Health Technology Assessment 1999; Vol. 3: No. 11

Review

Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis

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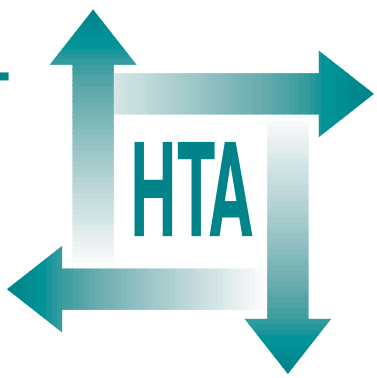
Health Technology Assessment
NHS R&D HTA Programme



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Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis

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Competing interests:
none declared

Published September 1999

This report should be referenced as follows:

Zeuner D, Ades AE, Karnon J, Brown J, Dezateux C, Anionwu EN. Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis. *Health Technol Assess* 1999;**3**(11).

Health Technology Assessment is indexed in *Index Medicus*/MEDLINE and *Excerpta Medica*/EMBASE. Copies of the Executive Summaries are available from the NCCHTA web site (see overleaf).

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The overall aim of the NHS R&D Health Technology Assessment (HTA) programme is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS. Research is undertaken in those areas where the evidence will lead to the greatest benefits to patients, either through improved patient outcomes or the most efficient use of NHS resources.

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This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care. It was identified as a priority by the Population Screening Panel and funded as project number 93/33/01.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The editors have tried to ensure the accuracy of this report but cannot accept responsibility for any errors or omissions. They would like to thank the referees for their constructive comments on the draft document.

ISSN 1366-5278

Published by Core Research, Alton, on behalf of the NCCHTA.
Printed on acid-free paper in the UK by The Basingstoke Press, Basingstoke.

Copies of this report can be obtained from:

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Contents

List of abbreviations

ARMS*	amplification refractory mutation system
$\alpha^0\alpha^0$	α^0-thalassaemia hydrops fetalis (genotype)
BA*	black African
Ban*	Bangladeshi
ββ	β-thalassaemia major (genotype)
BC*	black Caribbean
BMT*	bone marrow transplantation
BO*	black other
Chi*	Chinese
CVS	chorionic villus sampling
Cyp*	Cypriot
DdeI*	name of a restriction enzyme
Eβ	haemoglobin E β-thalassaemia (genotype)
GP	general practitioner
Hb	haemoglobin
Hb-pathy	haemoglobinopathy
HPLC	high-performance liquid chromatography
ICER	incremental cost-effectiveness ratio
IEF	isoelectric focusing
Ind*	Indian
Ita*	Italian
ITU*	intensive therapy unit
MCH	mean corpuscular haemoglobin
MCV	mean corpuscular volume
NE*	north European
OA*	other Asian
Oth*	other
Pak*	Pakistani
PCR	polymerase chain reaction
PKU	phenylketonuria
PND	prenatal diagnosis
Prg*	programme
QALY	quality adjusted life years
RFLP	restriction fragment length polymorphism
S*	selective screening strategy
Sβ	sickle cell β-thalassaemia (genotype)
SC	sickle haemoglobin C disease (genotype)
SCD*	sickle cell disease
SD	sickle haemoglobin D disease (genotype)
SMAC	Standing Medical Advisory Committee
SS	sickle cell anaemia (genotype)
thal	thalassaemia
TOP	termination of pregnancy
U*	universal screening on 'best plausable case' assumptions
U^{+*}	universal screening on baseline assumptions

* Used only in tables

Executive summary

Background

Antenatal haemoglobinopathy screening is intended to identify pregnancies that are at risk of an affected fetus. If the mother is identified as a carrier, testing is offered to her partner, with a view to offering prenatal diagnosis (PND) and termination of pregnancy (TOP) to carrier couples.

Neonatal testing is intended to identify newborns who are affected with sickle cell disease but not already diagnosed through PND, in order promptly to institute penicillin prophylaxis and comprehensive care, which reduce morbidity and mortality. Infants with presumed sickle cell disease are re-tested, and parents of affected and carrier infants are offered counselling.

Objectives of the review

The objectives were:

- to review alternative options for antenatal and neonatal haemoglobinopathy screening programmes in the UK
- to develop a decision model that compares the cost-effectiveness of universal testing and selective testing based on maternal ethnic status
- to apply the decision model to estimates of local health district ethnic composition
- to identify areas for further policy development and research.

Characterisation of alternative strategies

In a universal antenatal screening programme, all women are offered testing. In a selective programme, testing is offered to all non-north European women and to all women with a known low mean corpuscular haemoglobin (MCH) result, regardless of ethnic status. Antenatal screening for thalassaemia is therefore always universal. An alternative option, testing based exclusively on ethnicity regardless of MCH result, was examined in subsidiary analyses.

Neonatal screening would be either universal (all newborns not already diagnosed prenatally) or selective (undiagnosed babies of non-north European mothers), with selection being independent of the antenatal programme. A targeted programme, which would take account of parental carrier results to reduce the number of neonates requiring screening, was considered in subsidiary analyses. It was assumed that neonatal testing would be based on newborn heel prick samples collected on filter paper for routine phenylketonuria and congenital hypothyroidism tests. Explicit no antenatal testing and no neonatal testing policies were examined in subsidiary analyses.

Ethnic ascertainment was assumed to be part of routine antenatal booking and its costs were therefore not included in the analysis of screening, although costs were varied in sensitivity analyses.

It was assumed that the coverage of screening among ethnic minorities in a universal programme would never be less than the coverage achieved by a selective programme.

Methods

Disease progression models were developed in order to estimate the lifetime treatment costs and life expectancy of children with haemoglobinopathies and, where relevant, the effects of early diagnosis.

A computer model of the screening process was developed. For an antenatal population with any given ethnic composition, it predicted the fetal prevalence of haemoglobinopathies and calculated the costs and outcomes of each screening option.

The effectiveness of antenatal screening was measured by the expected number of women with affected fetuses who were offered choice over the outcome of a pregnancy. The number of affected live births prevented by screening was examined in subsidiary analyses. The effectiveness of neonatal screening was measured by the number of late diagnoses of sickle cell disease prevented. Costs were based on a health service perspective.

This model was applied to ethnic composition data for district health authorities in the UK, based on their 1993 boundaries. Parameter values and their ranges were identified from published and unpublished sources, informed by expert opinion. The preferred screening strategy in each district was estimated by using incremental cost-effectiveness ratios (ICERs), the additional cost of a universal compared with a selective programme per additional unit of effect.

It was assumed that districts would be willing to pay between £50,000 and £150,000 to offer an additional choice over the outcome of an affected fetus, based on an analysis of similar screening programmes, and between £10,000 and £50,000 to prevent an additional late diagnosis of sickle cell disease, based on review of other neonatal screening programmes and the estimated benefits of early diagnosis. Estimated lifetime treatment costs were used as benchmarks for affected live birth prevented ICERs in subsidiary analyses.

Results

Findings relevant to both antenatal and neonatal screening

- Neither antenatal screening of north European women nor neonatal screening of their children is cost-effective under the criteria used in the review, even under extreme assumptions about the frequency of the sickle cell trait and inter-ethnic unions.
- The rationale for universal screening is therefore based on the presumption that it will result in a higher coverage among ethnic minority women and their children.
- Lowering the failure to screen rate in a selective programme is always more cost-effective than changing to a universal policy.
- Selective screening is highly cost-effective compared with no screening.
- If costs of ethnic ascertainment and pretest counselling are included, the case for universal compared with selective screening is slightly strengthened, but the case for selective screening compared with no screening is substantially weakened.
- The use of economic criteria alone to determine whether a local screening policy should be universal or selective is not equitable: ethnic minority mothers and infants in lower-prevalence areas would receive a lower-coverage screening service than would be available to them in a high-prevalence area.

Findings relevant to antenatal screening alone

- Universal antenatal screening costs were estimated to be in the range £35,000–£145,000 per 10,000 antenatal population, and increased with prevalence. Selective screening costs were £30,000 less in low-prevalence areas and £18,000 less in high-prevalence areas.
- Adverse screening outcomes (PND-induced miscarriage, TOP with unaffected fetuses) would be very rare in both universal and selective strategies.
- If the purpose of antenatal screening was the prevention of affected live births rather than the offering of reproductive choice, universal screening would be difficult to justify in any district in the UK on the basis of costs averted, but selective screening would still be preferred to no screening.

Findings relevant to neonatal screening alone

- Universal neonatal screening was estimated to cost approximately £22,000 per 10,000 antenatal population. Selective neonatal screening costs range from less than £200 per 10,000 antenatal population to £11,500 in an area with 50% of the population from ethnic minorities.
- Antenatal screening, even if universal, would not render neonatal screening redundant at currently estimated rates of PND uptake (approximately 15% in black women). A high (80%) uptake of PND would considerably weaken the case for universal screening, but would not affect the case for selective neonatal screening in preference to no neonatal screening.
- The costs associated with neonatally identified carrier infants are small in relation to overall programme costs and do not alter the comparative cost-effectiveness of universal and selective strategies.
- The targeted screening of infants is a cost-effective alternative to selective screening, but would require robust information systems that have not yet been developed.

Conclusions

- Selective screening is cost-effective in comparison with no screening.
- Universal screening may be cost-effective in higher-prevalence districts, depending on the coverage of selective screening and economic willingness-to-pay criteria.

- On baseline assumptions, if coverage among ethnic minorities in selective screening was 5% lower than in universal screening, a universal antenatal strategy would be cost-effective at a fetal sickle cell disease prevalence above 5–12 per 10,000 antenatal population and a universal neonatal strategy would be cost-effective at a prevalence above 7–18 per 10,000.
- Based on the health districts pertaining in 1993, the model would imply that up to 15 out of 170 districts should consider universal antenatal and/or universal neonatal screening. However, if selective screening obtained a coverage only 1% lower than universal screening, the latter would be required in, at most, two districts.
- Equity considerations suggest that:
  - all districts could justifiably consider adopting explicit selective or universal strategies for antenatal and neonatal screening
  - local policy could be determined on the basis of the same economic and prevalence criteria, applied nationally
  - minimum standards for coverage of screening could be adopted and coverage monitored routinely
  - procedures for selection based on ethnicity could be standardised.

Implications and recommendations

- Research is needed to develop information protocols that can routinely deliver statistics on the coverage of antenatal and neonatal screening within ethnic groups. A pilot study in which such protocols are implemented should be considered.
- Research is needed to:
  - establish the prevalence of fetal haemoglobinopathies throughout the UK
  - ascertain the frequency and causes of: (1) the failure to offer reproductive choice to mothers with an affected fetus; and (2) the late diagnosis of haemoglobinopathies in children
  - determine the relationship between the timing of maternal carrier and couple testing and the uptake of PND and TOP.
- Medicolegal and ethical studies are needed to determine how much pretest information about antenatal and neonatal screening is required, in order that consent to testing can be considered to be informed.

Chapter 1
Introduction

Background

The haemoglobin (Hb) disorders comprise the sickle cell disorders and the thalassaemias. They are serious inherited medical conditions with a reduced life expectancy and require lifelong treatment.[1–3] They mainly affect black, Asian and Mediterranean ethnic minorities.[4,5] In the UK, about 10% of births are to women from these high-risk groups,[5,6] which, although heavily concentrated in major conurbations, occur in most districts.[6,7] Antenatal screening to give couples reproductive choice over the outcome of pregnancy, and neonatal screening to detect babies who are affected by sickle cell disorders and require prophylactic treatment, comply with the general principles of screening.[8–10] The offer is regarded as a standard part of healthcare delivery.[5,6,11–13] Many would consider it unacceptable for a district to have an explicit policy not to screen ethnic minorities who are at risk; from a legal point of view, the omission of this service has on occasion been judged to be negligent.[14,15] Instead, the main policy decision for both antenatal and neonatal screening components is between a universal and a selective approach, the latter limiting screening to ethnic minority groups who are considered to be at high risk. The workload created by universal screening, with its associated resource implications and potential increase in adverse screening consequences, has to be balanced against the possibility of missed cases[16,17] and the additional procedural and administrative costs due to the selection process,[18] especially in view of increasing inter-ethnic mixing.[19,20]

Current guidance

UK policies

In 1988 the British Society for Haematology formulated guidelines for haemoglobinopathy (Hb-pathy) screening. It recommended that, in principle, antenatal and neonatal screening should be selective, but acknowledged that for certain localities a universal neonatal approach might be necessary to cover all high-risk babies.[21] In 1993 the Standing Medical Advisory Committee (SMAC) on sickle cell, thalassaemia and other haemoglobinopathies[5] published recommendations that districts with more than 15% of the antenatal population at risk for sickle cell disorders should adopt a universal antenatal and neonatal screening strategy. The chosen cut-off figure was based on the neonatal screening experience of one locality and has been criticised for its lack of generalisability.[7,22] The more recent guidelines for screening for haemoglobin disorders from the NHS Centre for Reviews and Dissemination[6] reiterate the 15% figure for neonatal screening and emphasise the need for further research.

Policies in other countries

Other agencies, from the USA and Canada, and the WHO, have explicitly addressed the policy question of universal versus selective screening for Hb disorders and have published recommendations. Although influenced by the particular demography of different countries, three groups stand out:

- those who acknowledge that decisions about a universal or selective antenatal and neonatal approach should be addressed locally, taking into consideration disease prevalence, cost-effectiveness of individual screening programmes and available resources[23,24]
- those who, for neonatal screening, categorically propose a universal approach because of the fallibility of targeting high-risk populations by assigning ethnic origin[25,26]
- those who propose selective screening, especially antenatally and in geographical areas with a small population at risk, because of the considerable expense incurred in a universal approach.[27,28]

Current UK practice

Current screening practice in the UK is inconsistent.[29–35] Some districts have no explicit policy but eligibility for screening is decided in an *ad hoc* manner, while other districts with comparable ethnic compositions have adopted different combinations of antenatal and neonatal strategies. These discrepancies highlight potential inefficiency and inequity, and indicate uncertainty amongst policy makers about the most appropriate local configuration of services.

The project remit

The project was commissioned within the Research and Development Health Technology Assessment Programme under the title: *Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis*. Its remit was to develop a decision model that can predict the main screening outcomes and costs associated with **universal** and **selective** strategies **for any given ethnic distribution of the antenatal population**. The model is designed as a decision tool for policy makers. The main aims of the project are:

- to compare the cost-effectiveness of selective and universal antenatal screening strategies for all district health authorities in the UK
- to compare the cost-effectiveness of selective and universal neonatal screening options, given either a selective or a universal antenatal configuration
- to determine the most important parameters in the screening process that influence the cost-effectiveness of antenatal and neonatal programmes
- to identify areas where further research is required.

Parallel project

A second related project was commissioned from a group based at the Central Middlesex Hospital (lead applicant Professor Sally Davies) under the title: *Systematic review of screening for haemoglobinopathies*. This proposal encompassed a more general review of screening for Hb-pathies, and an assessment of the prevalence of Hb-pathy carriers in different ethnic groups in the UK. This work has not been duplicated here. After joint discussion, the two teams decided to proceed with separate studies because of the particular focus of each project. Where information has been shared this has been noted in the text.

Chapter 2

Review of haemoglobinopathy screening strategies

Purpose of the review and information sources

The purpose of the review was to characterise current antenatal and neonatal screening strategies that were relevant for inclusion in the decision model. To put current practice into perspective, future developments that are likely to change the role of screening or the screening process have been mentioned briefly. According to the remit of the project, alternative strategies considered are those that vary according to **who** should be screened, rather than **how** they should be screened. However, details of a 'generic' screening process, applicable to different antenatal and neonatal populations eligible for screening, had to be determined to inform the structure of the decision model and enable costing of the strategies. Details cover operational issues of the screening process, laboratory methods for screening and confirmatory tests, as well as education and counselling. They were chosen to reflect current UK practice and comply with minimum acceptable standards, to be relevant to the majority of districts. Information for the review was gathered from practising experts (appendix 1), published and unpublished literature, and routine data sources, and is referenced in the text. The literature search strategy employed is listed in appendix 2.

Haemoglobin disorders

The Hb-pathies are caused by a range of different deletional and non-deletional mutations of globin genes, which determine the structure as well as the amount of the various globin chains of the Hb molecule.[36] In sickle cell disorders, the mutations involve the β-globin gene and result in qualitative changes of the β-globin chain. The consequences are the aggregation of structurally abnormal Hb with subsequent vaso-occlusion and red cell destruction, leading to pain, anaemia and damage to various organs.[1] In thalassaemias the mutations affect α-, β- and rarely also δ-globin genes and corresponding globin chains. This leads to reduced production and increased destruction of Hb, causing severe haemolytic anaemia.[2,3]

Quantitative and qualitative globin chain changes can also occur together, for example in sickle cell β-thalassaemia. Hb disorders have a wide spectrum of severity and require lifelong treatment.

Hb disorders follow an autosomal-recessive pattern of inheritance, which gives a 1:4 chance of an individual being affected if both parents are carriers of an abnormal Hb gene (Hb-pathy trait). Carriers who have inherited a trait from one parent (heterozygotes) and are healthy must be distinguished from the much smaller number of people who have inherited a trait from both parents (homozygotes or compound heterozygotes) and may or may not be affected by a clinically significant disorder.[23]

Table 1 summarises the main Hb disorders, and their corresponding genotypes, that are included in the study. They represent the most commonly encountered types in the UK.[5,6,37] Because, to date, almost 700 Hb variants have been described,[38] a very large number of potential combinations exist. However, most of them are clinically insignificant.[36] Disease due to rare combinations of unusual Hb variants such as Hb^{Lepore} and HbO^{Arab} have

TABLE 1 *The main haemoglobin disorders included in this study*

Disorder	Genotype
Sickle cell disorders	
Sickle cell anaemia	*SS*
Sickle HbC disease	*SC*
Sickle cell β-thalassaemia	*Sβ*
Sickle HbD disease	*SD*
Thalassaemias	
β-Thalassaemia major	*ββ*
HbE β-thalassaemia	*Eβ*
α^0-Thalassaemia hydrops fetalis	$\alpha^0\alpha^0$

The genotypes ββ, Eβ, Sβ include β^0, β^+ and rare δβ gene mutations

The genotype $\alpha^0\alpha^0$ indicates absence or non-function of all four α genes

HbD disease refers to HbD^{Punjab}

Source: References 1–3

been omitted from the analysis because they constitute a very small proportion of the Hb-pathies encountered in the UK.[39]

Sickle cell disorders

Amongst the sickle cell disorders, the most common and generally most severe form is sickle cell anaemia.[40] Clinically, sickle HbD disease[41] and sickle β-thalassaemia ($S\beta^0$)[42] are of comparable severity to sickle cell anaemia, whereas sickle HbC disease[43] and sickle β-thalassaemia ($S\beta^+$)[42] often have a milder course.

In unscreened individuals with sickle cell anaemia the onset of specific symptoms is usually in early infancy, with the first manifestation occasionally being fatal.[44,45] In sickle HbC disease, presentation is later at an average age of about 5 years and is generally less dramatic.[46]

Sickle cell disorders may affect any organ system in the body and produce a wide range of symptoms, which vary with age, type of disease and also country of residence.[1] In the UK, the most common and important acute events include painful crisis, pneumococcal sepsis, splenic sequestration, acute chest syndrome, stroke and acute anaemia.[47–51] Sickle cell disorders are increasingly becoming chronic diseases, causing, for example, renal failure[52] and chronic lung disease.[53] In sickle HbC disease, avascular necrosis of the hip joint and retinopathy are common.[43] There is variation, mostly unpredictable, in the severity and pattern of disease within each condition as well as within individual patients.[1]

Life expectancy for sickle cell disorders has improved considerably over the last decades. In the 1960s and 1970s the majority of patients died in infancy or childhood.[54] In contrast, in 1994 a prospective US multicentre study of over 3700 patients reported a median survival for sickle cell anaemia of 42 years in men and 48 years in women, the corresponding figures for sickle HbC disease being 60 and 68 years respectively.[54]

Conventional treatment for sickle cell disorders includes penicillin prophylaxis to reduce the incidence of overwhelming pneumococcal infection, especially in the first 5 years of life,[55,56] when the risk is highest, and supportive treatment to alleviate symptoms.[57,58] Recent advances in the management of sickle cell disorders include bone marrow transplantation,[59,60] which can be curative but is associated with significant mortality and is currently restricted to selected patients,[61–63] and treatment with hydroxyurea to reduce the frequency and severity of sickle crises, which has recently been evaluated by a small randomised controlled trial in children in Belgium,[64] and a much larger one in adults in the USA.[65]

Thalassaemias

The most common type of thalassaemia is β-thalassaemia major. HbE β-thalassaemia occurs less frequently but most forms are clinically comparable.[66] α^0-Thalassaemia hydrops fetalis is a relatively rare condition in the UK. It is associated with maternal morbidity and mortality during pregnancy and is almost invariably fatal *in utero* or shortly after birth.[2]

The clinical course of β-thalassaemia major (and to a lesser degree HbE β-thalassaemia) is generally more predictable than that of sickle cell disorders. β-Thalassaemia major usually presents in the first year of life with progressive haemolytic anaemia.[67] Unless treated by regular monthly blood transfusions, combined with daily subcutaneous iron chelation therapy, patients do not usually survive the teenage years.[68] Morbidity is related to: anaemia, which, if it is uncontrolled, leads to bone marrow expansion, subsequent bony deformities, gross enlargement of the liver and spleen, and stunted growth; and the side-effects of blood transfusions, which include chronic organ damage due to iron overload, especially of the heart and endocrine organs, and the increased risk of viral infections.[58,69,70] The introduction of the chelating agent, desferrioxamine, has reduced morbidity and mortality due to iron overload,[71–73] but it can itself impair vision, hearing and growth.[74] Furthermore, compliance with the daily subcutaneous infusions can be a problem, especially during adolescence.[67,75,76]

Life expectancy for β-thalassaemia major has improved considerably since the introduction of iron chelation in the late 1970s.[68] The survival of members of a large Italian cohort of patients born after 1970 was reported to be 88% by age 20.[77] A smaller group of UK patients, the majority of whom had been receiving optimal treatment since 1977, showed 85% surviving at 36 years.[78] However, the survival of patients who commence optimal treatment from infancy is unknown and it is uncertain whether the favourable trend will continue.

Important advances in the treatment of β-thalassaemia major include the development

of an orally-active iron-chelating agent[79] and bone marrow transplantation.[80,81] The latter is curative and considered increasingly in patients for whom there is a compatible donor sibling available[82] and in whom pathological changes related to the disease or its treatment are not yet manifest.[80]

Future treatment alternatives

The main future therapeutic developments expected for both sickle cell disorders and β-thalassaemia major (including HbE β-thalassaemia) involve pharmacological modulation of the diseases,[83,84] especially through the augmentation of protective fetal Hb levels,[85,86] and attempts to cure the conditions, either through the transplantation of cells containing the normal β-globin gene or through direct gene therapy. Advances in transplantation technology include case reports of *in-utero* stem cell transplantation to overcome rejection[87] and transplantation of cord blood from unrelated donors to solve the problem of the limited availability of related donors.[88] Direct gene therapy,[89] the ultimate goal of curative treatment, is still in an experimental stage, with progress depending mainly on the development of an ideal vector system for gene transfer.[90]

Antenatal screening strategies

Outline of the screening process

Ascertainment of couples at risk for having an affected fetus

Antenatal screening for Hb disorders involves a **stepwise process** of carrier testing of expectant mothers and, if they are positive, their partners, to identify pregnancies at risk of an affected fetus. Carrier testing consists of a cascade of sequential laboratory tests, starting with measurement of the mean corpuscular Hb (MCH) and characterisation of structural Hb variants. There is no clear-cut difference between screening and diagnostic tests to ascertain carrier status; instead, the laboratory test sequence can best be characterised in the form of an algorithm (*Figure 1*), which is explained in detail later in this chapter (pp. 8–10). Not all couples in whom both partners are carriers of a Hb-pathy trait are at risk of an affected fetus because some combinations of Hb-pathy traits do not lead to disease. *Table 2* summarises the possible fetal genotype combinations resulting from the parental carrier states considered in this review and indicates those that lead to a clinically affected fetus.

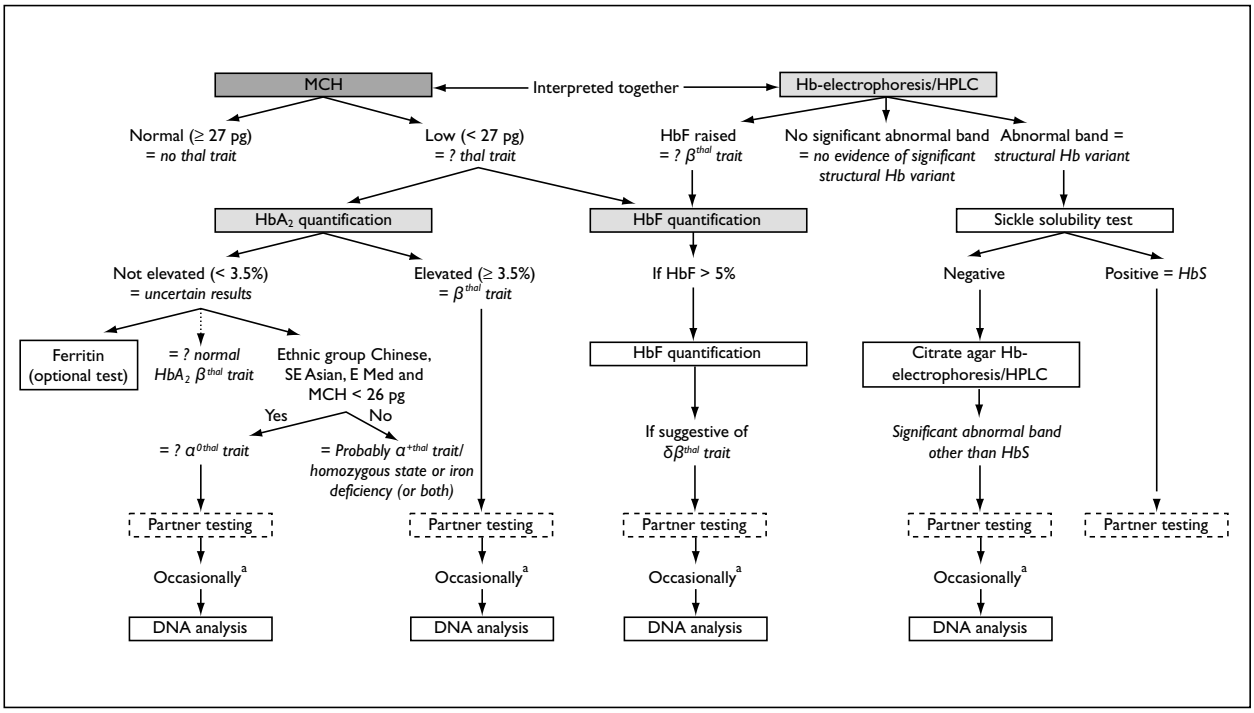

FIGURE 1 *Antenatal laboratory screening algorithm for carrier testing*

[a] When the risk assessment depends on the definite diagnosis of carrier results in the woman and/or her partner (SE Asian, south-east Asian; E Med, east Mediterranean; ·····>, rare 'normal HbA_2 β^{thal} trait' not considered in the report; ▭, part of routine obstetric care; ▭, with HPLC technology constitutes one test; italics, indicate test result interpretation; ▭▭, partner testing; ▭, laboratory test)

TABLE 2 *Fetal genotype combinations resulting from the parental carrier states considered in this review*

Paternal genotype	Maternal genotype						
	AS	***AC***	***AD***	***AE***	***Aβ***	***Aα***	***AA***
AS	*AA* (0.25) *AS* (0.50) *SS* (0.25)	*AA* (0.25) *AS* (0.25) *AC* (0.25) *SC* (0.25)	*AA* (0.25) *AS* (0.25) *AD* (0.25) *SD* (0.25)	*AA* (0.25) *AS* (0.25) *AE* (0.25) *SE* (0.25)	*AA* (0.25) *AS* (0.25) *Aβ* (0.25) *Sβ* (0.25)	*AA* (0.25) *AS* (0.25) *Aα* (0.25) *Sα* (0.25)	*AA* (0.50) *AS* (0.50)
AC	*AA* (0.25) *AS* (0.25) *AC* (0.25) *SC* (0.25)	*AA* (0.25) *AC* (0.50) *CC* (0.25)	*AA* (0.25) *AC* (0.25) *AD* (0.25) *CD* (0.25)	*AA* (0.25) *AE* (0.25) *AC* (0.25) *CE* (0.25)	*AA* (0.25) *AC* (0.25) *Aβ* (0.25) *Cβ* (0.25)	*AA* (0.25) *AC* (0.25) *Aα* (0.25) *Cα* (0.25)	*AA* (0.50) *AC* (0.50)
AD	*AA* (0.25) *AS* (0.25) *AD* (0.25) *SD* (0.25)	*AA* (0.25) *AC* (0.25) *AD* (0.25) *CD* (0.25)	*AA* (0.25) *AD* (0.50) *DD* (0.25)	*AA* (0.25) *AE* (0.25) *AD* (0.25) *DE* (0.25)	*AA* (0.25) *Aβ* (0.25) *AD* (0.25) *Dβ* (0.25)	*AA* (0.25) *AD* (0.25) *Aα* (0.25) *Dα* (0.25)	*AA* (0.50) *AD* (0.50)
AE	*AA* (0.25) *AS* (0.25) *AE* (0.25) *SE* (0.25)	*AA* (0.25) *AC* (0.25) *AE* (0.25) *CE* (0.25)	*AA* (0.25) *AE* (0.25) *AD* (0.25) *DE* (0.25)	*AA* (0.25) *AE* (0.50) *EE* (0.25)	*AA* (0.25) *AE* (0.25) *Aβ* (0.25) *Eβ* (0.25)	*AA* (0.25) *AE* (0.25) *Aα* (0.25) *Eα* (0.25)	*AA* (0.50) *AE* (0.50)
Aβ	*AA* (0.25) *AS* (0.25) *Aβ* (0.25) *Sβ* (0.25)	*AA* (0.25) *AC* (0.25) *Aβ* (0.25) *Cβ* (0.25)	*AA* (0.25) *Aβ* (0.25) *AD* (0.25) *Dβ* (0.25)	*AA* (0.25) *AE* (0.25) *Aβ* (0.25) *Eβ* (0.25)	*AA* (0.25) *Aβ* (0.50) *ββ* (0.25)	*AA* (0.25) *Aα* (0.25) *Aβ* (0.25) *αβ* (0.25)	*AA* (0.50) *Aβ* (0.50)
Aα	*AA* (0.25) *AS* (0.25) *Aα* (0.25) *Sα* (0.25)	*AA* (0.25) *AC* (0.25) *Aα* (0.25) *Cα* (0.25)	*AA* (0.25) *AD* (0.25) *Aα* (0.25) *Dα* (0.25)	*AA* (0.25) *AE* (0.25) *Aα* (0.25) *Eα* (0.25)	*AA* (0.25) *Aα* (0.25) *Aβ* (0.25) *αβ* (0.25)	*AA* (0.25) *Aα* (0.50) *αα* (0.25)	*AA* (0.50) *Aα* (0.50)
AA	*AA* (0.50) *AS* (0.50)	*AA* (0.50) *AC* (0.50)	*AA* (0.50) *AD* (0.50)	*AA* (0.50) *AE* (0.50)	*AA* (0.50) *Aβ* (0.50)	*AA* (0.50) *Aα* (0.50)	*AA* (1.0)

( ), Mendelian probabilities; α, α^{0thal} trait; A, normal Hb (includes HbF in the fetus/newborn)

Affected

SS, Sβ, SD, SC *(sickle cell disease)*
Eβ, ββ *HbE (β-thalassaemia, β-thalassaemia major)*
$\alpha^0\alpha^0$ *(α^0-thalassaemia hydrops fetalis)*

Parents of a fetus who has a chance to be affected are called 'at-risk couple/parents' and their pregnancy 'at-risk pregnancy'

Not affected

AS, AC, AD, AE, $S\alpha^0$, $C\alpha^0$, $D\alpha^0$, $E\alpha^0$ *(sickle carrier)*
$A\alpha^0$, Aβ, $\alpha^0\beta$ *(thalassaemia carrier)*
CC, CD, CE, Cβ, DE, EE, DD, Dβ, SE *(clinically non-significant combinations)*
AA *(normal)*

Ascertainment of affected fetuses

Once a high-risk pregnancy has been detected, prenatal diagnosis (PND) is the confirmatory test offered for definitive fetal diagnosis. Currently, this involves either chorionic villus sampling (CVS) or, much less commonly, amniocentesis, to obtain fetal material for subsequent DNA analysis.[39] Both sampling techniques are invasive and carry a small procedure-related risk of miscarriage.[91] In the future it can be anticipated that non-invasive methods to gain fetal material from maternal blood will be developed.[92,93]

Genetic termination of pregnancy

Once a fetus has been diagnosed as affected, genetic termination of pregnancy (TOP) is offered

to couples who wish to prevent an affected birth. Currently, there is no prenatal intervention available that would change the prognosis of an affected fetus. However, the option of *in-utero* stem cell transplantation, aiming at cure, might change this situation in the future.[87,94] The development of pre-implantation diagnosis, based on *in-vitro* fertilisation and genetic diagnosis before implantation, could become an alternative to current PND to avoid selective termination.[95]

Counselling

Education and non-directive counselling need to accompany each screening step to facilitate informed decision making.[5,6,11,12,23,96,97]

Objectives of antenatal screening

The main objective of antenatal screening is to give couples reproductive choice over the outcome of the pregnancy. The reduction of disease incidence *per se* is **not** the aim of antenatal Hb-pathy screening programmes, but only the prevention of **unwanted** affected births.[6,12,96,98]

In addition, antenatal screening identifies babies who are at risk of sickle cell disease and it can thus be used to determine eligibility for neonatal screening.

