

Ten-Year Survival of Down Syndrome Births

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Hayes C (Health Information Unit, Eastern Health Board, Dr Steevens Hospital, Dublin 8, Ireland), Johnson Z, Thornton L, Fogarty J, Lyons R, O'Connor M, Delany V and Buckley K. Ten-year survival of Down syndrome births. *International Journal of Epidemiology* 1997; **26**: 822–829.

Objective. To determine the survival status of children with Down syndrome (DS), and to document factors influencing survival. **Design.** Follow-up study of cases identified from the Dublin European Register of Congenital Anomalies and Twins (EUROCAT) Register. Follow-up was attempted for each case until death or 1992 or until the date last known to be alive. **Setting.** Eastern Health Board, Dublin.

Subjects. In all, 389 DS children, born between 1 January 1980 and 31 December 1989 were followed up. **Results.** Survival rates of 88% at one year and 82% at 10 years were found. There was a non-significant improvement in survival between the cohort born in 1980–1984 and that born in 1985–1989. Congenital heart defects reduced survival to 72% and complete atrio-ventricular canal defects (CAVD) had the poorest prognosis (58% survival at 10 years). Cases with CAVD showed a trend towards improved survival when surgically treated. Maternal age, mother's county of residence, sex of infant, season of birth and presence of additional non-cardiac congenital anomalies had no impact on survival.

Conclusions. Four out of five DS children now survive at least 10 years. Adequate educational and health service provision needs to be made for them, especially those with congenital heart defects. The need for studies which compare survival and quality of life in DS children with CAVD who undergo cardiac surgery versus those who do not, taking account of various selection factors, is identified.

Keywords: Down syndrome, survival, congenital heart disease, CAVD, cardiac surgery

Down syndrome (DS) is a major cause of congenital malformation and handicap. Life expectancy of children with DS has improved dramatically over the past 50 years particularly due to a large increase in the proportion of children surviving in the first year of life. Survival rates have improved from below 60% survival in mid 1940–1950 birth cohorts to 80% in 1950–1970 birth cohorts.^{1–3} Bell reported a survival rate of 87% in a mid 1970–mid 1980 birth cohort⁴ and McGrother has reported a survival of over 90% at 12 months in a 1981–1985 cohort.⁵ Data on survival of DS children born in Ireland has not been published previously.

The EUROCAT (*European Register of Congenital Anomalies and Twins*) project is a programme supported by the European community for the epidemiological surveillance of congenital anomalies in Europe which started in 1979. The EUROCAT registries are set up according to a number of general principles. They are population based, they cover congenital malformations in livebirths, stillbirths and induced abortions, they extend registration to cases diagnosed after the neonatal period and they use multiple sources of information and

active case finding.⁶ There are currently 26 participating registries.

The Dublin EUROCAT Registry which covers counties Dublin, Kildare and Wicklow, representing the Eastern Health Board (EHB) area (population 1.2 m), has contributed data to EUROCAT every year since 1980. Sources of information used by the Dublin Registry include the following: birth notification forms, death certificates for children aged <2 years, the Hospital In-Patient Enquiry Scheme (HIPE, a computerized system containing diagnostic and other details for cases discharged from paediatric and acute general hospitals) and paediatric unit karyotyping and autopsy records.

The availability of accurate information on survival of DS cases is an important requirement for clinical management, health care service provision and genetic counselling. The aim of this study was to document the survival of a cohort of DS children born in the EHB area between 1980 and 1989 using EUROCAT data and to identify factors influencing survival.

METHOD

All liveborn cases of DS, born to women resident in the EHB area between 1 January 1980 and 31 December

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1989, were identified from the EUROCAT register. Down syndrome children, whose mothers were resident in the EHB area at the time of birth, as established from birth notifications or from a list of names and addresses on the electoral register⁷ were considered eligible for the study. A small number of additional cases of DS were identified from a register of those in receipt of the Domiciliary Care Allowance (DCA) who were not on the EUROCAT register. (The DCA is a monthly allowance paid to parents of children aged between 2 and 16 years who require a level of care significantly above the norm for age.)

