study compared the occurrence of preoperative metabolic acidosis in patients with and without prenatal diagnosis of congenital heart defects</td>
<td>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</td>
</tr>
<tr>
<td>von Bernuth[22]</td>
<td>2000</td>
<td>TGA</td>
<td>Case series</td>
<td>Germany (n = 188) Age at surgery: (6 \text{ days (simple transposition), 9 days (complex)})</td>
<td>Mean 6 years after surgery</td>
<td>Actuarial survival; exercise capacity; neurodevelopment</td>
<td>Follow-up of case series of children receiving surgery in neonatal period, including deaths, neurodevelopmental outcome and exercise tests</td>
<td>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</td>
</tr>
</tbody>
</table>

continued
<table>
<thead>
<tr>
<th>Study</th>
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<th>Congenital heart defect</th>
<th>Study type</th>
<th>Country; sample size (n); age range; controls</th>
<th>Follow-up period</th>
<th>Outcomes</th>
<th>Method</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visconti</td>
<td>1999</td>
<td>ASD</td>
<td>Case–control study</td>
<td>USA (n = 26) (surgery), 19 (transcatheter) Mean age at surgery: 6 years Mean age at follow-up: 10 years (surgery), 12 years (transcatheter)</td>
<td>4–6 years after intervention</td>
<td>Cognitive outcome</td>
<td>Standardised neuropsychological testing was performed on children after closure of ASD through surgery or transcatheter device</td>
<td>IQ and achievement scores were in the normal range for both groups. Some differences noted on subscores but inconclusive</td>
</tr>
<tr>
<td>Wernovsky</td>
<td>2003</td>
<td>All congenital heart defects</td>
<td>Review</td>
<td>USA</td>
<td>Not applicable</td>
<td>Neurodevelopment</td>
<td>Editorial review of neurodevelopmental outcomes in children with complex congenital heart defects</td>
<td>--</td>
</tr>
<tr>
<td>Wetter</td>
<td>2001</td>
<td>TGA</td>
<td>Case series</td>
<td>Germany (n = 105) Median age at surgery: 24 days</td>
<td>Median 6 years after surgery</td>
<td>Actuarial survival; exercise capacity</td>
<td>Risk factors at the time of surgery were related to later follow-up. Outcomes reported were deaths, reoperation and exercise capacity</td>
<td>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</td>
</tr>
<tr>
<td>Williams</td>
<td>1980</td>
<td>COA</td>
<td>Case series</td>
<td>USA (n = 191) Age at surgery: &lt;1 year</td>
<td>Not reported</td>
<td>Actuarial survival; neurodevelopment</td>
<td>Follow-up of infants who underwent surgery during a 14-year period in a single centre</td>
<td>The 5-year mortality rate was 25%. Hypertension developed in 27% of the children followed more than 5 years after repair</td>
</tr>
<tr>
<td>Williams</td>
<td>2000</td>
<td>HLH</td>
<td>Case series and cross-sectional survey</td>
<td>USA (n = 106) (stage I = 106; stage II = 49; stage III = 25; 4 transplantations)</td>
<td>Not reported</td>
<td>Actuarial survival; neurodevelopment</td>
<td>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</td>
<td>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</td>
</tr>
</tbody>
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**continued**
<table>
<thead>
<tr>
<th>Study</th>
<th>Year of publication</th>
<th>Congenital heart defect</th>
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<th>Method</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson⁵⁰³</td>
<td>1998</td>
<td>TGA</td>
<td>Case series</td>
<td>USA (n = 113)</td>
<td>Up to 28 years</td>
<td>Actuarial survival</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Wray ⁸⁶</td>
<td>2001</td>
<td>All congenital heart defects</td>
<td>Case–control study</td>
<td>UK (n = 47) Age at assessment: 3–17 years. Two control groups: healthy children ((n = 51)) and children awaiting bone marrow transplantation ((n = 51))</td>
<td>1 year after surgery</td>
<td>Cognitive outcome</td>
<td>Prospective study in which children were assessed immediately before surgery and 12 months later to evaluate changes in cognitive functioning</td>
<td>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</td>
</tr>
<tr>
<td>Wray ⁷⁷</td>
<td>1999</td>
<td>All congenital heart defects</td>
<td>Case–control study</td>
<td>UK (n = 25) Age at assessment: 0–3 years. Two control groups: healthy children ((n = 15)) and children awaiting bone marrow transplantation ((n = 15))</td>
<td>1 year after surgery</td>
<td>Neurodevelopment; cognitive outcome</td>
<td>Three groups of children &lt; 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</td>
<td>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</td>
</tr>
<tr>
<td>Study</td>
<td>Year of publication</td>
<td>Congenital heart defect</td>
<td>Study type</td>
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<td>Main results</td>
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<tr>
<td>Wren96</td>
<td>2000</td>
<td>All congenital heart defects</td>
<td>Review of deaths</td>
<td>UK $n = 2523$ deaths Age at death: 1–20 years</td>
<td>Not applicable</td>
<td>Causes of death</td>
<td>A review of all sudden deaths at age 1–20 years in one English health region from 1985 to 1994</td>
<td>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.</td>
</tr>
<tr>
<td>Wren12</td>
<td>2001</td>
<td>All congenital heart defects</td>
<td>Cohort study</td>
<td>UK $n = 1942$ Age at diagnosis: &lt; 1 year old</td>
<td>15 years</td>
<td>Actuarial survival</td>
<td>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</td>
<td>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 underascertainment). 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.</td>
</tr>
<tr>
<td>Wren93</td>
<td>2002</td>
<td>All congenital heart defects</td>
<td>Review of deaths</td>
<td>UK</td>
<td>Not applicable</td>
<td>Causes of death</td>
<td>Review of literature concerning causes of sudden death in childhood</td>
<td>–</td>
</tr>
<tr>
<td>Zafra504</td>
<td>1993</td>
<td>Congenital AS</td>
<td>Case series</td>
<td>Spain $n = 107$ Mean age at surgery: 6 years (range 14 days–15 years)</td>
<td>Mean 5 years</td>
<td>Actuarial survival</td>
<td>Follow-up of children who underwent surgery in a single centre from 1969 to 1989</td>
<td>Actuarial survival of 95% at the age of 15 years</td>
</tr>
<tr>
<td>Study</td>
<td>Year of publication</td>
<td>Congenital heart defect</td>
<td>Study type</td>
<td>Country; sample size (n); age range; controls</td>
<td>Follow-up period</td>
<td>Outcomes</td>
<td>Method</td>
<td>Main results</td>
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<tr>
<td>Zehr505</td>
<td>1995</td>
<td>COA</td>
<td>Case series</td>
<td>USA $n = 179$ Age at surgery: &lt;1 year (majority &lt;3 months)</td>
<td>Not reported</td>
<td>Actuarial survival</td>
<td>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)</td>
<td>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</td>
</tr>
<tr>
<td>Zobel231</td>
<td>1993</td>
<td>All congenital heart defects</td>
<td>Case series</td>
<td>Austria $n = 441$ (128 developed cardiopulmonary insufficiency and were followed up)</td>
<td>Until hospital discharge</td>
<td>Predictive factors</td>
<td>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</td>
<td>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</td>
</tr>
</tbody>
</table>
## Appendix 3

### Actuarial survival and causes of death for different malformations

<table>
<thead>
<tr>
<th>Malformation</th>
<th>Actuarial survival</th>
<th>Main complications and causes of death</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TGA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>78–90% 5 years</td>
<td>Sudden cardiac death&lt;sup&gt;86,92,93&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>65–67% 15 years</td>
<td>Congestive heart failure&lt;sup&gt;92&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>90% 10–15 years</td>
<td>Reoperation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>84% 18 years</td>
<td>PVOD</td>
<td></td>
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<tr>
<td></td>
<td>82% 20 years</td>
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<tr>
<td></td>
<td>80% 20 years</td>
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<tr>
<td></td>
<td>75% 25 years</td>
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<tr>
<td></td>
<td>49% 30 years</td>
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<tr>
<td></td>
<td>Worse if:</td>
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<tr>
<td></td>
<td>Mustard operation</td>
<td></td>
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<tr>
<td></td>
<td>78% 3 years</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>64% 10 years</td>
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<td></td>
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<tr>
<td></td>
<td>67% 20 years</td>
<td></td>
<td></td>
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<tr>
<td><strong>AS</strong></td>
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</tr>
<tr>
<td></td>
<td>76% 3 years</td>
<td>Sudden cardiac death&lt;sup&gt;86,92,93&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>95–98% 5 years</td>
<td>Infective endocarditis&lt;sup&gt;98,99,102&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>73% 10 years</td>
<td>Reoperation in 20%&lt;sup&gt;99&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>90% 10 years</td>
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<tr>
<td></td>
<td>90% 15 years</td>
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<tr>
<td></td>
<td>85–87% 20 years</td>
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<td></td>
<td>Worse if:</td>
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<tr>
<td></td>
<td>Critical AS</td>
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<tr>
<td></td>
<td>70–80% 10 years</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>37% 15 years</td>
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<tr>
<td><strong>TAPVC</strong></td>
<td></td>
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<tr>
<td></td>
<td>23% 5 years (operated)&lt;sup&gt;93&lt;/sup&gt;</td>
<td>Congestive heart failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>42% 10 years (operated)&lt;sup&gt;93&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>73% 10 years</td>
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<tr>
<td></td>
<td>70% 15 years</td>
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<tr>
<td></td>
<td>84% 15 years</td>
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<td></td>
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<tr>
<td></td>
<td>Worse if:</td>
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<tr>
<td></td>
<td>Obstructed TAPVC, associated cardiac lesions, preoperative collapse</td>
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</tbody>
</table>