Health-related outcomes of screening

The main health-related outcomes of antenatal screening are unaffected and affected births, genetic TOPs and PND-induced miscarriages.

Unaffected births

The most desired outcome of any antenatal screening programme is to maximise the number of unaffected births. In the case of Hb-pathy screening, this could be achieved through treatment of affected fetuses during pregnancy. However, currently there are no interventions available that can reduce the proportion of affected fetuses.

Affected births and genetic termination of pregnancy

The numbers of affected births and genetic TOPs are frequently used as measures of the respective failure and success of antenatal screening programmes.[99,100] However, this approach is flawed if the objective of an antenatal programme is the **offer of reproductive choice** over the outcome of pregnancy. The prevention of **unwanted** affected births through genetic TOP only partially reflects such an objective. Affected births occurring as a consequence of informed decision making, for example after appropriately offered PND and TOP have been declined, also indicate that choice was offered and, **together** with genetic TOP, are an appropriate measure of the effectiveness of a programme. In contrast, affected births due to failure of the healthcare provider to offer choice (e.g. owing to a missed offer of screening or false laboratory results) truly represent programme failures.

Prenatal diagnosis-induced miscarriage

A significant adverse and readily measurable screening effect is PND-induced miscarriage. The **proportion** of screened women suffering this outcome is constant within procedure categories for sampling fetal material (i.e. amniocentesis and CVS),[101] although the absolute numbers in a locality will be higher the more women are screened, with the number of unaffected and affected births being reduced accordingly.

Other outcomes of screening

Other significant consequences of antenatal Hb-pathy screening programmes include psychological effects such as anxiety, stigmatisation and the need for reassurance.[102–107] Although these are important, their inclusion for the evaluation of screening has been hampered by the lack of reliable measurement tools and the added difficulty that the same effects can be viewed as positive or negative, depending on individual perception.[108–110]

Operational issues of the screening process

Ascertainment of at-risk couples

Sequential and couple screening. Currently, in the UK[5,6,12,29,111] and elsewhere,[23,112] partner screening is mostly sequential. Carrier testing is initially offered to mothers, with a sample requested from the partner only if the mother is found to be a carrier. In contrast, for cystic fibrosis, couple screening has been pioneered[113] and subjected to randomised controlled trials[114] and cost-effectiveness analysis.[115,116] Couple screening for Hb-pathies has so far not been evaluated, although it might be more effective in timely first-trimester identification of at-risk pregnancies and warrants further research. For characterisation of the screening process in this review, only sequential partner screening has been chosen.

Partner not available for screening. If the partner of a maternal Hb-pathy carrier is not available for testing, the potential risk of the mother carrying an affected fetus can be estimated only by taking the father's reported ethnic group into consideration.

For the majority of maternal carriers this risk is > 1%,[6] which is higher than the cut-off level of 1:250 often chosen for offering PND for Down's syndrome.[117] In the UK, it is thus recommended that in such a situation the woman should be given the option of individual counselling and the choice of PND,[5,6,111] an approach we have used in our review.

Ascertainment of affected fetuses

Timing of the offer of prenatal diagnosis. Within the screening process, the timing of the offer of PND in relation to length of gestation is an important policy issue because of its influence on the uptake of PND/TOP. With the introduction of CVS, first-trimester (< 13 weeks' gestation) PND and TOP have become technically feasible.[118] Subsequently, a number of studies worldwide have pointed to the increased acceptability of PND and TOP if they can be offered early.[119–122] The reasons cited for this preference are that early TOP is medically safer,[123] probably psychologically less traumatic[124] and often socially and ethically more acceptable[125] than if carried out at a later stage when the pregnancy has become more evident. This view, however, is not completely unchallenged. First-trimester PND and genetic TOP might actually increase unresolved grief because so few people will have known about the woman's loss and the availability of these options might increase social pressure on women who would otherwise prefer not to undergo an invasive procedure to seek a diagnosis prenatally.[126]

In the UK, a trend of increased acceptance of first-trimester PND/TOP has also been described, although the only published study lacks generalisability because it is set in a tertiary centre.[120] Other data, from community-based programmes (unpublished or published in abstract form only) seem to support this finding, but interpretation of the results is limited by small numbers of PNDs.[121,127] In the UK, a first-trimester offer of PND/TOP is currently achieved in about 50% of all PNDs for Hb-pathies.[128] For the purpose of this review, we assumed that the offer of PND, regardless of timing, signifies an offer of reproductive choice. The effects of different gestational ages at the time of PND will be examined indirectly by varying the uptake rates for PND/TOP.

A first-trimester offer of PND/TOP is organisationally difficult to achieve if the initial screening procedure is performed antenatally, especially if antenatal booking is done in hospital. Whereas the first contact with a general practitioner (GP) or community midwife for confirmation of pregnancy can be as early as 6–8 weeks' gestation,[129,130] antenatal booking visits in hospital generally occur later[131,132] and may be deferred to 16 weeks' gestation to allow serum screening for Down's syndrome, thus losing important time for Hb-pathy screening. In addition, women from ethnic minorities who most benefit from screening are often among those booking latest.[133]

The time constraints would be less were the maternal or couple carrier status known before conception. Preconceptional screening is one way to achieve this goal. In addition, it has the potential to extend reproductive choice to the further options of childlessness or partner change, although limited evidence from the UK[134] and Mediterranean countries[135,136] suggests that these seem to be rarely taken up.

Preconceptional screening, principally in primary care, or through contraceptive providers such as family planning or genitourinary medicine clinics, is widely recommended,[5,6,12,137] but current screening practice is rudimentary.[29,138] The obstacles in the health service to preconceptional screening seem to be: lack of awareness and training about Hb-pathies amongst GPs[139,140] and other primary care workers such as health visitors,[141] practice nurses[142] and midwives;[143] and concerns over the reliable information transfer about carrier status between different healthcare providers,[34] despite the increasing use of Hb-pathy cards as recommended by the Department of Health.[5] The possibility of future developments of preconceptional screening in primary care is the topic of ongoing pilot studies.[140] Because preconceptional screening is not currently an alternative to antenatal screening we have not evaluated it as a separate strategy but rather incorporated it as a variant of antenatal testing in which the woman's carrier state is already known at booking.

Laboratory tests and equipment

Ascertainment of parental carriers and at-risk couples

In the UK there is great variation in the sequence and type of laboratory tests performed to ascertain carrier status.[34] The basic methods for detecting the main Hb-pathy carrier states are unambiguous. They consist of the estimation of the red blood cell indices and quantification of HbA_2 and HbF levels as main indicators for thalassaemia traits, and the identification of structural Hb variants to identify sickle cell traits.[21,23,37,111,144] However, a number of samples with rarer traits (e.g. $\delta\beta^{thal}$ (thal = thalassaemia) trait or HbD^{Punjab}) or equivocal results (α^{+thal} trait/homozygous state and

$\alpha^{0\,thal}$ trait) require additional tests for phenotyping and sometimes genotyping. The proportion of such samples depends on the ethnic composition of the antenatal population screened and the coexistence of confounding conditions, especially iron deficiency.[6] For the purpose of this review we developed a laboratory algorithm (*Figure 1*) to describe carrier testing. It is based on current guidelines,[21,23,37,111,144] has been designed to reflect the most common and important laboratory screening pathways, and is made up of test components that can be used as units for costing. For the purpose of this review, rarely performed investigations to identify unusual carrier types have not been included.

Antenatal laboratory algorithm. To characterise the laboratory components of carrier testing in the form of an algorithm for inclusion in the model, a number of assumptions have been made.

1. There is no differential screening for thalassaemias and sickle cell disorders because of their frequent interactions.[111] Instead, the initial Hb-pathy screening step always encompasses the estimation of red blood cell indices in conjunction with the characterisation of Hb variants.
2. For the estimation of red blood cell indices, only the MCH is considered. Both the mean corpuscular volume (MCV) and the MCH are reduced in thalassaemia traits and these tests are often performed and interpreted together.[111] However, Rogers *et al.*[145] studied a cohort of antenatal patients in London and found that MCH is preferable to MCV because of better stability during storage. Furthermore, at a cut-off level of < 27 pg, MCH is an adequate single measure with which to identify thalassaemia trait.
3. The measurement of MCH is assumed to be part of routine obstetric care[146] and is undertaken in all women regardless of any Hb-pathy screening programme.
4. The detection of any structural Hb variant requires repeat testing of the initial sample.[21]
5. A low MCH result requires quantification of HbA_2 and HbF. An elevated HbA_2 is indicative of β^{thal} traits, whereas a substantially elevated HbF with heterocellular distribution is suggestive of a $\delta\beta^{thal}$ trait.
6. A low MCH with normal HbA_2 constitutes an uncertain result. In Chinese, south-east Asian and eastern Mediterranean ethnic groups (corresponding classifications used in the model are Chinese, other Asian, Cypriot) with considerably reduced MCH (< 26 pg), a possible diagnosis is $\alpha^{0\,thal}$ trait.[111] In all other groups, the most likely explanation is insignificant $\alpha^{+\,thal}$ trait/homozygous state or iron deficiency (or both).
7. The rare possibility of a normal HbA_2 β^{thal} trait[3] has been omitted from the analysis to reduce complexity. In practice, such individuals often, although not always, present with severely reduced red blood cell indices and other morphological indicators of thalassaemia trait, which should alert haematologists to the possibility of this trait and the need to initiate partner testing.[147]
8. Whenever the mother has been identified as a carrier or has a result suggestive of a trait, partner testing follows, according to the same algorithm as maternal carrier testing.
9. Partner testing is assumed to precede DNA analysis, if required, as the most cost-conservative approach.
10. DNA analysis is used when the assessment of an at-risk pregnancy depends on a carrier result that cannot be obtained reliably by phenotyping. This includes definite diagnosis for possible $\alpha^{0\,thal}$ trait, $\delta\beta^{thal}$ trait and HbD^{Punjab} in those in whom the other partner has a significant trait.[6,111,148]

Measurement of iron deficiency. The role of identifying iron deficiency, usually through ferritin measurement, **within a Hb-pathy screening programme** is controversial because of its limited diagnostic power: a diagnosis of iron deficiency cannot be used as a definite discriminatory result to exclude thalassaemia traits because both conditions might coexist.[111] Only a normal ferritin result, which rules out iron deficiency, can be used to reinforce the suspicion of a thalassaemia trait and prompt further investigation along the algorithm. However, if the aim of the Hb-pathy screening programme includes the identification of iron deficiency, ferritin measurement can been used for antenatal populations, although the interpretation of results in pregnancy is difficult.[149–151]

There are two principal points within the screening process where ferritin measurement could be used: either for all women with a low MCH,[21] or only for women with a low MCH in whom the HbA_2 level has not been found to be elevated (= uncertain result).[6,23]

In the model we have presented laboratory costs with and without ferritin measurement, the former as the more cost-conservative option in cases with an uncertain result, and we assume that ferritin

measurement does not alter the number of correct Hb-pathy carrier diagnoses.

Blood sampling. The ascertainment of a carrier state requires one anticoagulated venous blood sample for phenotyping. An additional sample is needed if DNA analysis is necessary. If ferritin measurement is included in the laboratory algorithm, it can be performed from the initial sample (provided an assay is used that allows the use of EDTA blood; Jones, R, Great Ormond Street Hospital, London: personal communication, 1997).

Laboratory equipment. The availability of particular laboratory equipment determines which methods are employed for the tests described in the algorithm. We have considered two main laboratory set-ups, namely 'standard' and 'high-performance liquid chromatography' (HPLC):

1. The **standard set-up** includes the use of Hb-electrophoresis on cellulose acetate for the initial detection of structural Hb variants,[152] quantification of HbA_2 by elution[111,152] and estimation of HbF using the Betke method.[111,153,154] Although HbA_2 quantification by microcolumn chromatography is another recommended method[111,152] and is in widespread use,[34] we have assumed the cheaper elution technique for cost calculations. For the repeat test method, when HbS has been detected on initial Hb-electrophoresis, we assume the use of a sickle solubility test as the cheapest method compared with newer tests based on immunoassays;[155] for other Hb variants, the method used is citrate agar Hb-electrophoresis.
2. The **HPLC set-up** uses cation-exchange HPLC, which concomitantly detects Hb variants, and quantifies HbA_2 and HbF.[156–158] HPLC is also employed for repeat testing after detection of a structural Hb variant other than HbS that can more easily be verified by a sickle solubility test (see above).

These laboratory set-ups represent two common and 'pure' configurations. A number of other set-ups encountered in the UK, using Hb-electrophoresis and HPLC, have not been considered in the analysis because they are mainly determined by local factors outside a Hb-pathy screening programme (e.g. use of laboratory equipment by other departments; Jarvis, M, North Middlesex Hospital NHS Trust, London: personal communication, 1997).

Isoelectric focusing (IEF) is another non-quantitative electrophoretic technique that differentiates reliably between various structural Hb variants.[26,159] IEF is a technically demanding procedure and interpretation of the results requires expertise,[26,144] although the resolution of Hb fractions is superior to conventional Hb-electrophoresis.[159] As our preliminary costing revealed substantially higher equipment and running costs for IEF than for the other methods, and a more detailed review of this technique is expected to be covered by Professor S Davies' team, we have not included this method in our analysis.

For the purpose of the model it has been assumed that the two laboratory set-ups discussed above are equally effective in detecting carriers[111,144,158,160] (see chapter 5; pp. 51–53).

The techniques currently used for DNA analysis are described in the next section. Future development of laboratory techniques, which might facilitate the ascertainment of Hb-pathy carriers, is discussed later in this chapter (p. 17).

Ascertainment of affected fetuses

Sampling of fetal material. Sampling methods to obtain fetal material for DNA analysis include CVS and amniocentesis.[161,162] Compared with mid-trimester amniocentesis, the risk of pregnancy loss seems slightly higher with CVS,[101] although comparison is difficult because of the different gestational ages at which the two procedures are performed. Technically, CVS can be performed from as early as 6 weeks' gestation, but it is usually delayed until after 10 weeks because of reports of several clusters of limb-reduction defects after earlier CVS.[163,164] In the context of Hb-pathy screening, CVS is currently the preferred technique in the UK[39] because it can be performed in the first trimester and the diagnosis is usually available within a few days of sampling.[118,165] In addition, for DNA studies (as opposed to chromosomal analysis), chorionic villi are the more reliable source of good-quality DNA and provide enough material for repeat analysis if necessary.[166] Fetal blood sampling is required for globin chain synthesis, an older technique for fetal diagnosis preceding the advent of DNA analysis (see below). For the model, we have considered only CVS as the PND sampling procedure.

Fetal diagnosis. Fetal diagnosis is primarily performed by DNA analysis of both parental and fetal samples.[37] It is now routine practice to repeat phenotyping of both parental blood samples before proceeding to fetal diagnosis to ensure reliability of the risk assessment of the pregnancy.[39]

For DNA analysis of Hb-pathies, the two main techniques currently employed are polymerase chain reaction (PCR) methods, and Southern blotting. They are used for fetal as well as newborn (see below) and adult samples. In our model we have followed the approach from the Oxford reference laboratory,[38,148] which complies with current guidelines,[37] namely: the use of PCR methods to identify structural Hb variants and β-thalassaemia mutations, the latter being confirmed if possible by restriction fragment length polymorphism (RFLP) linkage analysis; and the use of Southern blotting to detect α^0-thalassaemia mutations.

Globin chain synthesis is now rarely performed as a primary method of fetal diagnosis but is reserved as a back-up technology for the few cases in which DNA analysis cannot be performed for technical reasons or for late referrals of previously unstudied parents.[148] It has not been considered in the model.

Integration of haemoglobinopathy screening within other antenatal screening programmes

There are other conditions apart from Hb-pathies for which antenatal screening and PND exist to offer women choice over the outcome of their pregnancies. The main examples in the UK are antenatal screening for Down's syndrome[167] and cystic fibrosis.[168] Unless antenatal screening policies are developed in an integrated way, rather than in isolation, opportunities for the unnecessary repetition of invasive prenatal sampling procedures and duplication of pretest information provision cannot be avoided (Anionwu, EN, Institute of Child Health, London: personal communication, 1997).

Antenatal populations eligible for screening

Universal screening

Universal screening is offered to all expectant mothers. In areas with a low prevalence of high-risk groups this strategy will inevitably have a low yield.

Selective screening

Selective screening is offered only to women considered to be at increased risk of having a fetus affected by a Hb disorder. Two principal maternal risk factors are used for selection: non-north European ethnic origin and a low MCH.

Selection based on ethnic group. Ethnic group is used as a proxy indicator for the varying Hb-pathy carrier frequencies in different populations. The main relevant distinction for selective screening is between women of north European and non-north European origin. All of the latter are considered to be at high risk and are thus eligible for screening.[5,21] However, the concept of ethnicity is imprecise because it is socially constructed rather than biologically determined.[169–172] In addition, there is little consensus about the most appropriate way of ascertaining ethnic status in the context of Hb-pathy screening[5,173] and practice is highly variable.[29] For the purpose of this review, the term 'ethnic group' has been used in its widest sense, denoting shared origin or social background.[171] This has been necessary to allow the integration of information on ethnicity from the 1991 Census with other sources of information, particularly data about ethnic group-specific Hb-pathy carrier frequencies. The measurement of ethnicity in the 1991 Census followed the principle of self-perception and ten distinct summary output classifications were produced.[174] In contrast, other sources have used country of birth or ancestry to ascertain ethnic status and hence have defined different groups. The heterogeneity of data on ethnicity inevitably limits their comparability and validity as markers for Hb-pathy carrier frequency, but a better alternative is lacking.

Selection based on low mean corpuscular haemoglobin. Red blood cell indices (MCH, MCV) are estimated automatically with the full blood count carried out for every woman receiving antenatal obstetric care,[146] mainly for the detection of iron deficiency. Because low indices are associated with β^{thal} and α^{0thal} traits, an MCH result < 27 pg is used to select women who are eligible for Hb-pathy screening,[6,21,23,145] regardless of their ethnic status. This means that, in effect, **all** women are screened for thalassaemia traits. Iron deficiency and a clinically insignificant α^{+thal} trait/homozygous state also lower red blood cell indices,[2] and their prevalence in a given antenatal population chiefly determines how specific the selection is for thalassaemia traits. Most structural Hb variants are not associated with significantly reduced red blood cell indices,[111] although, in HbE trait, red cells often show a slight reduction of MCH and MCV.[175] The policy of screening all women with a low MCH for Hb-pathies has been recommended by the British Society for Haematology,[21] the SMAC report[5] and, most recently, a Centre for Reviews and Dissemination report,[6] and it is widely practised.[34] The rationale for this approach is as follows.

- Thalassaemia trait has been found in north European women, although it is rare (see p. 45).
- There are particular difficulties associated with ethnic distinction between north European groups at low risk for thalassaemia traits and high-risk non-north Europeans, including south and south-east Europeans.
- The abnormal finding of a low MCH is regarded as a diagnostic rather than a screening issue, which requires clarification of the underlying cause.
- The increasing use of HPLC technology in the UK[34] facilitates the investigation of a low MCH because characterisation of Hb variants, and quantification of HbA_2 and HbF, are performed simultaneously.[158]

Other selective strategies. A selective strategy that confines eligibility exclusively to ethnic minority mothers (i.e. does not screen women on grounds of a low MCH), has not been formally included in the main analysis, but has been briefly explored in a subsidiary analysis. According to this policy, north European women with a low MCH are assumed to have iron deficiency and are treated according to best obstetric practice without incurring costs for Hb-pathy screening.

A strategy that selects mothers with ethnic minority partners, as well as those with a low MCH and of non-north European origin, has not been included in the analysis. It is a logical strategy, the feasibility of which warrants further examination because it may be effective in identifying at-risk couples who are missed by current selective screening strategies, for example where the mother is a north European sickle carrier and her partner a Hb-pathy carrier from an ethnic minority group. However, currently, this strategy is rarely offered[29,34] because of its perceived administrative complexity.

In the rare event that a woman's partner is known to be a carrier, the mother requires screening regardless of her MCH result or ethnic group (Yardumian, A, North Middlesex Hospital NHS Trust, London: personal communication, 1997). To reduce complexity, this event has not been considered in the model.

Possibility of missing carrier women owing to selection

There are two principal mechanisms by which the selection process can lead to carrier mothers being missed: first, if the selection criteria are not 100% sensitive (e.g. a selective programme will by definition miss north European women who are sickle carriers because they are not eligible for screening); and, secondly, if coverage of the eligible population is not 100% (e.g. owing to failure to screen certain ethnic minority women).

Sickle carrier frequency in the north European population

The sickle carrier frequency in north European women determines the sensitivity of any selective screening programme that excludes these women. This is particularly pertinent if there is significant mixing between white women and partners from ethnic minorities with high Hb-pathy carrier frequencies, a situation that is found increasingly in the UK.[19,20] Although relatively rare, sickle carriers have been described in native north European individuals in the UK and elsewhere.[16,26,176–179] Reliable population estimates for the UK are not available; data from local universal neonatal screening programmes suggest, however, that frequencies might vary between geographical locations owing to different mixing patterns of the population.[180] In the USA, where there is a longer history of ethnic mixing, there are areas in which the indigenous white population is reported to have a 0.25% frequency of sickle carriers.[26] Accordingly, with the general trend of more inter-ethnic unions in the UK,[19,20] it can be anticipated that, in future, ethnic group will become more dissociated from genetic risk, thus diminishing its discriminatory power as a selection criterion.[181]

Failure to screen eligible women

The risk of failure to screen eligible women in a selective programme, either owing to failure to offer the screening test or to failure to carry out the test, is a frequently voiced concern and argument for a universal approach, based on anecdotal evidence of the births of unexpected affected children (Anionwu, EN, Institute of Child Health, London: personal communication, 1997). The reasons given for such failures include the administrative complexity required for a reliable selection process and uncertainty about ethnic ascertainment, leading to misclassification.[5,6,17] However, reliable estimates of the magnitude of this potential problem are lacking (see chapter 5; pp. 47–48) and it is not known how low a failure rate could realistically be expected and for what costs.

Neonatal screening strategies

Outline of the screening process

Neonatal screening detects newborns who are likely to be affected by a sickle cell disorder, who will then require an additional blood test for confirmation

of the definite diagnosis. Screening needs to be accompanied by parental education and counselling, depending on the results of the tests (see below, pp. 20–21). The screening procedure also identifies sickle carriers, most babies with β-thalassaemia major and other structural Hb variants, but does not reliably detect thalassaemia traits, although α-thalassaemia traits can often be suspected owing to the presence of Hb Barts (γ4).[144] *Table 3* summarises the main conditions detected by neonatal screening, the corresponding genotypes considered in the model and the need for confirmatory tests.

Objectives of neonatal screening

The main objective of neonatal screening is the early detection of babies with sickle cell disorders, so that penicillin prophylaxis and comprehensive care can be commenced, preferably before the age of 3 months.[21,144] Both interventions have been shown to reduce morbidity and mortality from sickle cell disorders. A multicentre, randomised double-blind, placebo controlled trial in the USA demonstrated that the administration of prophylactic oral penicillin to infants and young children with sickle cell disease reduced the incidence of pneumococcal septicaemia by 84%.[55] The effectiveness of comprehensive care in reducing morbidity and mortality, which includes education of caregivers about the signs and symptoms of illness in children with sickle cell disease, and the need for prompt intervention for life-threatening complications such as infection or splenic sequestration crises, has not been evaluated in randomised controlled trials but is described in longitudinal studies. This is summarised in three references.[24,26,27] A recent survival analysis of a Jamaican cohort of over 300 patients with sickle cell disease, who had been diagnosed and followed from birth, demonstrated significantly reduced mortality in the youngest group compared with older groups. Improved survival coincided with the introduction of early diagnosis followed by interventions such as penicillin prophylaxis and parental education, further suggesting that such measures are effective in reducing mortality.[182] Because penicillin prophylaxis reduces sepsis-related mortality through a reduction in the incidence of infection, it can be anticipated that other disease-related morbidity will also be reduced, in particular pneumococcal meningitis.[45,55,183] Amongst the most disabling consequences of pneumococcal meningitis are long-term sequelae such as mental retardation,[184–186] seizures[184,187] and deafness.[188–190]

The primary sickle cell disorders with proven benefit from early intervention include sickle cell anaemia and sickle cell β-thalassaemia. The number of children with sickle HbD disease is too small for separate analysis but, as the clinical features are comparable,[41] they can be expected to benefit similarly. Sickle HbC disease is generally less severe than the other forms.[43] However, infants with sickle HbC disease have increased mortality[191,192] and an increased incidence of bacterial infection in the first few years of life,[193,194] and are therefore likely to benefit from early intervention.

The recent worldwide emergence of penicillin-resistant strains of *Streptococcus pneumoniae*[195,196] has

TABLE 3 *Conditions detected by neonatal sickle cell screening that are considered in the model*

Suspected condition	Corresponding genotype considered in the model[a]	Need for confirmatory test
Sickle cell disorders	*SS, SC, SD, Sβ*	Yes
β-Thalassaemia major	*ββ*	Yes
HbE β-thalassaemia	*Eβ*	Yes
Sickle carriers	*AS, AC, AD, AE, Sα^0, Cα^0, Dα^0, Eα^0*	No
Clinically non-significant combinations of Hb-pathy traits	*CC, CD, CE, Cβ, DD, DE, Dβ, EE, SE*	Yes

[a] *To be read in conjunction with* Table 2

Conditions due to SS/Sβ, CC/Cβ, EE/Eβ, DD/Dβ *cannot be distinguished reliably by the neonatal screening test, but only by a later confirmatory blood test*

Some genotypes listed under clinically non-significant combinations are theoretical combinations considered for the purpose of the model – they are assumed to be benign states but, because of their extreme rarity, little is known about the possible range of clinical symptoms[178]

caused concern about the future effectiveness of penicillin prophylaxis in sickle cell disease.[56,197,198] So far, one death associated with such resistance in a Jamaican child with sickle cell anaemia has been reported.[199] Further research is required to study the clinical impact of the problem in the UK environment and to search for alternative means of prevention such as an improved vaccine because the currently available pneumococcal vaccine is of limited effectiveness.[200]

Neonatal screening also identifies sickle carriers and can thus alert the parents of an affected or carrier baby and their obstetric providers of the potential risk for the next pregnancy and the need for antenatal screening.[5] It is uncertain whether knowledge about carrier status of the newborn is perceived as beneficial for the individual and the community at risk;[201,202] and it is speculative whether such information will be preserved and could influence reproductive decision making in later life.[201] The early detection of β-thalassaemia major and HbE β-thalassaemia has no known beneficial influence on prognosis.[173]

The need for neonatal screening when antenatal screening is in place

Although antenatal Hb-pathy screening leads to the identification of some newborns with sickle cell disorders through PND and can indicate whether a pregnancy is at risk, additional neonatal sickle cell screening programmes are relevant for babies of women who were not carrier tested antenatally and of those identified as having an at-risk pregnancy, but who did not undergo PND. A neonatal programme would therefore be redundant only in the **theoretical** case that the preceding antenatal programme would have screened **all** eligible women and performed PND on **all** at-risk couples. Neonatal sickle cell screening, on the other hand, can **never** make up for a deficient antenatal screening programme because the objective of antenatal screening is to offer reproductive choice over the outcome of the pregnancy. A combined antenatal/neonatal Hb-pathy screening programme would therefore be justifiable in all districts.

Health-related outcomes of screening

The main direct outcome measures of neonatal screening are early and late diagnosis of sickle cell disease.

Early and late diagnosis of sickle cell disease

Early diagnosis refers to the detection of sickle cell disease through neonatal screening while the disorder is still asymptomatic (usually before 3–6 months of age), whereas late diagnosis refers to detection outside a neonatal screening programme, usually because of disease-related symptoms. However, the prevention of late diagnosis represents only an intermediate outcome and needs to be further converted into final outcome measures such as 'prevention of early death' and 'prevention of severe disability' to reflect the ultimate objectives of the screening programme to reduce the morbidity and mortality of sickle cell disease. Between the early diagnosis of a sickle cell disorder, through neonatal screening and the prevention of premature mortality, lie at least two further steps, namely the clinical follow-up of all babies with a confirmed positive diagnosis[203–205] and compliance with the prophylactic regimen of penicillin to prevent pneumococcal septicaemia,[55,206,207] both of which are often incomplete. Ensuring effective clinical follow-up of screen-detected individuals is an integral but frequently neglected part of screening, which requires reliable organisational links between those responsible for screening and those responsible for clinical care.

