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The effects of neonatal screening for sickle cell disorders on lifetime treatment costs and early deaths avoided: a modelling approach

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Abstract

Background The aim of the study was to calculate the cost to the UK National Health Service of providing treatment services for patients with sickle cell disorders. The rates of differential morbidity and mortality, in the first 10 years of life, between screen-detected early diagnosed and clinically presenting late diagnosed cohorts of sickle cell disorder patients are also estimated.

Method A cost model was developed, based on predictions of survival and the incidence of sickle cell disorder-related events. Direct data from the NHS are lacking, so data were incorporated from disparate sources. Patients with sickle cell disorders were divided into two categories: those with sickle cell anaemia and those with sickle HbC disease.

Results Differentiating between sickle cell anaemia and sickle HbC disorder patients, the results show that the undiscounted (discounted at 6 per cent) lifetime treatment costs range from £92 323 (£24 917) to £185 614 (£53 861). The number of early deaths avoided per 100 births, as a result of early diagnosis through screening, ranges from 0.57 to 1.25.

Conclusions The resulting estimates may act as a guide to those involved in the planning of health care provision with regard to the resources required to treat sickle cell disorder patients. Such information may also be incorporated into the evaluation of both antenatal and neonatal screening programmes for sickle cell disorders.

Keywords: sickle cell disorders, lifetime costs, early deaths avoided, morbidity prediction

Introduction

Sickle cell disorders are serious medical conditions that reduce life expectancy and require lifelong treatment.[1] They mainly affect black, Asian and Mediterranean ethnic minorities in the United Kingdom, and about 10 per cent of births are to women from these high-risk groups.[2] Although such high-risk births are heavily concentrated in major conurbations, they do occur in most districts.[3]

The most common and important acute events include painful crises, pneumococcal sepsis, splenic sequestration, acute chest syndrome, stroke and acute anaemia.[4–8] Increasingly, sickle cell disorders are chronic diseases causing, for example, renal failure, chronic lung disease, avascular necrosis of the hip joint and retinopathy,[9–11] and some of the acute conditions have irreversible sequelae involving mental retardation, seizures or deafness.[12]

Sickle cell disorders are autosomal recessive haemoglobinopathies, whereby the detection of a significant combination of defective traits in both parents signifies a one in four risk of the child suffering from the disorder. Antenatal screening for sickle cell disorders can detect defective traits in parents, following which, prenatal diagnosis may be offered as a confirmatory test for definitive foetal diagnosis. The primary objective of antenatal screening is to provide choice over the outcome of an affected pregnancy.[13] Within an antenatal screening programme, the detection of an antenatally diagnosed affected foetus may lead to the termination of the pregnancy. The calculation of a lifetime's use of resources in treating and caring for an affected patient may provide policy-makers with a possible benchmark for their assessment of screening programmes.

Neonatal screening is also available for sickle cell disorders, as the diagnosis of a child with a sickle cell disorder before presentation with symptoms improves the prognosis of affected infants. The early introduction of penicillin prophylaxis and comprehensive care has been shown to reduce mortality and

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morbidity caused by pneumococcal sepsis and splenic sequestration.[14] The resource consequences of neonatal screening for sickle cell disorders are reflected by the difference in lifetime treatment costs between early and late diagnosed individuals with sickle cell disorders. They include potential savings of health service costs as a result of reduced morbidity as well as potential expenditures as a result of improved survival in screen detected patients.

This paper should be read in the context of a programme of research funded by the NHS Health Technology Assessment (HTA) Programme, entitled 'Screening for haemoglobinopathies in the United Kingdom: review and economic analysis'.[15] Using, in the main, secondary data sources this programme's aim was to assess the costs and effectiveness of existing and alternative available screening models. Both antenatal and neonatal models were considered, including examination of the impact of antenatal screening on neonatal screening.

The presentation of the full economic evaluation and a comprehensive description of the calculation of lifetime treatment costs are beyond the scope of a single paper. Details of the results of the corresponding economic evaluations of both the antenatal and neonatal screening models will be forthcoming, although the implications of the lifetime treatment costs for the respective economic evaluations are discussed in this paper.

However, the estimates provided in this paper are not restricted to use in conjunction with economic evaluations. The treatment of sickle cell disorders will certainly have financial implications for health authorities in which sickle cell disorders are most common. Indeed, the calculation of the lifetime treatment costs makes explicit the costs incurred by such health authorities. If the costs incurred by health authorities with a high proportion of sickle cell disorder patients are not compensated by reductions in the cost of other disease areas, then they may be justified in claiming extra resources.

Methods

Lifetime treatment costs were estimated separately for sickle cell anaemia and sickle HbC disorder because of their different natural histories and management.[11] Other sickle cell disorders, including sickle HbD disease and sickle β^0 thalassaemia, were assumed to incur similar treatment costs to sickle cell anaemia.[16,17] The expected consequences of prevention of late diagnoses in both categories of sickle cell disorders, in terms of early deaths averted and severe disability prevented (mental retardation, seizures or deafness), are also presented.