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<sup>continued</sup>
<table>
<thead>
<tr>
<th>Malformation</th>
<th>Actuarial survival</th>
<th>Main complications and causes of death</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLH</td>
<td>33–59% 1 year</td>
<td></td>
<td>Other studies agree with survival 40–60% after operation[9,21,79,128]</td>
</tr>
<tr>
<td></td>
<td>58% survival to school age[178,179,433]</td>
<td></td>
<td>Few long-term studies as ‘new’ operation;</td>
</tr>
<tr>
<td></td>
<td>0% 15 years[12]</td>
<td></td>
<td>Antenatal diagnosis affects choice of palliative care and termination[72]</td>
</tr>
<tr>
<td></td>
<td>40% 15 years[78,464]</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Worse if: Unoperated (60 days)[458]</td>
<td></td>
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<tr>
<td>MA (MA is often classified as a univentricular heart, complex heart defect or severe HLH)</td>
<td>32% 15 years[12]</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>45% 15 years (for all univentricular hearts)[77]</td>
<td></td>
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</tr>
<tr>
<td>COA</td>
<td>90% 5 years[211,444]</td>
<td>Sudden cardiac death[86,92,93]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>90–100% 10 years</td>
<td>Reoperation for recurrent COA in 14–54%[490]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>86% 15 years[12]</td>
<td>Systemic hypertension in 17–27%[135,40,490]</td>
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</tr>
<tr>
<td></td>
<td>92% 15 years[77]</td>
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<tr>
<td></td>
<td>58% 27 years[505]</td>
<td></td>
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<tr>
<td></td>
<td>40–60% 5–10 years (complex)[211,467]</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Worse if: COA presenting in newborn</td>
<td></td>
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<tr>
<td>IAA</td>
<td>89% 8 years[497]</td>
<td>Sudden cardiac death[86,92,93]</td>
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</tr>
<tr>
<td></td>
<td>85% 12 years[451]</td>
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<tr>
<td>PA/IVS and PA/VSD</td>
<td>PA/IVS: 75% 1 year[443]</td>
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</tr>
<tr>
<td></td>
<td>77% 8 years[144,473,480]</td>
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<tr>
<td></td>
<td>31% 15 years[12]</td>
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<tr>
<td></td>
<td>PA/VSD: 80% 3 years[684]</td>
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<tr>
<td></td>
<td>48% 15 years[12]</td>
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<tr>
<td>VSD</td>
<td>64% 15 years[12]</td>
<td>PVOD</td>
<td>40–67% spontaneous closure by years of age[10,67,699]</td>
</tr>
<tr>
<td></td>
<td>83% 15 years[77]</td>
<td>Infective endocarditis[98,102,450]</td>
<td>19–25% require surgical closure by 5 years of age[67,699]</td>
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<tr>
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<td>94% 20 years[466]</td>
<td>Valve lesions occur if unoperated[78]</td>
<td>22% require follow-up after 5 years of age[67]</td>
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<td>20% close during adolescence (up to 19 years of age)[477]</td>
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continued
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<th>Malformation</th>
<th>Actuarial survival</th>
<th>Main complications and causes of death</th>
<th>Comments</th>
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<tr>
<td>TOF</td>
<td>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(^{106}) 86–89% 30 year(^{220,226,228})</td>
<td>Sudden cardiac death(^{86,92,93,156,457}) Reoperation(^{154,457,476})</td>
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</tr>
<tr>
<td>AT 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})</td>
<td>Congestive heart failure(^{216}) PVOD(^{216,436}) Atroventricular valve incompetency (10–15%)</td>
<td>Down’s syndrome is associated with 30% of AVSD</td>
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<tr>
<td>ASD</td>
<td>98% 10 years(^{475}) 84% 15 years(^{12}) 74% 30 years(^{471}) 94% 45 years(^{77})</td>
<td>Congestive heart failure(^{68}) PVOD Atrial arrhythmias(^{88})</td>
<td>Unoperated life expectancy of 50 years(^{88})</td>
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<tr>
<td>UVH</td>
<td>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})</td>
<td>Congestive heart failure</td>
<td>Actuarial survival rates vary between series depending on case mix and type of defect</td>
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<tr>
<td>Truncus arteriosus</td>
<td>80–90% &lt; 1 year(^{434,501}) 92% 1 year(^{498}) 31% 15 years(^{12})</td>
<td>Sudden cardiac death(^{86,92,93})</td>
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<tr>
<td>Congenitally corrected TGA</td>
<td>83% 10 years(^{489}) 96% 15 years(^{12})</td>
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</tr>
<tr>
<td>Miscellaneous and rare defects</td>
<td>Double outlet right ventricle(^{430,465}) Subaortic stenosis(^{493}) Congenital mitral valve defects(^{428,462,496}) Complex heart defects(^{204,433,432,444,448,470,483,492})</td>
<td>This is a mixed group for which overall survival rates cannot be given</td>
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</tr>
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Appendix 4

Screening classification for congenital heart defects
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

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 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 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 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 G: Unfavourable or transposition streaming
SHORT PRESYMPTOMATIC INTERVAL
• 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 H: Mixing with unrestricted pulmonary blood flow
MODERATE PRESYMPTOMATIC INTERVAL
• Unobstructed total anomalous pulmonary venous connection
• Univentricular heart with unrestricted pulmonary flow
• Truncus arteriosus
## Congenital heart disease classification system

### Short presymptomatic interval

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<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
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<tr>
<td><strong>Physiology</strong></td>
<td>Unfavourable streaming (transposition-streaming)</td>
<td>Duct-dependent pulmonary blood flow</td>
<td>Pulmonary venous hypertension</td>
</tr>
<tr>
<td><strong>Description</strong></td>
<td>Critical cyanosis (hypoxia) – worse if little intracardiac mixing; high pulmonary flow</td>
<td>Right ventricular outflow obstruction, right ventricular hypertrophy and right heart failure, oligaemic lungs, cyanosed body</td>
<td>Obstructed pulmonary venous return; pulmonary oedema</td>
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<table>
<thead>
<tr>
<th>Congenital heart defects included</th>
<th>PA + IVS</th>
<th>Critical PS</th>
<th>Obstructed TAPVC</th>
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<td>HLH syndrome</td>
<td>TGA + small ASD</td>
<td>Severe TOF</td>
<td>Critical mitral stenosis</td>
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<tr>
<td>Critical AS</td>
<td>TGA + VSD</td>
<td>Double-outlet right ventricle + PS</td>
<td>Severe cor triatriatum</td>
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<tr>
<td>IAA</td>
<td>Double-outlet right ventricle (transposition type)</td>
<td>UVH + TA + PA</td>
<td>Congenitally corrected TGA + PS/PA + VSD</td>
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<tr>
<td>Tight COA</td>
<td></td>
<td>Severe Ebstein's anomaly</td>
<td></td>
</tr>
<tr>
<td>Obstructed TAPVC</td>
<td></td>
<td>Congenitally corrected TGA + PS/PA + VSD</td>
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<th><strong>ICD 10 codes/OPCS4 codes</strong></th>
<th><strong>ICD 10 codes/OPCS4 codes</strong></th>
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<th><strong>Common symptoms and signs at presentation</strong></th>
<th><strong>Common symptoms and signs at presentation</strong></th>
<th><strong>Common symptoms and signs at presentation</strong></th>
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<td>Poor feeding</td>
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<td>Breathless</td>
<td>Poor feeding</td>
<td>Breathless</td>
<td>Breathless</td>
</tr>
<tr>
<td>Poor (femoral) pulses*</td>
<td>Shock</td>
<td>Cyanosis</td>
<td>Cyanosis</td>
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<tr>
<td>Cyanosis</td>
<td>Critical hypoxia</td>
<td>Murmur</td>
<td>Murmur</td>
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<tr>
<td>Shock</td>
<td>Critical hypoxia</td>
<td>Shock</td>
<td>Respiratory distress (pulmonary oedema)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
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</table>