Other outcomes of screening

Other consequences of neonatal screening are the detection of sickle carriers[201] and the detection of clinically non-significant combinations of Hb-pathy traits. Although they do not reflect the primary objectives of neonatal screening programmes, they are potentially important in terms of resource implications and psychological effects.[201]

Operational issues of the screening process

Newborn specimen collection

There are two most commonly encountered collection methods for newborn specimens in the UK: (1) blood samples are taken from the umbilical cord and submitted to the screening laboratory as a liquid sample (cord blood method); or (2) blood is collected by heel prick at the same time as the metabolic screening sample (about age 7 days) on dried filter paper (Guthrie card method). The collection of heel-prick samples into capillary tubes is rarely used and has thus not been considered separately from the Guthrie card method.[29] A review from the USA comparing the reliability of screening results from specimens obtained by all three different sampling methods found no differences,[26] although the SMAC report advised against the use of cord blood sampling because of the potential risk of maternal contamination of the specimen.[5] In the UK, cord blood analysis has traditionally been performed in local haematology laboratories[16,17] (Jarvis, M, North

Middlesex Hospital NHS Trust, London: personal communication, 1997). In contrast, Guthrie card samples can be analysed alongside phenylketonuria (PKU) and congenital hypothyroidism testing in regional metabolic neonatal screening laboratories,[30] although other individual arrangements exist, for example, the use of a separate Guthrie card, which is sent to a haematology laboratory.[208] Coverage achieved by the Guthrie card method in the UK is near 100% for universal metabolic screening,[209,210] indicating, in principle, the effectiveness of this approach. In contrast, programmes in the UK[16,17] and the USA[211–213] using the cord blood method have consistently reported difficulties in achieving full coverage after the initial screening event, especially in cases of home delivery, preterm birth or other labour complications. This necessitates tracing followed by screening of at-risk babies in the community[212] (Yardumian, A, North Middlesex Hospital NHS Trust, London: personal communication, 1997).

If both methods are to achieve a comparable coverage, cost calculations for cord blood sampling have to include the additional resources required for community screening of babies missed on the initial screen. In addition, cord blood sampling uses extra resources in terms of the professional and administrative time required to take specimens and report results, expenditures that can be avoided by the Guthrie card method through integration into an already existing screening programme.[26] Thus, only the Guthrie card method has been considered in the model.

Infant and parents' confirmatory blood samples

For confirmation of suspected sickle cell disorders, β-thalassaemia major (including HbE β-thalassaemia) and other clinically non-significant combinations of Hb-pathy traits (*Table 3*) in the baby, venous blood samples are required from the infant and preferably both parents.[144,160] Usually, the responsibility for confirmatory diagnosis lies with local clinicians, with samples being analysed in the local haematology laboratory (Jones, R, Great Ormond Street Hospital, London: personal communication, 1997). The optimal time to perform these blood tests depends on the condition suspected, the laboratory methods employed to analyse the samples, and whether parental blood specimens are available.[26,144,160,208] Babies with suspected sickle disease should be retested to confirm the provisional diagnosis before the age of 3 months.[21,26,144,160] However, if testing is delayed, penicillin prophylaxis should be started on the basis of the provisional diagnosis.[26]

Laboratory tests and equipment

The laboratory tests appropriate for neonatal screening for sickle cell disorders require modification from those employed for antenatal screening of adults because of the large amounts of HbF in the newborn. Care must be taken not to miss small amounts of HbA, HbS or other relevant structural Hb variants. For the purpose of this review, we have developed a laboratory algorithm for neonatal sickle cell screening (*Figure 2*). It is based on current guidelines[21,23,26,144] and is made up of test components that can be used as units for costing. Rarely performed investigations to identify unusual structural Hb variants have not been included.

Neonatal laboratory algorithm for sickle cell screening

To characterise the laboratory components of neonatal sickle screening in the form of an algorithm for inclusion in the model, a number of assumptions have been made.

1. The first step in the screening process is the characterisation of Hb variants.
2. The detection of any abnormal variant needs to be verified by a repeat test on the initial sample.
3. If a sickle cell disorder, β-thalassaemia major, HbE β-thalassaemia or a clinically non-significant combination of Hb-pathy traits (*Table 3*), has been detected in a baby, a confirmatory blood test from the infant and the parents is required to establish a definite diagnosis.
4. Without a screening programme, a definite diagnostic test would be necessary at the time of delayed diagnosis of sickle cell disorders and β-thalassaemia major (including HbE β-thalassaemia). In these cases, the diagnostic test is not attributed to the screening programme.
5. Confirmatory tests for infants found to have a clinically non-significant combination of Hb-pathy traits (*Table 3*) are included in the screening programme because these conditions would not necessarily be picked up in later life.
6. Confirmatory diagnostic blood tests on infants and parents are undertaken using the same methods as the screening tests.
7. A minority of diagnostic tests require DNA analysis for confirmation if complete family specimens are not received.[160] For this review, we assume that 1% of infants requiring confirmatory testing attributable to the screening programme have no parents available for tests and require DNA analysis.
8. Sickle carrier results are not verified by a confirmatory blood test.[21,144,160]

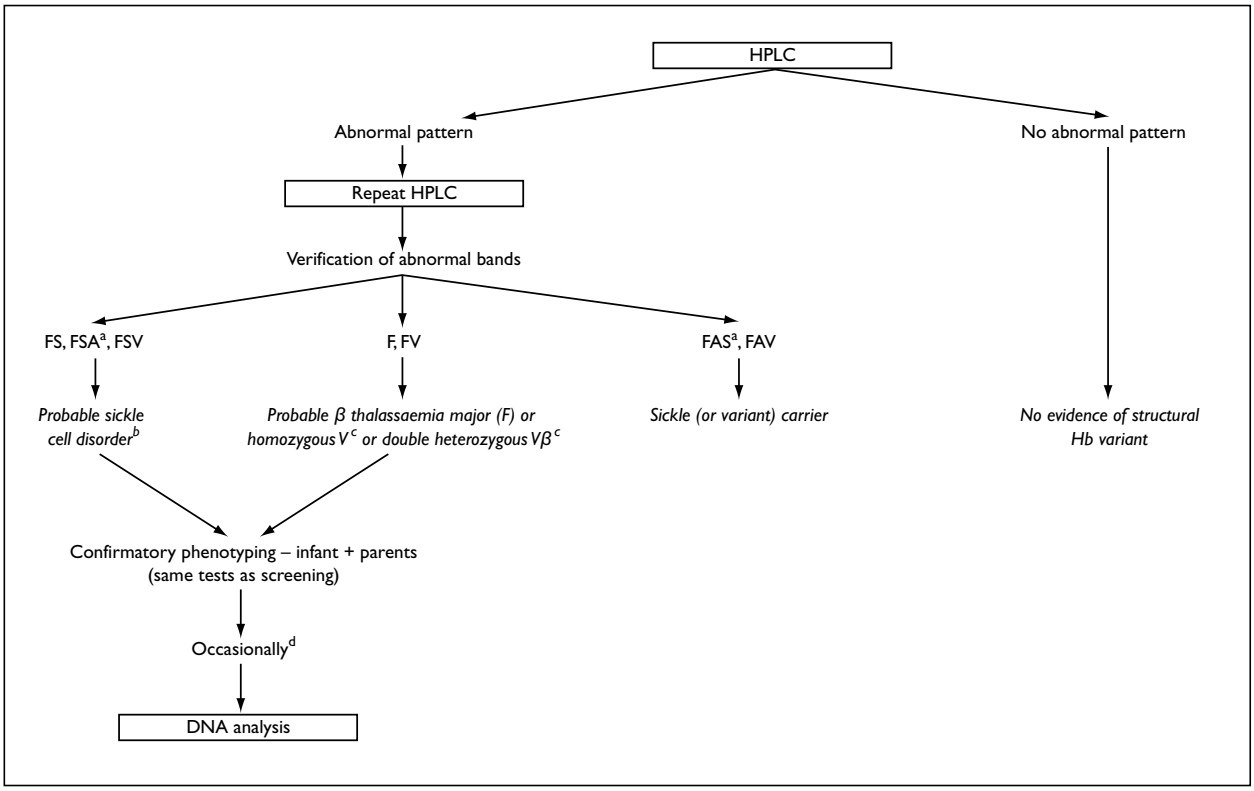

FIGURE 2 *Neonatal laboratory screening algorithm*

[a] FSA signifies amount of F > S > A; FAS signifies amount of F > A > S

[b] FS pattern can also indicate S/hereditary persistence of fetal Hb

[c] Clinically non-significant combinations of Hb-pathy traits

[d] In cases of unusual combinations of Hb-pathy traits and no parental samples available

(V, Hb variant other than S (such as C, D, E); F, fetal Hb; A, normal adult Hb; ▭, laboratory test; italics, test result interpretation)

Laboratory equipment

There are three main laboratory methods employed for neonatal screening, which use different equipment.

Haemoglobin-electrophoresis on cellulose acetate/citrate agar. The most basic method consists of initial screening with Hb-electrophoresis on cellulose acetate, followed by a repeat test on citrate agar for all samples with an abnormal band. Cellulose acetate electrophoresis distinguishes poorly between HbA or HbS and HbF, and it is thus essential that citrate agar electrophoresis is also undertaken.[159] Small amounts of HbA may not be detected at birth by these methods and may lead to a false-positive FS pattern. As a non-quantitative method, it can also be difficult to distinguish sickle cell β-thalassaemia ($S\beta^+$) from sickle cell trait. The distinction depends upon estimating whether the proportion of HbA is greater than that of HbS (sickle trait) or lower ($S\beta^+$).[26] Although early neonatal screening programmes in the UK[214] and elsewhere[26] have employed these methods effectively, they are now being gradually replaced by either IEF or HPLC technology, especially in large-scale programmes that are integrated into the national metabolic neonatal screening programme (Jones, R, Great Ormond Street Hospital, London: personal communication, 1997). We have therefore not considered this method in our analysis.

Isoelectric focusing. IEF is an electrophoretic technique that overcomes the limited sensitivity of cellulose acetate electrophoresis by its superior resolution of Hb fractions.[159] It is an effective neonatal screening method with test sensitivity and specificity approaching 100%,[26] and is widely used in the UK[208] and elsewhere.[159] However, abnormal bands identified on initial screening still require a repeat test with another method, for example, citrate agar electrophoresis or newer immunological methods. This method is technically demanding and expensive. The team working under Professor S Davies is expected to include IEF in their review. This technique has not been considered in our analysis.

High-performance liquid chromatography. For neonatal screening in a large-scale programme we

assume that HPLC is the laboratory method of choice. This is an automated, quantitative, highly effective neonatal screening method, suitable for large-scale screening programmes.[160,178] To date, the northern California screening programme has reported experience of over 3.3 million neonatal screens.[160,178] HPLC technology has been shown to detect small amounts of HbA, making easier the distinction between sickle cell trait and sickle cell β-thalassaemia ($S\beta^+$).[215] In the Californian programme, no known cases of sickle cell β-thalassaemia ($S\beta^+$) have been mistaken for sickle cell trait.[160] Repeat testing of all samples with an abnormal Hb variant on initial testing, employing a different method, is not required. In the Californian programme, no repeat testing is performed and sensitivity and specificity of the initial test approach 100%.[160] However, with less extensive experience, repeat testing might still be preferred as a precaution against possible laboratory errors,[144] but this does not require a different method and can therefore be carried out with HPLC. This approach has been used in the model.

For simplicity, we assume in our review that, for confirmation of a provisional diagnosis, the same laboratory tests as for screening are used. Instead of HPLC methodology, however, IEF or Hb-electrophoresis on cellulose acetate/citrate agar might equally be employed.[160]

Occasionally, the confirmatory diagnosis requires more sophisticated tests, usually DNA analysis, and, for unknown Hb variants, mass spectrometry.[160] However, for the model, only DNA analysis has been considered, which follows the same principles as described for fetal diagnosis (pp. 10–11). Examples of possible future developments in laboratory techniques to facilitate antenatal and neonatal screening include capillary electrophoresis[216] and primary use of automated DNA/RNA technology.[26,217,218]

Newborn populations eligible for screening

Universal screening

Universal screening is offered to all live-born babies, except those born after pregnancies in which PND was performed. For the latter, a neonatal confirmatory test is assumed to be a routine **diagnostic test** rather than part of screening, despite the fact that, for organisational purposes, it is often performed within a screening programme to ensure complete follow-up (Anionwu, EN, Institute of Child Health, London: personal communication, 1997). Universal screening inevitably has a relatively low positive yield, especially in areas with a low prevalence of high-risk groups, and leads to the detection of sickle carriers whose fathers, but not mothers, are carriers.[5,201]

Non-universal screening

Neonatal screening programmes for sickle cell disorders in the UK[29,30] and the USA,[213,219,220] which use the Guthrie card method for blood sampling and are integrated into large-scale neonatal metabolic screening programmes, are usually universal. However, experience of a programme that is screening only high-risk newborns, based on Guthrie cards, has been reported from France.[221] In the UK, some districts have reported the use of the Guthrie card method for non-universal neonatal screening, but there is no explicit account of whether such screening arrangements are integrated into the metabolic screening programme or whether they are free standing.[29]

For the purpose of this study we have assumed that the midwife who takes the Guthrie card sample is responsible for selecting neonates who are at risk of a sickle cell disorder. The requirement to test is communicated to the screening laboratory by flagging specimens accordingly. Laboratory personnel therefore only need to identify and test the Guthrie cards marked for additional sickle cell screening.

There are two principal approaches to non-universal neonatal screening, depending on whether selection is performed independently of the preceding antenatal screening programme (*de-novo* selection) or if information from the antenatal component of the programme is used to determine the risk status of the baby (targeted selection).

***De-novo* selection**. The main feature of this approach is that selection is performed post-natally and is independent of maternal and paternal carrier results from antenatal screening. It is based on an assessment of maternal ethnic group, with all babies of non-north European mothers being eligible for screening. This option has been described in the USA, where there is no systematic antenatal screening;[211] it is practised in other European countries,[221] and occurs in the UK where antenatal and neonatal parts of the screening programme are not connected and information transfer cannot be relied upon, as well as where there is no explicit screening policy.[29] In the context of such a strategy,

selection based on the infant's, rather than the mother's, ethnic origin has been discredited owing to ethnic misclassification of babies resulting from misleading judgement of skin colour at birth (Anionwu, EN, Institute of Child Health: personal communication, 1997).

For the purpose of this review, we have chosen universal and selective screening based on *de-novo* selection postnatally as the main strategies to be compared. However, targeted screening (see below) has been included in a limited subsidiary analysis because, although reliable access to parental antenatal carrier results might not currently be available in all districts, this strategy may become more widespread in the future.

Targeted selection. According to this approach, eligibility for neonatal screening is primarily determined by information about maternal and paternal carrier status from the antenatal programme. Various targeted options are currently practiced in the UK,[29] although they are often ill defined. There are two ways in which antenatal parental screening results can inform eligibility for neonatal screening.

First, antenatal information can be used to identify those neonates who **need screening** because parental carrier results suggest a risk of sickle cell disease in the baby. In this option, the default would be **not to screen** if the mother had not been tested antenatally because she was deemed non-eligible, or ***de-novo* selection for screening** if the mother had been too late for screening or had declined, or antenatal information about her carrier state had not been accessible.

Secondly, antenatal information can be used to identify those neonates **who do not need screening** because parental carrier results suggest no risk of sickle cell disease in the baby. In this case, the default is to undertake **neonatal screening** if there are antenatal results other than a negative maternal or paternal carrier test, and ***de-novo* selection for screening** if the mother has not been tested.

The latter approach is defensive and does not depend on the antenatal selection process but only on the sensitivity of the laboratory tests and on true paternity. For inclusion in the model, we have chosen this latter option as the more practical and reliable approach to targeted selection.

There is also variation in whether only maternal or both parental carrier results are used to make decisions about eligibility for neonatal screening. Relying only on maternal carrier results might be organisationally easier because sequential partner testing leads to paternal results, if available, being reported separately from the maternal results; but this approach does not use all relevant antenatal information for selection and thus inevitably results in redundant screening of babies known not to be at risk for sickle cell disease.

Possibility of missing the diagnosis in babies with sickle cell disease owing to selection

Sickle gene frequency in the north European population

With *de-novo* selection, newborns of north European mothers will inevitably be excluded from screening. This might lead to babies with sickle cell disease not being diagnosed neonatally, depending on the sickle carrier frequency in north European mothers and the frequency of such women having ethnic minority partners with high Hb-pathy carrier rates.

Failure to screen eligible babies

With *de-novo* selection, the risk of failure to screen eligible babies, either owing to failure to offer screening or to failure to perform the test, depends on the administrative and procedural difficulties associated with a selection process based on ethnic group. The principles are the same as for antenatal screening (pp. 11–12) but the process is a new one, with a new chance of error.

In a targeted programme, administrative and procedural difficulties associated with the selection process can also be anticipated, in addition to the small fixed failure rate predetermined by the laboratory performance and rate of non-paternity from the antenatal screening programme. As targeted selection is mainly based on antenatal parental carrier results, administrative structures and effective information technology are required to allow coordination and reliable information transfer between the antenatal and neonatal sides of the screening programme.

Counselling and related issues

Core ethical principles for antenatal and neonatal Hb-pathy screening are respect for the autonomy of the individual or couple, their right to full information, and confidentiality.[222] Education and non-directive counselling play an important part in ensuring that these principles are followed,

and that screening is only undertaken voluntarily and after meaningful informed consent, based on the knowledge of the significance of screening for health benefits, including reproductive outcomes, as well as the possible disadvantages of screening.[12,13,96,98,181]

For antenatal Hb-pathy screening, the main aim of counselling is to facilitate informed decision making with regard to reproductive choices. The effectiveness of genetic counselling generally has been evaluated by studying its impact on education, risk perception, and reported reproductive intentions and behaviour.[223] For the Hb-pathies there is evidence, mainly from US studies, that those who received counselling demonstrated a better understanding of the disease than controls when tested immediately after the session, and encouraged other individuals, such as their partners, to be tested.[224,225] Whether individual genetic counselling by itself can influence reproductive behaviour remains uncertain.[24,27,97]

For neonatal sickle cell screening, the main aim of counselling is to provide information about the importance of health maintenance as well as an understanding of the inheritance of the condition to enable informed family planning decisions. A review of studies on the techniques and impact of genetic counselling for sickle cell disorders can be found in a publication from the US Department of Health and Human Services.[26] All of these studies were observational and had small study populations.

In the UK, the impetus to develop Hb-pathy counselling services arose from a series of qualitative studies that explored the experience of parents of children who were affected with sickle cell disorders in Brent[33,226] and East London,[227] and with β-thalassaemia major in the north of England.[125] All of these studies revealed that many parents were made aware of the risk of having children with Hb disorders only after the symptomatic presentation of an affected child. They showed that: genetic counselling services were absent or inadequate; information was, if at all, provided in technical language with a lack of translation into ethnic minority languages and no use of written or visual materials; women were not informed that they had been screened in pregnancy or they were not given the results; there was cultural stereotyping of certain ethnic and religious groups with the assumption that they would not be interested in PND and were thus not informed; and there was evidence that women felt pressurised into undergoing PND or were not allowed PND without prior agreement that they would accept TOP if an affected fetus were diagnosed.

Although in the UK the need for counselling services for Hb-pathies is now undisputed,[5,6,11,12,228] the exact format of counselling sessions varies considerably between locations[29,31,35,229] and there is uncertainty about the most effective way of delivering the service. It was outside the remit of this project to assess formally the evidence of the effectiveness of counselling in the context of Hb-pathy screening. For this review, we have characterised the counselling requirements for antenatal and neonatal screening according to experience from Hb-pathy counsellors (appendix 1) and used these assumptions to inform the costing of counselling services for the model.

Education and counselling for antenatal haemoglobinopathy screening

Education and counselling accompanying antenatal screening has been divided into the following four main sections, reflecting the various steps in the screening process: maternal carrier testing; positive maternal carrier result; at-risk pregnancy/positive PND result; and post-TOP bereavement.

Maternal carrier testing

Pretest information. Maternal carrier testing requires general pretest information about Hb-pathy screening, including the purpose of antenatal screening and, possibly, neonatal screening. This allows meaningful consent to be obtained, which is a prerequisite of all screening policies and applicable to all women in universal and selective programmes. In a selective programme it is assumed that, for practical reasons, pretest information is given before the MCH result is available. Therefore, all women are potentially eligible for screening and require this counselling input, despite eventually not all of them being offered screening. Pretest information can be given in a variety of ways, ranging from written material with the option of personal education only on request, to face-to-face explanation for everybody, for example, given by a midwife. For the baseline analysis we have assumed the most cost-conservative approach of the integration of pretest information into already existing information materials, with no allocation of additional professional time. However, because of uncertainty about the adequacy of this approach, especially for some ethnic minority patients, we have subjected the assumption to a sensitivity analysis in which additional midwifery time has been allowed.

Ethnic ascertainment. Ascertainment of ethnic status and an explanation of the concept of high-risk groups is required for all antenatal women in a selective programme in order to determine who would qualify for screening on ethnic grounds.[12] The main distinction that is relevant for screening is between women of non-north European and north European ethnic origin, the former indicating an increased risk of Hb-pathy carrier status.[5,21] However, more refined classifications of some groups at risk for $\alpha^{0\,thal}$ trait, namely Chinese, south-east Asians and eastern Mediterraneans, are necessary to guide interpretation and further investigations of certain ambiguous screening results (pp. 8–10). Ethnic ascertainment in the context of selective Hb-pathy screening could be linked to routine NHS ethnic monitoring, which is currently mandatory for patients admitted to hospital in England,[230] as the majority of women are in hospital for the delivery of their babies, except for 1–3% of home births (data from Royal College of Midwifery, 1994). However, the standard format currently used for NHS ethnic monitoring[231] would have to be adjusted to allow distinction between north European and several Mediterranean and other groups at risk for Hb disorders; and the importance of ancestry would have to be emphasised if measurement were primarily based on self-definition.[5] For the purpose of the baseline analysis, we have assumed no additional professional time is required for ethnic ascertainment. However, in a sensitivity analysis, we have relaxed this assumption and allowed additional midwifery time, guided by the average time found to be necessary for the ethnic monitoring of most patients in a primary care setting.[232]

Positive maternal carrier result

Once a mother is found to be a carrier, counselling is required to explain the implications of the positive result and the options for further action.[226] Time allocated for this session also includes the organisation of partner testing.[233]

At-risk pregnancy/positive prenatal diagnosis result

In cases in which both parents are carriers, or when the partner of a maternal carrier is not available for testing, the main task for the counsellor is to assess the risk status of the pregnancy and to communicate this risk to the parents, together with the options of PND and TOP. Time allocation for this session allows additional counselling support for cases in which PND confirms an affected fetus.[226]

Post-termination bereavement

For women who opt for TOP after the diagnosis of an affected fetus, the last session comprises bereavement counselling, including discussion of the prospects for future pregnancies, to ameliorate the adverse psychological reactions described after genetic terminations.[234–236]

Parental education and counselling for neonatal screening

The two main parental education and counselling sessions accompanying neonatal screening are associated with the initial neonatal screening test and a positive screening result that is suggestive of a sickle cell disorder.

Initial neonatal screening test

Pretest information. As for antenatal screening, the initial neonatal screening test requires pretest information for the parents about the screening procedure and its purpose, so that informed consent can be given. The optimal time for consent for neonatal screening is not clear; obtaining consent from mothers around the time of delivery has been found to be difficult and unsatisfactory because of their preoccupation with obstetric issues.[237] A recent study in Cambridge of new mothers' knowledge of metabolic neonatal screening showed that, although two-thirds of mothers stated that the test had been fully explained at the time of the procedure, most did not know its purpose.[238] For neonatal Hb-pathy screening, we assumed that pretest information can most easily be given in the context of antenatal screening when the rationale of a combined Hb-pathy screening programme is explained, which is a cost-conservative approach that avoids the need for duplicating the task postnatally. However, mothers who have not been tested antenatally and who have babies eligible for neonatal screening, require special neonatal pretest information. As for antenatal screening, we assume no additional professional time is required for the provision of neonatal pretest information in our baseline analysis, but we allocate additional midwifery time per mother with a baby eligible for screening in a sensitivity analysis.

Ethnic ascertainment. The same principles as stated for antenatal screening apply for ascertainment of maternal ethnic group in the context of neonatal screening. Whereas a universal neonatal screening strategy obviates the need for ethnic ascertainment, all mothers with a live-born neonate who have not had PND require this procedure in a selective *de-novo* neonatal programme and all mothers not tested antenatally in a targeted programme. As

for antenatal screening, our baseline analysis assumes that no extra professional time is required, whereas additional midwifery time has been allocated per such mother in a sensitivity analysis.

Access to parental antenatal screening results. An additional duty that is applicable only to targeted neonatal screening programmes relates to the need to access antenatal parental carrier results to inform eligibility for neonatal screening. For our baseline analysis, we have assumed that such information transfer can be achieved reliably through established information technology and does not require additional professional time. However, there is uncertainty about the feasibility of this assumption and, for the purpose of a sensitivity analysis, we have allocated additional midwifery time per baby who is potentially eligible for screening, assuming that such coordination would most likely be the task of the midwife carrying out the neonatal screening procedure.

Positive screening result suggesting a sickle cell disorder

Screening results suggestive of a sickle cell disorder require counselling to explain the implication of the result, including the need to organise the necessary confirmatory diagnostic test and the importance of penicillin prophylaxis and comprehensive medical care. β-Thalassaemia major (including HbE β-thalassaemia) and clinically non-significant combinations of Hb-pathy traits also require diagnostic tests and thus counselling.

Positive diagnostic test results confirming a sickle cell disorder or β-thalassaemia major (including HbE β-thalassaemia) require further counselling. However, this has not been attributed to the screening programme but is assumed to be part of the treatment.

Positive sickle carrier screening result

Positive sickle carrier screening results are not routinely confirmed.[21,144,160] For the model, we have assumed the most cost-conservative counselling input, consisting of a letter explaining the implications of the carrier state. It is expected good practice that confirmatory tests and contact with a counsellor are offered on request.[201] Although experience has shown that uptake of such an offer is variable,[160,201] we have included in our baseline analysis additional counsellor time for the proportion of mothers with babies who are found to be sickle carriers for whom the result could be perceived as a surprise (e.g. mothers who were not screened antenatally or maternal non-carriers) (chapter 6; p. 63).

Notification of results

Active notification of all test results, both positive and negative, is assumed in the analysis. This is in agreement with published guidelines and current trends,[6,21] although in the UK some providers notify negative results only on request or not at all.[29]

Training for education/counselling

Hb-pathy counselling requires specialist knowledge and skills;[233] accordingly, training requirements for midwives and counsellors have been included, assuming in-service training for healthcare workers concerning pretest education, and attendance at a specialist course for training to undertake the counselling sessions.

Screening of relatives in families where a carrier or affected baby has been identified

When a Hb-pathy carrier has been identified by antenatal screening, or a sickle carrier or affected baby by neonatal screening, it is expected practice to offer screening to related family members (cascade screening).[5,6,12] Experience with Sardinia's thalassaemia screening programme has shown that this method was very effective in achieving a high coverage of screening amongst the total population at risk.[67] In addition, the offer of cascade screening potentially increases education and community awareness about Hb disorders and thus plays an important role in the wider health promotion approach.[23,228] However, cascade screening falls outside the remit of this study and has not been considered.

Chapter 3

Rationale for the economic approach

Purpose of this chapter

The main purpose of this chapter is to consider the economic methods and provide a rationale for the approach taken in the report with respect to the type of economic evaluation undertaken, the outcome measures chosen, the perspective and scope of the study, and the method of data synthesis. A wide range of sources were used, including a review of the published economic studies on screening for Hb-pathies.

Published economic studies

The main purpose of the review of published economic studies on screening for Hb-pathies was to establish the current state of knowledge and to confirm the need for the economic evaluation presented in this report. The focus of the review was on economic, or cost-related, articles associated with Hb-pathy screening. The search strategy is outlined in appendix 2.

The search identified 68 published articles that fulfilled the required criteria; that is, they included at least one of the group of terms used to identify:

- economic/cost-related articles
- Hb-pathy-related articles
- screening-related articles.

The abstracts of all the flagged articles were read. On the basis of these abstracts, only nine of the articles were considered to add to the 'state of knowledge' on the cost-effectiveness of Hb-pathy screening.[16,177,214,239–244] The findings are presented in *Table 4*. Also presented in this table are the findings of a study published only as a conference abstract.[245]

Although the selected articles presented a range of alternative screening strategies, two specifically considered the mass screening of senior high school students,[239,240] only two included antenatal screening as a screening option,[177,241] and one of the latter and the remaining articles included neonatal screening as a screening option.

Antenatal haemoglobinopathy screening

The French study by Le Gales and Moatti[177] incorporated both costs and effects, but it is not a conventional economic evaluation because it uses multicriteria decision analysis. After discussion with a study group of medical experts, 74 possible screening strategies for sickle cell and thalassaemia were considered. The strategies were defined by considering five variables. These included the place for screening (i.e. schools, premarital examinations, prenatal examinations, state funded community health centres for mothers and children, ambulatory examinations, and neonatal examinations), the diagnostic protocol, and the target population. In addition, the technical organisation (i.e. test performed by a specialised university laboratory or by any laboratory of the region) and institutional organisation (for example, screening included by law or regulation in the list of social security mandatory premarital or prenatal examinations, or voluntary participation) were considered. The strategies were compared, in terms of their effectiveness, total costs, technical feasibility, practical feasibility, ethical acceptability, information follow-up and impact on health education. To establish effectiveness, a laboratory test protocol was selected and the number of true-positives detected for each set of eligible populations was calculated, a true-positive being defined as a carrier of an abnormal haemoglobin trait. The cost components included the laboratory tests and any organisational requirements. The other qualitative criteria were quantified by experts and assigned weights ranging from very bad to very good. The multicriteria decision analysis selected a set of five preferable strategies. Three of the strategies were for screening to take place at state funded community healthcare centres for mothers and children, the strategies differing in terms of the diagnostic protocols and target population. The other preferred options were for strategies of screening school children and mandatory premarital screening.