The calculation of the lifetime treatment costs was based on the description of the survival rates of sickle cell disorder patients and the likely events experienced throughout their lifetime. A comprehensive literature review was undertaken, incorporating six medical databases and hand searches of a number of particularly pertinent sources, to estimate the relevant parameters.[15]

The baseline assessment of the lifetime treatment costs was based on the best available information on the prognosis of a sickle cell disorder patient born now, and only conventional management of the conditions was considered. Both complications as a result of shortcomings of previous therapy were avoided, and possible future developments in the treatment of sickle cell disorders were not included. The impact of progress in the treatment of sickle cell disorders, such as bone marrow transplantation (BMT), and the increased use of hydroxyurea to control painful episodes were explored in the sensitivity analysis.[18] Lower estimates of the incidence of stroke were also included in the sensitivity analysis, as were alternative costs of an in-patient day. The impact of increased community care was also considered.

A health service perspective was taken for this study, as it was felt that health service costs were most relevant to policymakers. The implications of this approach are raised in the discussion.

Baseline analysis

The estimation of the treatment costs of sickle cell disorder patients born now and managed according to current standards of care comprised a number of elements.

Data on the presentation of sickle cell disorders, in the absence of screening, were obtained from a 1985 study from Jamaica.[19] However, it was felt that diagnosis now would be earlier, so the distribution given by this study was shifted forward 1 year. This meant that 61 per cent of patients present by the end of the first year, 78 per cent by the end of the second year, and 86 per cent by the end of the third year. The remaining 14 per cent present gradually until the age of 10. Similar data for sickle HbC disease were taken from Williams *et al.*, although patients were assumed to present up to the age of 20.[20]

The incidence rates for pneumococcal sepsis and splenic sequestration are of particular importance as they are the major determinants of deaths averted, and severe disability prevented, as a result of early diagnosis. When a child presents clinically (in the absence of pneumococcal sepsis) treatment with penicillin prophylaxis is initiated, and the anticipated incidence rate for pneumococcal sepsis is reduced. The incidence rates of sepsis for sickle cell disease, with and without prior treatment with penicillin prophylaxis,[21] were combined with the yearly incidence rates for sickle cell anaemia and sickle HbC disease[22] to estimate the 'known' and 'unknown' diagnosis incidence rates reported in Table 1a and b. Gill *et al*. followed 694 patients over a 10 year period to establish the incidence rates of splenic sequestration used.[23]

The mortality experiences of early and late diagnosed cohorts of patients with sickle cell anaemia and sickle HbC disease were assumed to differ up to the age of 10 years as a result of increased incidence of pneumococcal sepsis[21] and case fatality of splenic sequestration[24,25] in late diagnosed individuals. Survival of patients with sickle cell disorders can be

Table 1a Age-specific incidence rates (per 100 person-years) of acute and chronic complications associated with sickle cell anaemia

Age (years)	Painful crisis[43,44]	Pneumococcal sepsis		Splenic sequestration[44]	Acute chest syndrome[44,46]	Acute anaemia[44]	Leg ulcers[47]	Hip replacement[b,48]	Other operations[c,48]	Retino-pathy[b,49]	Stroke[b,44,50]	Renal failure[b,10,28,51,52]	Chronic lung disease[b,9,28,51,52]
		Known[a,21,45]	Unknown[a,21,45]										
<1	6.2	0.02	0.09	3.25	11.6	3.95	0	0	1.43	0	0.93	0	0
–2	24	0.02	0.09	6.2	28	1.7	0	0	1.43	0	0.93	0	0
–3	38.3	0.02	0.09	5.3	26.3	3.3	0	0	1.43	0	0.93	0	0
–4	42.4	0.02	0.09	2	34.2	5.9	0	0	1.43	0	0.93	0	0
–5	49.6	0.02	0.09	1.5	25.5	3.9	0	0	1.43	0	0.93	0	0
–6	40.8	0.016	0.072	1.4	22.2	2	0	0	1.43	0	0.93	0	0
–7	39.2	0.012	0.054	1	28.9	9.3	0	0	1.43	0	0.93	0	0.52
–8	41.6	0.008	0.036	0.5	20.8	3	0	0	1.43	0	0.93	0	0.52
–9	37.9	0.004	0.018	0	15.2	1.9	0	0	1.43	0	0.93	0	0.52
–10	90	0	0	0	9.27	1	1.89	0.3	1.43	0.75	0.93	0.65	0.52
–20	110	0	0	0	8.78	1	11.58	0.3	1.43	1.9	0.25	0.65	0.52
–30	90	0	0	0	8.78	1	13.86	0.3	1.43	2.7	0.25	0.65	0.52
–40	55	0	0	0	8.78	1	13.33	0.3	1.43	2.5	0.25	0.65	0.52
>40	50	0	0	0	8.78	1	13.37	0.3	1.43	2.5	0.25	0.65	0.52

[a] Known and unknown refer to whether patients have presented and are receiving penicillin prophylaxis.
[b] Indirect estimation of age-specific incidence rates.
[c] Cholecystectomy or splenectomy.