* 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

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<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
<th>Group E</th>
<th>Group F</th>
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<td>Systemic ventricle outflow obstruction</td>
<td>Unfavourable streaming (transposition-streaming)</td>
<td>Low pulmonary blood flow</td>
<td>Pulmonary venous hypertension</td>
<td>Mixing with unrestricted pulmonary blood flow</td>
</tr>
<tr>
<td><strong>Description</strong></td>
<td>Left ventricular outflow tract obstruction</td>
<td>Cyanosis</td>
<td>Right ventricular outflow tract obstruction</td>
<td>High left atrial pressure</td>
<td>Progressive breathlessness as pulmonary vascular resistance falls; mild cyanosis</td>
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<tr>
<td><strong>Congenital heart defects included</strong></td>
<td>COA</td>
<td>TGA with large VSD</td>
<td>TOF</td>
<td>Mild/moderate mitral stenosis</td>
<td>Unobstructed TAPVC</td>
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<td></td>
<td>Moderate AS</td>
<td>Double-outlet right ventricle (Taussig–Bing type)</td>
<td>Severe PS</td>
<td>Mitral regurgitation</td>
<td>UVH with unrestricted pulmonary flow</td>
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<td>Pulmonary infundibular stenosis + VSD</td>
<td>Absent pulmonary valve</td>
<td>Cor triatriatum</td>
<td>Truncus</td>
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<td>Absent pulmonary valve Ebstein’s anomaly</td>
<td>Congenitally corrected TGA + VSD + PS</td>
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<th>Group D</th>
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<td>Congestive heart failure</td>
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## Asymptomatic in early childhood

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<td>Systemic ventricle outflow obstruction</td>
<td>Unfavourable streaming (transposition-streaming)</td>
<td>Low pulmonary blood flow</td>
<td>Pulmonary venous hypertension</td>
<td>Mixing with unrestricted pulmonary blood flow</td>
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<tr>
<td>Description</td>
<td>Left ventricular outflow obstruction</td>
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<td>Moderate or mild AS</td>
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<td>Partial anomalous pulmonary venous connection</td>
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Unlikely to present during this time period
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.
Appendix 5

Percentage of cases diagnosed

Group E

- A TAPVC
- B Truncus

Group F

- A CAVSD
- B ASD
- C Partial atrioventricular septal defect
- D VSD
- E PDA

Age at diagnosis (weeks)
Appendix 6

Prevalence of congenital heart defects by group in the screening classification
<table>
<thead>
<tr>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
<th>Group E</th>
<th>Group F</th>
</tr>
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<tbody>
<tr>
<td>Systemic ventricle outflow obstruction</td>
<td>Unfavourable streaming</td>
<td>Low pulmonary blood flow</td>
<td>Pulmonary venous hypertension</td>
<td>Mixing with unrestricted pulmonary blood flow</td>
<td>Left to right shunt</td>
</tr>
</tbody>
</table>

**Numbers**

<table>
<thead>
<tr>
<th>Total LB = 203,880</th>
<th>Total CHD = 1543 (7.6/1000)</th>
<th>Classifiable = 1420</th>
<th>Unclassifiable = 123 (Jackson[^264])</th>
</tr>
</thead>
<tbody>
<tr>
<td>COA = 72</td>
<td>TGA = 61</td>
<td>PA = 34</td>
<td>TAPVC = 32</td>
</tr>
<tr>
<td>HLH = 39</td>
<td></td>
<td>PS = 142</td>
<td>Mitral valve = 8</td>
</tr>
<tr>
<td>IAA = 11</td>
<td></td>
<td>TOF = 66</td>
<td></td>
</tr>
<tr>
<td>AS = 77</td>
<td></td>
<td>UVH = 23</td>
<td></td>
</tr>
<tr>
<td>Bicuspid = 19</td>
<td></td>
<td>Tricuspid atresia = 30</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total = 1/1000 (16%)</td>
<td>Total = 0.3/1000 (5%)</td>
<td>Total = 1.4/1000 (22%)</td>
<td>Total = 0.2/1000 (3%)</td>
</tr>
</tbody>
</table>

**Prevalence per 1000 live births**

| COA = 0.2 | TGA = 0.2 | PA = 0.1 | TAPVC = 0.1 | Truncus = 0.06 | AVSD = 0.4 |
| HLH = 0.3 | AS = 0.1  | PS = 0.2 | TOF = 0.3  | Tricuspid atresia = 0.04 | VSD = 0.9 |
| AS = 0.20 | TAPVC = 0.1 | Tricuspid atresia = 0.05 | Mitral atresia = 0.03 | |
| 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**

| COA = 0.24 | TGA = 0.30 | PA = 0.16 | TAPVC = 0.09 | Truncus = 0.09 | AVSD = 0.35 |
| HLH = 0.14 | AS = 0.20  | PS = 0.57 | TOF = 0.31  |                     | VSD = 2.38 |
| AS = 0.20  | TAPVC = 0.09 | Tricuspid atresia = 0.05 | Mitral atresia = 0.03 | |
| 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. coart$.ti,ab,kw.
7. (double adj outlet adj right adj ventricle).ti,ab,kw.
8. DORV.ti,ab,kw.
9. (double adj outlet adj2 ventricle).ti,ab,kw.
10. (endocardial adj cushion adj defect).ti,ab,kw.
11. (hypoplastic adj left adj heart).ti,ab,kw.
12. IHLS.ti,ab,kw.
14. Fontan.ti,ab,kw.
15. (interrupt$ 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.
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$).ti,ab,kw.
27. (switch adj operation).ti,ab,kw.
29. (switch adj procedure$).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
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>
<thead>
<tr>
<th>Reviewer 1</th>
<th>Eligible</th>
<th>Not eligible</th>
<th>Background</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible</td>
<td>29</td>
<td>0</td>
<td>15</td>
<td>44</td>
</tr>
<tr>
<td>Not eligible</td>
<td>1</td>
<td>191</td>
<td>39</td>
<td>231</td>
</tr>
<tr>
<td>Background</td>
<td>4</td>
<td>9</td>
<td>129</td>
<td>142</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>200</td>
<td>183</td>
<td>417</td>
</tr>
</tbody>
</table>

* Numbers in italics represent concordance between reviewers 1 and 2; numbers in bold represent disagreement on eligibility (n = 20).

* Some papers were also identified as providing useful background material, but no input data for the model.

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

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

<table>
<thead>
<tr>
<th>Reviewer 2</th>
<th>Eligible</th>
<th>Not eligible</th>
<th>Background</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligible</td>
<td>34</td>
<td>0</td>
<td>0</td>
<td>34</td>
</tr>
<tr>
<td>Not eligible</td>
<td>0</td>
<td>192</td>
<td>39</td>
<td>231</td>
</tr>
<tr>
<td>Background</td>
<td>0</td>
<td>9</td>
<td>143</td>
<td>152</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
<td>201</td>
<td>182</td>
<td>417</td>
</tr>
</tbody>
</table>

* See Table 34.
Appendix 8

Prevalence figures
TABLE 36  Prevalence table

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

continued
### TABLE 36 Prevalence table (cont’d)

<table>
<thead>
<tr>
<th>CHD combined</th>
<th>TGA</th>
<th>AS</th>
<th>TAPVC</th>
<th>HLH and MA</th>
<th>COA and IAA</th>
<th>PA</th>
<th>VSD (no echo)</th>
<th>Clinically significant CHD excluding VSD (no echo)</th>
<th>No. of infants excluded from routine newborn screening</th>
<th>Clinically non-significant VSDs (total VSD with echo)</th>
<th>Clinically non-significant CHD (PDA, PS, ASD with echo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.117</td>
<td>0.025</td>
<td>0.075</td>
<td>0.074</td>
<td>0.244</td>
<td>0.061</td>
<td>0.218</td>
<td>0.117</td>
<td>0.117</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NATIONAL ANTENATAL DETECTION DATA**

| No. of exclusions for antenatal diagnosis as proportion of condition-specific live births with congenital heart defects (national figures) |
| 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 |
| 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 |
| 67.0 | 0.3 | 1.0 | 0.7 | 0.7 | 1.0 | 0.7 | 12.0 | 49.2 |

| Number of exclusions per 100,000 live births (1–3) |
| 19.3 | 1.6 | 0.0 | 3.0 | 2.7 | 1.7 | 0.7 | 3.3 | 6.0 |

| Number of exclusions per 100,000 live births (due to antenatal diagnosis) BASE-CASE |
| 86.3 | 1.3 | 2.0 | 1.0 | 3.7 | 3.3 | 2.7 | 15.4 | 55.9 |

| Exclusions if screened at birth |
| 444 | 27 | 20 | 8 | 11 | 41 | 22 | 182 | 125 |

| Exclusions if screen at 24 hours |
| 107 | 12 | 4 | 1 | 3 | 5 | 7 | 48 | 27 |

| Exclusions if screened at birth = A1 |
| 4159 | 59 |

| Exclusions if screen at 24 hours = A1 |
| 319.5 | 235 |

continued
TABLE 36  Prevalence table (cont’d)

<table>
<thead>
<tr>
<th>CHD combined</th>
<th>TGA</th>
<th>AS</th>
<th>TAPVC</th>
<th>HLH and MA</th>
<th>COA and IAA</th>
<th>PA</th>
<th>VSD (no echo)</th>
<th>Clinically significant CHD excluding VSD (no echo)</th>
<th>No. of infants excluded from routine newborn screening</th>
<th>Clinically non-significant VSDs (total VSD with echo)</th>
<th>Clinically non-significant CHD (PDA, PS, ASD with echo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number left after exclusions per 100,000 LB if screen at 24 hours = A2</strong></td>
<td>337</td>
<td>15</td>
<td>16</td>
<td>7</td>
<td>8</td>
<td>36</td>
<td>15</td>
<td>134</td>
<td>98</td>
<td>4159</td>
<td>59</td>
</tr>
<tr>
<td>Exclusions if screen at 48 hours</td>
<td>209</td>
<td>20</td>
<td>8</td>
<td>4</td>
<td>8</td>
<td>15</td>
<td>14</td>
<td>69</td>
<td>71</td>
<td>421.5</td>
<td>337</td>
</tr>
<tr>
<td><strong>Number left after exclusions per 100,000 LB if screen at 48 hours = A3</strong></td>
<td>235</td>
<td>7</td>
<td>12</td>
<td>4</td>
<td>3</td>
<td>26</td>
<td>8</td>
<td>113</td>
<td>54</td>
<td>4159</td>
<td>59</td>
</tr>
</tbody>
</table>