Data collection was carried out in 1992. Information was collected on maternal age, maternal county of residence at time of delivery, parity, sex of child, karyotype, birthweight, presence or absence of other congenital anomalies with specific details about congenital heart disease, cases of leukaemia, episodes of hospital admission, survival status of child and cause of death. Information was collected from the following sources: EUROCAT, the death register, hospital records of paediatric units (including a leukaemia register and a cardiac surgery register), local public health nurse records and the DCA register. Follow-up was attempted for each case until death or time of data collection in 1992. In cases where no recent information was available the date on which the child was last known to be alive was recorded. As the cohort consisted of children born between 1980 and 1989, the period of follow-up varied from 12 years to 3 years in the case of youngest children.

Kaplan-Meier survival curves were calculated for the total cohort, for children born within the two time periods 1980–1984 and 1985–1989 and for other possible prognostic factors: maternal age <35 years and ≥ 35 years, birthweight <2500 g and ≥ 2500 g, parity <3 and 3+, maternal place of residence at time of birth, Dublin versus non-Dublin, and the presence or absence of additional anomalies. Survival curves were tested for heterogeneity using the log-rank test for censored data. A multivariate analysis was carried out using Cox's proportional hazards regression model to determine the effect of the different variables on survival. The data were analysed using SAS Version 6.07 (SAS is a registered trademark of SAS Institute Inc., Cary, NC, USA). The software package Confidence Interval Analysis (CIA) was used for calculating 95% confidence intervals (95% CI).⁸

RESULTS

There were 225 808 births in the EHB area between 1980 and 1989. In all, 389 DS livebirths were identified, a birth prevalence rate of 17.2/10 000 livebirths

(1 in 580). There were nine DS stillbirths. The male:female breakdown was 206 males (53%) and 183 females (47%). Information on survival status was obtained on 384 (98.7% of cases). Sixty-three deaths were identified during the follow-up period, 31 males and 32 females (16% of cases).

Information on karyotype was sketchy: reference was made to karyotyping in 58.6% (228/389) of cases and of these only 139 had the karyotype recorded. All of these were simple trisomy 21.

The cause of death was obtained for 55 of the 63 deaths (87%). Cardiac anomalies were cited as the cause of death in 26 (47.3%), with pneumonia as a stated complication in nine of these. Six deaths (10.9%) were due to leukaemia, six deaths (10.9%) were due to septicaemia/meningitis, five deaths (9.1%) were due to respiratory infection in the absence of congenital heart disease and two deaths (3.6%) were due to primary pulmonary hypertension. There was one accidental death, one Sudden Infant Syndrome Death and eight deaths (14.5%) due to other causes.

Information on the presence or absence of additional anomalies was available for 365 of the 389 children in the cohort (93.6%). At least one anomaly was present in 212 of these (54.5%) (Table 1). The 212 cases with at least one anomaly contributed 346 anomalies between them.

Cardiac defects occurred in 167 of the 365 children in the cohort (45.8%), gastrointestinal anomalies in 40 cases (11.0%) and other anomalies in 77 cases (21.2%). Of the 175 females in the cohort, 90 (51.4%) had congenital heart defects compared to 77/190 males (40.5%) ($P = 0.037$). Forty-three cases had more than one cardiac defect.

Of the total number of defects, 221/346 (63.9%) were cardiac; 48/346 (13.9%) were gastrointestinal and other anomalies accounted for 77/346 (22.2%).

Only 37 of the 167 cases of those known to have a cardiac anomaly had cardiac surgery (22.2%). Information regarding surgery was unobtainable for 10 cases. Although more females than males had cardiac surgery (22 females, 15 males), the difference was not statistically significant ($P = 0.11$). The median age at time of surgery was 27 months (range 1–96 months). Twenty-nine children (29/364), (8.0%), had surgery for non-cardiac conditions.

Of the 155 children with cardiac defects on whom information on survival status was obtainable, 37 (23.9%) had cardiac surgery. Survival was better among those who had surgery compared with those who did not have surgery; thirty-four of those who had surgery (91.9%) survived versus 80 (67.8%) of the 118 who did not have surgery (RR = 1.36, 95% CI : 1.16–1.57, $P = 0.004$).