Table 1b Age-specific incidence rates (per 100 person-years) of acute and chronic complications associated with sickle HbC disease

Age (years)	Painful crisis[43,44]	Pneumococcal sepsis		Splenic sequestration[44]	Acute chest syndrome[44,46]	Acute anaemia[44]	Hip replacement[b,48]	Other operations[c,48]	Retino-pathy[b,49]	Stroke[b,44,50]	Renal failure[b,10,28,51,52]	Chronic lung disease[b,9,28,51,52]
		Known[a,21,45]	Unknown[a,21,45]									
<1	1.9	0.0054	0.027	0	10.9	0	0	0	0	0	0	0
–2	8.5	0.0054	0.027	0.5	10.6	0	0	0	0	0	0	0
–3	15.3	0.0054	0.027	0	10.4	0	0	0	0	0	0	0
–4	28.5	0.0054	0.027	1.5	13.1	1.5	0	0	0	0	0	0
–5	23.3	0.0028	0.014	2.9	9.7	0	0	0	0	0	0	0
–6	33.6	0.0028	0.014	1.3	5.2	0	0	0	0	0	0	0
–7	29.1	0.0028	0.014	1.8	1.8	0	0	0	0	0	0	0
–8	40.3	0.0021	0.00405	0	5.8	0	0	0.538	0	0	0	0
–9	23	0.0014	0.0027	0	3.3	0	0	0.538	0	0.25	0	0
–10	40	0.0007	0.00135	0	3.95	0	0	0.538	4.3	0.25	0	0
–20	40	0	0	0	3.27	0.5	0	0.538	8.3	0.17	0	0
–30	40	0	0	0	3.27	0.5	0.241	0.538	7.4	0.17	0.402	0.08
>30	40	0	0	0	3.27	0.5	0.241	0.538	3.5	0.17	0.402	0.08

[a] Known and unknown refer to whether patients have presented and are receiving penicillin prophylaxis.
[b] Indirect estimation of age-specific incidence rates.
[c] Cholecystectomy or splenectomy.

expected to vary between sickle cell anaemia and sickle HbC disease[26,27] as well as between screened and unscreened cohorts.[21] Overall mortality was set to be consistent with current literature, which also informed survival estimates in early and late diagnosed groups after the age of 10 years.[26,27] The main assumptions underlying the calculation of differential mortality in early and late diagnosed individuals with sickle cell disorders up to the age of 10 years are shown in Table 1a and b.

The age-specific frequency of major health service interventions was based on sickle cell disorder-related morbidity and current protocols for diagnosis, routine follow-up and management of complications. Hospital- and community-based services were both considered. Acute complications can occur with different degrees of severity, and chronic organ damage caused by sickle cell disorders can affect almost all organ systems.[28] For the purpose of this study only complications requiring initial hospitalization were considered to incur health service costs.

The incidence rates for the multiple complications associated with sickle cell disorders were considered to reflect sickle cell disorder-specific events. These studies presented their results in a variety of ways and individuals were recruited at different ages, which made it necessary to derive age-specific incidence rates indirectly by estimating age-specific years under observation.

Unit costs for the various intervention categories were obtained from a number of sources, including hospital trusts, mainly London based, the published literature, the British National Formulary and the Personal Social Services Research Unit (PSSRU). All costs have been uprated to 1998 values using the NHS pay and prices index.

The costs associated with each of the included acute and chronic events were estimated by describing the interventions involved in the treatment of the respective conditions and then attaching the relevant unit costs to each component. Table 4a and b (see below) describes this process. For each patient year, the proportions of patients experiencing the respective acute and chronic conditions were estimated using the data presented in Table 1a and b. These proportions were then multiplied by the episodic or annual cost of each condition. Summing the costs of treatment for the individual conditions produced an estimate of the annual cost per surviving sickle cell disorder patient for each year. These annual costs were then multiplied by the respective survival rates, and aggregated to estimate the lifetime treatment costs. Costs were included up to the age of 60 years, and were subject to a discount rate of 0 and 6 per cent.

Sensitivity analysis

Treatment of sickle cell disorders is an evolving process, so it was considered necessary to investigate the impact on the cost of treatment of fundamental alternative treatment schedules in the sensitivity analysis. The sensitivity analysis was conducted on a single patient group – sickle cell anaemia patients who are diagnosed early – because such disorders are the most severe and increased uptake of screening makes early diagnosis more likely.

For some children who can find a compatible bone marrow donor, BMT can cure sickle cell disorders, although there are associated risks.[29] The main UK centre for BMT in children with sickle cell disorders has estimated that only 17 such operations have been undertaken. The current scope is small, which is mainly due to genetic factors, but also to environmental constraints such as the unpredictable nature of the disease and an immediate mortality rate of around 10 per cent.[30,31] To test the upper bounds of the use of BMT, it was assumed that 5 per cent of patients could receive such treatment in the future. Cost estimates were obtained from a hospital trust experienced in undertaking BMT. Transplantations are preferably completed by the age of 10 years, and it was assumed that the 5 per cent would be uniformly distributed over the ages of 6–10 years.