**NORTHERN REGION CASES DETECTED BETWEEN 1 AND 16 YEARS**

| Number per 100,000 live births 1–16 = B | 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 | 0.99249 | 0.00235 |

Atrial septal defects (71), persistent ductus arteriosus (81), pulmonary stenosis (135) = 287; tetralogy of Fallot (99), complete atrioventricular septal defects (81), truncus arteriosus (24), miscellaneous (80) = 284.
### TABLE 37  Prevalence figures from Eurocat surveillance data

<table>
<thead>
<tr>
<th>Condition</th>
<th>Eurocat prevalence (1996–99) per 100,000 live-births</th>
</tr>
</thead>
<tbody>
<tr>
<td>Down’s syndrome</td>
<td>106.2</td>
</tr>
<tr>
<td>Lethal trisomy 18</td>
<td>8.1</td>
</tr>
<tr>
<td>Lethal trisomy 13</td>
<td>5.4</td>
</tr>
<tr>
<td>Gastroschisis</td>
<td>29.3</td>
</tr>
<tr>
<td>Omphalocele</td>
<td>12.5</td>
</tr>
<tr>
<td>Anorectal atresia</td>
<td>31.7</td>
</tr>
<tr>
<td>Tracheo-oesophageal atresia</td>
<td>21.1</td>
</tr>
</tbody>
</table>

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)**

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

*<sup>a</sup> The range of subjective probabilities are only relevant where data were derived from expert opinion.*
### TABLE 39  Aortic stenosis (AS)

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

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

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

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

* The range of subjective probabilities are only relevant where data were derived from expert opinion.
### TABLE 41  Hypoplastic left heart/mitral atresia (HLH/MA)

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

* 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)

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

* The range of subjective probabilities are only relevant where data were derived from expert opinion.
### TABLE 43 Pulmonary atresia (PA)

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

\(^a\) The range of subjective probabilities are only relevant where data were derived from expert opinion.

### TABLE 44 Ventricular septal defect (VSD)

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

\(^a\) 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 \((\alpha, \beta)\) 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>
<thead>
<tr>
<th>Parameter type</th>
<th>Distribution type</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathway probabilities</td>
<td>Beta</td>
<td>Beta distributions are bounded by 0 and 1. The distribution’s parameters ((\alpha, \beta)) represent the number of two possible complementary events such as success/failure, positive/negative test result, collapse/no collapse or life/death(^{276,277})</td>
</tr>
<tr>
<td>Prevalence data</td>
<td>Dirichlet</td>
<td>Generalisation of the beta distribution to more than two categories(^{507})</td>
</tr>
<tr>
<td>Staff time to perform screening test and diagnostic echocardiography</td>
<td>Gamma</td>
<td>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 &lt;0 for smaller samples(^{507,509})</td>
</tr>
<tr>
<td>Unit costs, e.g. equipment for screening, management of collapsed infants, ambulance transport, post-mortem examination of collapsed infants</td>
<td>Uniform</td>
<td>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})</td>
</tr>
</tbody>
</table>
parameters \((\alpha, \beta)\) for the beta distribution such that \(\alpha + \beta = n\) for all probability ranges elicited.\(^2\)\(^7\)\(^9\) 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 \((\alpha, \beta)\), 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 \(\alpha\) and \(\beta\). For more detail, see Spiegelhalter and colleagues (1994)\(^2\)\(^7\)\(^9\) and for a formal overview of different methods used to elicit prior distributions see Spiegelhalter and colleagues (2000).\(^5\)\(^1\)\(^0\)

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.\(^5\)\(^0\)\(^7\) 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 \(\alpha\) and \(\beta\) 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.\(^5\)\(^0\)\(^7\)

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 I I

Outcome tables
<table>
<thead>
<tr>
<th>Life-threatening congenital heart defects</th>
<th>Life-threatening congenital heart defects</th>
<th>Life-threatening congenital heart defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transposition of the great arteries</td>
<td>Aortic stenosis</td>
<td>Total anomalous pulmonary venous connection</td>
</tr>
<tr>
<td>CE</td>
<td>PO</td>
<td>SE</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Expected number affected at birth</td>
<td>28.0</td>
<td>28.0</td>
</tr>
<tr>
<td>Number recognised before newborn screen</td>
<td>13.7 (0.7)</td>
<td>13.7 (0.7)</td>
</tr>
<tr>
<td>Expected number affected at screen</td>
<td>14.3</td>
<td>14.3</td>
</tr>
<tr>
<td>Number screened&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13.3</td>
<td>13.3</td>
</tr>
<tr>
<td>Proportion of all affected and screened who are detected by newborn screen&lt;sup&gt;b&lt;/sup&gt;</td>
<td>38.9% (5.2)</td>
<td>95.0% (12.7)</td>
</tr>
<tr>
<td>Proportion of all affected who are detected by newborn screen</td>
<td>18.5%</td>
<td>45.2%</td>
</tr>
<tr>
<td>Number affected with positive screen&lt;sup&gt;c&lt;/sup&gt; who collapse or die before definitive diagnosis&lt;sup&gt;d&lt;/sup&gt; (failures of initial management)</td>
<td>0.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Number of timely diagnoses&lt;sup&gt;e&lt;/sup&gt; (receiving a definitive diagnosis after screen and without collapse or death)</td>
<td>4.5</td>
<td>11.1</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Screening strategy</th>
<th>Hypoplastic left heart/mitral atresia</th>
<th>Coarctation of the aorta/interrupted aortic arch</th>
<th>Pulmonary atresia</th>
</tr>
</thead>
<tbody>
<tr>
<td>CE</td>
<td>PO</td>
<td>SE</td>
<td></td>
</tr>
<tr>
<td>Expected number affected at birth</td>
<td>15.8</td>
<td>15.8</td>
<td>15.8</td>
</tr>
<tr>
<td>Number recognised before newborn screen (number antenatally)</td>
<td>7.0 (3.0)</td>
<td>7.0 (3.0)</td>
<td>7.0 (3.0)</td>
</tr>
<tr>
<td>Expected number affected at screen</td>
<td>8.8</td>
<td>8.8</td>
<td>8.8</td>
</tr>
<tr>
<td>Number screened ⁷</td>
<td>8.2</td>
<td>8.2</td>
<td>8.0</td>
</tr>
<tr>
<td>Proportion of all affected and screened who are detected by newborn screen (n)</td>
<td>37.5% (3.1)</td>
<td>95.0% (7.8)</td>
<td>99.0% (7.9)</td>
</tr>
<tr>
<td>Proportion of all affected who are detected by newborn screen</td>
<td>19.4%</td>
<td>49.2%</td>
<td>50.2%</td>
</tr>
<tr>
<td>Number affected with positive screen ⁷ who collapse or die before definitive diagnosis (n) (failures of initial management)</td>
<td>1.1</td>
<td>2.7</td>
<td>2.8</td>
</tr>
<tr>
<td>Number of timely diagnoses (n) (receiving a definitive diagnosis after screen and without collapse or death)</td>
<td>2.0</td>
<td>5.1</td>
<td>5.2</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Clinical significant congenital heart defects</th>
<th>Ventricular septal defects</th>
<th>Other congenital heart defects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CE</td>
<td>PO</td>
</tr>
<tr>
<td>Expected number affected at birth</td>
<td>251.3</td>
<td>251.3</td>
</tr>
<tr>
<td>Number recognised before newborn screen (number antenatally)</td>
<td>33.3 (3.3)</td>
<td>33.3 (3.3)</td>
</tr>
<tr>
<td>Expected number affected at screen</td>
<td>218.0</td>
<td>218.0</td>
</tr>
<tr>
<td>Number screened(^a)</td>
<td>202.7</td>
<td>202.7</td>
</tr>
<tr>
<td>Proportion of all affected and screened who are detected by newborn screen (n)</td>
<td>49.3% (99.9)</td>
<td>71.4% (144.8)</td>
</tr>
<tr>
<td>Proportion of all affected who are detected by newborn screen</td>
<td>39.7%</td>
<td>57.6%</td>
</tr>
<tr>
<td>Number affected with positive screen(^b) who collapse or die before definitive diagnosis (n) (failures of initial management)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Number of timely diagnoses (n) (receiving a definitive diagnosis after screen and without collapse or death)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

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

\(^a\) 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 = \(\text{number of all congenital heart defects cases detected antenatally + number of all congenital heart defects cases recognised after birth but before screening + number of cases with Down's syndrome, lethal trisomy, gastrointestinal malformations not associated with congenital heart defects (128)}\) × 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)