TABLE 1 Breakdown of additional anomalies by type^a

Category	Type of anomaly	No. of anomalies detected	% of total anomalies
Cardiac	Ventricular septal defect	62	17.9
	Complete atrio-ventricular defect	62	17.9
	PDA ^b	46	13.3
	ASD ^c	33	9.5
	Tetralogy of Fallot	3	0.87
	Other specified	9	2.6
	Other unspecified	6	1.7
Alimentary tract	Duodenal atresia	21	6.1
	Hirschsprungs disease	11	3.2
	Imperforate anus	4	1.2
	Cleft lip/palate	3	0.87
	Other gastrointestinal	3	0.87
	Tracheo-oesophageal fistula	6	1.7
Other anomalies	Miscellaneous	77	22.2
Total		346	100.0

^a There were 212 children included in this analysis. Some cases had more than one additional anomaly. Thus the total number of anomalies is 346.

^b Patent ductus arteriosus.

^c Atrio-septal defects.

The combinations of defects treated surgically are set out in Table 2. Patent ductus arteriosus (PDA) closure was the commonest operative procedure carried out. Corrective surgery for PDA alone or in combination with other defects gave an excellent result with 100% survival. Surgery for isolated ventricular septal defects (VSD) and for atrio-septal defects (ASD) and VSD combined was successful in the small number of cases where this was carried out.

The largest subgroup comprised of children with isolated complete atrio-ventricular canal (CAVD) defects (49 cases). Eight of these had surgery of whom 75% survived, compared with survival of 46.3% among the 41 cases who did not have surgery. However, this difference was not statistically significant (Table 2). We then combined cases with isolated CAVD (49) with those having other cardiac defects in addition to CAVD (12), where information on cardiac surgery was known, giving a total of 61 cases. Sixteen (26.2%) had surgery of whom 14 (87.5%) survived compared to 46.7% survival among the 45 children who did not have surgery (RR = 1.88, 95% CI : 1.3–2.7, $P = 0.01$). All seven of the 10 children who had surgery for combined CAVD and PDA survived. Surgery was less successful in the case of isolated Tetralogy of Fallot where only one of the two children who had corrective surgery survived (Table 2).

The estimated probability of survival to one year was 0.88 (Figure 1), (95% CI : 0.85–0.91) and to 10 years was 0.83 (Figure 2) (95% CI : 0.79–0.87). Twelve of the

63 deaths occurred in the first 28 days, 34 between one month and one year and 16 between one and 3 years. One child died at 4.5 years. The infant mortality rate for our cohort was 118/1000 live births.

Presence of additional anomalies was significantly associated with decreased survival on univariate analysis after 10 years ($P < 0.001$, 95% CI : 0.15–0.28). However when cardiac, gastrointestinal and other anomalies were analysed separately, only congenital heart disease was significantly associated with reduced survival. The probability of infants without heart disease reaching the first year was 96% compared to 80% of children with congenital heart disease ($P < 0.001$, 95% CI for difference: 0.91–0.23). Of children without congenital heart disease, 94% survived 10 years compared with 72% of children with congenital heart disease ($P < 0.001$, 95% CI : 0.15–0.30).

When specific groups of cardiac defects were analysed, only CAVD defects either alone or in combination emerged as having a statistically significant impact on survival, with 68% surviving to one year and 58% to 10 years compared to 93% at one year and 90% at 10 years for children without CAVD (Figure 3) ($P < 0.001$, 95% CI for difference: 0.18–0.45).

Survival was significantly worse in children who developed leukaemia ($P < 0.001$). Six of the 384 children in the cohort had leukaemia (1.6%), of the acute myeloid type, all of whom died. Their ages at death ranged from 1.5 to 4.4 years.