In a US trial, hydroxyurea has been shown to reduce the frequency of both painful crises and the incidence of acute chest syndrome.[32] However, no similar trial has been undertaken in the United Kingdom, mainly because of apprehension on the part of patients[33], although more recently it has been reported that a European register of sickle cell disorder patients treated with hydroxyurea was being set up.[34] It was assumed that the uptake of hydroxyurea may increase in the future and the impact of a 50 per cent uptake across all ages was tested in the sensitivity analysis. The cost of the drug was added, and the rates of painful crises requiring hospitalization and acute chest syndrome were decreased by 58 and 53 per cent, respectively.[32]

The cost of treating patients with stroke is high, so that the lifetime treatment cost of sickle cell disorders may be sensitive to assumptions about the prevalence of stroke. The estimates of the incidence of stroke were halved, prompted by recent estimates that were lower than the baseline assessment. The cost of a day in both an intensive care unit and a normal ward were halved and doubled to test the impact of the largest individual cost components.

The final sensitivity analysis explored the possible impact of expanded programmes of community care that can reduce the time spent in hospital for episodes of painful crisis. A before-and-after study has been completed that implemented a home pain management programme to improve the quality of care and educate sickle cell disorder patients in handling painful crises.[29] The results showed that such programmes can reduce the total number of in-patient days per year associated with painful crises by 32 per cent through a reduction in hospital admissions.

Results

The unit costs of the main components of the interventions used for the monitoring and treatment of sickle cell disorder patients are listed in Tables 2 and 3.

Table 2 Diagnosis, routine monitoring and preventive interventions for patients with sickle cell disorders, and their corresponding unit costs

Interventions	Unit cost (£)	Years (inc.)	Frequency per year
Family studies	44.89	0–1	1
Physical examination	22.47	0–1	8
		2–5	4
		>5	3
Penicillin prophylaxis			
Child (per year)	5.25	15–60	1
Adult (per year)	10.50	0–14	1
Counselling (per hour)	27.07	0–1	2
		1–60	1
Haematology out-patient visit[a]	173.64	0–1	6
		1–5	3
		>5	2
Abdominal ultrasound	30.64	>10	0.5
Cardiology out-patient visit[b]	76.61	>5	0.5
Stress echocardiogram	64.35	>5	0.5
Respiratory medicine out-patient visit[c]	62.31	>5	0.5
Ophthalmology out-patient visit	76.61	>10	1
Nutrition assessment	56.18	>10	1
Pneumococcal vaccine	10.15	2	1
Hepatitis B vaccine (Engerix B)	38.45	1	1
Influenza vaccine	5.21	1–60	1

Costs are from finance departments, apart from the vaccines (British National Formulary). Frequency of interventions based on Refs 53–55.
[a] Haematology out-patient visit includes cost of basic tests such as full blood count ferritin, liver function tests, hepatitis B and C tests, creatinine, uric acid and urine analysis.
[b] Cardiac out-patient visit includes the cost of ECGs.
[c] Respiratory medicine out-patient visit includes cost of pulmonary function tests and chest X-ray.

The type and frequency of acute complications are described in Table 4a, and their respective episodic costs reported, as well as the annual costs of any sequelae. Table 4b presents the treatment assumptions made for the chronic conditions associated with sickle cell disorders, as well as the relevant lengths of survival.

Table 5a and b presents the baseline results to 60 years. The costs per surviving patient comprise the aggregation of the annual costs for the relevant treatment categories, which are multiplied by the survival rate to calculate the cost per original patient. A discount factor is applied to each year's total to estimate the discounted lifetime treatment costs. The

Table 3 Unit costs of interventions used in the treatment of patients with sickle cell disorders

Costs associated with blood transfusion		Costs associated with complications	
Intervention	**Unit cost (£)**	**Intervention**	**Unit cost (£)**
Hepatitis B immunization (Engerix B)	38.45	Intensive care unit (per day)	827.00
Day case nursing/hotel charge	33.71	Normal ward (per day)	209.00
Unit of blood[a]	59.17	Doppler echocardiography	74.56
Skeletal survey	73.54	CT scan	73.54
Complex eye assessment	82.73	Dialysis session	188.96
Full audiology assessment	81.71	Home oxygen therapy[b]	303.23
Hearing test	28.60	GP (per visit)	16.34
		Ultrasound scan	30.64
		Laser treatment	122.57
		Caesarean delivery[c]	787.00
		Bone marrow transplantation	50000.00
		Hydroxyurea (per day)	0.12

Unless stated otherwise, costs are from finance departments, the British National Formulary (desferal and Engerix B) or Personal Social Services Research Unit, University of Kent (GP visit).[56]
[a] A unit of blood includes costs of cross matching, a cannula and a filter.
[b] Cost from Midwest Medical Repair, Oxygen Sales & Service.
[c] Cost of caesarean delivery minus the cost of a normal delivery.