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

\(^a\) See Table 48.
## TABLE 50  Estimated screening performance of alternative screening strategies by condition (birth)

<table>
<thead>
<tr>
<th>Life-threatening congenital heart defects</th>
<th>Transposition of the great arteries</th>
<th>Aortic stenosis</th>
<th>Total anomalous pulmonary venous connection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening strategy</td>
<td>CE</td>
<td>PO</td>
<td>SE</td>
</tr>
<tr>
<td>Expected number affected at birth</td>
<td>28.0</td>
<td>28.0</td>
<td>28.0</td>
</tr>
<tr>
<td>Number recognised before newborn screen (number antenatally)</td>
<td>1.3 (0.7)</td>
<td>1.3 (0.7)</td>
<td>1.3 (0.7)</td>
</tr>
<tr>
<td>Expected number affected at screen</td>
<td>26.7</td>
<td>26.7</td>
<td>26.7</td>
</tr>
<tr>
<td>Number screened*</td>
<td>24.8</td>
<td>24.8</td>
<td>24.3</td>
</tr>
<tr>
<td>Proportion of all affected and screened who are detected by newborn screen (n)</td>
<td>38.9% (9.6)</td>
<td>95.0% (23.6)</td>
<td>90.0% (21.8)</td>
</tr>
<tr>
<td>Proportion of all affected who are detected by newborn screen</td>
<td>34.4%</td>
<td>84.1%</td>
<td>79.7%</td>
</tr>
<tr>
<td>Number affected with positive screen* who collapse or die before definitive diagnosis (n) (failures of initial management)</td>
<td>1.2</td>
<td>2.9</td>
<td>2.7</td>
</tr>
<tr>
<td>Number of timely diagnoses (n) (receiving a definitive diagnosis after screen and without collapse or death)</td>
<td>8.4</td>
<td>20.6</td>
<td>19.1</td>
</tr>
</tbody>
</table>

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

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

<sup>a</sup> Numbers may not add up due to rounding.  
<sup>b</sup> Number affected with positive screen who collapse or die before definitive diagnosis.
**TABLE 50** Estimated screening performance of alternative screening strategies by condition (birth) (cont'd)

<table>
<thead>
<tr>
<th>Clinically significant congenital heart defects</th>
<th>Ventricular septal defects</th>
<th>Other congenital heart defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CE</td>
<td>PO</td>
<td>SE</td>
</tr>
<tr>
<td>Expected number affected at birth</td>
<td>251.3</td>
<td>251.3</td>
</tr>
<tr>
<td>Number recognised before newborn screen (number antenatally)</td>
<td>15.4 (3.3)</td>
<td>15.4 (3.3)</td>
</tr>
<tr>
<td>Expected number affected at screen</td>
<td>236.0</td>
<td>236.0</td>
</tr>
<tr>
<td>Number screened¹</td>
<td>219.5</td>
<td>219.5</td>
</tr>
<tr>
<td>Proportion of all affected and screened who are detected by newborn screen (n)</td>
<td>49.3% (108.1)</td>
<td>71.4% (156.8)</td>
</tr>
<tr>
<td>Proportion of all affected who are detected by newborn screen</td>
<td>43.0%</td>
<td>62.4%</td>
</tr>
<tr>
<td>Number affected with positive screen² who collapse or die before definitive diagnosis (n) (failures of initial management)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Number of timely diagnoses (n) (receiving a definitive diagnosis after screen and without collapse or death)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

CE, Clinical examination alone; PO, pulse oximetry with clinical examination; SE, screening echo with clinical examination.

¹ Coverage: CE 93%, PO 93% and SE 91%.
² 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.
³ Excluding all non-clinically significant cases that will be detected by echocardiography.
<table>
<thead>
<tr>
<th>Life-threatening congenital heart defects</th>
<th>Transposition of the great arteries</th>
<th>Aortic stenosis</th>
<th>Total anomalous pulmonary venous connection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected number affected at birth</td>
<td>CE 28.0</td>
<td>PO 28.0</td>
<td>SE 28.0</td>
</tr>
<tr>
<td></td>
<td>34.0</td>
<td>34.0</td>
<td>34.0</td>
</tr>
<tr>
<td>Number recognised before newborn screen</td>
<td>CE 21.7 (0.7)</td>
<td>PO 21.7 (0.7)</td>
<td>SE 21.7 (0.7)</td>
</tr>
<tr>
<td></td>
<td>10.3 (1.6)</td>
<td>10.3 (1.6)</td>
<td>10.3 (1.6)</td>
</tr>
<tr>
<td>Expected number affected at screen</td>
<td>6.3</td>
<td>6.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Number screened</td>
<td>CE 5.9</td>
<td>PO 5.9</td>
<td>SE 5.8</td>
</tr>
<tr>
<td></td>
<td>22.0</td>
<td>22.0</td>
<td>21.6</td>
</tr>
<tr>
<td>Proportion of all affected and screened who are detected by newborn screen (%)</td>
<td>38.9% (2.3)</td>
<td>95.0% (5.6)</td>
<td>90.0% (5.2)</td>
</tr>
<tr>
<td>Proportion of all affected who are detected by newborn screen</td>
<td>8.2%</td>
<td>20.0%</td>
<td>18.6%</td>
</tr>
<tr>
<td>Number affected with positive screen who collapse or die before definitive diagnosis (%)</td>
<td>0.3</td>
<td>0.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Number of timely diagnoses (n) (receiving a definitive diagnosis after screen and without collapse or death)</td>
<td>2.0</td>
<td>4.9</td>
<td>4.5</td>
</tr>
</tbody>
</table>

continued
### Table 51 Estimated screening performance of alternative screening strategies by condition (48 hours) (cont’d)

<table>
<thead>
<tr>
<th></th>
<th>Life-threatening congenital heart defects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypoplastic left heart/mitral atresia</td>
</tr>
<tr>
<td></td>
<td>Screening strategy</td>
</tr>
<tr>
<td>Expected number affected at birth</td>
<td>15.8</td>
</tr>
<tr>
<td>Number recognised before newborn screen (number antenatally)</td>
<td>11.3 (3.0)</td>
</tr>
<tr>
<td>Expected number affected at screen</td>
<td>4.5</td>
</tr>
<tr>
<td>Number screened</td>
<td>4.2</td>
</tr>
<tr>
<td>Proportion of all affected and screened who are detected by newborn screen</td>
<td>37.5% (1.6)</td>
</tr>
<tr>
<td>Proportion of all affected who are detected by newborn screen</td>
<td>9.9%</td>
</tr>
<tr>
<td>Number affected with positive screen who collapse or die before definitive diagnosis</td>
<td>0.5</td>
</tr>
<tr>
<td>Number of timely diagnoses (n)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*continued*
<table>
<thead>
<tr>
<th></th>
<th>Clinically significant congenital heart defects</th>
<th>Other congenital heart defects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ventricular septal defects</td>
<td>Other congenital heart defects</td>
</tr>
<tr>
<td></td>
<td>CE</td>
<td>PO</td>
</tr>
<tr>
<td>Expected number affected at birth</td>
<td>251.3</td>
<td>251.3</td>
</tr>
<tr>
<td>Number recognised before newborn screen (number antenatally)</td>
<td>84.4 (3.3)</td>
<td>84.4 (3.3)</td>
</tr>
<tr>
<td>Expected number affected at screen</td>
<td>167.0</td>
<td>167.0</td>
</tr>
<tr>
<td>Number screened</td>
<td>155.3</td>
<td>155.3</td>
</tr>
<tr>
<td>Proportion of all affected and screened who are detected by newborn screen (n)</td>
<td>49.3% (76.5)</td>
<td>71.4% (110.9)</td>
</tr>
<tr>
<td>Proportion of all affected who are detected by newborn screen</td>
<td>30.5%</td>
<td>44.1%</td>
</tr>
<tr>
<td>Number affected with positive screen(\ast) who collapse or die before definitive diagnosis (n) (failures of initial management)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Number of timely diagnoses (n) (receiving a definitive diagnosis after screen and without collapse or death)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

CE, Clinical examination alone; PO, pulse oximetry with clinical examination; SE, screening echocardiography with clinical examination.

\(\ast\) Coverage: CE 93%, PO 93% and SE 91%.

\(\ast\) 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.