The article by Modell and Kuliev[241] considered the option of a community-based programme of prospective carrier screening and counselling, with first-trimester prenatal diagnosis for thalassaemia,

TABLE 4 *Economic studies of haemoglobinopathy screening*

Author, year, country	Screening strategies	Costs included	Main outcome measure used	Results
Scriver *et al.,* 1984, Canada[239] Ostrowsky *et al.,* 1985, Canada[240]	Mass screening of senior high school students	Laboratory tests Educational programmes Sample collection Genetic counselling PND Treatment	Cases prevented	The cost per case prevented was $6,754 or $6,638, depending on the method of PND. The cost per case prevented was slightly higher that the average cost of 1 year of treatment or about 4% of the undiscounted total treatment cost incurred in the first 25 years of treatment.
Horn *et al.,* 1986, UK[16]	Selective neonatal screening in Camberwell, London	Laboratory costs	Cases detected	The cost per case detected was £295.59. Screening all infants at birth for haemoglobinopathies would not be cost-effective and should be confined to infants of non-white mothers.
Griffiths *et al.,* 1988, UK[214]	Universal neonatal screening in Birmingham	Not stated	Number of cases detected, not tested and missed	The additional cost, above the cost of existing neonatal services, of providing universal haemoglobinopathy testing for the five districts in Birmingham was 33 pence per baby tested.
Le Gales and Moatti, 1990, France[177]	74 strategies, including preconceptual, antenatal and neonatal screening	Laboratory test Organisational aspects	Number of carriers detected	Multicriteria decision analysis selected five preferable options. Three of the strategies were for screening to take place in state funded community health centres. The others were for a strategy for screening school children and one involving mandatory premarital screening.
Modell and Kuliev, 1991, UK[241]	Community-based antenatal carrier screening and counselling compared with five other approaches to the problem	Laboratory tests Counselling PND	Percentage of the expected affected births detected	Community-based screening and counselling is most effective in terms of expected affected births. It is also the most expensive option in terms of running costs, but in the long run is most effective at limiting costs.
Tsevat *et al.,* 1991, USA[242]	Neonatal screening of three hypothetical neonatal populations: black, non-black with a relatively high prevalence of HbS genes, and non-black with a low prevalence of HbS genes	Laboratory tests Treatment costs	Lives saved	Screening and treating affected black infants costs $3100 more per life saved than no screening. Screening non-black populations with a high prevalence would cost $1.4 million per life saved and non-black low-prevalence populations would cost $450 billion per life saved, compared with no screening.
Sprinkle *et al.,* 1994, USA[243]	Universal versus non-universal selective neonatal screening throughout the USA	Laboratory tests	Cases detected	If the value of finding a case of sickle cell disease were no more than half that of finding a case of PKU, seven of the 19 states that do not currently conduct universal screening would do so and six of the 34 that currently do so would stop.
Gessner *et al.,* 1996, USA[244]	Universal versus selective neonatal screening in Alaska	Laboratory tests Organisational aspects Treatment Education Home care Institutional care	Deaths averted	Selective screening would cost $206,192 per death averted, compared with no screening; universal screening would prevent 50% more deaths at an incremental cost of $2,040,000 per death averted, compared with selective screening.
Pinepinto *et al.,* 1997, USA[245 a]	No screening versus selective infant versus universal neonatal screening in the USA	Screening Follow-up Confirmatory testing Treatment	Life years saved (within first 3 years)	Selective infant screening would cost $4,000 per life year saved using a 3% discount rate on both costs and benefits ($2,100 without discounting) compared with no screening. Universal neonatal screening would cost $66,000 per life year saved using a 3% discount rate ($35,000 without discounting) compared with selective infant screening.

[a] *Pinepinto* et al. *is a conference abstract, which was identified by an author of this review*

compared with five other approaches to the problem. The other approaches included the following situations: no treatment, no genetic counselling and no prenatal diagnosis; the recurrence risk was known but laboratory diagnosis was not possible; only mid-trimester diagnosis was possible for immune deficiency syndromes that must be diagnosed by fetal blood sampling after 20 weeks' gestation; first-trimester prenatal diagnosis was available on a retrospective basis for many inherited conditions; and, finally, only mid-trimester diagnosis for thalassaemia was possible. The alternative approaches essentially describe the successive stages in the evolution of treatment, carrier diagnosis and PND for an inherited disorder. The financial costs of each policy in the UK were considered together with the effects in terms of the percentage of affected births detected. A policy of community-based screening and counselling was found to be the most effective in terms of reducing the percentage of expected affected births, but it was the most expensive in terms of running costs. However, when treatment costs were included, this policy was considered the most cost-effective.

In the studies described above, the comparisons were not restricted to antenatal screening. As described in chapter 2, however, the issue in the UK is whether to provide universal or selective antenatal screening in areas with different ethnic compositions, and not, for example, whether to provide antenatal or neonatal screening. The study by Modell and Kuliev[241] only considered screening a population at risk (i.e. selective screening) and, although Le Gales and Moatti[177] investigated universal versus selective screening, it was for a single French region only.

Neonatal Hb-pathy screening

As discussed previously (chapter 2; pp. 12–13), neonatal Hb-pathy screening is relevant only for sickle cell disorders. The neonatal screening options pertinent to the UK are described in chapter 2 (pp. 17–18). These are universal or selective screening, whereby the latter can comprise either *de-novo* or targeted selection. In addition, we have proposed that a neonatal screening policy can be determined only in the context of an antenatal screening policy, since it is the antenatal policy that determines the population available for neonatal screening.

Of the five published studies specifically evaluating neonatal screening, one considered universal screening alone, one selective screening alone and the remainder universal versus selective screening. The selective screening strategy evaluated was always de novo and antenatal screening was assumed not to be in place.

The paper by Horn *et al.*[16] published in 1986, reported a cohort study identified by selective neonatal screening, using cord blood diagnosis of infants of non-white mothers in Camberwell, London. The cost per sample was £1.70, which gave a cost per case detected of £295.59. The authors suggested that screening all infants for Hb-pathies would not be cost-effective because the incidence of heterozygous states in white individuals was extremely low. However, it was recognised that the increasing intermarriage between ethnic groups would eventually lead to a wider distribution of heterozygous states.

In 1988, Griffiths *et al.*[214] reported on a cohort study of universal antenatal screening in Birmingham. Although no detailed breakdown of the costs were given, they estimated the additional cost of providing universal Hb-pathy testing using capillary whole blood samples to be 33 pence per baby tested. No cost was given per case detected. The authors advocated screening the total neonatal population in areas where the incidence of sickle disease is high, in view of the perceived risks of missing affected infants through errors in ascertaining ethnic origins.

Tsevat *et al.*[242] used a decision model to analyse the cost-effectiveness of screening in three hypothetical populations with different genetic frequencies of the HbS gene: black, non-black with a relatively high prevalence of the HbS gene, and non-black with a low prevalence of the HbS gene. They concluded that screening black infants was worth while, but was unjustified where the HbS gene is rare. The analysis has been criticised, however, as not being relevant to decisions regarding universal screening because it compared screening black infants with screening infants with virtually no risk of sickle disease.[18] A more appropriate analytical approach would have been to compare screening targeted towards African–American and other high-risk groups with universal screening of all infants, allowing projections of cost-effectiveness to be obtained by varying the percentage of at-risk infants in the population. In response to this criticism, Tsevat *et al.*[242] used the racial composition and prevalence of sickle cell disease among neonates in Texas to calculate the incremental cost of screening only black infants. They argued that the estimated incremental cost of $4.1 million per additional life saved for universal compared with selective

screening was too high to justify a universal screening policy.

The article by Sprinkle *et al.*[243] considered, for each state throughout the USA, the cost per case detected for a universal and a selective screening programme and related this to the cost per cased detected for a universal PKU screening programme. They suggested that, if the 'value' of a case of sickle cell disease were no more than half that of finding a case of PKU, seven of the 19 states currently not screening universally should start to do so, and six of the 34 currently screening universally should cease.

Gessner *et al.*[244] compared universal and selective screening in Alaska. They estimated that selective screening would cost $206,192 per death averted, compared with no screening. Universal screening would prevent 50% more deaths at an incremental cost of $2,040,000 per death averted, compared with selective screening.

In a conference abstract by Pinepinto *et al.*,[245] these authors estimated the additional cost per life year saved for selective as opposed to no screening to be $4000, and, for universal compared with selective, to be $66,000 (discounted both costs and benefits at 3%). The authors argued that selective screening is a cost-effective alternative to universal screening.

The remaining two articles selected report on a study of mass screening of high school students in the Quebec province of Canada.[239,240]

The relevance of published cost-effectiveness analyses of Hb-pathy screening to decision making is thus limited. In the UK, neonatal screening requires to be considered in the context of antenatal screening, where it would be appropriate to consider screening policies for districts with differing ethnic composition. The selected articles can, however, be used to explore the economic methods and approach taken in this review.

Rationale for the economic approach taken in this review

Type of economic evaluation

A full economic evaluation requires a comparison of two or more alternative options in terms of both their costs and effects.[246] One of these options may be equivalent to doing nothing or not screening. Economic evaluations are generally categorised into four main types of analyses, namely: cost minimisation, cost-effectiveness analysis, cost–benefit analysis and cost–utility analysis. Each type of analysis values resource use in monetary terms, but differs in how the outcomes or non-resource-use consequences are reported.

Cost minimisation is conducted when there is evidence to suggest that the outcomes of the alternatives under evaluation are the same. In the case of selective and universal antenatal screening or the neonatal screening options, this cannot be assumed to be the case.

Cost–benefit analysis measures and values the outcomes, or non-resource-use consequences, of the options under consideration in monetary terms. Measuring outcomes in monetary units is, however, notoriously difficult. Hence, previous so-called cost–benefit analyses of antenatal and neonatal screening programmes have tended to present financial savings as the sole 'benefit' of screening and the non-resource consequences have not been valued.[241,306] Methods such as using 'willingness to pay' to obtain monetary outcome values do exist and have been used in the context of antenatal screening for cystic fibrosis,[248] but are generally considered to be experimental.[246,306]

Cost–utility analysis measures outcome in terms of 'utility', most commonly expressed in terms of quality adjusted life years (QALY). The quality of life associated with a health state is measured on a scale of zero to one, where death is assigned a value of zero and good health is assigned a value of one. Various techniques, such as the time trade-off and standard gamble, exist to elicit such values.[249] The duration of each health state is multiplied or weighted by its utility value. Where an option leads to a series of health states, the weighted durations are summed to give the QALY. In the case of antenatal screening, cost–utility analysis is complicated by the fact that the future, or expected, utility of at least three groups of individuals are affected in a significant manner, namely, the pregnant woman, her family and the fetus (or child-to-be).[110,250] The effect on their utility is likely to change considerably, depending on the path, and the decisions, taken throughout the screening process.[110] The process of delivering a programme may also be utility- or disutility-bearing, such as the manner by which results are delivered (e.g. in person, by telephone or by letter), or the standard of counselling provided.[110,251,252] Future research might consider how best to measure and value the range of utility effects associated with the provision of an antenatal screening programme but, so far, methods have not

been developed to take full account of all the utility effects.[108–110,253]

Cost-effectiveness analysis is theoretically more limited inasmuch as the outcomes are presented as a single 'natural' unit on a unidimensional scale. Ideally, the outcome measure should be all-embracing, but at least capture the main objective of the programme. The most common outcome measure used in evaluations of antenatal screening programmes tends to be the number of affected fetuses detected,[115,251,254] the number of affected births prevented[239–241] or the number of carriers detected.[116,177] In the case of neonatal screening, the outcome measures most commonly used are cases detected,[16,214,243,247,255,256] lives saved[242] or deaths averted.[244]

Outcome measures

The wide range of possible outcomes, both positive and negative, resulting from antenatal and neonatal screening have been discussed by others and include, for example: raised anxiety on being informed that a pregnancy is at risk, pain and discomfort caused by the PND procedures, distress over termination or miscarriage, reassurance that the pregnancy is not at risk, reduced uncertainty and greater information.[108–110,252,253,257] Given this wide range of possible outcomes, cost–utility or cost–benefit analyses may be considered to be theoretically more suitable. However, for reasons discussed above, the required methodological tools are not currently available to allow confidence in applying such forms of analysis to antenatal screening programmes. Thus, the approach taken in this report is that of a cost-effectiveness analysis.

As discussed in chapter 2 (p. 7), the main objective of antenatal screening for Hb disorders is to offer reproductive choice over the outcome of the pregnancy, which includes as one option the prevention of unwanted affected births. In order to reflect these objectives, the main outcome measures presented in the cost-effectiveness ratios in this review are the number of mothers with affected fetuses to whom choice was offered ('choice offered') and the number of affected live births prevented as a result of a mother's decision to terminate the pregnancy ('live birth prevented') (chapter 4; pp. 33–35). The number of affected fetuses born alive or lost through PND or lost otherwise, the number of unaffected fetuses either born alive or genetically terminated, lost through PND or lost otherwise, and the number of live births for whom no choice was offered, were presented for consideration but not included in the cost-effectiveness ratios.

Trading off the various outcomes is, however, by necessity a value judgement. Psychological consequences of antenatal screening were not included in the analysis owing to the lack of appropriate measurement tools.

The main objective of neonatal sickle cell screening is the early detection of the condition in newborns, to reduce morbidity and mortality through the timely introduction of penicillin prophylaxis and the institution of comprehensive care (chapter 2; pp. 13–14). In order to reflect this objective, the main outcome measure chosen to be incorporated into a cost-effectiveness ratio was the number of late diagnoses of sickle cell disease prevented through screening ('late diagnosis prevented'). Also presented for consideration, but not included in the cost-effectiveness ratios, was the number of late cases detected (chapter 4; p. 36). As the ultimate goal of the screening programme is to prevent premature deaths and disability, the review also presents for consideration the estimated number of early deaths averted and severe disabilities avoided through prevention of the late diagnosis of sickle cell disorders (chapter 7; pp. 76–77).

Study perspective

The resource consequences of a programme may, broadly, be categorised as the resources used and saved as a result of the programme. The chosen perspective of a study is particularly important when looking at the resource consequences of a programme because the burden of resource provision, and the benefit of resource savings, may fall on different sectors of society, for example, the health service, social services, education services, voluntary sector or relatives.[110,246] As decisions taken with regard to the provision of antenatal and neonatal screening are largely taken by commissioning agencies with respect to a health service budget, the perspective or viewpoint taken in this review was that of the health service, and only costs that fall on the health service were considered.

Scope of the study

Given the chosen perspective, the scope of a study depends on how far, in terms of the set of consequences included, the evaluation proceeds. The costs incurred by the health service as a result of an antenatal Hb-pathy screening programme can be categorised as those associated with the laboratory screening tests, PND, TOP and counselling throughout the screening and diagnosis processes. It can be seen in *Table 4* that previous economic studies relating to antenatal Hb-pathy screening have not considered these costs

comprehensively.[18,177,241] In part, the inclusion of costs in previous studies that evaluated antenatal screening programmes for genetic disorders have reflected the outcome measure chosen. For example, Morris and Oppenheimer[116] estimated the cost per carrier couple detected for an antenatal screening programme for cystic fibrosis. Only GP, counselling and laboratory costs incurred to detect a carrier were included. Costs associated with PND, TOP and counselling were not included. Similarly, the cystic fibrosis study by Cuckle *et al.*[115] estimated the cost per affected pregnancy detected and included only the costs up to and including PND.

The main outcome measure for antenatal screening used in this review was that of reproductive choice. It was considered that commissioning agencies would be interested in all the costs listed above. Thus, the costs associated with the laboratory screening tests, PND, TOP and counselling throughout the screening and diagnosis processes are considered in detail in chapter 6. Moreover, the costs and outcomes considered were those directly related to Hb-pathy disorders; excluded were those related to the potential detection of other conditions and the potential cascade screening in families where a carrier or an affected baby has been identified, which was seen as being outside the remit of this review (chapter 2; p. 21).

In the case of antenatal screening, saved resources, or averted costs, are associated with the termination of pregnancies where there is an affected fetus. Had the affected pregnancy not been detected through screening and then terminated, the child would have incurred costs throughout its lifetime in order to treat the condition for which it was screened. These are costs over and above the cost of a child without the condition.[110] If the health service perspective is adopted, the excess costs avoided can be considered equivalent to the health service costs of treating the condition, which would otherwise have been detected late. It should be noted that, when comparing the costs of a universal antenatal screening programme with a selective programme, averted costs are associated only with the additional terminated affected fetuses due to the universal screening programme. These would otherwise have been missed by a selective programme and thus detected late. When comparing a universal, or a selective, antenatal screening programme with a policy of no screening, all terminated pregnancies are associated with an averted cost because they would otherwise have been detected late.

In addition, saved or averted costs can be associated with those affected pregnancies that are detected early by antenatal screening but are not terminated. Here the saved, or averted, costs relate to improved prognosis owing to the early detection of an affected newborn (i.e. the difference in cost between treating an early and a late detected case). Again, it should be noted that, when comparing the costs of a universal antenatal programme with a selective programme, the averted costs are associated only with the early affected cases born with a universal screening programme which would otherwise have been missed by a selective programme and thus detected late. When comparing a universal, or selective, antenatal screening programme with a policy of no screening, all detected affected cases are associated with an averted cost because they would otherwise have been detected late.

Not all conditions, however, will be associated with averted costs owing to the improved prognosis of an early detected affected case. The treatment for thalassaemia, for example, is not altered through early detection. In addition, for some conditions it might be that early detected cases actually cost more because they survive longer.

The issue is more complicated if the implications for other sectors of society are contemplated. For example, consideration would have to be given to the avoided excess costs associated with educational and institutional care, as well as with voluntary services and care incurred by the family. In addition, antenatal screening may affect family size, for example, dissuading couples from having further children, in which case, it could be argued that the cost of caring for these children is saved. On the other hand, the fact that an antenatal screening programme gives couples a clearer definition of risk, plus the opportunity to terminate an affected fetus, may actually encourage the conception and birth of unaffected children who would otherwise not have been born. Whether reproductive behaviour is affected remains, however, uncertain (chapter 2; p. 19). The effect of the number of additional children on total costs and the cost-effectiveness ratio could be explored by modelling different assumptions. This, however, does not complete the equation because the forgone intangible future benefits of the unborn child to the mother, the family and the unborn child itself are excluded.[241] There also exists the moral dilemma of the inclusion of averted costs related to a TOP.

If it is believed that the costs should reflect the outcome measure used, then it can be argued that only the costs incurred by the screening programme up to, and including, TOP are relevant when considering choice over the outcome of a pregnancy with an affected fetus. Averted lifetime treatment costs are then only relevant when affected births prevented are considered. Thus, the approach adopted in this review with respect to antenatal screening is to present the lifetime treatment costs incurred by the health service that are associated with sickle cell disorders and thalassaemia (chapter 7) for consideration by decision makers, but not to include these costs in the cost-effectiveness ratios. This is similar to the approach taken by others, whereby the lifetime treatment costs of an affected individual are presented for comparison purposes.[239,240]

The costs incurred by the health service resulting from a neonatal Hb-pathy screening programme can be categorised as those associated with the laboratory screening tests and counselling throughout the screening process. Although acknowledged, counselling costs were not included in the studies presented in *Table 4*.[16,214,242] Both laboratory screening tests and counselling are considered in detail in chapter 6. Costs may be saved, or averted, in relation to an improved prognosis owing to the early detection of an affected newborn (i.e. the difference in cost between an early and a late detection of a child with a sickle cell disorder). As discussed in chapter 2, the early detection of sickle cell disorders allows the early administration of penicillin prophylaxis and comprehensive care, which has been shown to reduce mortality. The differences in lifetime costs associated with early and late treatment of sickle cell disorders are addressed in the analysis presented in chapter 7 for consideration by decision makers, but they were not included in the cost-effectiveness ratios.

The incremental approach to cost-effectiveness analysis

Given that any district starts with a selective or a universal antenatal screening programme, it is the cost and effectiveness implications of moving from a selective to a universal programme, or vice versa, that are of interest to commissioning agencies. An incremental approach should be adopted whereby the difference in cost and effectiveness between the options is estimated.[258,259] If one option costs less and is more effective, this option is said to be dominant and it makes sense to implement it. Situations of dominance are, however, rare. Usually, one option is found to be more effective and more costly. Where this is the case, the additional costs and the additional effects are presented as a cost-effectiveness ratio or, more precisely, as an incremental cost-effectiveness ratio (ICER).

The use of average cost-effectiveness ratios, whereby the total cost of each programme is divided by the total effectiveness, rather than by ICERs, can lead to inefficient decisions because the cost and effectiveness of the existing policy are ignored. Thus, an incremental approach to cost-effectiveness ratios is taken in this review. It is interesting to note, however, that an incremental approach has not always been taken in the published articles. For example, Sprinkle *et al.*[243] (see *Table 4*) presented the average cost-effectiveness ratios for universal and selective neonatal screening, rather than the additional costs and additional effectiveness of universal compared with selective screening. The way in which the use of average cost-effectiveness ratios can lead to inefficient decisions is explored below.

Illustrative example of how average cost-effectiveness ratios can lead to inefficient decisions

Table 5 presents an illustrative example of the total costs and total effectiveness associated with three hypothetical policy options and the resulting average cost-effectiveness ratios. The options could, for example, be: (1) targeted, (2) selective and (3) universal neonatal screening programmes. A decision maker is interested in whether it is cost-effective to move from an existing policy, say, option 1, to one of the other options. If decisions were made on the average cost-effectiveness ratio, then options 2 and 3 would be deemed to be the same in terms of cost-effectiveness. *Table 6* shows, however, that, with option 3, it is possible to produce more effectiveness but only at a higher cost per unit of additional effectiveness, compared with option 2. The decision maker then needs to consider whether the higher cost per unit of effectiveness associated with option 3 is worth

TABLE 5 *Example of average cost-effectiveness ratios*

Option	Total cost (C)	Total effectiveness (E)	Average cost-effectiveness ratio (C/E)
1	3,000	100	30
2	4,000	200	20
3	6,000	300	20

TABLE 6 *Example of incremental cost-effectiveness ratios*

Option	Total cost	Total effectiveness	ΔC[a]	ΔE[b]	ICER (ΔC / ΔE)
1	3,000	100			
2	4,000	200	1,000[c]	100[c]	10
3	6,000	300	2,000[d]	100[d]	20

[a] *Difference in cost*
[b] *Difference in effectiveness*
[c] *Difference between option 2 and option 1*
[d] *Difference between option 3 and option 2*

paying for or, indeed, whether the cost per unit of additional effectiveness associated with option 2 is worth paying.

Maximum acceptable incremental cost-effectiveness ratio

This raises the issue of a maximum acceptable ICER; that is, the maximum amount that society is willing to pay for an additional unit of effectiveness. This is an empirical question that needs further, more general, research. Chapter 8 discusses the maximum acceptable ICERs chosen for this review in order to provide examples of the decisions that districts may take, given the information provided.

Given a maximum acceptable ICER, the implication is that the most effective option with an acceptable ICER should be implemented. Even if the ICER for a particular programme is acceptable to decision makers, it still may be, however, that the current budget is not sufficient to implement that programme. Where mutually exclusive and indivisible options for the same population, or patient group, are being considered it is not practical for some individuals to receive one option and others another. For example, it may not be practical for some individuals in a district to receive universal screening (for example, until the budget runs out), or for some individuals to receive universal and others selective screening. In such cases, where the budget is not sufficient to support an option with an acceptable ICER, provision would have to be made to shift resources from another budget or activity with a higher ICER, otherwise that district will necessarily implement a less effective policy with a lower ICER (even though the ICER for a more effective policy is acceptable), which implies a more generally inefficient use of resources. For some districts, implementing the most effective option with an acceptable ICER might actually mean budgetary savings if their current programme is found not to have an acceptable ICER.

Efficiency versus equity

It should be noted that the above approach to decision rules relates to efficiency and does not allow for equity considerations (i.e. offering the same provision of service to women with the same risk of an affected pregnancy). Equitable service provision requires either the implementation of a universal screening programme or for selective screening to be as effective as universal screening. Thus, equity may be at the expense of efficiency and may imply that a higher acceptable cost-effectiveness ratio is necessary.

Synthesis of data

The approach taken in this reiew was to synthesise the data using a model programmed in a general-purpose programming language, SAS. Modelling was thought to be the appropriate approach in view of the large quantities of data and their associated uncertainties.[260] Moreover, the cost-effectiveness of different polices is likely to vary for districts with different ethnic compositions. Modelling allows cost-effectiveness to be explored and projected for populations of varying ethnic composition.[18] The model is described in detail in chapter 4.

Chapter 4
The model

Terms of reference

Assumptions and definitions

We have assumed that the antenatal population screened consists of women who are either carriers of one of six significant Hb-pathy traits, namely S, C, D, E, β^{thal} and α^{0thal}, or are non-carriers. In addition, we assumed that each woman has a given probability of being iron deficient and a given probability of being a clinically non-significant α^{+thal} heterozygote/homozygote.

The α^{0thal} trait is defined by the genotype *αα*/– –, denoting two α-gene deletions (or non-deletional mutations) on one chromosome; α^{+thal} heterozygotes and homozygotes are defined by the genotypes *αα*/*α*– and *α*–/*α*– respectively.

Non-significant α^{+thal} heterozygotes/homozygotes have been considered only for estimation of the frequency of a low MCH (< 27 pg) in a given population. The prevalence of homozygotes has been calculated from the known prevalence of heterozygotes by applying the Hardy–Weinberg equation.[23,261] It has been assumed that 69% of α^{+thal} heterozygotes and 100% of α^{+thal} homozygotes have an MCH < 27 pg, based on their mean MCH values of 26 ± 2 pg (one standard deviation) and 22 ± 2 pg (one standard deviation) respectively.[2] The α^{+thal} trait and the homozygous state have otherwise been counted as normal HbA.

A low MCH (< 27 pg) has also been assumed for all carriers of β^{thal} and α^{0thal} traits, and all mothers and partners with iron deficiency.

To reduce unnecessary complexity of the model, overlap between α^0- and β-gene mutations has not been considered. In most populations, mutations of both genes are uncommon and thus combined carrier states are rare. For populations where both mutations are common, however, the simplification will lead to a slight overestimation of the prevalence of a low MCH.[147]

Parameter values entered into the model are all probabilities/proportions. In cases in which numbers are very small, data have been presented as percentages to increase readability.

When district-specific results are shown, these are applied to a hypothetical figure of 10,000 women (= pregnancies) for comparability.

For this analysis we have assumed that each pregnant woman carries one fetus.

Twelve ethnic groups have been used in the model. They are based on 1991 Census output classifications,[174] which have been extended,[6,7] and comprise the following: black Caribbean, black African, black other, Indian, Pakistani, Bangladeshi, Chinese, other Asian, other, Cypriot, Italian and north European. All categories other than north European are termed non-north European.

Costs

Costs resulting from administering selective and universal Hb-pathy screening programmes have been considered in the model. Potential savings of treatment costs owing to the prevention of unwanted affected births through antenatal screening and morbidity through neonatal screening, potential expenditure of routine follow-up, and treatment costs owing to decreased mortality through neonatal screening, have been calculated for comparison (chapter 7), but not formally included in the analysis.

Health-related screening outcomes

The main health-related outcomes of antenatal and neonatal screening are described later in this chapter in the section concerned with functions of the model (pp. 33, 35, 36).

Scope

The scope of the model has been limited to the effects of screening on Hb-pathy-related outcomes and does not include the potential detection of other conditions. In addition, the costs and consequences of potential cascade screening in families in which a carrier or affected baby has been identified have not been included.

Perspective

The perspective is from that of the NHS policy maker and costs incorporated are only to the healthcare sector.

Time horizon

The time horizon of the analysis covers one pregnancy, birth, termination or other pregnancy loss unrelated to screening. It does not include the potential effects of an antenatal and neonatal screening cycle on future pregnancies.

Antenatal strategies

The two main antenatal strategies to be compared are to offer carrier testing and, if indicated, partner testing, PND and TOP, with each step accompanied by education/counselling to:

- all pregnant women (**universal strategy**)
- all pregnant women with low MCH and all non-north European pregnant women regardless of the MCH (**selective strategy**).

In a limited subsidiary analysis, two further strategies have been examined:

- to offer carrier testing and, if indicated, partner testing, PND and TOP, with each step accompanied by education/counselling, to non-north European pregnant women but not to north European pregnant women with low MCH (**selective strategy based on ethnicity without regard to MCH**)
- **no screening**.

Neonatal strategies

The two main neonatal strategies to be compared are to offer screening and, if indicated, confirmatory blood tests, with both steps accompanied by parental education/counselling to:

- all newborns (**universal strategy**)
- all newborns of non-north European mothers, identified postnatally (**selective strategy**).

In a limited subsidiary analysis, two further strategies have been examined:

- to offer screening and, if indicated, confirmatory blood tests, with both steps accompanied by parental education/counselling to all newborns of mothers tested antenatally, except those whose mother or father was identified not to be a sickle or β^{thal} carrier; and to all newborns of non-north European mothers, identified postnatally and not tested antenatally (**targeted strategy**)
- **no screening**.

The model functions

The model was implemented in a general purpose programming language, SAS.[262]

Characterisation of antenatal populations

The first function of the model is to characterise any given antenatal population. The model holds information about:

- the ethnic composition of antenatal populations of all districts in England, Wales and Scotland
- the ethnic distribution of the male partners of women in each ethnic group (inter-ethnic unions)
- the frequency of the six significant Hb-pathy carrier states and the non-carrier state in each of the 12 ethnic groups
- Mendelian recessive inheritance patterns which determine a 1:4 probability of the fetal genotype to be homozygous or double heterozygous if both parents are carriers of a single trait.[23]

This allows the calculation of the number of homozygous, heterozygous and normal fetuses, with their corresponding genotypes, expected each year by the antenatal population of a given district. In effect, the model matrix calculates the number of fetuses in each of 28,224 ($12 \times 12 \times 7 \times 7 \times 4$) subgroups determined by possible combinations of parental ethnic status and Hb-pathy carrier state. *Figure 3* depicts schematically the characterisation of antenatal populations.

The screening process

The second function of the model is to put each of these subgroups of an antenatal population through an antenatal and neonatal screening process, presented below in the form of two flow diagrams (*Figures 4* and *5*). The antenatal and neonatal screening flow diagrams describe the chronological sequence of steps during the screening process. Each step represents an event with a given probability, from where the individual screened can either proceed with screening, following the main vertical flow, or leave the screening process along the horizontal flow, joining again at the final outcomes.

The antenatal screening flow diagram

Figure 4 depicts the antenatal screening flow diagram. Every woman of a given antenatal population is considered at the beginning of the screening process. The first step (**step 1**) allows for known and unknown maternal carrier status.