Table 4a Main assumptions for the costing of the treatment of acute complications in patients with sickle cell disorders, and the treatment costs per episode, or yearly equivalent costs for treatment of sequelae

Condition	Length of hospital stay		Special interventions[a]	Sequelae and survival assumptions[b]	Episode(E)/annual(A) cost (£)
	ITU	Normal			
Painful crisis[5]	–	7	–	–	1466.00(E)
Pneumococcal sepsis[12,24,43,57]	3	8	–	18% meningitis, of whom 31% die, of survivors:	4157.00(E)
				20% are deaf,	521.00(A)[c]
				5% are mentally retarded and	1404.00(A)[c]
				8% suffer permanent seizures	2554.00(A)[c]
Splenic sequestration[5,24,25,53,58,59]	1	6	simple transfusion	case fatality rate 0.033 and 0.06 with early and late diagnosis, respectively	2143.00(E)
Acute chest syndrome[5,58,60,61]					
child	2	5	exchange transfusion	–	2932.00(E)
adult	2	5	exchange transfusion	–	3162.00(E)
Stroke[50,62,63]	2	16	CT scan, exchange transfusion	20% die <3 weeks, another 10% die <1 year, of survivors; 25% need temporary rehabilitation for 2 years, 10% permanent care	64914.00(A)[d]
Acute anaemia[5,59,64]					
child	–	7	simple transfusion	–	1505.00(E)
adult	–	7	simple transfusion	–	1542.00(E)
Hip replacement[48]	–	–	–	–	4111.00(E)
Cholecystectomy[48]	–	–	–	–	1675.00(E)
Splenectomy[48]	–	–	–	–	1170.00(E)
Pregnancy care[44,64–68]	5	10	cared for as a high-risk pregnancy, 17 per cent higher rate of caesarian delivery	–	1682.00(E)[e]

[a] Special interventions are costed in addition to the aggregated average costs per hospital day. Assumptions about transfusion requirements are based on Refs 43, 48 and 54–56.
[b] Survivors of sequelae, and patients with conditions with non-specific survival effects, are assumed to have an average life expectancy similar to other patients with sickle cell diseases.
[c] Reference 12; US dollars are converted at $1.6 = £1, and sequelae are considered independently.
[d] Reference 62; an average cost per stroke survivor is presented.
[e] Extra antenatal and postnatal care is costed.

Table 4b Main assumptions for the costing of the treatment of chronic conditions in patients with sickle cell disorders, and the yearly equivalent costs

Condition	Length of hospital stay		Special interventions[a]	Survival assumptions	Episode(E)/annual(A) cost (£)
	ITU	Normal			
Leg ulcers[47,69,70]	–	–	cared for as out-patients and in the community	–	2255.00(A)
Retinopathy[58,71–73]	–	–	laser photocoagulation and out-patient care	–	298.00(A)
Renal failure[10]	–	–	haemodialysis	mean survival from onset of 4 years	29478.00(A)
Chronic lung disease[9]					
child	–	7 p.a.[b]	hypertransfusion, home oxygen therapy	mean survival from onset of 5 years	4680.00(A)
adult	–	7 p.a.[b]		mean survival from onset of 5 years	6926.00(A)

[a] Special interventions are costed in addition to the aggregated average costs per hospital day.
[b] Per annum.

Table 5a Average lifetime treatment costs for patients with sickle HbC disorder with respect to time of diagnosis (early and late diagnosed), and their calculation from annual treatment costs and survival[a,b]

	Early diagnosis				Late diagnosis			
Year	Cost per surviving patient	Survival rate (%)	Cost per original patient	Discounted cost per original patient	Cost per surviving patient	Survival rate (%)	Cost per original patient	Discounted cost per original patient
1	1560	99.81	1557	1557	555	99.63	553	553
2	1081	99.61	1076	1015	1221	99.28	1212	1143
3	1208	99.42	1201	1069	1208	98.97	1196	1064
4	1543	99.23	1531	1286	1543	98.67	1523	1278
5	1357	99.07	1344	1065	1404	98.47	1382	1095
6	1284	98.92	1270	949	1300	98.28	1277	955
7	1150	98.74	1135	800	1165	98.13	1143	806
8	1401	98.58	1382	919	1417	98.00	1389	924
9	1102	98.47	1085	681	1117	97.89	1094	686
10	1545	98.36	1520	900	1561	97.79	1526	903
11–15	7776	97.30	7599	3788	7838	96.74	7616	3797
16–20	8038	95.95	7765	2890	8038	95.39	7720	2873
21–25	11187	93.41	10548	2893	11187	92.87	10486	2877
26–30	12817	91.23	11788	2450	10495	90.70	9606	2022
31–35	13043	90.23	11820	1838	9171	89.70	8263	1284
36–40	13234	87.29	11810	1373	9362	86.78	8306	965
41–45	13425	77.31	10900	949	9553	76.86	7711	671
46–50	13616	69.63	9822	639	9744	69.22	6988	454
51–55	13807	67.09	9402	456	9935	66.70	6726	326
56–60	13998	64.64	9184	333	10127	64.27	6606	239
Total			113739	27848			92323	24917

[a] All costs are in £ uprated to 1998 values.
[b] Discount rate 6 per cent.