\(\ast\) Excluding all non-clinically significant cases that will be detected by echocardiography.
### TABLE 52  Scenarios investigated within the economic analysis using the primary outcome

<table>
<thead>
<tr>
<th></th>
<th>Clinical examination alone</th>
<th>Pulse oximetry with clinical examination</th>
<th>Screening echocardiography with clinical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs (£)</td>
<td>Base-case analysis using primary outcome</td>
<td>Costs (£)</td>
<td>Timely diagnoses</td>
</tr>
<tr>
<td></td>
<td>296,891</td>
<td>34.0</td>
<td>–</td>
</tr>
<tr>
<td>Scenarios using primary outcome</td>
<td>289,803</td>
<td>33.0</td>
<td>–</td>
</tr>
<tr>
<td>National antenatal detection rate</td>
<td>269,937</td>
<td>30.0</td>
<td>–</td>
</tr>
<tr>
<td>National antenatal detection rate doubled</td>
<td>340,909</td>
<td>43.9</td>
<td>–</td>
</tr>
<tr>
<td>Screening at birth</td>
<td>243,986</td>
<td>23.7</td>
<td>–</td>
</tr>
<tr>
<td>Probability of collapse after a positive screen is zero</td>
<td>298,060</td>
<td>34.0</td>
<td>–</td>
</tr>
<tr>
<td>Coverage for screening echocardiography with clinical examination is 93%</td>
<td>297,942</td>
<td>33.8</td>
<td>–</td>
</tr>
<tr>
<td>Sensitivities of screening echocardiography with clinical examination are 100%</td>
<td>306,039</td>
<td>50.5</td>
<td>–</td>
</tr>
</tbody>
</table>

ICER, incremental cost-effectiveness ratio.
<table>
<thead>
<tr>
<th>Scenario Description</th>
<th>Clinical examination alone</th>
<th>Pulse oximetry with clinical examination</th>
<th>Screening echocardiography with clinical examination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Costs (£)</strong></td>
<td>Costs (£)</td>
<td>Timely diagnoses</td>
<td>ICER (£)</td>
</tr>
<tr>
<td>Base-case analysis using secondary outcome</td>
<td>297,627</td>
<td>222.4</td>
<td>222.4</td>
</tr>
<tr>
<td><strong>Scenarios using secondary outcome:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>National antenatal detection rate</td>
<td>289,427</td>
<td>210.2</td>
<td>210.2</td>
</tr>
<tr>
<td>National antenatal detection rate doubled</td>
<td>269,265</td>
<td>192.5</td>
<td>192.5</td>
</tr>
<tr>
<td>Screening at birth</td>
<td>341,236</td>
<td>252.2</td>
<td>252.2</td>
</tr>
<tr>
<td>Screening at 48 hours</td>
<td>243,377</td>
<td>170.0</td>
<td>170.0</td>
</tr>
<tr>
<td>Probability of collapse after a positive screen is zero</td>
<td>268,541</td>
<td>228.2</td>
<td>228.2</td>
</tr>
<tr>
<td>Coverage for screening echocardiography with clinical examination is 93%</td>
<td>297,643</td>
<td>222.4</td>
<td>222.4</td>
</tr>
<tr>
<td>Sensitivities of screening echocardiography with clinical examination are 100%</td>
<td>296,990</td>
<td>222.4</td>
<td>222.4</td>
</tr>
<tr>
<td>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%)</td>
<td>305,169</td>
<td>259.8</td>
<td>259.8</td>
</tr>
</tbody>
</table>

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: 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: 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: 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
Appendix 13

**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
- Visits hospital and doctor quite frequently; 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. infant$
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. anx$i$
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

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Setting: country; participants; sample size</th>
<th>Methods</th>
<th>Results (relevant to screening for congenital heart defects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bekker $^{351}$</td>
<td>1994</td>
<td>UK; general practice; 441 adults (18–45 years)</td>
<td>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</td>
<td>Positive carrier result associated with transient increased anxiety (&lt;3 months); negative carrier status believed no risk to future children; results had no effect on perceptions of own health</td>
</tr>
<tr>
<td>Jarvinen $^{352}$</td>
<td>1999</td>
<td>Finland; hospital genetics clinic; 46 women relatives of males with genetic disorders</td>
<td>Women tested as children with parents' consent, followed up 10–15 years later with postal questionnaire; asked about knowledge of carrier status and HRQoL</td>
<td>7 carriers, 17 non-carriers, 22 uncertain; normal HRQoL scores (standardised instrument); transient psychological effects (anxiety) as children</td>
</tr>
<tr>
<td>Sorenson $^{356}$</td>
<td>1984</td>
<td>USA; hospital clinic; 60 infants and their parents</td>
<td>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)</td>
<td>No increased anxiety due to false-positive result. 36% were concerned about infant's health because they felt they were given too little information</td>
</tr>
<tr>
<td>Gibson $^{422}$</td>
<td>1997</td>
<td>UK; hospital maternity unit; 83 mothers of screen-positive infants and 54 control mothers</td>
<td>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)</td>
<td>No differences in maternal adjustment or anxiety; a few anxious mothers remained anxious after a normal result</td>
</tr>
<tr>
<td>Watkin $^{357}$</td>
<td>1998</td>
<td>UK; audiology clinic; 288 mother–infant pairs; control group of mothers</td>
<td>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)</td>
<td>Anxiety increased at 6-week retest but still not significantly different compared with control mothers</td>
</tr>
<tr>
<td>Parsons $^{359}$</td>
<td>2002</td>
<td>UK; Duchenne muscular dystrophy pilot screening study; 42 families in pilot and 43 control families</td>
<td>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</td>
<td>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)</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Setting: country; participants; sample size</td>
<td>Methods</td>
<td>Results (relevant to screening for congenital heart defects)</td>
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<tr>
<td>Yu511</td>
<td>1999</td>
<td>US; clinic; 8 mothers</td>
<td>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</td>
<td>No difference in changes in parenting stress and TSS between the two groups</td>
</tr>
<tr>
<td>Bell368</td>
<td>1994</td>
<td>UK research screening programme for neuroblastoma; parents of 7 infants</td>
<td>Parents of infants given a false-positive result interviewed 13 months after normal test</td>
<td>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</td>
</tr>
<tr>
<td>Dobrovolski369</td>
<td>2003</td>
<td>Austrian neuroblastoma screening programme; 32 parents of 16 infants</td>
<td>Included infants with false-positive results from programme involving 270,000 infants; telephone interviews about psychological responses</td>
<td>31 parents still supported screening; anxiety low at screen but high during hospital admission for investigation (severe anxiety in 19 parents)</td>
</tr>
<tr>
<td>Stuart360</td>
<td>2000</td>
<td>USA; audiology clinic; 40 mothers</td>
<td>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</td>
<td>No significant differences in PSI scores between the two groups; initial hearing retest does not increase parenting stress</td>
</tr>
<tr>
<td>Owen361</td>
<td>2001</td>
<td>UK; local health clinics; parents of 621 infants</td>
<td>Short written survey of anxiety; given after newborn hearing test</td>
<td>Mean anxiety score increased with successive repeat tests; parents liked tests as simple, quick, could be done on young infants and no discomfort</td>
</tr>
<tr>
<td>Vohr362</td>
<td>2001</td>
<td>USA; audiology clinic; 307 mothers at initial screen, 40 mothers at retest</td>
<td>Questionnaire asked mothers about worry, knowledge and demographic data in 1997 and 1999</td>
<td>Maternal worry significantly greater at rescreen. Maternal knowledge increased between 1997 and 1999</td>
</tr>
<tr>
<td>Clemens363</td>
<td>2000</td>
<td>USA; 2% of parents of 5010 screened infants</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Magnuson358</td>
<td>1999</td>
<td>Sweden; 49 parents of 26 children</td>
<td>Parents of infants given newborn hearing screening were interviewed about anxiety and attitudes to test</td>
<td>Positive attitudes to screening overall but less if infant retested; more anxiety if retested but this resolved after a definitive diagnosis or normal retest</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Setting: country; participants; sample size</td>
<td>Methods</td>
<td>Results (relevant to screening for congenital heart defects)</td>
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<tr>
<td>Thelin374</td>
<td>1985</td>
<td>Sweden; primary care; parents of 61 children (59 mothers, 48 fathers)</td>
<td>Parents of children identified with alpha 1-antitrypsin disorder on newborn screening were interviewed for attitudes to follow-up and future screening recommendations</td>
<td>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</td>
</tr>
<tr>
<td>Holtzman376</td>
<td>1983</td>
<td>USA; newborn screening for phenylketonuria (PKU); 418 study mothers, 210 control mothers</td>
<td>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</td>
<td>Knowledge greater in mothers given more information before consenting</td>
</tr>
<tr>
<td>Bell378</td>
<td>1994</td>
<td>UK research screening programme for neuroblastoma; parents of 85 infants</td>
<td>Parents of recently screened infants interviewed about knowledge of the test and disorder and anxiety</td>
<td>Knowledge was poor and 13% did not know infant was tested; one-third were anxious, increasing if retested; information provided was often inadequate</td>
</tr>
<tr>
<td>Weichbold375</td>
<td>2001</td>
<td>Austria; maternity unit; 90 mothers</td>
<td>Mothers of infants given newborn hearing screening were given a knowledge and attitude questionnaire by interview on the postnatal unit</td>
<td>84% of mothers supported newborn screening despite knowledge of false-positive rates; women supporting screening were better informed overall</td>
</tr>
<tr>
<td>Young373</td>
<td>2001</td>
<td>UK; critical review of literature about newborn hearing screening</td>
<td>Review of studies reporting the effects on parents of screening, especially where parent experiences directly assessed</td>
<td>Implications for universal newborn hearing screening in the UK outlined</td>
</tr>
<tr>
<td>Luterman379</td>
<td>1999</td>
<td>USA; postal survey of 75 parents of hearing-impaired children aged 3 months–24 years</td>
<td>Retrospective survey of parents</td>
<td>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</td>
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<tr>
<th>Study</th>
<th>Year</th>
<th>Setting: country; participants; sample size</th>
<th>Methods</th>
<th>Results (relevant to screening for congenital heart defects)</th>
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<tbody>
<tr>
<td>Oliver377</td>
<td>1996</td>
<td>UK; hospital maternity unit; 26 pregnant women, 14 midwives, ultrasonographers</td>
<td>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</td>
<td>No increased anxiety in women with increased information; resistance to new leaflet from ultrasonographers; welcomed by midwives</td>
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<tr>
<td>Sorenson356</td>
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<tr>
<td>Bell368</td>
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<td>Parsons359</td>
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<td>Clemens363</td>
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<td>Study</td>
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<td>Setting: country; participants; sample size</td>
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<tr>
<td><strong>Cystic fibrosis screening</strong></td>
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<tr>
<td>Al-Jader(^{385}) 1990</td>
<td>UK; screening programme; families of 18 screened and 11 unscreened infants</td>
<td>Pilot newborn screening programme for cystic fibrosis; parents of infants diagnosed early (screened) and late (clinically) interviewed (40 questions)</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Cobb(^{390}) 1991</td>
<td>UK; school; 216 pupils (14–16 years)</td>
<td>Pupils given information about screening then tested on knowledge retained and attitudes to cystic fibrosis screening</td>
<td>Good increase in knowledge; over 80% supported carrier and antenatal screening</td>
<td></td>
</tr>
<tr>
<td>Mischler(^{398}) 1998</td>
<td>USA; Wisconsin cystic fibrosis screening project</td>
<td>Several questionnaires to families with cystic fibrosis children diagnosed clinically or on screening, control families, and families receiving false-positive results</td>
<td>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</td>
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<tr>
<td><strong>Duchenne muscular dystrophy screening</strong></td>
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<tr>
<td>Bradley(^{370}) 1993</td>
<td>UK; pilot screening programme; 9 families</td>
<td>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</td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>Smith(^{393}) 1990</td>
<td>UK; hospital maternity unit; 201 mothers</td>
<td>Structured questionnaire with interview to assess attitudes towards the newborn screening for Duchenne muscular dystrophy</td>
<td>68% aware screening was carried out; majority would like screening, would like to know of disability at birth and would probably terminate affected pregnancies</td>
<td></td>
</tr>
<tr>
<td>Firth(^{394}) 1983</td>
<td>UK; 53 families of boys with Duchenne muscular dystrophy nationally</td>
<td>Boys aged 4 years to adulthood. Families interviewed about diagnosis, family impact and newborn screening</td>
<td>Parents complained about delay in diagnosis and lack of information; siblings and marriages were affected; 75% supported newborn screening</td>
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<tr>
<td>Parsons(^{339})</td>
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<td>See Table 54</td>
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<tr>
<td><strong>Newborn hearing screening</strong></td>
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<tr>
<td>Moulin(^{586}) 2001</td>
<td>France; mothers of 124 screened infants</td>
<td>Anonymous questionnaire to mothers whose newborn infants received hearing screening test</td>
<td>95% supported screening; 35% experienced low anxiety; knowledge about hearing loss was low</td>
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</tbody>
</table>
### TABLE 56 Parents’ support for screening (cont'd)