TABLE 2 Differences in survival of cases with and without surgery for different categories of cardiac defects

Category	Surgery	No. alive	% Alive	No. dead	% dead	Relative risk ^a	95% CI	P
^b CAVD ^c	Y	6	75.0	2	25.0	1.62	0.96–2.72	0.25
n = 49	N	19	46.3	22	53.7			
PDA ^d	Y	8	100.0	0	0	1.14	0.88–1.49	1.00
n = 16	N	7	87.5	1	12.5			
VSD ^e	Y	1	100.0	0	0	1.15	1.00–1.33	1.00
n = 31	N	26	86.7	4	13.3			
ASD ^f	Y	0	0	0	0	–	–	–
n = 10	N	8	80.0	2	20.0			
ASD + ^b CAVD	Y	1	100.0	0	0	–	–	–
n = 1	N	0	0	0	0			
ASD + VSD	Y	2	100.0	0	0	1.38	0.96–1.98	1.00
n = 13	N	8	72.7	3	27.3			
ASD + ^b CAVD+PDA	Y	0	0	0	0	–	–	–
n = 1	N	1	100.0	0	0			
ASD + VSD + PDA	Y	1	100.0	0	0	–	–	–
n = 2	N	0	0	1	100.0			
ASD + PDA	Y	1	100.0	0	0	–	–	–
n = 3	N	2	100.0	0	0			
VSD + PDA	Y	5	100.0	0	0	1.2	0.84–1.72	1.00
n = 11	N	5	83.3	1	16.7			
^b CAVD + PDA	Y	7	100.0	0	0	3.0	0.61–14.9	0.07
n = 10	N	1	33.3	2	66.7			
Falloots	Y	1	50.0	1	50.0	0.50	0.13–2.00	1.0
n = 3	N	1	100.0	0	0			
Other CHD ^g	Y	1	100.0	0	0	–	–	–
n = 1	N	0	0	0	0			

^aRelative risk refers to the risk of being alive following surgery.

^bThe total no. of cases of CAVD in this analysis was 61 which is one less than the 62 cases shown in Table 1. This is due to missing information on surgery in one case.

^cComplete atrio-ventricular defect.

^dPatent ductus arteriosus.

^eVentricular septal defect.

^fAtrio-septal defect.

^gCongenital heart defect.

Survival of the 1980–1984 birth cohort was 87% at one year versus 90% for the 1985–1989 cohort. At 5 years, survival among the 1980–1984 cohort had fallen to 82% versus 86% for the 1985–1989 cohort. The log-rank test gave a non-significant result ($P = 0.27$).

None of the following factors emerged as statistically significant prognostic factors using the log-rank test: female sex ($P = 0.47$), birthweight <2500 g ($P = 0.58$), parity 3+ ($P = 0.07$), maternal age ≥ 35 ($P = 0.96$), maternal place of residence outside Dublin at delivery ($P = 0.87$), presence of cardiac anomalies other than CAVD alone or in combination ($P = 0.33$) and presence of all other additional anomalies ($P = 0.86$).

The data were re-analysed using Cox's proportional hazards model and including only those variables significant on bivariate analysis i.e. CAVD and leukaemia.

The results of this analysis were as follows: presence of CAVD, (Risk Ratio [RR] = 5.56, 95% CI : 3.19–9.69, $P < 0.001$), leukaemia (RR = 11.18, 95% CI : 3.89–32.15, $P < 0.001$).

DISCUSSION

The Dublin EUROCAT Registry has the largest number of liveborn Down syndrome children of any of 18 registries who collected data from 1980–1989.⁶ It should be noted that induced abortion is illegal in Ireland, and thus the findings of our study may be quite different from what pertains in countries where abortion is legal.