Table 5b Average lifetime treatment costs for patients with sickle cell anaemia with respect to time of diagnosis (early and late diagnosed), and their calculation from annual treatment costs and survival[a,b]

	Early diagnosis				Late diagnosis			
Year	Cost per surviving patient	Survival rate (%)	Cost per original patient	Discounted cost per original patient	Cost per surviving patient	Survival rate (%)	Cost per original patient	Discounted cost per original patient
1	1963	99.11	1967	1967	958	98.60	945	945
2	2180	98.14	2162	2040	2514	97.33	2447	2308
3	2419	97.20	2376	2115	2613	96.21	2514	2237
4	2719	96.37	2648	2223	2912	95.27	2775	2330
5	2541	95.57	2455	1945	2751	94.38	2596	2056
6	2260	94.82	2167	1619	2470	93.59	2311	1727
7	2586	94.16	2461	1735	2795	92.89	2597	1830
8	2313	93.56	2187	1454	2554	92.30	2357	1567
9	2164	93.04	2035	1277	2374	91.78	2178	1367
10	5477	92.57	5125	3033	5704	91.32	5209	3083
11–15	19530	89.80	17941	8936	20515	88.59	18394	9163
16–20	22842	86.40	20323	7567	21594	85.24	18764	7028
21–25	25990	80.46	21728	6034	23263	79.37	18979	5267
26–30	25901	74.31	20151	4197	23175	73.30	17596	3665
31–35	26537	66.38	18632	2903	23811	65.48	16316	2542
36–40	27257	58.34	17043	1985	24530	57.55	14969	1743
41–45	27976	48.05	14700	1281	25249	47.40	12948	1128
46–50	28695	38.81	12373	806	25969	38.28	10928	712
51–55	29415	29.00	9716	474	26688	28.61	8603	420
56–60	30134	21.67	7424	271	27407	21.38	6602	241
Total			185614	53861			170026	51360

[a] All costs are in £ uprated to 1998 values.
[b] Discount rate 6 per cent.

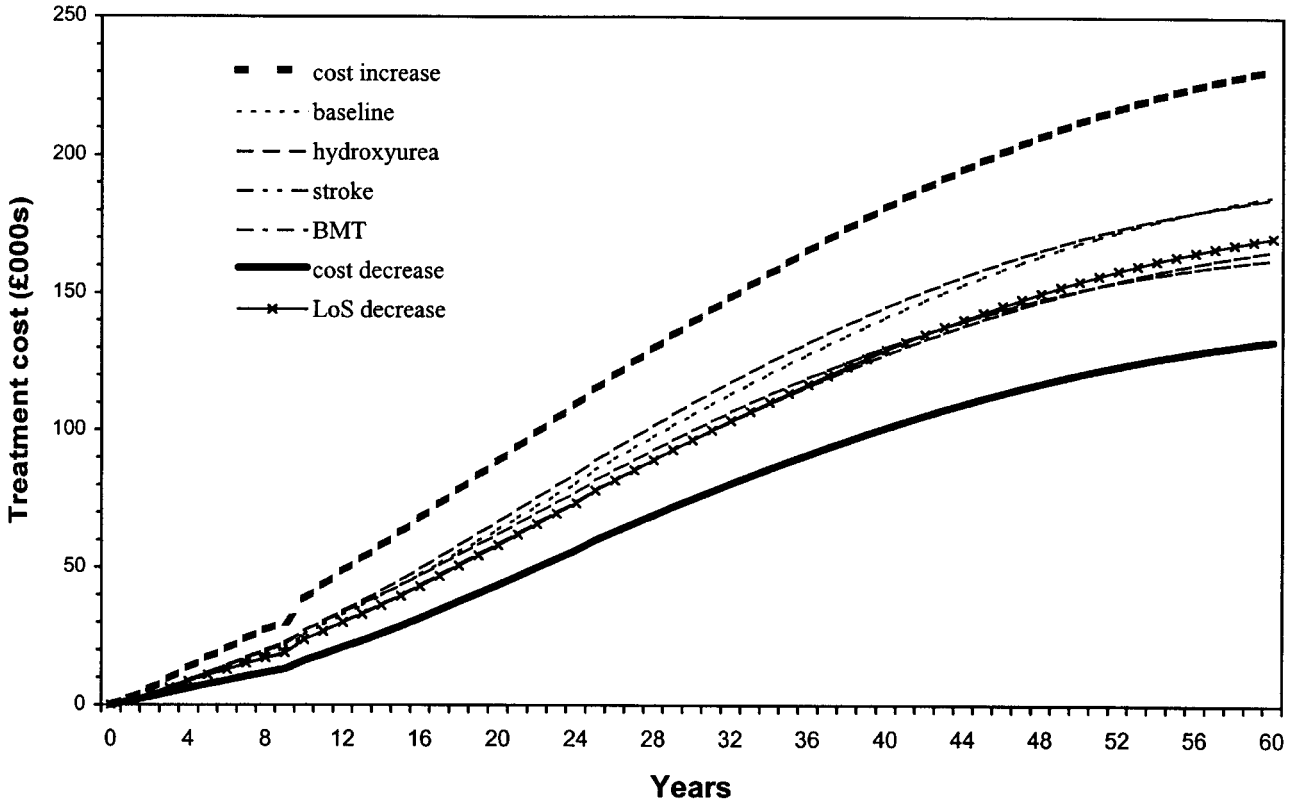

Figure 1 Cumulative undiscounted treatment costs of sickle cell anaemia, early diagnosed, according to alternative treatment and cost assumptions.

undiscounted total lifetime treatment costs for a patient with sickle cell anaemia was estimated to either £185 614 (early diagnosis) or £170 026 (late diagnosis), depending on whether the child was diagnosed via a screening programme. The discounted figures (6 per cent discount rate) were £53 861 and £51 360, respectively. The respective estimates for patients with sickle HbC disease were £113 739 and £92 323, and £27 848 and £24 917 discounted.