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Setting: country; participants; sample size</th>
<th>Methods</th>
<th>Results (relevant to screening for congenital heart defects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hergils387</td>
<td>2000</td>
<td>Sweden; audiology clinic; parents of 87 infants (6 months old)</td>
<td>Parents of screened children given a written questionnaire about attitudes to screening, knowledge and anxiety</td>
<td>95% positive towards screening; 4% against newborn screening; 77% had sufficient information; repeat testing increased anxiety</td>
</tr>
<tr>
<td>Weichbold375</td>
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<tr>
<td>Young373</td>
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<tr>
<td>Clemens363</td>
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<tr>
<td>Magnuson358</td>
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<tr>
<td>Metabolic and other screening programmes</td>
<td></td>
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<tr>
<td>Warren392</td>
<td>1982</td>
<td>USA; State screening programme for haemoglobinopathy; 18 parents</td>
<td>Parents interviewed about child’s health, their knowledge of sickle cell disease and views on newborn screening</td>
<td>Parents had fair knowledge of sickle cell disorder; many felt isolated and some felt anxious or depressed; majority supported newborn screening for earlier detection</td>
</tr>
<tr>
<td>Read397</td>
<td>2002</td>
<td>USA; six-State regional survey; 230 parents</td>
<td>Parents of children with metabolic disorders participated in telephone interviews using standardised questionnaires for health behaviour, parenting stress and adaptive behaviour</td>
<td>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</td>
</tr>
<tr>
<td>Sveger512</td>
<td>1999</td>
<td>Sweden; primary care; parents of 85 children with ATD and 89 matched controls</td>
<td>Parents of 22–23 year-old children identified with alpha1-antitrypsin disorder (ATD) on newborn screening were interviewed for attitudes to follow-up study, physical and psychosomatic problems compared with controls</td>
<td>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</td>
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<tr>
<td>Thelin374</td>
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<td></td>
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<tr>
<td>Dobrovoljšk369</td>
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<tr>
<td>Bell368</td>
<td></td>
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</tbody>
</table>
TABLE 57 Technologies used in screening for congenital heart defects

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Setting: country; participants; sample size</th>
<th>Methods</th>
<th>Results (relevant to screening for congenital heart defects)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical examination in newborn infants</strong></td>
<td></td>
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<tr>
<td>Owen[361]</td>
<td>2001</td>
<td>UK; local health clinics; parents of 683 infants</td>
<td>Short written survey of anxiety; given after newborn hearing test</td>
<td>Mean anxiety score increased with successive repeat tests; parents liked tests as simple, quick, could be done on young infants and no discomfort</td>
</tr>
<tr>
<td>Wolke[382]</td>
<td>2002</td>
<td>UK; district general hospital maternity unit; 826 mother–infant pairs</td>
<td>RCT assigning infants to newborn examination by midwife or SHO; excluded 47% of all births (higher risk); maternal satisfaction questionnaire</td>
<td>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</td>
</tr>
<tr>
<td>McCrindle[381]</td>
<td>1995</td>
<td>Canada; hospital paediatric cardiology department; parents of 182 children (1 day–18 years)</td>
<td>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</td>
<td>Parents often did not understand concept of heart murmur; 10% believed a heart malformation was present even after reassurance that the heart was normal</td>
</tr>
<tr>
<td>McDonald[383]</td>
<td>1996</td>
<td>UK; hospital cardiology outpatients; 40 consecutive patients</td>
<td>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</td>
<td>28 murmurs associated with normal heart, but 20 anxious short term and 11 anxious longer term</td>
</tr>
<tr>
<td><strong>Ultrasound (and echocardiography) of infants</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Garcia[384]</td>
<td>2002</td>
<td>UK; structured review of women’s views of antenatal ultrasound screening</td>
<td>Review of research directly reporting women’s views of antenatal ultrasound screening, including early and late (detailed, including heart) scans</td>
<td>Women have minimal fear of ultrasound technology; prefer to have some explanation during the scan</td>
</tr>
</tbody>
</table>
### TABLE 58 ‘Early’ screening diagnosis compared with ‘late’ clinical diagnosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Setting: country; participants; sample size</th>
<th>Methods</th>
<th>Results (relevant to screening for congenital heart defects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pollitt342</td>
<td>1997</td>
<td>UK; systematic review of the psychosocial effects of newborn screening for inborn errors of metabolism</td>
<td>Review of literature; comparing screening and clinical diagnosis, the acceptability of screening and management of the screening process</td>
<td>Psychological benefits of screening outweigh the costs; particular problem areas are repeat testing and information provision</td>
</tr>
<tr>
<td>Merelle400</td>
<td>2003</td>
<td>The Netherlands; cystic fibrosis regional centre; parents of 45 children with cystic fibrosis</td>
<td>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</td>
<td>Groups with early (&lt;3 months old) versus later diagnosis were compared; early diagnosis was associated with less negative feelings and more confidence in the medical profession</td>
</tr>
<tr>
<td>Baron401</td>
<td>1997</td>
<td>USA; hospital outpatients; 51 parents of children with cystic fibrosis and 47 control parents</td>
<td>14 false-positive results at newborn screen; 20 true-positive screening diagnoses and 17 clinical diagnoses; postal questionnaire with parenting stress index (PSI)</td>
<td>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</td>
</tr>
<tr>
<td>Al-Jader385</td>
<td></td>
<td></td>
<td>See Table 56</td>
<td></td>
</tr>
<tr>
<td>Firth402</td>
<td>1983</td>
<td>UK; community setting; 69 parents of boys with Duchenne muscular dystrophy</td>
<td>Interview survey of parent views about newborn screening for Duchenne muscular dystrophy and their experiences of diagnosis</td>
<td>Most parents favoured newborn screening and expressed dissatisfaction with current delays, methods of disclosure and support</td>
</tr>
<tr>
<td>Firth394</td>
<td></td>
<td></td>
<td>See Table 56</td>
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<tr>
<td>Smith393</td>
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<td>See Table 54</td>
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<tr>
<td>Parsons339</td>
<td></td>
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<td>See Table 54</td>
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<tr>
<td>Warren392</td>
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<td>See Table 56</td>
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<tr>
<td>Bradley370</td>
<td></td>
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<td>See Table 56</td>
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</tr>
<tr>
<td>Magnuson403</td>
<td>2000</td>
<td>Sweden; audiology clinic; 10 parents of 8 children with hearing impairment</td>
<td>Interviews with parents whose children were diagnosed late with hearing impairment</td>
<td>Parents describe 4 phases: unawareness, suspicion, confirmation, habilitation; diagnosis results in relief and sorrow; all parents supported newborn hearing screening</td>
</tr>
<tr>
<td>Green404</td>
<td>1996</td>
<td>UK; parents of 158 boys with Duchenne muscular dystrophy</td>
<td>Postal questionnaire to parents asking about experiences of diagnosis</td>
<td>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</td>
</tr>
<tr>
<td>Watkins405</td>
<td>1995</td>
<td>UK; audiology clinic; 208 parents of children with hearing impairment</td>
<td>Parents were asked about their satisfaction with the way in which the diagnosis was made</td>
<td>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</td>
</tr>
</tbody>
</table>
### TABLE 59 Results of screening tests