In our study, it was difficult to obtain complete data, particularly on karyotype and on cardiac surgery despite

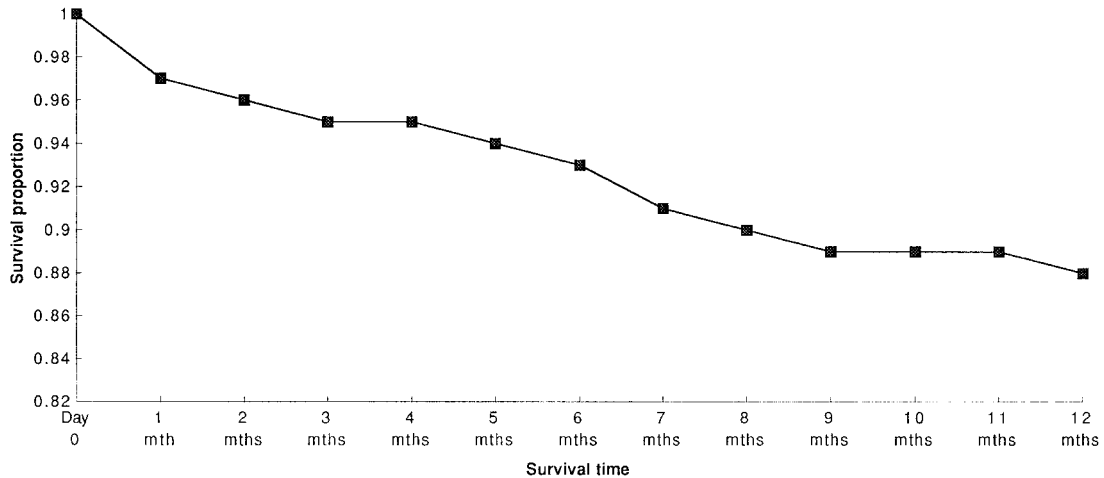


FIGURE 1 Monthly survival to 12 months of Down syndrome children

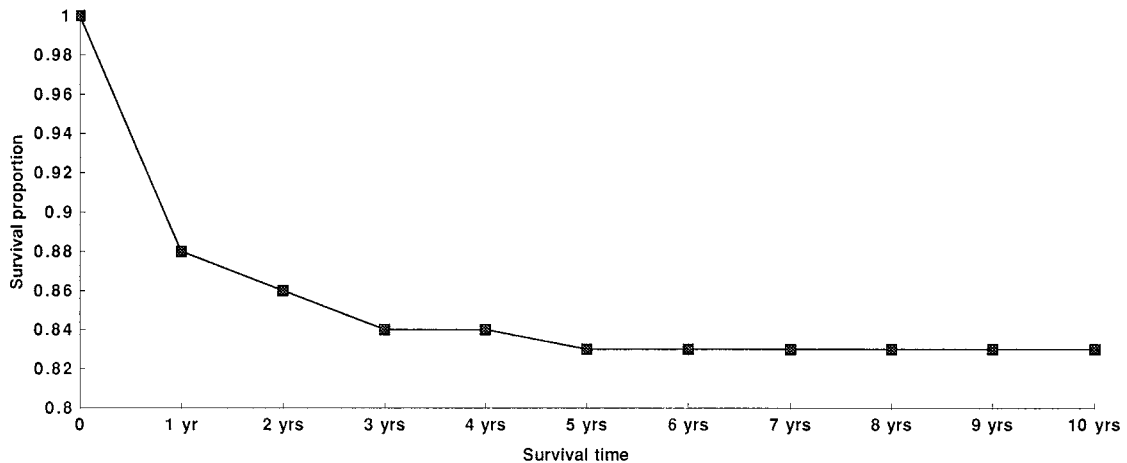


FIGURE 2 Ten-year survival of Down syndrome children

access to a number of different data sources, highlighting the need for improved and compatible information systems.

The overall crude prevalence rate of Down syndrome at 17.2 per 10 000 live births is amongst the highest prevalence rates documented in 18 EUROCAT registries for the years 1980–1990.⁶ However, when maternal age specific prevalences were compared for EUROCAT registries, there was no significant variation between centres.⁶ The rate is comparable to the crude prevalence rate for DS of 17.7/10 000 live births reported in the EHB for the years 1978 and 1979 combined⁹ and the rate of

18.3/10 000 live births for the 10-year period 1981–1990.¹⁰ Using the capture-recapture method, we have estimated that the ascertainment of Down syndrome in the Dublin Registry is 93% complete.¹⁰