The observed differences up to 10 years are illustrative: for sickle cell anaemia patients the extra costs associated with early diagnosis have been reversed by the age of 10, as a result of the prevention of serious sequelae, and late-diagnosed patients have higher cumulative treatment costs. However, the cost of treating early-diagnosed sickle HbC cases remains around £800 higher than for late-diagnosed children by the age of 10. After 60 years, additional treatment costs associated with the prevention of a late diagnosis of sickle cell anaemia have reversed again, because of the lower mortality rate, so that early diagnosed patients require over £15 000 in treatment costs (£2500 discounted). The respective differences for sickle HbC cases are £21 416 and £2931.

The sensitivity analyses, presented in Figure 1, demonstrate the impact of five alternative scenarios. Doubling the cost of in-patient bed days has the largest effect, moving the undiscounted lifetime treatment costs to over £231 000 (discounted £53 860), a 25 per cent (34 per cent) increase. All the other assumptions reduced the lifetime costs. Increased use of BMT would reduce the undiscounted lifetime treatment cost by 12 per cent (5 per cent undiscounted), whereas a 50 per cent reduction in the incidence of stroke cuts undiscounted treatment costs by 11 per cent (£165 680), and discounted costs by 9 per cent (£49 010). Increased uptake of hydroxyurea to control painful crises reduced undiscounted costs considerably, by 17 per cent (£153 470), although discounted costs fell by only 1 per cent (£53 540). However, it must be borne in mind that the use of BMT and hydroxyurea, and reduced stroke incidence also improve overall morbidity and mortality rates.

Implementing the community-based model of caring for patients experiencing painful crises, assuming a 32 per cent reduction in the number of in-patient days, resulted in a reduction in the discounted and undiscounted lifetime treatment costs of 8 per cent (£49 363 and £170 496, respectively). The largest decrease in the lifetime costs arises when the cost of an in-patient bed day was halved, resulting in an undiscounted cost of £132 820 (£37 470 undiscounted), a reduction of over 28 per cent (30 per cent).

The process of calculating the differential treatment costs for early and late diagnosed sickle cell disorder patients produced

Table 6 Differential morbidity and mortality between screen-detected early diagnosed and clinically presenting late diagnosed cohorts of sickle cell disorder patients up to the age of 10

Patient category	Early deaths/ 100 patients	Early deaths averted/100 late diagnoses prevented	Cases of severe disability/ 1000 patients	Cases of severe disability prevented/1000 late diagnoses prevented
Sickle cell anaemia				
late diagnosis	8.68		2.1	
early diagnosis	7.43		0.5	
Difference		1.25		1.6
Sickle HbC disease				
late diagnosis	2.21		0.5	
early diagnosis	1.64		0.1	
Difference		0.57		0.4

additional data describing the morbidity and mortality avoided through early diagnosis. The results are presented in Table 6. Early deaths averted are defined as the difference in the mortality rate, between the screened and unscreened cohorts, up to the age of 10. For sickle cell anaemia and sickle HbC disease, it was found that 1.25 and 0.57, respectively, early deaths were averted for every 100 early-diagnosed children. This means that a screening programme, to prevent one early death, must diagnose 80 sickle cell anaemia cases; the equivalent figure for sickle HbC cases is 175. Early diagnosis also reduces the frequency of serious disability, as a result of the reduction in the incidence pneumoccocal sepsis. It was estimated that for sickle cell anaemia and sickle HbC disease, respectively, 1.6 and 0.4 cases of severe disability would be avoided every 1000 early diagnoses. Thus, a screening programme, to prevent one early death, must diagnose 625 sickle cell anaemia cases; the equivalent figure for sickle HbC cases is 2500.

Discussion

The resource usage presents a best estimate given the available state of knowledge. There remains considerable uncertainty, however, about the survival of cohorts of patients with sickle cell disorders who are currently born and the possible development of new complications or new interventions. The method adopted in this study allows parameters, in particular resource use and cost parameters, to be varied according to local conditions, as well as facilitating the inclusion of new interventions, and their associated impact on survival and complications.

The baseline results show that sickle cell anaemia in particular is currently an expensive condition to treat, although it appears to be significantly less costly than other haemoglobinopathies, such as β thalassaemia major.[35] The annual number of pregnancies affected with sickle cell disorders in the United Kingdom has recently been put at around 170, with sickle cell anaemia accounting for 74 per cent of cases, and sickle HbC disease for 26 per cent.[15] Thus, a maximum estimate of the cost to the NHS of treating sickle cell disorders in any given year would be 170 multiplied by the undiscounted total lifetime treatment costs, or £28.37 million.

The geographical distribution of cases of sickle cell disorders around the United Kingdom is highly skewed, with the majority of districts experiencing a single case only very rarely. Indeed, only eight districts in the United Kingdom have been found to have a foetal sickle cell disorder prevalence of over 10 per 10 000 pregnancies.[15] If these districts can prove that the incursion of costs associated with the treatment of sickle cell disorders is not balanced by a reduction in the costs of treating other expensive conditions they may justifiably argue for additional funding.