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Setting: country, participants; sample size</th>
<th>Methods</th>
<th>Results (relevant to screening for congenital heart defects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelchat[416]</td>
<td>1999</td>
<td>Canada; 144 parents (72 couples)</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Rona[406]</td>
<td>1998</td>
<td>UK; fetal and paediatric cardiology outpatients; 108 mothers</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Clark[371]</td>
<td>1999</td>
<td>USA; hospital ward; 8 fathers</td>
<td>Fathers of children hospitalised with a congenital heart defect interviewed about experiences</td>
<td>Fathers experience conflicting emotions: joy at fatherhood, sadness at illness, attachment and fear, loss of control, and the need to remain strong for partners</td>
</tr>
<tr>
<td>Luterman[379]</td>
<td></td>
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<tr>
<td>Kaden[380]</td>
<td>1985</td>
<td>USA; Baltimore–Washington Infant Study; 285 mothers</td>
<td>Interview including questionnaire about information gained from cardiology consultation</td>
<td>One-third of mothers demonstrated poor understanding of the heart malformation; parents in biomedical occupations answered better</td>
</tr>
<tr>
<td>False-negative results</td>
<td></td>
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</tr>
<tr>
<td>Petticrew[348]</td>
<td>2000</td>
<td>UK</td>
<td>Review of the impact of false negative results in screening programmes</td>
<td>Discusses relevant psychosocial issues</td>
</tr>
<tr>
<td>Hall[317]</td>
<td>2000</td>
<td>UK; home interviews with parents of 179 children with Down’s syndrome</td>
<td>Children aged 2–6 years old; parents asked about anxiety, depression, parenting stress, attitudes towards child, attributions of blame for the birth</td>
<td>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</td>
</tr>
<tr>
<td>Rona[406]</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>True-negative results</td>
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<tr>
<td>Bekker[351]</td>
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</tbody>
</table>

continued
**TABLE 59 Results of screening tests (cont’d)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Setting: country; participants; sample size</th>
<th>Methods</th>
<th>Results (relevant to screening for congenital heart defects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murray³⁴⁶</td>
<td>1999</td>
<td>UK</td>
<td>Expert review; single chapter in wider review</td>
<td>Review of psychosocial issues of Down’s syndrome screening</td>
</tr>
<tr>
<td>Hergils³⁸⁷</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>False-positive results</strong></td>
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</tr>
<tr>
<td>Statham³⁹⁹</td>
<td>1993</td>
<td>UK; 20 women</td>
<td>Of 20 women who had had serum screening for Down’s syndrome and amniocentesis, 8 were false positives; telephone interviews</td>
<td>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</td>
</tr>
<tr>
<td>Bodegard⁴²⁰</td>
<td>1983</td>
<td>USA; congenital hypothyroid screening; 102 families</td>
<td>Interviews about anxiety and psychological distress 6 months after a false-positive result</td>
<td>78 families had strong initial reactions but 18 remained anxious at 6 months after test; possible effects on parenting adjustment</td>
</tr>
<tr>
<td>Fyro⁴²¹</td>
<td>1987</td>
<td>USA; congenital hypothyroid screening; 32 families</td>
<td>Interviews about anxiety and psychological distress four years after a false-positive result</td>
<td>19 families anxious at 4 years after test; 8 children with behaviour problems</td>
</tr>
<tr>
<td>Rona³⁰⁶</td>
<td></td>
<td></td>
<td></td>
<td>See above</td>
</tr>
<tr>
<td>McCrindle³⁸¹</td>
<td></td>
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<td>See Table 57</td>
</tr>
<tr>
<td>Bekker³⁵¹</td>
<td></td>
<td></td>
<td></td>
<td>See Table 54</td>
</tr>
<tr>
<td>Bell³⁶⁸</td>
<td></td>
<td></td>
<td></td>
<td>See Table 54</td>
</tr>
<tr>
<td>Dobrovoljski³⁶⁹</td>
<td></td>
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<td>See Table 54</td>
</tr>
<tr>
<td>Pollitt³⁴²</td>
<td></td>
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<td>See Table 58</td>
</tr>
<tr>
<td><strong>Detection of ‘non-disease’</strong></td>
<td></td>
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</tr>
<tr>
<td>Laane⁴²⁴</td>
<td>1997</td>
<td>Sweden; 51 children born 1986–91 and 83 matched controls</td>
<td>Children with VSDs diagnosed neonatally and closing within first 24 months of life; quality of life questionnaires administered to cases and control group</td>
<td>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</td>
</tr>
</tbody>
</table>

*continued*
**TABLE 59** Results of screening tests (cont’d)

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Setting: country; participants; sample size</th>
<th>Methods</th>
<th>Results (relevant to screening for congenital heart defects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harding$^{25}$</td>
<td>1999</td>
<td>UK; 70 parents of affected children, 52 controls</td>
<td>Parents of infants with abnormal urinary tracts on fetal scans sent postal questionnaire about follow-up, problems and concerns</td>
<td>Follow-up is unselective and too intense for the majority who have spontaneously resolving or insignificant lesions; high levels of concern generated</td>
</tr>
<tr>
<td>Axworthy$^{47}$</td>
<td>1996</td>
<td>UK; six cystic fibrosis screening centres; 280 carriers and 466 controls</td>
<td>Postal survey of cystic fibrosis gene carriers and controls</td>
<td>Uncertainty for some about meaning of carrier status; no difference in anxiety; carriers had poorer perception of own health; no difference in reproductive intentions</td>
</tr>
<tr>
<td>Henneman$^{513}$</td>
<td>2002</td>
<td>The Netherlands; 9 cystic fibrosis carrier couples</td>
<td>Seven couples were interviewed and 2 completed a questionnaire; 2–8 years after receiving result</td>
<td>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</td>
</tr>
<tr>
<td>Luterman$^{379}$</td>
<td></td>
<td></td>
<td></td>
<td>See Table 55</td>
</tr>
</tbody>
</table>
## TABLE 60  Genetic testing

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Setting: country; participants; sample size</th>
<th>Methods</th>
<th>Results (relevant to screening for congenital heart defects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marteau³⁹¹</td>
<td>1998</td>
<td>Expert review of psychological responses to genetic testing</td>
<td>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</td>
<td>Considers impact on individuals, society and families of different genetic tests</td>
</tr>
<tr>
<td>Michie⁵¹⁴</td>
<td>2001</td>
<td>UK and Australia; 8 regional genetics centres; 148 adults, 60 children</td>
<td>--</td>
<td>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</td>
</tr>
<tr>
<td>Umans-Eckenhausen⁵¹⁵</td>
<td>2002</td>
<td>The Netherlands; familial hypercholesterolaemia (FH) screening programme; 35 couples</td>
<td>Parents with FH gene offered genetic testing for their children; telephone survey of parents' attitudes to FH screening</td>
<td>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</td>
</tr>
<tr>
<td>Whitelaw⁵¹⁶</td>
<td>1996</td>
<td>UK; hospital outpatients; 62 adults with familial adenomatous polyposis</td>
<td>62 adults asked about attitudes to antenatal, newborn and childhood genetic testing for familial adenomatous polyposis in a semi-structured interview</td>
<td>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</td>
</tr>
<tr>
<td>Bassett³⁸⁹</td>
<td>2001</td>
<td>Australia; hospital antenatal clinic; 135 women and partners</td>
<td>Women given information and offered newborn genetic testing for hereditary haemochromatosis</td>
<td>Test accepted in over 90%; low level of anxiety about the test</td>
</tr>
<tr>
<td>Senior³⁷¹</td>
<td>1999</td>
<td>UK; newborn screening programme for familial hypercholesterolaemia; parents of 24 children</td>
<td>Interviews with parents after positive screening test result received for their children; asked about response to screening and knowledge</td>
<td>Parents were more anxious if they saw the risk as genetic and uncontrollable as opposed to dietary and controllable; genetic testing might induce fatalism</td>
</tr>
</tbody>
</table>
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.
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.

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

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