The rate of reported additional congenital anomalies is similar to the 52% reported by McGrother.⁵ The incidence of congenital heart defects is similar to Matthew *et al.*, (41%).¹¹ As with previous studies, the commonest cardiac defects were CAVD and VSD.^{11–13}

As expected congenital heart defects and their complications were the most frequent cause of death. It was possible to establish a cause of death for 55 of

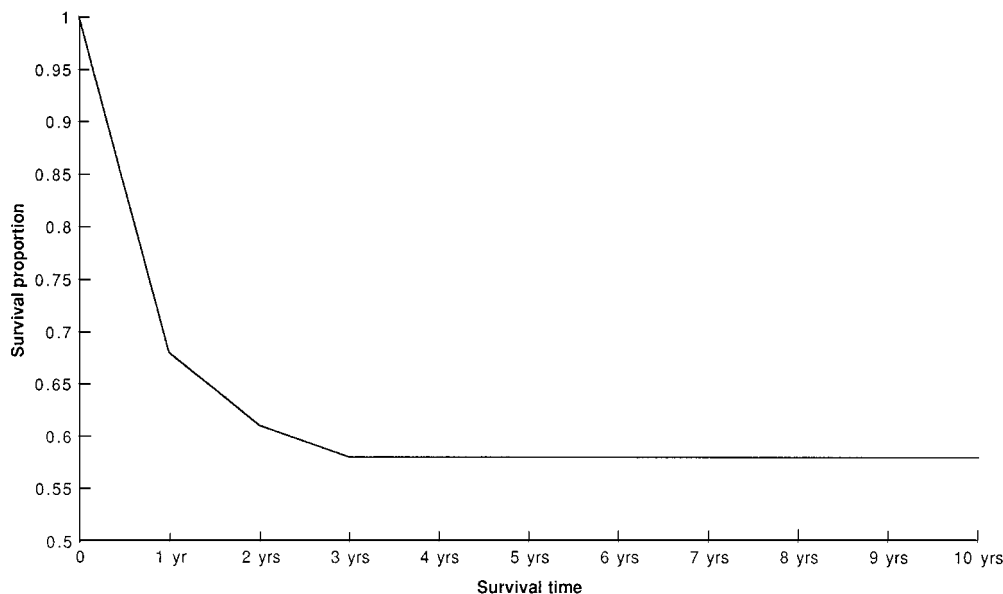


FIGURE 3 Ten-year survival of Down syndrome children with complete atrio-ventricular defects

the 61 total deaths (90.2%). Eleven of the 55 deaths (20%) were due to infection in the absence of congenital heart disease. This compares with a national figure of 12.1% for deaths from infections in children under 15 years.¹⁴

The survival rate to one year of 88% for DS children is consistent with rates of between 83% and 94% reported over the past two decades.^{2,4,5,15} Mikkelsen *et al.* reported a rate of death which was highest between 22 days and one year.¹⁶ In our study the highest death rate occurred between 28 days and one year. The infant mortality rate was 13.5 times higher (118/1000 live births) than the 1985 Irish infant mortality rate (8.7/1000 live births).¹⁷ Our study showed that infection caused a substantial proportion of deaths, 20% of all deaths being due to infection, with pneumonia being a complicating factor in those dying of congenital heart disease. Of the children in our study, 9.1% died of respiratory infection which compares unfavourably with the 5% mortality reported by McGrother in England and Wales for the period 1976–1985.⁵

In a study of DS in Northern Ireland, Elwood and Darragh reported mortality among cases born to mothers aged ≥ 35 years to be twice that for younger mothers.¹⁸ Our study, in common with Bell's work⁴ showed no difference in mortality related to maternal age at delivery.

Some early studies showed a higher mortality rate in females with DS,^{2,3} however, other studies have shown

no difference between male and female survival.^{5,16,19} Studies have reported a significantly higher proportion of female DS cases with congenital heart defects^{20,21} which may account for the trend towards lower survival rates in females in some reports. Our study had approximately equal numbers of males and females although more females had cardiac defects.