Sensitivity analyses were used to explore the impact of some alternative treatment and cost assumptions; they suggested that most developments will not have a major impact on the lifetime treatment costs, although the increased uptake of hydroxyurea could be a significant factor.

The estimates of lifetime treatment costs derived in this paper are intended to serve as indicators for the approximate magnitude of expenditure in treating patients with sickle cell disorders. Although the estimated survival rates show a large proportion of patients surviving to 60 years, especially of sickle HbC disease, it was felt that any survival assumptions made beyond that age would be sufficiently uncertain to justify 60 years as a cut-off point for the inclusion of treatment costs. Moreover, discounting the annual costs minimizes the impact of excluding costs incurred past 60 years.

The costs used in the study were chosen, as far as possible, to represent the costs faced by decision-makers within the UK NHS. Although the cost estimates were obtained from a variety of sources, the majority of costs were estimated in conjunction with hospital finance departments. Drug costs were taken from the British National Formulary, which may tend to overestimate the unit costs paid by hospitals, which may negotiate some reductions in price.

The only costs obtained from the literature referred to the long-term costs of caring for patients with chronic sequelae. The costs of treating stroke patients were taken from a

UK-based paper,[62] although the costs of treatment of sepsis sequelae were available only from a US-based paper.[12] More detailed analysis of such costs was beyond the resources of the current study, but it was felt that the published estimates were suitably rigorous for inclusion in the study. Moreover, the impact of the cost of stroke was analysed by looking at the effect of halving the incidence rate of stroke in the sickle population.

The estimates are likely to present minimum values, as only major health service interventions have been included. It is recognized that non-health care expenditure, related to sickle cell disorders, will also be required during the course of a lifetime. The accuracy of the results should not be affected significantly, as a US study has found that 90 per cent of medical costs for sickle cell disorder patients resulted from hospitalization.[37] The possible impact of community-based models of care for patients with sickle cell disorders was explored in the sensitivity analysis. Treating and educating patients experiencing painful crises in the home was found to reduce the total lifetime treatment costs, although the overall impact on costs was not huge. However, the increased ability to care for themselves could also positively affect patients' quality of life, so such programmes could benefit all concerned.

It was recognized that recent guidelines for economic evaluation have recommended that resource use be identified and valued from the societal perspective,[38] thus requiring the inclusion of such non-health care resources as child care and transportation, as well as some form of measurement of the effects of lost productivity. The estimation of the non-health care resources required by patients with sickle cell disorders would be an interesting exercise, as would the prediction of the employment pathways of sickle cell disorder patients. However, it was felt that the complexities and uncertainties inherent in such an exercise would dwarf those imposed in the estimation of the lifetime treatment costs. It was also felt that policy-makers would be most likely to include health care costs alone in their allocation decisions.

The calculation of differential morbidity and early mortality rates between early diagnosed (screened) and late diagnosed (unscreened) cohorts was based on the differential survival presented in Table 5a and b, which includes assumptions that all children identified by a screening programme with sickle cell disorder were given appropriate care, and that patients had a compliance to prophylactic penicillin therapy similar to that achieved by Gaston *et al*.[21] Both assumptions are conservative[39,40] and likely to exaggerate the number of early deaths averted as a result of the early management of the disease.

Gessner *et al*. have previously calculated the number of deaths averted as a result of screen detection as 2.44 per 100 cases.[12] The difference between their estimate and the estimate of 1.25 presented here is due to assumptions made regarding the presentation of non-screen detected patients with sickle cell disease. Gessner *et al*. have assumed that all non-screen detected patients present at exactly 1.75 years, whereas the data used in this paper reflect an assumption of earlier presentation with symptoms. The potential of screening to avert deaths is increased in locations where non-screened patients present later, because there is a greater risk reduction in the incidence of serious illness.

Cross-sectional analyses of the costs associated with sickle cell disorders have been published,[37,41] as have the lifetime treatment costs of other disease areas.[42] The calculation of the lifetime treatment costs of sickle cell disorders provides health authorities with information regarding the likely burden on resources of sickle cell disorder patients over the course of their lifetime. This information may be used at a local level, in conjunction with information on the age-specific prevalence of sickle cell disorders in the area, to ensure that an adequate capacity of resources is available. The details provided in this paper could then be used at the disaggregated level of the categories of interventions.

Alternatively, lifetime treatment costs should also be of interest to those involved in the provision of screening programmes, antenatally and neonatally, as well as to policy-makers interested in increasing the information base on which policy is decided. Screening for sickle cell disorders alters the level of resources used in two, opposite, directions. First, both antenatal and neonatal screening improve the prognosis of an affected baby through early diagnosis, preventing morbidity and mortality, with the subsequent effect that the treatment costs of early diagnosed patients are, on average, more than those of their late diagnosed counterparts. Secondly, antenatal screening saves the full lifetime treatment costs whenever an affected pregnancy is terminated. Such calculation of lifetime costs for sickle cell disorders may be used to aid policy-makers with respect to the provision of antenatal and neonatal screening programmes.

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