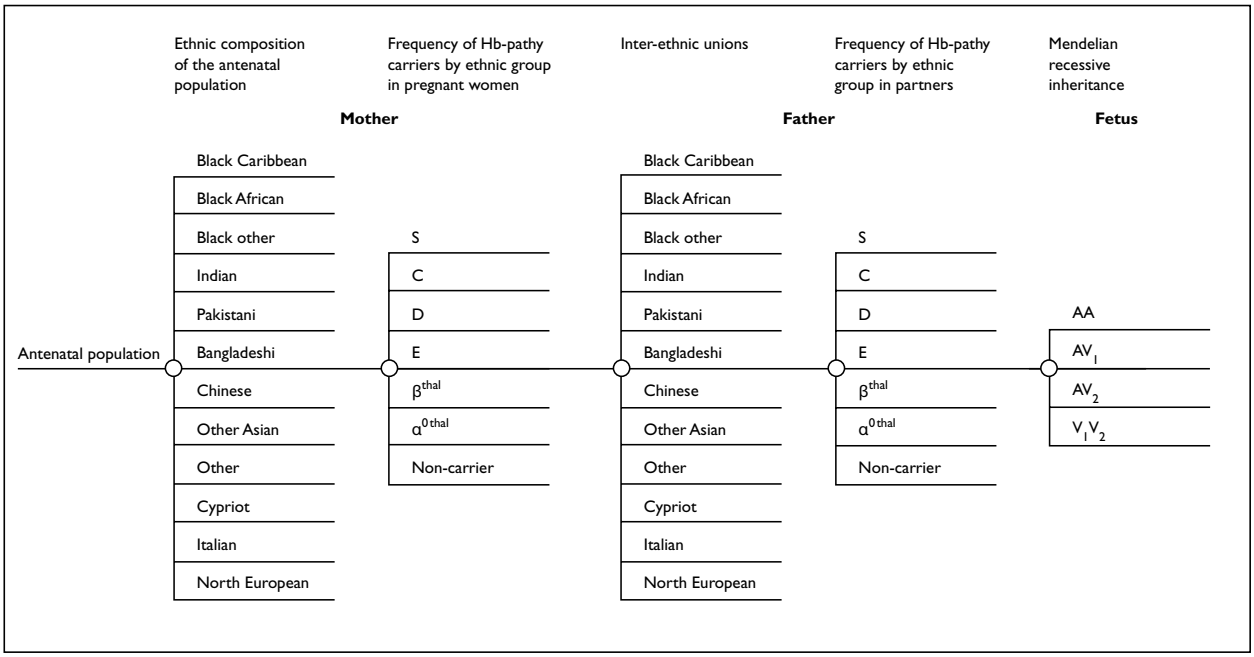

FIGURE 3 *Characterisation of antenatal population (○, probability; A, normal Hb; V_1, maternal Hb-pathy trait; V_2, paternal Hb-pathy trait)*

Depending on whether the known result is positive or negative, such women either continue directly with partner testing or leave the screening process. The next step (**step 2**) accounts for women who book too late to enter the screening cascade, and **step 3** distinguishes between mothers who are eligible for screening and those who are not eligible. The proportions of mothers in each group vary, depending on whether it is a selective or a universal programme; in a selective programme, they are determined by low MCH and ethnic group (p. 32). Acceptance or decline of the offer of screening is the subsequent step (**step 4**), followed by failure to screen eligible women (**step 5**), which again is dependent on a selective or universal strategy. To simplify the diagram, the step 'failure to offer screening' prior to step 4 has been omitted; all errors are considered at the level of step 5. Once a woman has been tested, the result can be either positive for one of the six significant Hb-pathy traits or negative (**step 6**). If the maternal carrier test is positive and the partner accepts screening (**step 7**), the couple tests interpreted together might indicate an at-risk pregnancy (**step 8**). This leads to the offer of PND, which can be accepted or declined (**step 9**). If the partner is not available for testing, the maternal carrier will be counselled and offered PND, which can result in a PND-induced miscarriage (**step 10**). This represents a final outcome or, if pregnancy continues, in an affected or unaffected fetal diagnosis (**step 11**). If a fetus is found to be affected, TOP is offered (**step 12**). TOP can be accepted or declined (**step 13**), leading to the final outcome categories of genetic termination, live birth and other pregnancy loss unrelated to screening. The latter two outcomes are also joined by pregnant women who have left the screening pathway at some earlier stage. All outcome categories apply to either affected or unaffected fetuses, depending on the antenatal subgroups going through the screening process. Education and counselling are part of the screening process (not shown in the diagram). Counselling takes place when a woman has been found to be a carrier, when the couple carrier tests show an at-risk pregnancy, when the fetus is diagnosed as affected, and after TOP. Information is give to all women before testing (for more details see chapter 6).

Antenatal screening outcomes

The main antenatal screening outcomes from the model include the **number of affected** and **unaffected fetuses** (**born alive**, **genetically terminated**, **lost through PND** or **lost otherwise**) and **screening costs**. For affected fetuses, specific outcomes have been defined.

Mothers with **affected fetuses** have been divided into those to whom reproductive choice was offered ('**choice offered**') and those to whom choice was denied ('**choice not offered**'). All affected fetuses of women who were not given the opportunity to terminate the pregnancy were counted as 'choice not offered'. These include affected fetuses not identified owing to: non-eligibility in a selective programme; failure

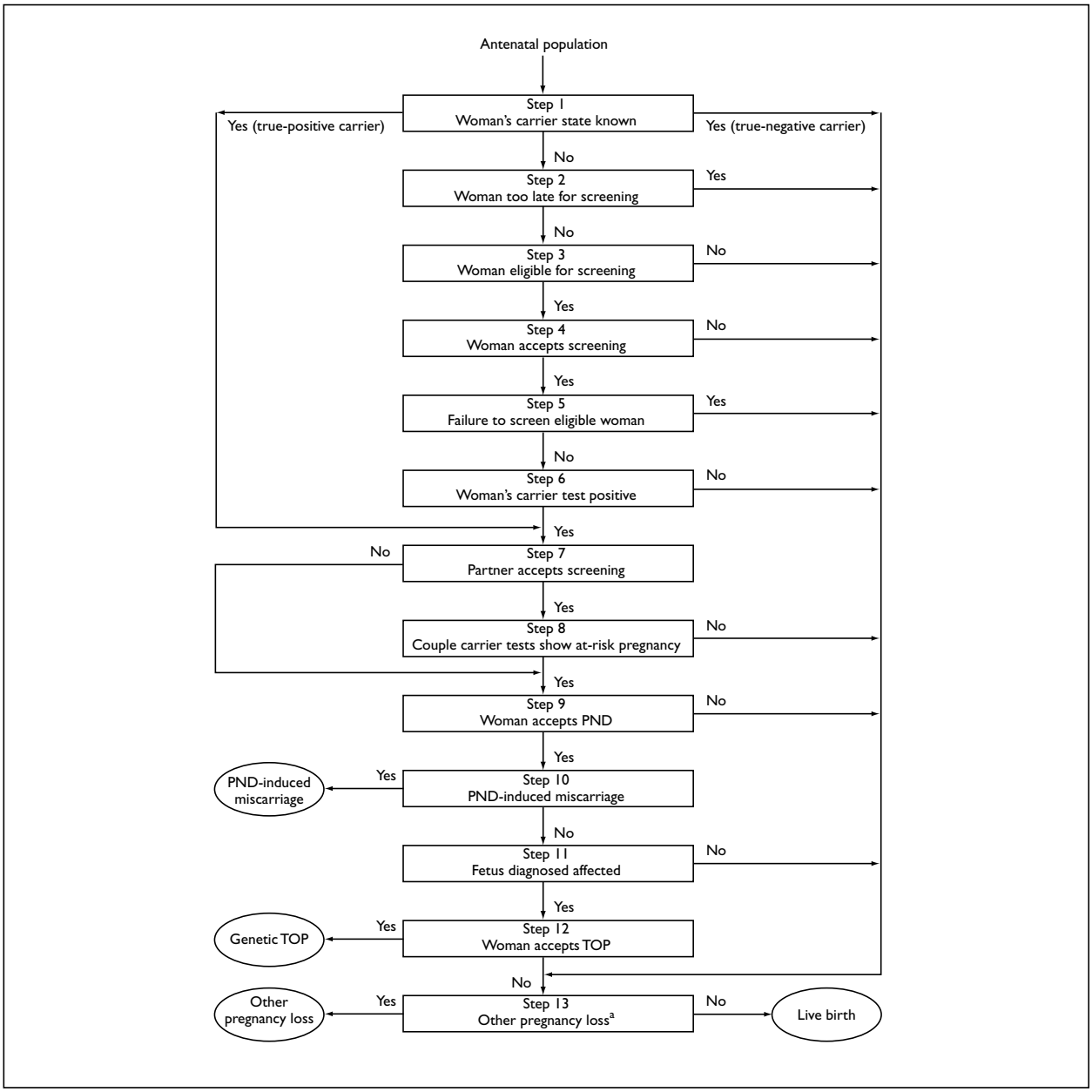

FIGURE 4 *Antenatal screening flow diagram*

[a] Pregnancy loss unrelated to screening

(carrier, significant Hb-pathy carrier; ⬭, final outcome)

to offer screening to an eligible woman; and false-negative laboratory results (carrier tests including risk assessment, and PND). The birth of affected fetuses (live births or other pregnancy losses unrelated to screening) after refusal of maternal carrier testing, PND or TOP, and affected fetuses genetically terminated or lost through PND-induced miscarriage, are defined as 'choice offered' outcomes. Affected fetuses due to non-paternity are also counted in the 'choice offered' outcome category because they are assumed to be the responsibility of the afflicted couple rather than the health service. Affected fetuses as a consequence of late booking have been excluded from the choice category (**'choice not applicable'**).

Screening costs have been divided into the following cost categories:

- **maternal and paternal laboratory carrier tests**
- **PND**
- **TOP**
- **education/counselling**.

For the main analysis, the ICERs calculated by the model present the additional screening

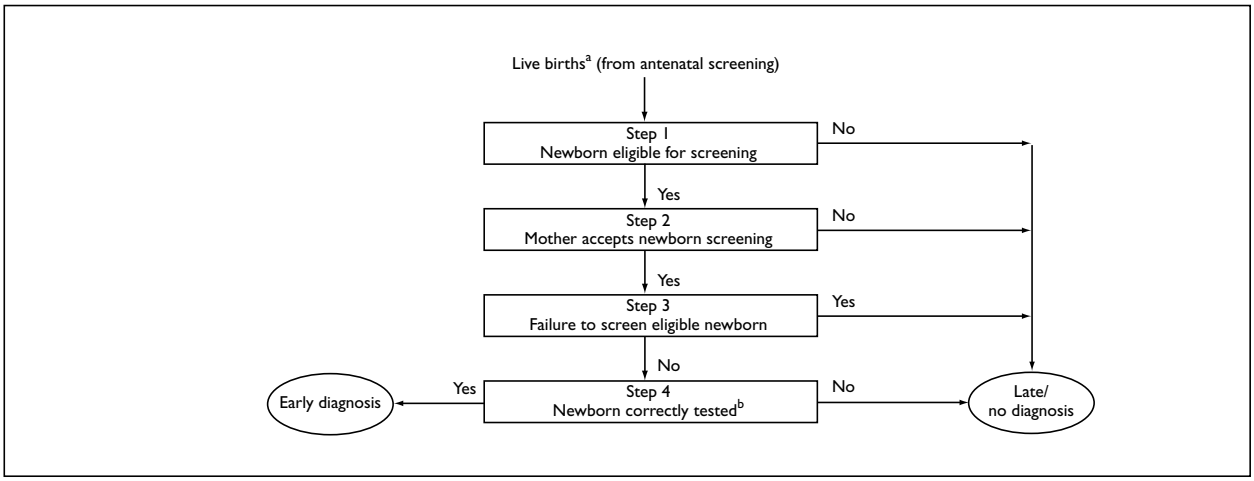

FIGURE 5 *Neonatal screening flow diagram*

[a] Excluding all babies who underwent PND and babies with α^0-thalassaemia hydrops fetalis (assumed mortality 100%)
[b] Test includes screening and, if indicated, confirmatory diagnosis
(⬭, final outcome)

costs incurred per additional choice offered (**'choice' ICER**) when changing from a selective to a universal antenatal screening programme. For a limited subsidiary analysis, the additional screening costs incurred per additional unwanted affected live birth prevented (**'affected live birth prevented' ICER**) when changing from a selective to a universal antenatal screening programme, have also been shown.

Table 7 lists the screening steps in the flow diagram where an affected pregnancy could arise with the corresponding outcome classifications: 'choice offered', 'choice not offered' and 'choice not applicable'.

The neonatal screening flow diagram

The neonatal screening flow diagram is presented in *Figure 5*. All babies from a given antenatal population who are alive at the time of Guthrie card sampling (age about 7 days) and whose mothers did not undergo PND are considered to enter the neonatal screening process.

TABLE 7 *Outcome classification of affected fetuses into 'choice offered', 'choice not offered' and 'choice not applicable'*

Antenatal screening step		**Outcome classification of affected fetus**
Step 2	Woman too late for screening	Choice not applicable
Step 3	Woman not eligible for screening	Choice not offered
Step 4	Woman declines screening	Choice offered
Step 5	Failure to screen eligible woman	Choice not offered
Step 6	Woman's carrier test false-negative	Choice not offered
Step 8	Couple carrier tests false-negative Couple carrier tests negative owing to non-paternity	Choice not offered Choice offered
Step 9	Woman declines PND	Choice offered
Step 10	PND-induced miscarriage	Choice offered
Step 11	Fetal diagnosis false-negative	Choice not offered
Step 12	Woman accepts or declines TOP	Choice offered
Steps 1 and 7 do not lead directly to an affected fetus		

This starts by distinguishing between newborns who are eligible for screening and those who are not (**step 1**). The proportions in each group vary, depending on a selective, targeted or universal strategy. **Step 2** allows acceptance or decline of the offer of screening. This is followed by the possibility of failure to screen eligible babies (**step 3**). To simplify the diagram, the step 'failure to offer screening' prior to step 3 has been omitted and all errors are considered at the level of step 4. If the newborn was screened, the test result can be correct or false (**step 4**), leading to the final outcomes, which are early diagnosis or late/no diagnosis of the baby's sickle cell disease state (and other conditions, see *Figure 5*).

Characterisation of newborn populations entering the neonatal screening process

In order to compare the different neonatal strategies, the newborn populations entering the screening process were characterised according to their presumed risk of sickle cell disorders as judged from the preceding antenatal screening programme. *Table 8* summarises the risk status of newborns arising from various points in the antenatal screening cascade. The following categories have been used:

- 'considered at risk' for all babies of couples, and mothers without partners, identified to be at risk who declined PND
- 'considered not at risk' for babies of mothers who are known to be non-carriers or have been tested negative, and for babies of couples identified not to be at risk
- 'risk not known' for babies of mothers who were too late for screening, were not eligible, declined or failed to be screened despite being eligible.

Neonatal screening outcomes

The main model outcomes from the neonatal screening programme are **early** and **late/no diagnosis of sickle cell disease**, and **screening costs**. Screening costs have been divided into two categories: costs due to **laboratory tests** and to **education/counselling**.

The ICER calculated by the model presents the additional screening costs incurred per additional late diagnosis of sickle cell disease prevented (**'late diagnosis prevented' ICER**) when changing from a selective to a universal neonatal screening programme.

Combined antenatal and neonatal outcomes

Neonatal screening outcomes are not presented in isolation but always calculated in combination with the preceding antenatal screening programme. This means that all PNDs that identified a fetus with a sickle cell disorder are counted in the combined analysis as early diagnosis of the sickle status of a baby. In this way the model takes into account that an antenatal screening programme can also lead to the early diagnosis of sickle cell disorders in newborns and allows the theoretical possibility, that a neonatal programme might be

TABLE 8 *Newborn risk status for sickle cell disease as presumed from antenatal screening*

Antenatal screening step		**Newborn risk status**
Step 1	Woman's carrier state true-negative	Considered at no risk
Step 2	Woman too late for screening	Risk not known
Step 3	Woman not eligible for screening	Risk not known
Step 4	Woman declines screening	Risk not known
Step 5	Failure to screen eligible woman	Risk not known
Step 6	Woman's carrier test negative	Considered at no risk
Step 8	Couple carrier tests do not show at-risk pregnancy	Considered at no risk
Step 9	Woman declines PND	Considered at risk
Step 11	Fetus diagnosed not affected Fetus diagnosed affected	Considered at no risk Considered at risk
Step 12	Woman declines TOP	Considered at risk
Steps 7 and 10 do not lead to a live birth		

redundant if the preceding antenatal programme would screen all mothers and perform PNDs on all at-risk couples.

Probabilities

The probabilities of branching one way or the other at each step of either of the two flow diagrams are all parameters that can be varied according to best estimates derived from the literature and experts (chapter 5). In addition, these probabilities can be made to be dependent on any combination of parental ethnic status or carrier status because the entire flow chart is calculated afresh for each of the combinational subgroups. For example, in the antenatal screening flow diagram, the probability that a woman who is screened will be diagnosed as a carrier must depend on whether or not she really is a carrier. This probability is one minus the false-negative rate if the mother is a carrier and is the false-positive rate if she is not. Both carrier and non-carrier mothers proceed down the same path, albeit with different probabilities. The same principle applies to the neonatal screening flow diagram.

Chapter 5

Parameter probabilities

Methodology

Parameter probabilities for the model are indicative estimates. Their main purpose is to allow, in principle, exploration of the impact of each of the parameters on the predicted outcomes of universal and selective screening strategies.

As most parameters are strongly dependent on the local demographic context and policy implementation, meta-analysis based on a systematic literature search was not considered an appropriate way of obtaining estimates. Rather, the emphasis was on obtaining plausible baseline values and ranges that would convey general trends that were applicable to the current and future UK environment. The dearth of available information made it necessary to derive parameter estimates from a wide range of published and unpublished data sources as well as from experts. This section describes the rationale for the choice of all probability estimates and their ranges employed in the baseline and sensitivity analysis. They are summarised with corresponding references in *Tables 9–11*. The literature search strategy employed is listed in appendix 2.

Characterisation of antenatal populations

Ethnic composition of the antenatal population

The ethnic composition of the antenatal populations for all districts (1993 distribution) and former regional health authorities (1991 distribution) in England, Wales and Scotland has been estimated from the corresponding proportions of ethnic group-specific births.[6,7,228] District-specific proportions of births by ethnic group were calculated from the number of children aged 0–4 years recorded in the 1991 Census, adjusted for underenumeration[174] and divided by 5. Ethnic groups were used according to the Census output classification,[174] with the addition of Cypriot and Italian groups. Births in the latter groups were estimated from birth recordings of parents' country of birth, multiplied by 2.25 to allow for the young age at immigration and subsequent reproduction in these groups. Italian and Cypriot categories were subtracted from the white ethnic group, the remaining group being renamed north European.

The above calculation is likely to underestimate the proportion of ethnic minority births, and thus mothers, because Census figures refer to births that occurred between 1986 and 1991, since when births in ethnic minority groups are reported to have risen.[133,247,359] The ethnic composition data were therefore adjusted before use in the model (for details see chapter 9; pp. 83–84) and subjected to a sensitivity analysis. Baseline data are summarised in appendix 3 (*Table 81*).

Inter-ethnic unions

In the context of antenatal Hb-pathy screening, the importance of inter-ethnic unions is twofold.

- Compared with unions between similar ethnic minority groups, inter-ethnic unions between white groups with low Hb-pathy carrier frequency and ethnic minority groups with high Hb-pathy carrier frequency can be expected to lead to a smaller number of affected homozygous or double heterozygous fetuses and a higher number of unaffected heterozygous fetuses.[23]
- In the long term, increasing inter-ethnic unions can be expected to lead to higher Hb-pathy carrier frequency in the north European population.[23]

The vast majority of couples in the UK comprise partners of the same ethnic group. Overall, it is estimated that 1.11% are inter-ethnic unions, mostly between an ethnic minority individual and a white individual. There is little mixing within the Asian or black ethnic minorities or between them.[19] Levels of inter-ethnic union have increased since the late 1980s and are reported to be rising, especially between black and white ethnic groups.[19,20]

Data about the ethnic distribution of male partners of women from different ethnic groups was used from the 1991 Census (1% household sample of anonymous records),[19] based on information about marriage and cohabitation patterns at the time of the Census. For inclusion in the model we have chosen data from a subgroup of women of reproductive age (16–34 years). As the Italian and Cypriot ethnic groups were not part of the Census

TABLE 9 *Probabilities for characterisation of antenatal populations*

Parameter	Description	Baseline values (sensitivity analysis)	Reference source
Ethnic composition of the antenatal populations by district	*p* that a woman of a given antenatal population belongs to one of 12 ethnic groups	***Table 81*** (% black African women x 1.3)	6, 7, 133, 228, 247, 359
Inter-ethnic unions	*p* that a woman from one of the 12 ethnic groups has a partner from one of the 12 ethnic groups	***Table 12*** (among north Europeans x 5)	19, 263
Hb-pathy carrier frequency by ethnic group	*p* that a woman from one of the 12 ethnic groups is a carrier of one of six significant Hb-pathy traits or is a non-carrier	***Table 13*** (ethnic minority groups all traits x 1.25; north Europeans S trait x 5)	6, 7, 228
	p that a partner from one of the 12 ethnic groups is a carrier of one of six significant Hb-pathy traits or is a non-carrier	***Table 13*** (ethnic minority groups all traits x 1.25; north Europeans S trait x 5)	6, 7, 228
Mendelian recessive inheritance	*p* that, if both parents are carriers of a significant Hb-pathy trait, the fetus inherits both traits, one trait or no trait;	**0.25, 0.5, 0.25**	23
	and, if one parent is a carrier of a significant Hb-pathy trait, the fetus inherits one trait or no trait	**0.5, 0.5**	23

Baseline values are emphasised in bold; values used in sensitivity analysis are given in brackets

p, probability; woman, woman of a given antenatal population; partner, partner of a woman of a given antenatal population

output classification,[174] the ethnic distribution of their male partners was estimated, based on published experience from a group of UK Cypriots.[263] *Table 12* summarises the baseline assumptions about inter-ethnic unions.

It is important to note that data about the frequency of inter-ethnic unions has been aggregated from the whole of the UK and thus might conceal potential variations, depending on the ethnic minority density and particular distribution of a location. The possible impact of higher levels of inter-ethnic unions between north European and ethnic minority groups on the cost-effectiveness of universal screening has been explored in a sensitivity analysis by arbitrarily multiplying the baseline rates by a factor of 5.

Haemoglobinopathy carrier frequency by ethnic group

Data concerning Hb-pathy carrier frequency by ethnic group are based on estimates by B Modell and colleagues.[6,7,228] There are no direct epidemiological data obtainable from UK studies or screening programmes because of small sample sizes or incomplete recording of ethnic group. Estimates for ethnic minority groups were therefore based on studies carried out in their countries of origin, compiled by Livingstone[264] and updated by the WHO.[23,265–268] Estimates for the north European population were informed by case series that reported families of British descent with Hb-pathy traits or disease.[269,270] Carrier frequency estimates for all Hb-pathy traits were subjected to sensitivity analysis. Ranges were derived by multiplying the original estimates of the frequency of sickle trait in north Europeans by an arbitrary factor of 5 and the frequency of all Hb-pathy traits in ethnic minority groups by a factor of 1.25. Maximum and minimum figures have been compared with epidemiological data available from France[177] and the USA[26,178] to ensure plausibility. In certain ethnic groups, especially British Pakistanis, consanguineous marriage continues to be common[271,272] and increases the chance of a couple having an at-risk pregnancy. To adjust for this effect we have increased the frequency of β^{thal} trait in Pakistani men.[6] *Table 13* summarises baseline estimates of Hb-pathy carrier frequency by ethnic group.

Antenatal screening flow diagram

Coverage of screening

Woman's carrier status known

Theoretically, Hb-pathy screening needs to be done only once in a lifetime because the result will not change. If a woman's carrier status could reliably be known, repeat testing could be avoided. This would save resources and, in cases of positive

TABLE 10 *Probabilities for the antenatal screening flow diagram*

Parameter	Description	Baseline value (sensitivity analysis)	Key	Reference source
Woman's carrier state known	*p* that a woman of a given antenatal population has a known carrier state or is known to be a non-carrier	**0** (0.45)	Step 1	131,132
	p that such a woman is a true-positive or true-negative carrier	***Table 13***		6, 7, 228
Woman too late for screening	*p* that a woman whose carrier state is not known books at > 26 weeks' gestation	***Table 14*** (x 2, ÷ 2)	Step 2	133
Woman eligible for screening in a universal programme	*p* that a woman who books ≤ 26 weeks' gestation is eligible for screening	**1**	Step 3	By definition
Woman eligible for screening in a selective programme	*p* that a woman who books ≤ 26 weeks' gestation has an MCH < 27 pg due to iron deficiency or α^{+thal} trait/homozygous state	***Table 15*** *(Table 15)*	Step 3	149, 151, 282–284
	p that a woman who books ≤ 26 weeks' gestation belongs to one of 11 non-north European ethnic groups	***Table 81***		6, 7, 133, 228, 247, 359
Woman accepts screening	*p* that a woman who is eligible for screening accepts the offer	**1**	Step 4	Anionwu, EN, Institute of Child Health, London: personal communication, 1997
Failure to screen eligible woman in a universal programme	*p* that in a universal programme a woman who accepts screening is not screened	**0.005**	Step 5	No reference; see 'Failure to screen eligible women' (pp. 47–48)
Failure to screen eligible woman in a selective programme	*p* that a woman eligible for screening in a selective programme on grounds of a low MCH who accepts screening is not screened	**0.005**	Step 5	No reference; see 'Failure to screen eligible women' (pp. 47–48)
	p that a woman eligible for screening in a selective programme on grounds of non-north European ethnic group who accepts screening is not screened	**0.055** (0.005, 0.015, 0.03)		17, 34, 286
Woman's carrier test positive	*p* that the carrier test result of a true maternal carrier is positive (1 – false-negative rate)	**0.999** (0.990)	Step 6	21, 23, 37, 111
	p that the carrier test result of a true maternal non-carrier is positive (false-positive rate)	See note[a]		21, 23, 37, 111

Baseline values are emphasised in bold; values used in sensitivity analysis are given in brackets

Key refers to steps in the antenatal screening flow diagram Figure 4

p, *probability; woman, woman of a given antenatal population; partner, partner of a woman of a given antenatal population*

[a] *In Chinese, other Asian and Cypriot ethnic groups, non-carrier women with low MCH due to* α^{+thal} *trait/homozygous state or iron deficiency are assumed to be offered partner testing because of the risk of* α^{0thal} *trait and are called 'false-positive' if they proceed with partner testing. For all other women, the false-positive rate for carrier testing is assumed to be 0 (see 'Carrier testing', pp. 52–53)*

continued

TABLE 10 contd *Probabilities for the antenatal screening flow diagram*

Parameter	Description	Baseline value (sensitivity analysis)	Key	Reference source
Partner accepts screening	*p* that the partner of a woman with a positive β^{thal} or α^{0thal} carrier test result accepts screening	**0.95** See note[b]	Step 7	127, 226, 287, 288
	p that the partner of a woman with a positive S, C, D, E carrier test result accepts screening	**0.70** See note[b]		127, 226, 287, 288
	p that the partner of a woman with a 'false-positive' carrier test result[a] accepts screening	**0.95** See note[b]		127, 226, 287, 288
Couple carrier tests show at-risk pregnancy	*p* that the partner who accepts screening is not the biological father of the woman's pregnancy (non-paternity)[c]	**0.005** (0.015)	Step 8	39, 309
	p that the non-biological partner is a Hb-pathy carrier[d]	***Tables 12, 13***		6, 7, 19, 228, 263
	p that the couple carrier test results of a true at-risk pregnancy are positive (1 – false-negative rate)	**0.999** (0.990)		21, 23, 37, 111
	p that the couple carrier test results of a true non-risk pregnancy are positive (false-positive rate)	**0**		21, 23, 37, 111
	p that the carrier test result of a true maternal non-carrier without a partner test result is positive (false-positive rate)	**0**		21, 23, 37, 111
Woman accepts PND	*p* that a woman who has been offered PND after partner testing accepts the offer	***Table 17*** See note[b]	Step 9	39
	p that a woman who has been offered PND without partner testing accepts the offer	***Table 17*** See note[b]		39
PND-induced miscarriage	*p* that a woman who has accepted PND has a miscarriage due to the procedure (CVS)	**0.015**	Step 10	101, 310
Fetus diagnosed affected	*p* that a truly affected fetus is diagnosed as affected (1 – false-negative rate)	**0.9925**	Step 11	39
	p that a truly not affected fetus is diagnosed as affected (false-positive rate)	**0.001**		39
Woman accepts TOP	*p* that a woman with a fetus diagnosed with *ββ*, *Eβ*, $\alpha^0\alpha^0$ accepts the offer of TOP	**0.95** See note[b]	Step 12	39, 121, 127
	p that a woman with a fetus diagnosed with *SS*, *SC*, S*β* accepts the offer of TOP	**0.70** See note[b]		39, 121, 127
Other pregnancy loss	*p* that a woman loses a fetus affected by $\alpha^0\alpha^0$ after 16 weeks' gestation due to late miscarriage, TOP other than genetic TOP for a fetus affected by Hb-pathy, or stillbirth	**0.5**	Step 13	2, 299, 313
	p that a woman loses a fetus affected by all other significant Hb-pathies or not affected after 16 weeks' gestation due to late miscarriage, TOP other than genetic TOP for a fetus affected by Hb-pathy, or stillbirth	**0.0014**		310

Baseline values are emphasised in bold; values used in sensitivity analysis are given in brackets

Key refers to steps in the antenatal screening flow diagram Figure 4

p, *probability; woman, woman of a given antenatal population; partner, partner of a woman of a given antenatal population*

[b] *Explored in sensitivity analysis as summary parameter 'net TOP rate' (further explanation in 'Partner accepts screening', pp. 48–49)*

[c] *Assuming 100% carrier test sensitivity and specificity for test results from non-biological partners*

[d] *Assuming* p *that the non-biological partner is a Hb-pathy carrier* = p *that the biological father is a Hb-pathy carrier*

TABLE 11 *Probabilities for the neonatal screening flow diagram*

Parameter	Description	Baseline value (sensitivity analysis)	Key	Reference source
Newborn eligible for screening in a universal programme	*p* that a newborn is eligible for screening	**1**	Step 1	By definition
Newborn eligible for screening in a selective programme	*p* that a newborn has a non-north European mother (identified postnatally)	***Table 81***	Step 1	6, 7, 133, 228 247, 359
Newborn eligible for screening in a targeted programme	*p* that a newborn has a mother who was tested antenatally, except where mother or father were identified not to be a sickle or β^{thal} carriers	***Table 13***	Step 1	6, 7, 228
	p that a newborn has a mother who was not tested antenatally and is non-north European (identified postnatally)	***Table 81***	Step 1	6, 7, 133, 228 247, 359
Mother accepts newborn screening	*p* that a mother of a newborn accepts screening for her baby	**1**	Step 2	247
Failure to screen eligible newborn in a universal programme	*p* that a newborn whose mother accepted screening is not screened	**0.002** (0.050)	Step 3	209, 379
Failure to screen eligible newborn in a selective or targeted programme	*p* that a newborn whose mother accepted screening is not screened	**0.055** (0.015, 0.03)	Step 3	No reference; see 'Failure to screen eligible newborns' (p. 55)
Newborn tested correctly	*p* that the a screening result of a baby truly affected by a sickle disorder is positive for *SS, SC, SD, Sβ* (1 – false-negative rate)	**0.999**	Step 4	21, 23, 144, 160
	p that the screening result of a baby truly not affected by a sickle disorder but truly being a sickle carrier is positive for *SS, SC, SD, Sβ* (false-positive rate)	**0.999**	Step 4	21, 23, 144, 160
	p that the confirmatory test of a false-positive screening result is positive for *SS, SC, SD, Sβ* (false-positive rate for confirmatory test)	**0**	Step 4	21, 23, 144, 160
	p that any other screening and confirmatory test result is correct	**1**	Step 4	21, 23, 144

Baseline values are emphasised in bold; values used in sensitivity analysis are given in brackets

Key refers to steps in the neonatal screening flow diagram Figure 5

p, *probability; newborn, baby born to a mother from a given antenatal population, without* α^0*-thalassaemia hydrops fetalis, with no PND, and is alive at the time of Guthrie card sampling (age about 7 days)*

TABLE 12 *Inter-ethnic unions: percentage ethnic distribution of male partner*

Ethnic group of male partner	Ethnic group of female partner (age 16–34 years)											
	BC	BA	BO	Ind	Pak	Ban	Chi	OA	Oth	Cyp	Ita	NE[a]
Black Caribbean	79.1	–	–	–	–	–	–	–	–	–	–	0.320
Black African	–	91.1	–	–	–	–	–	–	–	–	–	0.070
Black other	–	–	48.1	–	–	–	–	–	–	–	–	0.110
Indian	–	–	–	95.9	–	–	–	–	–	–	–	0.140
Pakistani	–	–	–	–	97.8	–	–	–	–	–	–	0.042
Bangladeshi	–	–	–	–	–	100	–	–	–	–	–	0.007
Chinese	–	–	–	–	–	–	77.6	–	–	–	–	0.050
Other Asian	–	–	–	–	–	–	–	61.7	–	–	–	0.060
Other	–	–	–	–	–	–	–	–	55.6	–	–	0.290
Cypriot	–	–	–	–	–	–	–	–	–	70.0	–	0.010
Italian	–	–	–	–	–	–	–	–	–	–	70.0	0.010
North European	20.9	8.9	51.9	4.1	2.2	–	22.4	38.3	44.4	30.0	30.0	98.890

All data are percentages

[a] Figures for NE female partner are very small, therefore additional decimal places shown

–, very small numbers, set to 0

Ethnic group abbreviations: BC, black Caribbean; BA, black African; BO, black other; Ind, Indian; Pak, Pakistani; Ban, Bangladeshi; Chi, Chinese; OA, other Asian; Oth, other; Cyp, Cypriot; Ita, Italian; NE, north European

Source: References 19, 263

trait, would allow faster progress to partner screening. In addition, if indicated and desired, it would allow earlier PND and TOP.