Survival of children with DS has improved over time for those with and without congenital heart disease. However, the presence of congenital heart disease is the biggest factor influencing survival. In our study, children with congenital heart disease who had CAVD defects had poorest survival. While the difference in survival between children with isolated CAVD who had surgery and those who did not was not significant, there was a tendency for the surgically treated cases to do better. Indeed, those with other cardiac defects in addition to CAVD did significantly better if they had surgery. This raises the issue of the appropriateness of cardiac surgery for DS children, especially those with CAVD. Our data suggests but does not confirm that surgery may improve the prognosis in those with CAVD. Likewise, Culpepper *et al.*²² showed a 64% survival in children having surgery for CAVD and Sheehan *et al.*¹² reported 66% survival. However, Bull *et al.*²³ have suggested that there is no significant difference in outcome between those who are conservatively managed and those who have had surgery, although quality of life was not considered in detail.

Our findings should be interpreted bearing in mind that information on whether surgery was carried out or not was missing in 6% of children known to have had cardiac anomalies. However, our information on survival status in the case of those known to have had cardiac surgery was complete. No information was available on what criteria were used to select children for surgery and it is likely that babies with less complex lesions were operated on as indicated by Sheehan *et al.* in 1990.¹² Although overall survival was significantly better in those who had surgery and we were able to demonstrate a trend towards an improved survival in some subgroups, statistical power to detect significant differences in subgroups was limited by small numbers.

We consider that the question of surgery in DS children with CAVD should be addressed by specific studies which compare survival in surgical and non-surgical cases and which take account of various selection criteria.

The incidence of leukaemia is higher in DS children than in non-affected children. All children in our study had acute myeloblastic leukaemia (AML) and all had died by age four and a half years. The incidence of leukaemia in our study was very high with 1:65 cases affected (an incidence rate of 1.6%). This is similar to the 2% rate reported by Brookes and Alberman for a cohort of DS children diagnosed with leukaemia in 1989.²⁴ This is a 20-fold increase over that in the general population. A British study noted an incidence of leukaemia in DS 14 times that of normal children indicating that approximately one in 150 DS children will develop leukaemia.²⁵ Most leukaemia in DS is of two types: Acute lymphatic leukaemia (ALL) in older children and AML almost exclusively in children <4 years.²⁶ Acute myeloblastic leukaemia is very rare in non-DS children.

There have been no previous studies on the survival of children with DS in Ireland. As in the study of Bell *et al.*, there was no significant difference in survival between cohorts of children born in the two 5-year periods which we studied.⁵ However, although our study showed no significant difference in the cohort born 1980–1984 and that born 1985–1989 there was a tendency for the latter group to survive longer, and so improvement in survival may not have plateaued yet. Eight out of 10 children born alive will now survive long term. Once children reach 5 years old, they are likely to survive to adulthood. The long-term requirement for health care, education and provision of support services is likely to be significant for these individuals. Of particular importance is the need for residential services for people with DS when their parents die or become unable to care for them through illness.

Couples who are planning a pregnancy who have a substantial risk of having a DS child (as in the case of older mothers) or indeed couples to whom a DS child is born can now be told by genetic counselling services that there is an eight out of 10 chance of survival to 10 years. This is important in a country where termination of pregnancy is not legal.

Extension of life expectancy is not an end in itself unless accompanied by an associated improvement in quality of life. More detailed studies on quality of life of DS children and adults and their families are necessary.

ACKNOWLEDGEMENTS

Dr Desmond Duff, Consultant Paediatric Cardiologist, Our Lady's Hospital, Dublin, Dr Finn Breathnach, Consultant Paediatric Oncologist, Our Lady's Hospital, Dublin, Dr Leslie Daly, Lecturer in Medical Statistics, University College, Dublin. The staff of the records departments at Our Lady's Hospital, The Children's Hospital Temple Street, and The National Children's Hospital, Dublin, Public Health Nursing staff, Eastern Health Board, Dublin and the staff of the Health Information Unit, Eastern Health Board, Dr Steevens Hospital, Dublin 8, Ireland.

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(Revised version received October 1996)