However, currently, retesting is the norm. An unpublished survey of present antenatal screening practice[34] found that 22/37 (59.5%) laboratories questioned would not accept a previous result, retesting even if a Hb-pathy card had been issued by their own staff. If the card had been issued by another laboratory, the figure rose to 28/37 (75.7%). The main reason given for retesting was the difficulty of achieving reliable and timely information transfer, with its associated administrative problems, which is an unresolved issue despite the introduction of Hb-pathy cards.[5] Two instances, where women had taken another patient's identity before TOP, highlight the problem, because they led to results being recorded in the laboratory that did not relate to the names attached to them.[34]

If in the future such problems could be overcome (e.g. through improved information technology), it can be envisaged that retesting will decrease. A plausible assumption of how many pregnant women could be expected already to have reliable test results would be the proportion who are multiparous and had their previous pregnancy care in the UK. Data from two London maternity information systems suggest a figure of about 55% multipara.[131,132] To explore the potential impact of this parameter on predicted outcomes, we used a baseline value of zero and a maximum estimate of 45% known maternal carrier state.

Woman too late for screening

There are no technical[273] or legal (Human Fertilisation and Embryology Act 1990) time limits to performing carrier testing, PND and genetic TOP. However, in practice there seems to be a limit, owing to the minimal time required to organise the various screening steps (Yardumian, A, North Middlesex Hospital NHS Trust, London: personal communication, 1997) and the reluctance of obstetric providers to perform late genetic terminations.[274]

Thus, the practical cut-off after which time the screening cascade cannot reliably be completed is dependent on local policy factors. We used data on numbers of women booking after 26 weeks' gestation from a recent survey in six London hospitals.[133] They are average ethnic group-specific figures taken from booking records spanning the

TABLE 13 *Haemoglobinopathy carrier frequency by ethnic group*

Ethnic group	Percentage Hb-pathy carrier					
	Sickle cell carrier (%)				Thalassaemia carrier (%)	
	S	C	D	E	β^{thal}	α^{0thal}
Black Caribbean	11.00	4.00	0.05	0.05	0.90	–
Black African	20.00	3.00	–	–	0.90	–
Black other	11.00	4.00	0.05	–	0.90	–
Indian	1.00	–	1.50	0.05	3.50	–
Pakistani (female)	0.05	0.05	0.05	0.05	4.50	–
Pakistani (male)	0.05	0.05	0.05	0.05	13.50[a]	–
Bangladeshi	–	–	0.05	4.00	3.00	–
Chinese	–	–	0.05	–	3.00	5.00
Other Asian	–	–	0.05	0.05	3.00	1.00
Other	5.00	–	0.05	–	1.00	–
Cypriot	0.75	–	–	–	16.00	2.00
Italian	0.05	–	0.05	–	4.00	–
North European	0.05	–	0.05	–	0.10	–

–, very small numbers, set to 0; percentage non-carrier = 100 – percentage carrier
[a] *Adjustment for consanguineous marriage*
Source: Modified from references 6, 7, 228

year 1995–1996. Ethnic groups were adjusted to fit the extended Census classification used in the model. Baseline estimates are summarised in *Table 14*.

Woman eligible for screening

The proportion of women from the antenatal population who are eligible for screening depends on whether a universal or a selective approach is being used. It is one of the functions of the model to predetermine the assumed true proportions of eligible women for any antenatal population broken down into ethnic groups. This is achieved by taking into consideration maternal ethnic group and Hb-pathy carrier state, as well as information about the prevalence of iron deficiency and clinically non-significant α^{+thal} trait/homozygous state (see below), both of which can lead to a low MCH. This parameter must be distinguished from the later one of 'failure to screen eligible woman', which reflects screening practice and takes account of the fact that, in any screening programme, not all women predetermined as eligible will actually be screened.

Prevalence of iron deficiency in pregnant women. Iron deficiency in pregnancy is a problem related

TABLE 14 *Probability of a woman booking after 26 weeks' gestation by ethnic group*

Ethnic group	Probability of a woman booking after 26 weeks' gestation (woman too late for screening)
Black Caribbean	0.046
Black African	0.081
Black other	0.041
Indian	0.078
Pakistani	0.078
Bangladeshi	0.078
Chinese	0.070
Other Asian	0.078
Other	0.061
Cypriot	0.056
Italian	0.056
North European	0.041

Woman, woman of a given antenatal population
Source: Modified from reference 133

to inadequate nutritional intake to meet the increased demand,[275] with prevalence usually increasing from the first to the third trimester.[276] Iron deficiency is primarily associated with low socio-economic status, which might explain the high prevalence reported in some ethnic minority groups, although dietary habits, such as vegetarianism and the customary avoidance of certain foods in pregnancy, might also contribute.[277] Iron deficiency occurs with different degrees of severity, starting with the depletion of iron stores, followed by hypochromic and microcytic red blood cell indices and, finally, a reduction in Hb level and anaemia.[151]

The parameter of relevance for the model is the prevalence of iron deficiency (which causes a low MCH < 27 pg and occurs at the beginning of pregnancy: first/second trimester) by maternal ethnic group. It is a parameter that is strongly influenced by local demographic factors and appropriate figures could be expected to stem from antenatal Hb-pathy screening programmes. However, there are no such published data available for UK antenatal populations. Only one survey, from a deprived inner London area with a high proportion of Asian ethnic groups, was found to be informative. It reported that, amongst ethnic minority groups, 38% of pregnant women were found to be iron deficient on grounds of a low serum ferritin concentration (10 µg/l), with no differences between ethnic groups; 24% of pregnant women had an MCH < 27 pg, which, after exclusion of α- and β-thalassaemia traits, left a minimum of 15% with an MCH < 27 pg, most likely due to iron deficiency.[151] The proportion of iron-deficient women who had coexisting thalassaemia traits was not reported. In a concurrent study, the prevalence of iron deficiency in Caucasian pregnant women was 62% but no corresponding MCH values were reported.[151]

Indirect data about the overall prevalence of iron deficiency or low Hb levels in pregnancy are difficult to interpret. The main problems are that: evidence of iron deficiency in pregnancy is usually demonstrated by decreased ferritin concentrations, with variable cut-off levels (10–20 µg/l); corresponding levels of MCH are not regularly reported or, if they are, they do not show a consistent association with ferritin concentration;[278,279] and prevalence values are not related to gestation. Because in the early stages of iron deficiency, not all women with a low ferritin concentration will have a low MCH, and the prevalence of iron deficiency increases with gestation, such results would be biased towards overestimation.

The prevalence of low Hb levels in pregnancy is only a very crude proxy for the parameter value of interest because physiological haemodilution in pregnancy makes the definition of a normal and decreased level of Hb contentious,[149] and iron deficiency with a decreased MCH can occur before Hb levels fall. A retrospective analysis of 8684 maternity records from a cohort of pregnant women who delivered between 1987 and 1989 in an affluent area of the UK (John Radcliffe Hospital Oxford) showed that 9.8% of these women had a Hb < 10 g/dl at some time during their pregnancy.[280] An analysis using 153,602 records from the North West Thames Region between 1988 and 1991 reported the lowest recorded measurements over the whole gestation period of Hb (< 10.5 g/dl) in 18.3% of white women; certain ethnic groups, notably black and Indo-Pakistani, were found to have significantly lower mean Hb concentrations than the white population.[281] However, interpretation of these results as being indicative of increased iron deficiency has to be cautious because there are ethnic variations in normal Hb levels.[149]

Published data could thus be used only for a crude estimation of the likely magnitude of the effect. As baseline values, we have chosen a probability of 0.1 for all ethnic groups as a conservative estimate to demonstrate the possible impact of iron deficiency on screening outcomes.

Apart from the Hb-pathy carrier state, iron deficiency is only one parameter that contributes to the prevalence of a low MCH amongst pregnant women, the other being the α^{+thal} trait/homozygous state. Uncertainty about the prevalence of iron deficiency has been explored, together with the prevalence for α^{+thal} trait (see below) by varying a newly created summary parameter called 'low MCH due to iron deficiency or α^{+thal} trait/homozygous state', which combines both variables. *Table 15* shows baseline values and ranges of the summary parameter.

Prevalence of α^{+thal} trait by ethnic group. Data concerning the prevalence of α^{+thal} trait by ethnic group were based on estimates by Petrou and Modell[282] and the WHO.[283] The α^{+thal} trait/homozygous state is not clinically significant and cannot be diagnosed definitely, but only suspected by routine haematological tests showing an otherwise unexplained decrease in MCH and, in cord blood samples, by a band suggestive of Hb Barts.[111,144] Definite diagnosis requires genotyping and there are a variety of deletional and non-deletional mutations described.[2] There are no

TABLE 15 *Prevalence of 'low MCH due to iron deficiency or α^{+thal} trait/homozygous state' by ethnic group*

Ethnic group	Prevalence of α^{+thal} trait (%)	Prevalence of low MCH due to α^{+thal} trait/ homozygous state[a] (%)	Prevalence of low MCH due to iron deficiency or α^{+thal} trait/homozygous state (%) at different levels of iron deficiency		
			Level of iron deficiency		
	Baseline value	Baseline value	Baseline value	Low	High
			10%	5%	30%
Black Caribbean	30	24	32	28	47
Black African	30	24	32	28	47
Black other	30	24	32	28	47
Indian	50	59	64	62	72
Pakistani	50	59	64	62	72
Bangladeshi	25	19	27	23	44
Chinese	5	4	13	8	32
Other Asian	3	2	12	7	31
Other	3	2	12	7	31
Cypriot	25	19	27	23	44
Italian	3	2	12	7	31
North European	3	2	12	7	31

Data are all percentages

[a] Calculation of prevalence of low MCH due to α^{+thal} trait/homozygous state has been explained in chapter 4 (p. 31)

Source: References 149, 151, 282, 283, 284

published epidemiological data available from UK studies or screening programmes. Estimates for ethnic minority groups residing in the UK were therefore mainly based on studies in their countries of origin, using random cord blood samples or, more recently, with available DNA technology, population samples. Data for the north European population were informed by case series reporting families of British descent with α^{+thal} trait.[284] Estimates for Asian and Cypriot ethnic minority groups and north Europeans have been checked against the observed frequency of otherwise unexplained low MCH measurements in haematological samples.[283] Overall, however, there remains considerable uncertainty about the accuracy of the estimates, which, together with estimates about the prevalence of iron deficiency (see above), have been varied in a sensitivity analysis (*Table 15*).

Woman accepts screening

There was no specific information available regarding the percentage of women accepting antenatal screening after informed consent, but it is estimated to approach 100% (Anionwu, EN, Institute of Child Health, London: personal communication, 1997). Nationally and internationally there is a broad consensus about the voluntary character of antenatal screening and the need for consent.[12,13,96–98] Historically, however, testing for Hb-pathies and for sickle carrier status was seen as part of routine antenatal care for the optimal management of pregnant women.[96] Uptake might thus vary according to the way in which consent is sought, ranging from assumed acceptance of comprehensive antenatal care including diagnostic and screening procedures (implied consent) to screening-specific consent, either in the form of generic consent for genetic screening for a variety of conditions[285] or as explicit disease-specific opt-out and opt-in policies.[96]

A baseline value of 100% acceptance was therefore assumed and not varied in a sensitivity analysis.

Failure to screen eligible women

There is concern about an inherent risk of failure to screen eligible women in a selective programme, either owing to failure to offer screening or to

failure to carry out the necessary tests.[5,17,173] However, there are no reliable published UK quantitative studies directly addressing these issues. An unpublished audit from University College Hospital London over a period of 3 months found that 3.4% (9/268) of non-north European mothers from the antenatal clinic had no laboratory test results available.[286] Adjaye *et al.*[17] reported that, over a 3-year period, six out of 10 mothers of babies diagnosed with sickle cell disease postnatally had not been identified in a selective antenatal programme; three were due to non-attendance and one (10%) to failure to offer screening despite eligibility. Indirect evidence of the potential problem is given by an unpublished survey of antenatal laboratory screening practice in the UK, in which only four out of 23 (17.4%) laboratories with selective screening strategies reported that they had information about the ethnic origin of the mother for more than 80% of patients.[34] As directly applicable data were lacking, it was necessary to use best estimates and explore the influence of this parameter value in a sensitivity analysis.

A range of arbitrary values have been employed, depending on the purpose of particular analyses:

- 0.5%: the best estimate, similar to the average value assumed to be achieved in a universal programme
- 1.5%: representing a well-run selective programme
- 3.0%: representing a moderately well-run programme
- 5.5%: representing a poorly-run programme; without definite evidence to the contrary, it has been assumed that districts cannot achieve a failure to screen rate better than this value.

As baseline values, we assumed a 0.5% failure rate for screening eligible women in a universal programme in contrast to 5.5% in a selective programme, representing a 5% difference. The failure rate in a selective programme is applicable only to women selected solely by ethnic group but not those selected on grounds of a low MCH. The latter were subjected to the same 0.5% failure to screen rate as those in a universal programme, because MCH measurement is a universal test performed on all antenatal women.

Partner accepts screening

There is a lack of current published information from UK screening programmes regarding the proportion of partners of carrier mothers who accepted screening and possible factors influencing the uptake, such as ethnic group and the conditions potentially affecting the fetus. In addition, there is often a lack of clarity about the denominator used when reporting proportions. Confusion between the proportion of partners screened related to 'all carrier women detected', and the proportion of partners screened related to 'all carrier women who accepted counselling' makes comparison difficult. Data used in this analysis refer to the denominator of 'women with a positive carrier test result'.

An earlier study[226] from the antenatal screening programme at the Central Middlesex Hospital, London (which was initially selective, later universal), identified 335 carrier women over a 4-year period, mainly with sickle cell trait, and tested 71% of their partners. Averaged estimates of partner testing, reported to the 25th meeting of the North London Working Group on Haemoglobin Disorders for 1991–1992 from four hospitals in the former North East Thames Regional Health Authority and from Brent, range from 95% for maternal β^{thal} carriers (523 carriers had 496 partners screened) to 81% for maternal sickle carriers (1177 carriers had 951 partners screened).[287] However, it was not possible to check the quality of these data concerning completeness, accuracy and consistency in reporting. More recent data from the George Marsh Centre in North London show, over a 3-year period from 1993 to 1996, an uptake rate of partner screening of 76.8% (985 maternal carriers had 756 partners tested), without distinction between ethnic groups or maternal carrier trait. The rate was consistent over the period reported, with yearly fluctuations of 78.9%, 77.0% and 76.8% respectively.[288] A retrospective cohort study from a large community-based antenatal screening programme centred on the Central Middlesex Hospital, London, for the period 1986–1995, reported that, amongst 1688 carrier women identified, 1192 partners were tested (71%). Mothers with a sickle trait had a lower uptake (64%) than those with β^{thal} trait (88.3%).[127]

Examples from experience in other countries also show wide variations. They include the USA,[289] where, in a universal programme in Rochester, over a 5-year period 810 women were identified antenatally to be carriers (sickle and thalassaemia traits), and only 314 (38.8%) had their partners tested. Factors predicting partner testing included gestational age ≤ 18 weeks, the perceived burden of having an affected child, and unmarried partners living together. A selective programme from California (1990–1991) reported 1019 women with Hb-pathy trait (sickle and thalassaemia) and 79% partner screening.[212] The main UK data have been summarised in *Table 16*.

TABLE 16 *Uptake of partner testing, UK experience*

Population	No. women carriers	% partners screened (of women carriers)	Reference
Central Middlesex Hospital, London, 1982–1986	335 (mainly sickle trait)	71	226
4 hospitals in North London, 1991–1992	523 β^{thal} trait 1,177 sickle trait	95 81	287
Central Middlesex Hospital, London, 1986–1995	1,023 sickle trait 675 thalassaemia trait	63 81	127
George Marsh Centre, North London, 1993–1996	985 sickle and β^{thal} trait	77	288

Best estimates for the baseline value were 70% uptake of partner screening if the woman has sickle trait and 95% uptake if she has a thalassaemia trait. For non-carrier mothers from Chinese, Cypriot and other Asian ethnic groups at risk of α^{0thal} trait who are either α^{+thal} heterozygotes/homozygotes or iron deficient, and were therefore assumed to be tested false-positive as (probable) α^{0thal} trait (p. 53), we also assumed an uptake rate of 95% for partner screening. The main impact of varying proportions of partners being tested is its effect on the uptake of PND and TOP. Sensitivity analysis of partner uptake was therefore not performed in isolation but incorporated into a sensitivity analysis of a newly created summary parameter called 'net TOP rate', describing the proportion of women with affected fetuses who request TOP. The summary parameter is influenced by: the proportion of women booking too late to enter the screening cascade; acceptance of maternal carrier testing and partner testing; and uptake of PND and TOP. High and low values for the 'net TOP rate' have been arbitrarily set as follows:

- high rate = baseline late booking rates, acceptance of maternal carrier testing 100%, acceptance of partner testing minimum 90% (otherwise baseline level), uptake of PND minimum 80% (otherwise baseline level), uptake of TOP 95%
- low rate = baseline late booking rates, acceptance of maternal carrier testing 100%, acceptance of partner testing reduced by 10% from baseline, uptake of PND reduced by 25% from baseline, uptake of TOP baseline.

Woman accepts prenatal diagnosis/termination of pregnancy

Acceptance of PND/TOP are complex parameters and difficult to study. Estimates are influenced by a variety of factors:

- individual experience, including religious, moral and cultural motives, as well as prior experience of an affected child[226] (Such motives, however, are not generalisable. Experience from Catholic Mediterranean countries[290–292] has shown very high uptake of PND; in-depth qualitative studies of British Pakistani Muslims[125] have found that difficulty in accessing counselling services is the main reason for rejection; and data are conflicting about whether and how the experience of an affected child will influence subsequent requests for PND/TOP.[120,121,124])
- availability, format and content of culturally sensitive counselling services, including the use of appropriate language[293–295]
- predictability of the severity of the condition that is preventable by genetic termination (Acceptance rates for PND/TOP have universally been found to be higher for thalassaemias than for sickle cell disorders, and, among sickle cell disorders, higher for sickle cell anaemia than sickle HbC disease. For example: WHO register,[296] USA,[212,297] Cuba,[298] UK,[120,127] Italy.[292])
- timing of the PND/TOP offer with regard to length of gestation. (A number of studies worldwide have pointed to the increased acceptance of PND and TOP if it is offered early in pregnancy, preferably in the first trimester (Italy,[119] USA[122]) and UK experience is in line with this trend.[120,121,127])

Prenatal diagnosis uptake. There were no generalisable studies from the UK to inform the parameter values for the model. Figures used to estimate PND uptake are recent PND utilisation rates (1990–1994) calculated from the discrepancy between theoretically expected numbers of at-risk couples – or maternal carriers without a partner result – and actual numbers of PNDs performed.[39] Ethnic groups used in the PND register had to be supplemented with indirect estimates for Chinese[299] and Italians.[119,300] Other Africans were assumed to be similar to black Caribbean, other Asians to other, and white to Cypriot. Baseline figures employed in the model are summarised in *Table 17*.

TABLE 17 *Prenatal diagnosis uptake by ethnic group*

Ethnic group	Probability that woman accepts PND
Black Caribbean	0.13
Black African	0.15
Black other	0.13
Indian	0.37
Pakistani	0.24
Bangladeshi	0.19
Chinese	0.98
Other Asian	0.50
Other	0.50
Cypriot	0.98
Italian	0.98
North European	0.98

Woman, woman of a given antenatal population found to have a pregnancy at risk of an affected fetus

Probability that a woman who has been offered PND without the partner being available for testing is 0.003 times the values in the table

Source: Modified from references 6, 39

These baseline values are low, especially for black, Pakistani and Bangladeshi ethnic groups, and are probably an underestimate because low PND utilisation rates are likely to reflect not only low acceptance of PND but also that some at-risk couples and maternal carriers without a partner result have not been offered PND. For the purpose of the model, however, where we assumed a 100% PND offer for couples who were identified to be at risk and carrier mothers with no partner available for testing, these figures represent current reality in terms of numbers of PNDs performed.

Data from some UK community-based programmes support low estimates of PND/TOP acceptance. A retrospective survey from south London of 199 women with pregnancies at risk for sickle cell disorders who were referred for genetic counselling between 1987 and 1992, showed an overall uptake of PND of 35.2% (70/199). The uptake varied according to genetic risk, being highest for sickle cell anaemia (45%) and lower for sickle HbC disease (18.6%) and sickle cell β-thalassaemia (12.5%).[121] The George Marsh Centre in north London has reported that, over a 3-year period (1993–1996) at-risk couples accepted 41/91 PND offers (45.1%), fluctuating between 43.8%, 48.6% and 40.9% over the three years respectively.[288] A retrospective cohort study from the Central Middlesex Hospital, covering a 10-year period (1986–1995)[127] described even lower uptake for their population: from a total of 135 pregnancies identified to be at risk for a Hb-pathy in which the mother attended for follow-up interview, 35 underwent PND (26%). There was a marked difference of PND uptake between 14.5% for mothers carrying a fetus at risk of a sickle cell disorder and 85.5% for β-thalassaemia major. However, these figures hide variations within each disease category, especially when PND uptake for sickle cell disorders is analysed separately (14/65 at risk of sickle cell anaemia, sickle HbD disease, sickle cell β-thalassaemia; 1/39 at risk of sickle HbC disease; 1/6 for other sickle cell disorders), and less so for β-thalassaemia (19/21 at risk of β-thalassaemia major; 0/1 at risk of HbE β-thalassaemia), but numbers are very small. Amongst the three pregnancies at risk for α^0-thalassaemia hydrops fetalis, PND was accepted for none, an unusual finding for this risk group, which is otherwise reported almost universally to accept PND and TOP.[299] In none of 142 pregnancies in which a maternal carrier did not have her partner tested was PND performed.[127]

Published experience from a tertiary London referral centre demonstrates that, under particular circumstances, much higher uptake is achieved: an earlier study from 1980[134] reports that, of 50 Cypriot couples and 22 Indian/Pakistani couples at risk of a fetus with β-thalassaemia major, 47 (94%) and 13 (59%) respectively accepted PND. More recent experience from the same centre indicated that PND was requested by 80% of Pakistani at-risk couples if they were referred in the first trimester.[294] A retrospective analysis of 29 pregnancies at risk of α^0-thalassaemia hydrops fetalis found acceptance of PND in 28 (97%).[299] Between 1979 and 1990, 170 couples with 188 pregnancies at risk for sickle cell disorders were referred to the centre for counselling. Overall, PND was requested for 58% of pregnancies (109/188). This figure increased to 82% when the mother was seen in the first trimester of pregnancy but fell to 49% in the second trimester.[120] A differential acceptance rate for PND depending on the type of sickle cell disorder expected in the fetus was confirmed in this study: overall PND uptake for sickle cell anaemia was 58%, compared with 47% for sickle cell β-thalassaemia and 17% for sickle HbC disease. It is important to note that all the above data relate to the denominator of 'at risk pregnancies

counselled' rather than 'at risk pregnancies identified', which is the appropriate denominator for the model parameter. It can be assumed that figures relating to the former are higher than those relating to the latter, because not all mothers with pregnancies identified as at risk will actually attend for follow-up counselling.[127] *Table 18* summarises the UK experience of PND uptake.

Termination of pregnancy uptake. The national PND register for Hb-pathies in the UK reports on the outcomes of all pregnancies found to carry a fetus affected by thalassaemia (genotypes $\beta\beta$, $E\beta$, $\alpha^0\alpha^0$), showing an overall uptake rate of TOP for these conditions of 98%.[39] There are no comparable figures for sickle cell disorders. Worldwide experience suggests that the TOP uptake rate for sickle cell disorders is lower than for thalassaemias.[296] This is consistent with UK data from local community-based programmes, which indicate a figure around 75%,[121,127] although absolute numbers are very small.

Currently, most women who accept PND also accept subsequent TOP if the fetus is found to be affected. However, since the introduction of CVS as a less invasive fetal sampling technique than the previously used fetal blood sampling, a trend has been described internationally of increasing discordance between the acceptance of PND and TOP, especially for fetuses with sickle cell disorders.[301] In addition, a change in attitude towards PND as a legitimate way of reassurance or psychological preparation for the birth of an affected child might explain this development.[5,274]

The main question that is relevant to the model remains what proportion of women could be expected to request PND and TOP after an appropriate offer of screening services (including a timely offer of carrier tests and non-directive counselling) and what proportion would genuinely choose not to take up the option.

This uncertainty is explored by varying the summary parameter 'net TOP rate' as previously explained (p. 49).

Laboratory test performance

The overall performance of the laboratory tests employed for carrier testing and PND has been assumed to be highly accurate, in line with current UK consensus guidelines from the British Society of Haematology[21,37,111] and international expert opinion,[23,256] and supported by evidence from the PND register[39] and results from the National Confidential Inquiry into Counselling for Genetic Disorders, which includes β-thalassaemia major.[229] These sources indicate that adverse outcomes at the end of the screening cascade owing to conditions that are undetectable by the laboratory tests employed for screening, such as silent β-thalassaemia, are probably extremely uncommon. Technical and clerical laboratory errors also seem rare. However, a formal quantitative analysis of the distribution of the various screening cascade test results between carriers and non-carriers, and a review of the recommended cut-off levels, were beyond the scope of this report. Because uncertainty about these parameters does not differentially influence selective and universal

TABLE 18 *Uptake of prenatal diagnosis, UK experience*

Population	No. at-risk pregnancies offered PND (after attending follow-up counselling)	% uptake of PND (of at-risk pregnancies offered PND)	Reference
Community programmes			
Central Middlesex Hospital, London, 1982–1986	21	57	226
King's College Hospital, South London, 1987–1992	199	35.2	121
Central Middlesex Hospital, London, 1986–1995	135	26	127
George Marsh Centre, North London, 1993–1996	91	45.1	288
Tertiary referral centre: University College, London			
1974–1979	50 Cypriot couples	94	134
	22 Indian/Pakistani couples[a]	13	
1979–1990	29 at risk for $\alpha^0\alpha^0$	97	299
1982–1991	188 at risk for sickle cell disease	58	120

[a] *Data refer to at-risk couples rather than at-risk pregnancies*

screening outcomes (see sensitivity analysis (chapter 9; pp. 95–98), the issue was only tangential to this study.

Laboratory test performance and the interpretation of results with regard to the risk assessment of a pregnancy have been considered together because there are no data available that would support different parameters. There is evidence from the PND register that, formerly, referrals for PND have occurred for pregnancies that were not at risk.[39] However, centres performing PNDs now routinely recheck parental results before proceeding with fetal diagnosis (Modell, B, UCLMS, London: personal communication, 1997), thus minimising the probability of false-positive laboratory results and risk assessments.

Carrier testing

The objective of carrier testing is the detection of **couples at risk** for a fetus with a Hb-pathy, not the detection of maternal and paternal Hb-pathy carriers in isolation. In this context, maternal carrier testing aims to identify all mothers who could have a significant Hb-pathy trait, whereas the role of partner testing is to exclude or confirm the possibility of an at-risk pregnancy. In cases in which the partner is found not to be a carrier, this is the end of the screening process and definitive diagnosis of the maternal carrier state, if not already made, is not sought. In contrast, if partner testing cannot exclude the possibility of an at-risk pregnancy without definitive diagnosis of maternal and sometimes also paternal traits, DNA analysis is added into the screening process accordingly.

Carrier testing consists of several tests, performed in parallel to cover all significant Hb-pathy carrier states and increase sensitivity, and in sequence to increase specificity. All tests used are well established and have been subjected to quality control to ensure accuracy and reliability. The cut-off levels chosen are based on national and international recommendations.[21,23,37,111,144,152,302]

False-negative rate for carrier testing. For the model, it has been assumed that the false-negative rate for carrier testing is similar for maternal and paternal tests, and for all Hb-pathy traits. The false-negative rate is principally determined by the sensitivity of the initial tests of the screening cascade. For the detection of structural Hb variants, these are either Hb-electrophoresis on cellulose acetate or HPLC. Both technologies are able to identify reliably the Hb variants HbS, C, D and E included in the model.[21,152] For the detection of thalassaemia traits, the main determinants of the false-negative rate are the MCH measurement. To a lesser extent the false-negative rate also depends on the accuracy of the HbA_2 quantification, $\delta\beta^{thal}$ on the HbF level, and α^{0thal} on the correct determination of ethnic group (see *Figure 1*).

The MCH cut-off values chosen for further testing are high enough to ensure that not only the usual β^{thal} and α^{0thal} traits, which show profoundly decreased MCH levels, are detected, but also the much rarer double heterozygous conditions such as β^{thal} trait/homozygous α^{+thal} state and β^{thal} trait/α^{0thal} trait, which have MCH values closer to the normal range.[147] The only thalassaemia trait that cannot be detected on the basis of a low MCH measurement is silent β^{thal} trait because it is not reliably associated with a reduction of red blood cell indices. However, mutations known to be silent (e.g. Mediterranean-101 and Indian CAP+1) are currently very rare in the UK.[111] The use of HPLC technology, which includes HbA_2 estimation among the initial tests, will detect most of these traits on the grounds of an elevated HbA_2.[111]

The majority of β^{thal} traits are associated with an elevated HbA_2.[111] Cases of 'normal HbA_2 β^{thal} traits' are known but rare, and often have severely reduced red blood cell indices and a blood film showing other morphological markers characteristic of thalassaemia trait.[303] There has been evidence that severe iron deficiency coexisting with β^{thal} trait reduces HbA_2 levels.[111] However, in practice, this reduction rarely seems profound enough to bring the HbA_2 level down to normal values and usually does not interfere with the diagnosis of β^{thal} trait.[23,151]

Most cases of $\delta\beta^{thal}$ trait, which are less common than β^{thal} trait,[304] are not associated with elevated HbA_2 levels but show HbF levels above 5%.[111]

Further investigation for possible α^{0thal} trait is limited to certain ethnic groups who are considered to be at risk, namely Chinese, south-east Asian and eastern Mediterranean,[37] their corresponding extended Census output classifications being Chinese, other Asian and Cypriot. In the UK, there are no published data available about the ethnic group distribution of cases of confirmed α^{0thal} trait, but their prevalence outside the at-risk groups is assumed to be rare (Modell, B, UCLMS, London: personal communication, 1997).

The false-negative rate for carrier testing informs two parameters in the model, namely 'woman's carrier test positive' and 'couple carrier tests show

at-risk pregnancy'. For the purpose of this review, both probabilities have been assumed to be 0.001.

False-positive rate for maternal carrier testing. The false-positive rate for maternal carrier testing was assumed to depend on the maternal ethnic group, carrier state and iron deficiency. Non-carrier women of all ethnic groups, except those at risk for α^{0thal} trait (Chinese, Cypriot, other Asian), were assumed not to be wrongly identified as carriers of a significant Hb-pathy trait (false-positive rate = 0). This assumption was based on the very high specificity of the laboratory tests at the end of the screening cascade. The relevant test sequence for a potentially false-positive screening result of β^{thal} trait is the MCH in conjunction with HbA_2 quantification. An elevated HbA_2 is highly specific for β^{thal} trait after the third month of life.[69,305] Other conditions that can cause a slight increase, such as pernicious anaemia and some unstable Hb variants,[111] are usually either not associated with a low MCH or are likely to be detected during screening by Hb-electrophoresis or HPLC.

A separate maternal false-positive rate for $\delta\beta^{thal}$ trait, most likely in non-carriers with a hereditary persistence of fetal Hb,[111] has not been considered because of the rarity of both conditions.

A false-positive screening result of one of the structural Hb variant S, C, D or E is equally rare, the main reason for false-positive test results being unusual non-significant Hb variants, which are mistaken for significant variants because of a similar migration pattern on electrophoresis.[144,160]

In contrast, the identification of α^{0thal} trait is more ambiguous because iron deficiency and non-significant α^{+thal} trait/homozygous state cannot easily be distinguished. In Chinese, other Asian and Cypriot ethnic groups, non-carrier women with a low MCH due to iron deficiency or α^{+thal} trait/homozygous state are assumed to be offered partner testing because of the risk of α^{0thal} trait. For the purpose of the model, all those women who proceed with partner testing are assumed to have a 'false-positive' maternal carrier test result; all those who have no partner available for testing are assumed to receive a definite DNA analysis to resolve the uncertainty about possible α^{0thal} carriage and the false-positive rate is zero. As there is ambiguity in the screening literature about the exact definition of 'false-positive',[306] it is important to note that the term in this context was chosen to take account of redundant partner testing. However, a maternal carrier test that indicates 'probable α^{0thal} trait' is, strictly speaking, an uncertain rather than a false-positive result, requiring further confirmation.

False-positive rate for couple tests showing an at-risk pregnancy. The probability that both parental results taken together at the end of the screening cascade lead to a false-positive assessment of an at-risk pregnancy has been assumed to be zero, provided that:

- DNA analysis would be used for the definite diagnosis of possible α^{0thal} and $\delta\beta^{thal}$ traits, and HbD^{Punjab} in women in whom the partner has a significant trait, which, in combination could result in an affected fetus
- all parental samples were rechecked by the PND laboratory before fetal diagnosis (see above).

The assumption of a zero false-positive rate is likely to slightly underestimate the number of PNDs performed on fetuses not at risk of a Hb-pathy because DNA analysis, although highly specific, has a false-positive rate of about 0.001 (see 'Prenatal diagnosis' below). However, as expected numbers are very low, the assumption was justified to simplify the model and consider only those PNDs for fetuses not at risk that were due to partners not screened or to non-paternity (see below).

Prenatal diagnosis

Error rates for PND have been based on information from laboratory records of all PNDs performed in the UK from 1974 to 1994.[39] Errors were included only for DNA analysis, not for globin chain synthesis, an older less accurate method for fetal diagnosis that preceded the advent of DNA technology and is not now routinely performed. There was a total of seven known misdiagnoses out of 1551 prenatal DNA analyses (0.45%). This number might be an underestimate because fetuses terminated after a positive PND of a Hb-pathy are not routinely re-examined and false-positive misdiagnoses can thus go unrecognised. The figure is comparable with an international estimate of 0.5% misdiagnoses, computed from WHO register data from over 6000 prenatal DNA analyses for Hb-pathies from 1986 to 1989,[296] although the data are relatively old, reflecting the beginning of DNA analyses; in addition, the reporting of errors was not based on the systematic follow-up of all PNDs. Recently reported experience from Sardinia's programme, which has been in place since 1976, showed one error out of 2837 PNDs based on DNA technology,

an error rate of 0.04%.[67] For inclusion in the model, the parameters required were the false-positive and false-negative rates for PND, based on DNA analysis. Among the seven misdiagnoses reported from the UK register, three were false-negatives, one was false-positive, and the other three were diagnoses of Hb-pathy traits in fetuses, which, on follow-up, turned out to be non-carriers. Only the false-negative and false-positive diagnoses of a Hb-pathy, not of the carrier state, have been used to calculate the corresponding rates, which were 0.0075 (3/399) and 0.001 (1/1151) respectively.

If the partner of a maternal carrier is not available for testing and PND is carried out under these circumstances, certain Hb-pathy gene mutations (mainly thalassaemia mutations) cannot be definitely excluded because the paternal genotype is unknown. Therefore, some uncertainty might remain concerning whether the fetus is affected or not.[37,307] For the model, however, we have not modified the false-positive and false-negative PND rates for these cases because, currently, they are very rare in the UK.

Non-paternity

In the context of this review, non-paternity, when a woman's partner is not the biological father of her child, is only of relevance if the biological father and the partner have different Hb-pathy carrier states. The main impact of non-paternity in an antenatal screening programme is under-estimation of the number of at-risk couples and, consequently, affected fetuses, in cases in which a partner screening result is negative, despite the biological father being a carrier. This effect is deleterious for targeted neonatal screening programmes, which rely on antenatal information about parental carrier state to determine eligibility for neonatal screening and will inevitably miss affected infants. Although non-paternity can also lead to false PND results, this dependence has not been incorporated into the model because, in the majority of cases, non-paternity can be detected through incompatibility between fetal and partner DNA.[39]

The prevalence of non-paternity is difficult to establish. Earlier reports that quote rates ranging from 1% to 30% are all limited by poor quality or lack of applicability to the general and ethnic population of the UK.[308] The UK PND register recorded a very low probability of non-paternity of 0.0025, based on findings of incompatible fetal and paternal DNA.[39] A low estimate of about 0.01 has also been reported from nine UK laboratories carrying out PND for cystic fibrosis.[309] For the model we have chosen a probability of non-paternity of 0.005, relaxed in a sensitivity analysis to 0.015, and assume that the ethnic group of the biological and 'apparent' father are the same.

Pregnancy loss

Prenatal diagnosis-induced miscarriage

Procedure-related pregnancy loss due to CVS is not easy to assess because, for ethical reasons, there has been no randomised controlled trial conducted to compare the risk of PND-induced fetal loss against the spontaneous background miscarriage rate at similar gestations. Instead, comparison has been carried out with standard mid-trimester amniocentesis. A recently updated systematic review[101] concluded that the risk of fetal loss was up to 52% higher in the CVS group than in the amniocentesis group. As amniocentesis has been compared with no intervention in a randomised controlled trial of low-risk women[310] and was found to increase loss by 1% over background spontaneous miscarriages, the probability of CVS-induced loss has been estimated to be 0.015.

Other pregnancy loss

This parameter incorporates pregnancy loss due to late spontaneous miscarriages, stillbirths and TOPs that are not screening related. To make the outcome applicable for women who have entered the screening process, figures include only events occurring after 16 weeks' gestation. This parameter has considerable influence on estimates of the proportion of unwanted affected births prevented by antenatal screening.

There is no evidence that pregnancies are at an increased risk of loss in cases in which either the mother is a Hb-pathy carrier[69,311] or the fetus is affected by a sickle cell disorder or β-thalassaemia major.[1,312] A probability of pregnancy loss of 0.014 has been assumed in such cases, similar to that in the normal population,[310] with spontaneous miscarriage between 16 and 28 weeks' gestation accounting for a probability of 0.007, stillbirth greater than 28 weeks' gestation for a probability of 0.005, and induced abortion other than genetic TOP for a probability of 0.002. In contrast, fetuses with α^0-thalassaemia hydrops fetalis are not viable; usually, about half of them die in the third trimester, the rest shortly after birth.[2,299,313] For the model, we thus used a probability estimate for pregnancy loss of 0.5.

Neonatal screening flow diagram

Coverage of screening

Newborns eligible for screening

The proportion of newborns of a given antenatal population who are eligible for screening depends on the neonatal screening strategy as well as the preceding antenatal screening programme. It is one of the functions of the model to calculate the expected proportions. This parameter must be distinguished from the later one, 'failure to screen eligible newborns', which reflects **screening practice** and takes account of the fact that, in any programme, not all eligible newborns will actually be screened.

Mother accepts newborn screening

There is no available information about maternal refusal of neonatal sickle cell screening offered in the context of a metabolic screening programme using the same Guthrie card sample. Refusal rates for metabolic screening are negligible.[247] Although, theoretically, acceptance of metabolic screening might be expected to differ from acceptance of screening for sickle cell disorders because of their association with certain ethnic groups and the consequent potential for stigmatisation,[201] current integrated neonatal programmes do not usually allow for differential acceptance of the metabolic and sickle cell screening components.[314]

Failure to screen eligible newborns

As with selective antenatal screening, there is the same concern with selective neonatal screening about an inherent risk of failure to either offer screening to eligible babies or to carry out the test. The reasons are similar and include complex administration and possible ethnic misclassification (chapter 2; pp. 17–18). For example, Githens *et al.*[220] reported from a universal neonatal screening programme in Colorado, where the screening forms requested ethnic information from the parents, that, in 30% of cases, this was inaccurate or incomplete. With targeted neonatal screening, which relies on accessing antenatal parental carrier results, there is the additional risk of missing eligible babies owing to errors in the information transfer between the antenatal and neonatal sides of the screening programme.[17] However, quantitative data about the magnitude of these errors are difficult to interpret because results are very dependent on local organisational factors. In particular, most published studies of selective neonatal screening that report the frequency of missed neonatal screening samples, either from the UK[16,17,315] or from the USA,[211,212] relate to programmes using cord blood samples. These studies cannot inform the parameter value in question as it is not clear whether reported failure rates of screening eligible babies are the result of a selective screening approach or whether they are confounded by the inferior coverage achieved by cord blood compared with Guthrie card sampling. The only published study of selective neonatal sickle cell screening based on Guthrie card samples and associated with a neonatal metabolic screening programme is from metropolitan France (Paris area).[221] However, programme errors with this approach have not been reported.

Although there are different plausible failure mechanisms between selective and targeted programme approaches (see above), it is not known whether overall proportions of missed babies in the two programmes vary significantly.

Confronted with no current reliable information, we assumed neonatal selection to have similar failure to screen rates as antenatal selection (0.5%, 1.5%, 3.0%, 5.5%). In particular, we chose a baseline value of 5.5% and, for all combined analyses, we have used the same values for antenatal and neonatal components. Furthermore, we assumed no difference between selective and targeted strategies.

In universal neonatal Hb-pathy screening programmes, the risk of failure to offer screening to eligible newborns has been assumed to be minimal, similar to experience from the metabolic neonatal screening programme. In an analysis of over 25,000 Guthrie cards matched to child health records in North East Thames, a coverage rate of 99.76% was reported when failure to test a child was distinguished from failure to record the test correctly.[209] In the Birmingham area, where a link between the laboratory and the local child health computers assures very high ascertainment of coverage, in most districts this is reported as being in excess of 99.8%.[210] Ethnic minority status, which has previously been associated with poorer coverage[316,317] is also a risk factor for poorer ascertainment of coverage owing to variable naming conventions and the practice of staying with relatives during the neonatal period. Thus, for the purpose of this review, no differential estimates between ethnic groups have been used, but an overall estimate of 99.8% was assumed. This has been decreased to 95% in a sensitivity analysis.

Laboratory performance

Neonatal sickle cell screening, based on Guthrie card sampling and analysis by HPLC technology, and integrated into a large-scale metabolic

screening programme, has been assumed to achieve high sensitivity and specificity, in line with current guidelines from the UK,[21,144] the USA[26] and the WHO.[23] There is no register for sickle cell disease in this country, so no systematic data are available to back up this assumption, but experts agree that the methodology is highly accurate (Jones, R, Great Ormond Street Hospital, London: personal communication, 1997) and very few false results have been encountered in the UK (Anionwu, EN, Institute of Child Health, London: personal communication, 1997). As discussed in the section concerning laboratory performance in antenatal screening (pp. 51–52), a formal quantitative analysis of neonatal screening and confirmatory test sensitivity and specificity was beyond the remit of this report.

Probability of correct neonatal screening and confirmatory test results

Experience from northern California, where over 2 million infants have now been screened by HPLC methodology, has shown no false-negative and very few false-positive screening results, the latter being mainly due to unusual Hb variants being mistaken for HbS.[160] For the purpose of the model, we have estimated a sensitivity and specificity for the screening tests of 99.9%, assuming that misdiagnoses occur only between sickle cell disorders and sickle cell traits, and do not involve other conditions detectable by neonatal screening. Confirmatory diagnosis is assumed to have no false-negative and false-positive results. *Table 19* summarises the probabilities that the neonatal screening test identifies the true conditions.

TABLE 19 *Probabilities that the neonatal screening test identifies true conditions*

True condition	Probability of test results		
	Sickle cell disorder	Sickle carrier	Other conditions
Sickle cell disorder	0.999	0.001 (false-negatives)	0
Sickle carrier	0.001[a] (false-positives)	0.999	0
Other conditions	0	0	1

[a] *Confirmatory diagnosis is assumed to rectify the false-positive screening result*

Source: Modified from reference 160

Chapter 6

Screening programme costs

Methodology

Perspective

The provision of screening programmes, both antenatally and neonatally, incurs a wide range of costs. The perspective taken in this report refers only to the costs incurred by the health service.

Categories of costs

The total costs of antenatal and neonatal screening programmes will depend on the characteristics of the antenatal population, including its ethnic composition, Hb-pathy carrier frequencies, and rate of inter-ethnic unions.

In order to derive total programme costs, the costs associated with providing an antenatal screening programme were divided into four categories:

- maternal and paternal laboratory carrier tests
- PND
- TOP
- education/counselling.

The costs associated with neonatal screening were divided into two categories:

- laboratory screening and confirmatory tests
- education/counselling.

Where necessary, categories were further divided into component costs, which could be integrated directly into the model.

Cost sources

Cost data were collected from a wide range of sources, including various hospital trusts, the published literature and one independent laboratory. The sources of the costs are listed in the relevant sections. All data on costs were uprated to 1997 values using the NHS price index. *Tables 20* and *21* summarise the main antenatal and neonatal costs included in the model.

Antenatal screening programme costs

Laboratory costs for ascertainment of parental carriers and at-risk couples

Assumptions for the cost analysis

The sequence and type of laboratory tests required for ascertainment of parental carriers and at-risk couples has been summarised in chapter 2 (pp. 8–10) and *Figure 1,* which depicts the antenatal laboratory algorithm. The parental carrier states considered in the model, namely S, C, D, E, β^{thal} and α^{0thal} traits, are ascertained by using different laboratory pathways. In addition, to establish that an individual is not a significant Hb-pathy carrier requires a variable sequence of laboratory tests. These tests depend on:

- whether the individual screened has iron deficiency or α^{+thal} trait/homozygous state, conditions that need to be distinguished from significant Hb-pathy traits
- the individual's ethnic group.

As Chinese, other Asians and Cypriots have an increased risk of α^{0thal} trait, these groups need additional laboratory investigations in cases of ambiguous results ('uncertain result' in the laboratory algorithm, *Figure 1*), whereas in all other groups such results are interpreted as negative without further tests. *Table 22* summarises the laboratory tests necessary to identify the different significant Hb-pathy carrier states, iron deficiency, α^{+thal} trait/homozygous state and the normal state (with neither of these conditions) in mothers and their partners.

If assessment of an at-risk pregnancy depends on a carrier result that cannot reliably be done by phenotyping, DNA analysis is required (chapter 2; p. 9). The following list specifies such cases and the number of DNA analyses required for a risk assessment.

- If either partner is found to have HbD and the other HbS, one DNA analysis is undertaken to specify the HbD as HbD^{Punjab}.
- To account for the rare cases of β^{thal} and $\delta\beta^{thal}$ trait, it was assumed that 1% of all β^{thal} trait results require DNA analysis.

TABLE 20 *Antenatal screening costs included in the model: costs per item per woman screened (£)*

Item	Baseline value by ethnic group												Sensitivity analysis
	BC	BA	BO	Ind	Pak	Ban	Chi	OA	Oth	Cyp	Ita	NE	
Laboratory cost for carrier testing[a]	5.34	5.76	5.28	5.70	5.52	4.79	37.39	23.58	3.84	46.54	3.84	3.50	x 1.5, ÷ 1.5
Education/counselling session[b]													
Pretest information							0						+ 0.39, + 0.78
Ethnic ascertainment							0						+ 0.39, + 0.78
Positive maternal carrier test	22.10	26.60	22.10	22.10	25.10	26.60	22.10	22.10	22.10	20.60	20.60	20.60	x 2, ÷ 2
Positive couple test/PND	36.78	44.28	36.78	36.78	41.78	44.28	36.78	36.78	36.78	34.28	34.28	34.28	x 2, ÷ 2
Post-TOP bereavement	36.78	44.28	36.78	36.78	41.78	44.28	36.78	36.78	36.78	34.28	34.28	34.28	x 2, ÷ 2
Surgical TOP							470.50						–

	Baseline value by suspected disorder			
	ββ, Eβ	$\alpha^0\alpha^0$	Sβ	SS, SC, SD
PND (CVS and laboratory tests)	1639.80	1315.89	1205.32	1165.47

Sources of cost data: three hospital trusts, one independent laboratory, two training centres for counsellors and the leading manufacturer of HPLC technology (BioRad). In addition, published sources of data were used (Personal Social Service Research Unit, Association for Community Interpreters, Translators, Advocates and Link Workers)

[a] *Laboratory costs for carrier testing per woman screened comprise maternal carrier test and, if required, paternal carrier test and DNA, assuming use of HPLC, 10% iron deficiency in the antenatal population and exclusion of ferritin measurement They are based on the algorithm described in* Figure 1

[b] *Counselling costs include allocation for professional training courses. Variations in counselling costs between ethnic groups result from different requirements of interpreting services, informed by estimates from Hb-pathy counsellors (appendix 1)*

- If both partners have $\alpha^{0\,thal}$ trait, two DNA analyses are required.
- If a woman has $\alpha^{0\,thal}$ trait and her partner has $\alpha^{+\,thal}$ trait/homozygous state or iron deficiency, two DNA analyses are required.
- If a woman is from a Chinese, other Asian or Cypriot ethnic group and has $\alpha^{+\,thal}$ trait/homozygous state or iron deficiency, and her partner has $\alpha^{0\,thal}$ trait, $\alpha^{+\,thal}$ trait/homozygous state or iron deficiency, one DNA analysis is required.
- If a woman is from a Chinese, other Asian or Cypriot ethnic group and has $\alpha^{0\,thal}$ trait, $\alpha^{+\,thal}$ trait/homozygous state or iron deficiency, and her partner is unavailable, one DNA analysis is required.

Cost measurement and valuation

Costs for the individual tests were derived from a Hb-pathy screening laboratory with an annual throughput of about 4000 samples. If larger, cross-district laboratories were established, it could be anticipated that the unit costs of the laboratory tests would decrease. This has been explored in a sensitivity analysis (see below).

The cost elements associated with the laboratory tests include consumables, direct labour of laboratory technicians, general overheads (secretarial support, general repairs, quality control) and specific overheads for the Hb-pathy screening laboratory, including the cost of obtaining the blood samples (costing the phlebotomist's salary and the associated consumables).

Table 23 summarises the individual test costs, depending on laboratory equipment. The two laboratory set-ups considered are the 'standard' and 'HPLC', as defined in chapter 2 (p. 10).

Table 24 shows laboratory costs per women tested by ethnic group, comparing HPLC and standard laboratory equipment. The laboratory costs comprise mother's carrier

TABLE 21 *Neonatal screening costs included in the model: costs per item per newborn screened (£)*

Item	Baseline value by ethnic group												Sensitivity analysis
	BC	BA	BO	Ind	Pak	Ban	Chi	OA	Oth	Cyp	Ita	NE	II
Laboratory cost[a]													
Initial screening	2.12												x 1.5, ÷ 1.5
Repeat test on initial sample	2.12												x 1.5, ÷ 1.5
Confirmatory test	3.11 (phenotyping), 147 (DNA analysis)												x 1.5, ÷ 1.5
Education/counselling session[b]													
Pretest information	0												+ 0.39, + 0.78
Ethnic ascertainment	0												+ 0.39, + 0.78
Access to parental carrier results	0												0.39, 0.78
Positive sickle screening result	22.10	26.60	22.10	22.10	25.10	26.60	22.10	22.10	22.10	20.60	20.60	20.60	x 2, ÷ 2
Positive sickle carrier result	0.98, 2.46	1.18, 2.96	0.98, 2.46	0.98, 2.46	1.12, 2.79	1.18, 2.96	0.98, 2.46	0.98, 2.46	0.98, 2.46	0.92, 2.29	0.92, 2.29	0.92, 2.29	x 2, ÷ 2

Sources of cost data: three hospital trusts, one independent laboratory, two training centres for counsellors and the leading manufacturer of HPLC technology (BioRad). In addition, published sources of data were used (Personal Service Research Unit, Association for Community Interpreters, Translators, Advocates and Link workers)

[a] *Laboratory costs for neonatal screening assume use of HPLC. They are based on the algorithm described in* Figure 2

[b] *Counselling costs include allocation for professional training courses. Variations in counselling costs between ethnic groups result from different requirements of interpreting services, informed by estimates from Hb-pathy counsellors (appendix 1). Two values for counselling for sickle carrier status assumed 2 or 5 minutes of counsellor's time (see* Table 27*)*

TABLE 22 *Laboratory tests required for ascertainment of significant haemoglobinopathy carrier states, iron deficiency, α^{0thal} trait/homozygous state and normal state in mothers and partners*

Individual laboratory tests	Significant Hb-pathy carrier states						Confounding conditions		Normal
	S	C	D	E	β^{thal}	α^{0thal}	α^{+thal}[a]	Iron deficiency	
MCH[b]	✓	✓	✓	✓	✓	✓	✓	✓	✓
Characterisation of Hb variants	✓	✓	✓	✓	✓	✓	✓	✓	✓
Repeat testing for HbS	✓	✓	✓	✓					
Repeat testing for other Hb variants		✓	✓	✓					
HbA_2 quantification					✓	✓	✓	✓	
HbF quantification					✓	✓	✓	✓	
Measurement of iron deficiency (optional)[c]						✓	✓	✓	
DNA analysis			d		d	d	d	d	

The probability of iron deficiency in partners has been conservatively assumed to be 0.01 [151]

[a] *α^{+thal} trait/homozygous state*

[b] *For women, the cost of the MCH test is assumed to be attributed to obstetric care; for partners, to the screening programme*

[c] *The cost of ferritin measurement has not been included in the baseline analysis, but the effect of inclusion on total laboratory costs has been shown in chapter 9; p. 97*

[d] *See explanation in the text (pp. 57–58)*

TABLE 23 *Costs per individual laboratory test according to laboratory equipment used*

Individual laboratory test	Standard laboratory set-up		HPLC laboratory set-up	
	Method	Cost (£)	Method	Cost (£)
MCH	Automated	1.55	Automated	1.55
Characterisation of Hb variants	Hb-electrophoresis (cellulose acetate)	2.56	HPLC	3.11
Repeat testing for HbS	Sickle solubility	1.85	Sickle solubility	1.85
Repeat testing for other Hb variants	Hb-electrophoresis (citrate agar)	6.39	HPLC	3.11
HbA_2 quantification	Elution	7.50	HPLC	0.00[a]
HbF quantification	Betke	3.39	HPLC	0.00[a]
Measurement of iron deficiency (optional)	Ferritin	3.32	Ferritin	3.32
DNA analysis	Chapter 6; p. 61	147.00	Chapter 6; p. 61	147.00

[a] *HPLC characterises Hb variants and quantifies HbA_2 and HbF simultaneously*

test, father's carrier test and any additional DNA testing required, under baseline assumptions including 10% iron deficiency in the antenatal population. It is evident that the use of HPLC is cheaper than the standard equipment in every ethnic group. (This is the case at any level of iron deficiency above 5%; results not shown separately.)

TABLE 24 *Laboratory costs per woman tested, by ethnic group, using HPLC and standard laboratory equipment, assuming 10% iron deficiency in antenatal population*

Ethnic group	Laboratory cost per woman screened (£)	
	HLPC	Standard
Black Caribbean	5.34	7.42
Black African	5.76	7.94
Black other	5.28	7.31
Indian	5.70	10.40
Pakistani	5.52	10.24
Bangladeshi	4.79	6.63
Chinese	37.39	38.44
Other Asian	23.58	24.21
Other	3.84	4.27
Cypriot	46.54	49.67
Italian	3.84	4.49
North European	3.50	3.88

Costs do not include ferritin measurement

Hence, for inclusion in the model, laboratory costs based on HPLC technology have been used. The HPLC equipment considered was a relatively old model, supplied by Bauer. As HPLC technology is progressing, future costs can be expected to decrease. This possibility has been accounted for in a sensitivity analysis by varying the total laboratory costs for antenatal carrier testing by a factor of 1.5 (chapter 9; p. 96).

Laboratory costs for carrier testing were integrated into the model for mothers and partners according to their ethnic group and carrier state.

Costs for ascertainment of an affected fetus

Costs for sampling of fetal material

For the purpose of this study, we assume that fetal material for PND is derived by CVS, the most common method used in the UK.[39] Cost estimates for CVS were taken from the literature[318] and provided by a hospital trust. A total cost of £320 was included in the model.

Costs for fetal diagnosis

Assumptions for the cost analysis. Methods of fetal diagnosis have been discussed in chapter 2 (pp. 10–11). We have assumed that fetal diagnosis is performed by DNA analysis of both parental and fetal samples, following the approach of the Oxford Haemoglobinopathy Reference Laboratory,[38,148] which complies with current guidelines.[37] This is now always preceded by repeat phenotyping of both parental blood samples to ensure reliability of the risk assessment of the pregnancy.[39]

TABLE 25 *DNA techniques used for diagnosis of fetal haemoglobinopathies*

Suspected disorder	Technique used	
	Initial test	**Repeat test**
β-Thalassaemia major/HbE β-thalassaemia	ARMS–PCR[a]	RFLP linkage analysis[b]
α^0-Thalassaemia hydrops fetalis	Southern blot	Southern blot
Sickle cell β-thalassaemia	ARMS–PCR[c]	DdeI–PCR
Other sickle cell disorders	ARMS–PCR	DdeI–PCR

ARMS, amplification refractory mutation system; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; DdeI, name of restriction enzyme

[a] In cases of rare mutations of β-thalassaemia major, a second ARMS–PCR test is undertaken prior to linkage analysis. 10% of mutations have been assumed to be rare (Old, J, John Radcliffe Hospital, Oxford: personal communication, 1997)

[b] For RFLP linkage analysis, it was assumed that 70% of cases required analysis of samples from three family members, while the remainder required analysis of samples from six family members (Old, J, John Radcliffe Hospital, Oxford: personal communication, 1997)

[c] Two initial ARMS–PCR tests are always required for suspected sickle cell β-thalassaemia

The fetal diagnosis of each of four disease groups, namely, β-thalassaemia major and HbE β-thalassaemia, α^0-thalassaemia hydrops fetalis, sickle cell β-thalassaemia, and other sickle cell disorders, require different DNA techniques. They are summarised in *Table 25*.

Cost measurement and values. Calculations of cost estimates per PND were obtained in collaboration with the Oxford Reference Laboratory. They are listed in *Table 20*.

The costs of the individual tests were estimated by considering consumable items, labour, capital and overheads.

The labour component of the costs comprises a grade C clinical scientist (the head of the laboratory), who performs a supervisory role, grade B clinical scientists, who perform the analysis, and a secretary. The overheads make up a substantial proportion of the costs; included are the usual components, such as rent and heating, as well as an annual charge for the use of capital equipment and maintenance costs shared by several departments. Capital costs specific to Hb-pathy screening were divided amongst all the tests undertaken by the laboratory, including tests unrelated to the screening programme. A lifetime of 10 years was assumed for all capital equipment.

PND costs were integrated into the model for each woman accepting the test, according to the genotype of the fetus.

Costs for genetic termination of pregnancy

In the UK, the majority of TOPs carried out after the diagnosis of a fetus affected by a Hb-pathy are performed in the late first or second trimester.[39] The current standard method of termination for these gestations is surgical removal,[123,319] which has been considered in the model.

The cost of a surgical termination was taken from two sources, a hospital finance department and a non-profit making charity organisation. The costs obtained were comparable, with a mean total of £470.50.

TOP costs were integrated into the model for each woman accepting genetic termination.

Neonatal screening programme costs

Laboratory costs for the initial neonatal screening test, repeat test and confirmatory diagnostic test

Assumptions for the cost analysis

We have assumed that the collection of neonatal specimens follows the Guthrie card method, with integration of the whole screening process into an existing large-scale metabolic neonatal screening programme. The sequence and type of laboratory tests required for initial neonatal sickle cell screening, repeat testing of abnormal results and confirmatory diagnostic tests have been summarised in chapter 2 (p. 15) and in *Figure 2,* which depicts the neonatal laboratory algorithm. It has been assumed

TABLE 26 *Cost estimates for neonatal screening test, repeat test and confirmatory diagnostic test*

Laboratory test	Cost of annual laboratory sample throughput (£)	
	< 50,000	50,000–100,000
Initial screening	2.12	1.88
Repeat[a]	2.12	1.88
Confirmatory[b]		
Phenotyping	3.11	
DNA analysis	147.00	

[a] *The repeat test is undertaken on the same Guthrie card sample as the initial test*
[b] *The cost of the confirmatory test is included only for false-positive sickle cell disease results and non-significant combinations (chapter 2; pp. 15–16).The sample is taken during the course of counselling for a positive screening result, so no transport costs are included.The sample is tested in the local haematology laboratory*

that the primary laboratory method used for all tests is HPLC; confirmatory diagnosis includes phenotyping of the infant and parents, and, in 1% of infants (without parents available for testing), DNA analysis.

Cost measurement and valuation

Table 26 summarises the cost estimates of individual tests. The combination of screening for metabolic disorders and sickle cell disease, using the same Guthrie card specimens and laboratories, reduces considerably the cost of the initial and repeat screening because no additional blood sampling costs are incurred. Laboratory costs for initial screening and repeat tests are based on hypothetical laboratories with an annual throughput of < 50,000 and 50,000–100,000 samples, using prices quoted by a leading manufacturer of HPLC technology (Bio-Rad), in conjunction with preliminary estimates prepared by R Jones (Great Ormond Street Hospital, London). The costs comprise labour, consumables, capital and overheads, with the cost of consumables comprising the largest proportion. For laboratories processing < 50,000 samples per year, no further differential costs between larger and smaller laboratories have been considered because it has been assumed that, if HPLC equipment is not used to full capacity for sickle cell screening, it can be utilised for biochemical tests (i.e. measurement of glycosylated HbA[156]). The estimated costs are comparable with those quoted from neonatal screening programmes in other countries (costs are converted at $1.6:£1 and Ff10:£1 and uprated to 1997 prices): Le Gales and Galacteros[256] calculated the cost per initial neonatal screen using HPLC technology for an annual laboratory throughput of 50,000–100,000 specimens to be about £2.90, and for a throughput of < 50,000 between £3.20 and £4.20. In 1994, the cost per neonatal test in California's universal screening programme was reported to be equivalent to about £2.50 at a laboratory throughput of approximately 65,000 specimens per year, with the expectation that costs would decline in the future.[160]

The confirmatory test was assumed to be undertaken in a haematology laboratory; thus the cost was based on the set-up used to calculate the cost of antenatal screening laboratory tests. The cost of the DNA analysis was estimated from the Reference Laboratory in Oxford (see above).

For inclusion in the model, the higher estimate of £2.12 for the initial laboratory test was used as baseline value; but laboratory costs were varied by a factor of 1.5 in a sensitivity analysis (chapter 9; p. 96).

Laboratory costs for neonatal screening tests, repeat tests and confirmatory diagnosis were integrated into the model for all screened newborns according to their genotype.

Education and counselling costs for antenatal and neonatal screening

Assumptions for the cost analysis

Antenatal education and counselling requirements have been outlined in chapter 2 (pp. 18–20). They have been divided into four main sections, reflecting the various steps in the screening process and are summarised in *Table 27*.

Neonatal education and counselling requirements are discussed in chapter 2 (pp. 20–21). They comprise three main sections and are summarised in *Table 28*. Assumptions have been based on published evidence, which is referenced in chapter 2 (pp. 20–21) and on the experience of Hb-pathy counsellors (appendix 1).

Neonatal educational and related duties before the initial screening test vary according to the neonatal screening strategy adopted and the preceding antenatal programme. This has been summarised in *Table 29*.

For our baseline analysis we have assumed that no additional professional time is required for

TABLE 27 *Education and counselling assumptions for antenatal haemoglobinopathy screening*

Education and counselling	Antenatal screening steps			
	Maternal carrier testing	**Positive maternal carrier result**	**At-risk pregnancy/ positive PND result**	**Post-TOP bereavement**
Content	Pretest information[a] (including antenatal and neonatal screening), ethnic ascertainment (selective strategy)	Hb disorders, carrier status, partner testing (including organisation), PND/TOP	Pregnancy risk assessment, PND/TOP, support if PND positive, future pregnancies, implications for other family members	Bereavement, future prospects
Personnel	None/midwife grade G	Counsellor nursing grade H		
Time (min)	0–2 pretest information, 0–2 ethnic ascertainment[b]	45	75	75
Training	In-service	Accredited course (modular, 15 days, every 5 years)		

Variable use of interpreting services depending on ethnic group has been assumed (see p. 64)

[a] In a universal programme, all women require pretest information, none require ethnic ascertainment; in a selective programme, all women require pretest information and ethnic ascertainment

[b] Assumptions for baseline and sensitivity analysis

TABLE 28 *Education and counselling assumptions for neonatal sickle cell disease screening*

Education and counselling	Neonatal screening steps		
	Initial neonatal screening	**Positive sickle cell disease screening result[a]**	**Positive sickle carrier result[b]**
Content	Pretest information, ethnic ascertainment, access of antenatal parental carrier results (targeted screening only)	Sickle cell disorders, need for confirmatory blood test, penicillin prophylaxis and comprehensive care	Sickle carrier status
Personnel	None/midwife grade G	Counsellor, nursing grade H	Counsellor, nursing grade H
Time (min)	0–2 pretest information, 0–2 ethnic ascertainment, 0–2 access of antenatal parental carrier results[c]	45	5 if mother booked late (= no screening information received antenatally), 2 if mother non-carrier
Training	In-service	Accredited course (modular, 15 days, every 5 years)	Accredited course (modular, 15 days, every 5 years)

Variable use of interpreting services depending on ethnic group has been assumed (see p. 64)

[a] For other screening results that require confirmation, the following counsellor times have been allocated: results indicating β-thalassaemia major and HbE β-thalassaemia 45 min; results indicating clinically non-significant combinations 30 min

[b] A positive sickle carrier screening result is assumed to incur additional counselling costs if perceived as unexpected: either because the woman had no antenatal screening and hence no screening information antenatally, or was found on antenatal screening to be a non-carrier

[c] Assumptions for baseline and sensitivity analysis

either pretest information or ethnic ascertainment in the context of antenatal or neonatal screening, or access to parental carrier results in the context of neonatal targeted screening. However, because of uncertainty, 1 and 2 minutes of midwifery time have been allocated to each of these tasks in sensitivity analyses (chapter 9; p. 96).

Cost measurement and values

Table 30 summarises the costs of the main education and counselling components. These costs include the salaries of the relevant personnel, taken at the mid-point of the salary scale. The specialist nurse counsellors were assumed to be grade H nurses, the midwives grade G. The

TABLE 29 *Variable neonatal educational and other precounselling duties according to neonatal screening strategy*

Neonatal strategy	Neonatal educational and related duties		
	Pretest information[a]	**Ascertainment of maternal ethnic status postnatally**	**Access to parental antenatal carrier results**
Universal	Mothers not tested antenatally[b]	None	None
Selective	Mothers not tested antenatally with babies eligible for screening	All mothers	None
Targeted	Mothers not tested antenatally with babies eligible for screening	All mothers not tested antenatally	All mothers

[a] It is assumed that mothers tested antenatally have already received pretest information about neonatal screening
[b] Mother, woman of a baby alive at the time of Guthrie card sampling, without α^0-thalassaemia hydrops fetalis and who did not have PND

TABLE 30 *Costs of the main education and counselling components*

Cost description (per min)	Cost (£)
Midwife	0.39
Specialist counsellor	0.46
Interpreter	0.33

cost of providing an interpreter for a counselling session was provided by the Association for Community Interpreters, Translators, Advocates and Link Workers.

In addition, oncosts of 25% were included in the cost of a midwife's time, allowing for working unsociable hours,[320] and a fixed overhead cost per hour of counselling time was added to the salary of the specialist counsellors. The cost of training specialist counsellors was estimated by using information from two centres (Nottingham Sickle and Thalassaemia Service and the Institute of Child Health, London). Training was assumed to cover 5 years of counselling. The annual equivalent training cost for specialist counsellors was estimated as £83.09. It was assumed that a counsellor works for 1687.5 hours per year (45-week year, 37.5 hours per week) and that the ratio of client to non-client contact is 1.00:0.75. This gave a training cost per client contact of approximately £0.09 per hour.

The assumed proportions of each ethnic group requiring an interpreter are presented in *Table 31*. These proportions were estimated after consultation with Hb-pathy counsellors (appendix 1). The cost of an interpreter was added for the

TABLE 31 *Proportion of each ethnic group requiring an interpreter*

Ethnic group	Proportion requiring an interpreter
Caribbean	0.10
African	0.40
Black other	0.10
Indian	0.10
Pakistani	0.30
Bangladeshi	0.40
Chinese	0.10
Other Asian	0.10
Other	0.10
Cypriot	0.00
Italian	0.00
North European	0.00

proportion of each ethnic group requiring the service for the whole of the relevant counselling session.

Using the above estimates, costs for each of the four main antenatal and three main neonatal education and counselling sessions were calculated, depending on ethnic group where appropriate. They are presented in *Tables 20* and *21* respectively.

Costs were incorporated into the model for each woman and newborn respectively, according to the screening steps passed.

Chapter 7

Lifetime treatment costs for patients with β-thalassaemia major and sickle cell disorders

Purpose of estimating lifetime treatment costs

In the context of antenatal screening for Hb-pathies, the issue of lifetime treatment costs arises when an affected pregnancy has been identified and the parents request genetic termination. Had the pregnancy continued, the child would have incurred lifelong costs to treat the condition for which screening was performed, whereas, in the case of termination, these future costs to the health service would be averted. Policy makers might therefore wish to take these costs into consideration for long-term planning purposes. However, only very crude estimates of treatment costs for Hb-pathies in the UK are currently available.[6]

In this review we present an estimation of lifetime treatment costs separately from the main analysis because there is an ongoing debate about the appropriateness of their inclusion in or exclusion from an economic evaluation of antenatal screening programmes, on conceptual as well as ethical grounds.[110,250,253,321]

The resource consequences of neonatal screening for sickle cell disorders are reflected by the difference in lifetime treatment costs between screened and unscreened individuals. They include potential savings of health service costs owing to reduced morbidity as well as potential expenditure of treatment costs because of improved survival in the screened compared with the unscreened child. For the analysis of neonatal screening (in combination with antenatal screening) we have chosen as the primary outcome measure the prevention of late diagnoses of sickle cell disorders. However, because the ultimate goal of neonatal screening is the reduction of morbidity and mortality, we present here the expected consequences of prevention of a late diagnosis of sickle cell disease in terms of lifetime treatment costs, early deaths averted and severe disability prevented (mental retardation, seizures or deafness).

Methodology

Conditions considered

The focus of the review is the comparison between selective and universal antenatal and neonatal Hb-pathy screening strategies. If selective antenatal screening includes all women with a low MCH, as recommended by the British Society for Haematology,[21] the SMAC report[5] and the Centre for Reviews and Dissemination report,[6] screening for β-thalassaemia major is in effect always **universal**. The number of additional live births with β-thalassaemia major that are preventable by changing from a selective to a universal policy can therefore be expected to be very small, limited to rare cases of HbE β-thalassaemia, when the mother did not have a low MCH on antenatal screening. Nevertheless, as we have explored in a sensitivity analysis, a selective strategy in which only ethnic minority status, but not low MCH, would be used to identify pregnant women eligible for antenatal screening, we have included the estimation of lifetime treatment costs for β-thalassaemia major (including HbE β-thalassaemia) as well as sickle cell disorders. Lifetime treatment costs have been estimated separately for sickle cell anaemia and sickle HbC disease because of their different natural histories and management. Other sickle cell disorders (genotypes *Sβ*, *SD*) are assumed to incur similar treatment costs to sickle cell anaemia. α^0-Thalassaemia hydrops fetalis is assumed to lead to late miscarriage, stillbirth or early neonatal death,[2] and thus does not consume treatment resources.

Perspective

The cost burden associated with patients suffering from β-thalassaemia major or sickle cell disorders are incurred by several sectors of society, including the health service, social services, the affected individuals and their families. Costs included in this chapter refer only to those incurred by the healthcare sector.

Estimation of lifetime treatment costs

Lifetime treatment costs of interest for this study are those that can be expected to be incurred by

individuals with Hb-pathies who are born **now**, avoiding complications due to past shortcomings of therapy. A hypothetical cohort of 100 patients is followed through a model for each of the three categories of Hb-pathies of interest. Calculation consisted of several steps:

- estimation of expected age-specific frequency of major health service interventions owing to the condition, based on the natural history of Hb-pathies and current protocols for diagnosis, routine follow-up and management of complications (for this review, hospital and community-based services have been considered)
- estimation of average annual treatment costs per surviving patient with a Hb-pathy, based on costs associated with major health service interventions
- estimation of the survival of patients with a Hb-pathy born now and managed according to current standards of care
- calculation of the expected annual treatment costs (discounted and undiscounted) per original cohort member, by multiplying the average annual treatment cost per surviving patient by the proportion of surviving patients for each year of life
- calculation of the total lifetime treatment costs per patient with Hb-pathy (discounted and undiscounted) by adding the annual treatment costs per original cohort member from zero to a maximum of 60 years.

For the current estimation of lifetime treatment costs, only conventional management of the conditions has been considered as the most frequent and established form of treatment. However, new progress in the treatment of Hb-pathies, especially the increasing use of bone marrow transplantation, may necessitate future adjustment of these estimates.

Estimates of lifetime treatment costs derived by the above described method are intended to serve as indicators for the approximate magnitude of expenditure associated with the treatment of Hb-pathies. As recent, direct age-specific data about frequency and type of health service use for UK cohorts of patients are very limited,[48] information from various sources (see below) had to be combined to calculate the expected treatment costs, an approach likely to decrease the accuracy of the estimates. The estimates used are likely to present minimum values, as only major health service interventions have been included. There remains considerable uncertainty about the survival of cohorts of patients with Hb-pathies who are born currently and the possible development of new complications, decreasing the confidence with which these estimates may be projected into the future.

Information sources

Survival data and age-specific incidence rates of major complications of Hb-pathies were derived from published cohort studies, where available, mainly from Mediterranean countries for β-thalassaemia major patients and from the USA and Jamaica for patients with sickle cell disease.

Information about the current management of Hb-pathies, UK hospital admission rates and the average length of stay was collected from selected literature, including current standard textbooks, and from practising experts (Dr B Wonke, Whittington Hospital, London and Dr A Yardumian, North Middlesex Hospital, London).

Unit costs for the various intervention categories were obtained from the finance departments of a number of hospital trusts (mainly London based), the published literature, the British National Formulary, the Personal Social Services Research Unit and from independent laboratories. All costs have been uprated to 1997 values using the NHS pay and prices index.

Information sources are referenced in the appropriate sections below. The literature search strategy is summarised in appendix 2.

Lifetime treatment costs for patients with β-thalassaemia major

Conventional treatment

The course of β-thalassaemia major is relatively predictable and dominated by problems of anaemia and iron overload, with their associated complications.

The current conventional treatment consists of lifelong monthly blood transfusions of screened blood (negative for hepatitis B, C and HIV) combined with daily subcutaneous iron chelation therapy with desferrioxamine, from about 2 years of age onwards.[58,67,322] Transfusion and chelation therapies need to be balanced carefully because too little or too much of either carries significant side-effects:[58,67,74] blood transfusions are associated with the risk of iron overload and subsequent organ damage, mainly of the heart and endocrine organs, and the risk of transfusion-acquired

hepatitis B and C. If these patients are not transfused, the result is anaemia and its complications, such as growth failure, bone deformity and enlargement of the liver and spleen. Desferrioxamine treatment is used to prevent iron overload but it can itself cause growth failure and visual and hearing impairment.

The monitoring of complications remains a vital part of the management of β-thalassaemia major, especially as compliance with the chelation regimen can be a problem,[67,75,76] but complications due to iron overload can be reversible when detected early.[74]

Iron overload, desferrioxamine toxicity and liver dysfunction due to transfusion-acquired chronic hepatitis have all been responsible for complications in the past. Cohorts of younger patients who have avoided these complications are still too young and small in number to make a reliable prediction of the incidence of residual complications.[67,323] It is uncertain whether other complications will appear as the survival times of patients with β-thalassaemia major increase.

Type and frequency of major health service interventions and associated costs

The assumptions about the type and frequency of major health service interventions made for the calculation of lifetime treatment costs are described below. They take into consideration imperfect compliance with current standard treatment. The unit costs of the main components of the interventions used for the monitoring and treatment of β-thalassaemia major patients are listed in *Table 32*. The calculation of the average annual costs per category of intervention based on the unit costs, the period of years over which they are incurred, and the percentage of patients incurring them per year during that period, are shown in *Table 33*.

Diagnosis

The diagnosis of β-thalassaemia major (at between 0 and 2 years of age) includes haematological tests (full blood count, Hb-electrophoresis, quantification of HbA_2 and HbF), DNA analysis, and counselling for the affected child and the family. In addition it has been assumed that three other family members are screened for thalassaemia trait and HLA typed with a view to possible bone marrow transplantation.

Basic haematology outpatient visits and tests

From the time of diagnosis, patients are assumed to attend a haematology outpatient clinic 4-weekly during their lifetime. Basic regular tests include:

TABLE 32 *Unit costs of interventions used in the monitoring and treatment of patients with β-thalassaemia major and sickle cell disorder*

Intervention	Unit cost (£)
Costs associated with diagnosis	
DNA analysis	148.54
HLA typing (for BMT)	76.37
Counselling (per hour)	26.79
Costs associated with blood transfusion	
Hepatitis B immunisation (Engerix B)	38.04
Day-case nursing/hotel charge	33.35
Unit of blood[a]	58.54
Infusion pump	707.35
Desferrioxamine (Desferal, per g)	5.80
Skeletal survey	72.76
Complex eye assessment	81.85
Full audiology assessment	80.84
Hearing test	28.29
Outpatient visits[b]	
Haematology	171.79
Endocrinology	50.53
Cardiology	75.79
Ophthalmology	40.42
Antenatal	90.95
Costs associated with complications	
Intensive care unit (per day)	818.51
Normal ward (per day)	207.15
Psychotherapist (per session)	82.06
Splenectomy	1,157.02
Glucose tolerance test	25.26
Extended endocrine tests[c]	283.95
Testosterone (Sustanon 100, per 1 ml)	1.12
Oestrogen (Prempac-C, per 1 tab)	0.10
Somatropin (Genotropin, per unit)	7.71
Chorionic gonadotrophin (Profasi, per 2000 units)	2.12
Human menopausal gonadotrophins (Pergonal, per 75 units)	10.29
Doppler echocardiography	73.77
Bone densitometry	121.26
Disodium etidronate (Didronel, per pack)	40.62
Computed tomographic scan	72.76
Dialysis session	186.94
Home oxygen therapy[d]	299.99
GP (per visit)	16.17
Ultrasound scan	121.26
Caesarean delivery[e]	778.59

Unless stated otherwise, costs are from finance departments, the British National Formulary or the Personal Social Services Research Unit

BMT, bone marrow transplantation

[a] A unit of blood includes costs of cross-matching, a cannula and a filter; [b] Haematology outpatient visit includes cost of diagnosis and basic tests; endocrinology outpatient visit includes cost of thyroid function tests and gonadal function tests; cardiology outpatient visit includes cost of electrocardiography; [c] Hypothalamic–pituitary-stimulation test or growth provocation test; [d] Costs are from Midwest Medical Repair, Oxygen Sales and Service; [e] Cost of caesarean delivery minus the cost of a normal delivery

TABLE 33 *Average annual cost per category of intervention associated with treatment of β-thalassaemia major, years over which costs are incurred, and the percentage of patients incurring them in each year*

Category	Annual cost (£)	Ages at which intervention may be experienced (incl)	% Patients per year
Diagnosis	343.80	1–2	50
Haematology outpatient visits	73.97	1–60	100
Transfusion	1,667.28	0–10	100
	2,362.60	11–20	100
	3,057.91	21–60	100
Desferrioxamine	1,392.62	2–5	100
	2,209.22	6–10	100
	3,434.10	11–15	100
	4,659.00	16–20	100
	5,067.29	21–60	100
Psychosocial support	24.62	0–10	10
	49.24	11–20	10
	73.86	21–30	10
Splenectomy	1,157.02	5–20	1.17
Diabetes			
Monitoring	75.79	10–15	25
		16–60	100
Treatment[a]	496.84	10–30	0–18
		31–60	18
Gonadal function			
Monitoring and treatment	184.83	14–19	50
Growth			
Monitoring	283.95	14	50
Growth hormone deficiency treatment	11,018.24	14–19	4
Growth hormone resistance treatment	22,036.48	14–19	1
Reproduction	741.67	24 & 31	75
Pregnancy care	1,455.12	25 & 32	50
Cardiac complications			
Monitoring	149.55	12–60	100
Treatment[b]	15,789.06	20–35	0.27
Osteoporosis			
Monitoring	128.33	15–60	20
Treatment	162.49	20–40	4.5

[a] *Reference 381;* [b] *Reference 382*

3-monthly measurement of ferritin, calcium, phosphate, zinc; liver function tests; and yearly virology (hepatitis B and C antibodies, HIV antibodies)

Blood transfusion and iron chelation

Prior to the start of transfusion therapy, after initial diagnosis, patients are immunised against hepatitis B and undergo a number of special tests (including red blood cell typing and antibody screen, cytomegalovirus antibodies). Patients are assumed to require 4-weekly lifelong blood transfusions. Costs include regular pretransfusion tests (full blood count, cross-matching), units of blood, filters, cannulae and day-case nursing. The cost per transfusion varies according to the age of the patient because of increasing requirements for units of blood and filters. It was assumed that patients aged 0–10 years require one unit of blood,

aged 11–20 years two units and aged over 20 years three units.[23]

Iron chelation therapy (starting at age 2 years) involves the daily subcutaneous administration of desferrioxamine by infusion pump.[322] It was assumed that an average patient requires two infusion pumps over the course of a lifetime. The amount of drug given varies with age, according to the weight of the patient. This is summarised in *Table 34*. In addition, patients receive 6 g of desferrioxamine with every blood transfusion (Wonke, B, Whittington Hospital, London: personal communication, 1997).

TABLE 34 *The assumed weight of patients with β-thalassaemia major and their respective daily desferrioxamine dosage, at different ages*

Age range (years)	Weight (kg)[a]	Daily desferrioxamine dose (mg)
2–5	15	675
6–10	25	1,125
11–15	40	1,800
16–20	55	2,475
21+	60	2,700
[a] *Reference 23*		

Monitoring for the toxic effects of chelation therapy[74] was assumed to include a yearly hearing test and ophthalmology outpatient visit, with a complex assessment every 5 years, including a full audiological assessment, skeletal survey and complex eye tests.

Psychosocial support

Psychosocial support is required, particularly at the time of diagnosis, at the introduction of chelation therapy, during adolescence, when compliance with treatment may be a problem, and between the ages of 21 and 30 years because of difficulties concerning reproduction[76] (see below). It was assumed that 10% of patients aged 0–10 years require an average of three sessions with a psychotherapist, that 10% of patients aged 11–20 years require six sessions, and 10% of patients aged 21–30 require nine sessions. The sessions are assumed to be evenly distributed over each 10-year period.

Endocrine complications

Diabetes. Monitoring for diabetes (including a glucose tolerance test) through yearly endocrine outpatient visits was assumed to commence in patients with a family history of diabetes (25% of patients with β-thalassaemia major) from age 10 onwards, and for those without a family history from age 15.

With current management, it was assumed that the prevalence of insulin-dependent diabetes type 1 increases steadily from age 10 onwards and reaches 18% by age 30.[323] An average prevalence of 1.5% in the normal population[324] has been subtracted from the total, so the prevalence figures reflect diabetes due to β-thalassaemia major.

Thyroid and parathyroid function. Both hypothyroidism and hypoparathyroidism are rare in well-managed patients.[323] Monitoring was assumed to include a yearly thyroid function test for hypothyroidism, and calcium and phosphate measurements for hypoparathyroidism, already covered by the basic tests.

Gonadal function. It was assumed that 50% of all β-thalassaemia major patients experience pubertal problems, males and females suffering to the same degree.[77,325] These patients require 4-monthly follow-up in an endocrinology outpatient clinic between the ages of 14 and 19 years, which includes an initial assessment with hypothalamic–pituitary stimulation tests, subsequent gonadal function tests, and hormonal treatment (see below). All patients with pubertal problems are assumed to require lifelong hormone replacement therapy for secondary hypogonadism from the age of 19 years onwards, assuming the use of the same drugs (oestrogens (Prempac-C) for women); testosterone (Sustanon 100) for men) as for pubertal hormone treatment, albeit in adult doses.

Growth. Growth impairment requiring endocrinology outpatient visits (the same as for gonadal problems) and a growth hormone provocation test were assumed to affect 50% of patients.[323,326] Of these, 10% were assumed to warrant treatment for growth failure between the ages of 14 and 19, 20% with growth hormone deficiency and 80% with growth hormone resistance. Treatment consists of somatropin (Genotropin) 0.5 u/kg per week for growth hormone deficiency and 1 u/kg per week for growth hormone resistance. The average weight of a patient of 14–19 years of age was assumed to be 55 kg.[23]

Reproduction. Patients with β-thalassaemia major that is well controlled can now achieve pregnancy.[327,328] Although pregnancies are managed as high risk, there are no important

increases in complications reported in the UK.[328] We assumed that, prior to conception, 75% of patients experiencing pubertal problems would need induction of spermatogenesis/ovulation to achieve conception. This includes visits to an endocrinology outpatient clinic and hormonal treatment (chorionic gonadotrophin (Profasi); human menopausal gonadotrophin (Pergonal)). It was assumed that the average length of treatment per pregnancy was 1 year, that the average number of pregnancies achieved per female patient was two, and that they occurred at the ages of 25 and 32 years.

Other complications

Cardiac function. Cardiac failure through iron overload has been the major cause of death in patients with β-thalassaemia major,[72,73,77] but has decreased considerably with the introduction of effective chelation therapy.[77] All patients above the age of 12 years require yearly monitoring with electrocardiography and Doppler® echocardiography in a cardiology outpatient clinic. It was assumed that 4% of patients between the ages of 20 and 35 years would develop severe cardiac failure leading to death after 1 year.[78]

Hypersplenism. It is unclear what proportion of well-managed patients develop hypersplenism and need splenectomy. We assumed that 17.5% of patients between the ages of 5 and 20 years require a splenectomy.[329] The costs include the operation itself as well as pre- and post-operative care.

Osteoporosis. Osteoporosis is a relatively recently described complication that has only just become manifest as cohorts of patients grow older.[330–333] It was assumed that all patients from age 20 years onwards are monitored by 5-yearly bone densitometry and 24-hour urinary calcium and phosphate profile, with 30% of patients between the ages of 20 and 40 years requiring treatment with disodium etidronate (Didronel) for 3 years.

Estimation of survival in patients with β-thalassaemia major who are born now and managed according to current standards of care

Before the availability of iron chelation therapy, the majority of patients with β-thalassaemia major died in their teenage years as a result of cardiac complications caused by iron overload.[78] Chelation therapy started in the mid-1970s with intramuscular desferrioxamine treatment and became more effective with the introduction of subcutaneous daily administration regimens in the early 1980s.[68] All patients with β-thalassaemia major routinely receive iron chelation therapy from a young age to prevent iron overload, which initially can be reversible, but, after prolonged exposure leads to permanent organ damage.[74] Thus, currently, complications due to iron overload are seen mainly in patients who incurred irreversible organ damage before chelation therapy became part of routine management and in those who are not compliant with treatment.

Current data on the survival of patients with β-thalassaemia major are based on cohorts of patients who received variable lengths of effective chelation therapy.[68,77] In order to estimate the survival of a patient born now, we used the mortality data from three different cohorts of patients to model a hypothetical average survival curve. The first two cohorts used comprise patients with β-thalassaemia major born between 1960 and 1964,[68] and 1970 and 1979,[77] reflecting no chelation therapy through childhood and intramuscular desferrioxamine treatment respectively. The third cohort comprises the normal population.[334] The survival data from the three cohorts were combined according to the assumed proportions of currently born β-thalassaemia major patients incurring the corresponding severe, moderate and no iron overload represented by the three cohorts chosen. Fifteen per cent of patients were assumed to have a survival experience corresponding to a severe degree of iron overload, 15% to a moderate degree, the remaining 70% to none. The percentages were informed by the currently observed frequency of non-compliance with chelation treatment (Wonke, B, Whittington Hospital, London: personal communication, 1997).

The estimated survival of currently born patients with β-thalassaemia major is summarised in appendix 3 (*Table 82*). The survival curve predicts an average life expectancy of 63 years (not shown).

Calculation of the total lifetime treatment costs

The undiscounted total lifetime treatment costs for a patient with β-thalassaemia major has been estimated to be over £490,000; the discounted figure (6% discount rate) is about £123,000.

Appendix 3 (*Table 82*) shows the calculation, which is based on the summation of the average annual treatment costs per original β-thalassaemia major cohort member up to a hypothetical age of 60 years.

Lifetime treatment costs for patients with sickle cell disorders

Conventional treatment for sickle cell disorders

The sickle cell disorders follow an unpredictable clinical course, characterised by intermittent episodes of acute complications, caused by the aggregation of abnormal Hb, and the concomitant development of a variable degree of irreversible chronic organ damage.

The mainstay of conventional treatment for sickle cell disorders is penicillin prophylaxis and regular comprehensive care, including education of carers, to reduce the incidence of pneumococcal infection and other life-threatening complications such as splenic sequestration, especially in the first 5 years when the risk is highest. For the effective reduction of disease-related morbidity and mortality, the presymptomatic detection of sickle cell disorders through neonatal screening is a prerequisite. Conventional therapy also comprises specific supportive treatment to alleviate the wide range of symptoms encountered by patients with sickle cell disorders.

Type and frequency of major health service interventions and associated costs

The assumptions about the type and frequency of major health service interventions and the associated costs used for calculating lifetime treatment costs are described below and summarised in a series of tables.

Routine monitoring and preventive interventions

Table 35 presents the type and frequency of routine monitoring and preventive interventions for patients with sickle cell disorders, together with the corresponding unit costs per intervention.

Treatment of acute complications (including sequelae)

Acute complications can occur with different degrees of severity. For the purpose of this study, only those complications requiring initial hospitalisation have been considered to incur health

TABLE 35 *Routine monitoring and preventive interventions for patients with sickle cell disorders, and their corresponding unit costs*

Intervention	Unit cost (£)	Years (incl)	Frequency per year
Penicillin prophylaxis			
Child (per year)	5.19	0–14	1
Adult (per year)	10.39	15–60	1
Counselling (per hour)	26.79	1–60	1
Haematology outpatient visit[a]	171.79	0–1 2–5 > 5	6 3 2
Abdominal ultrasound	30.32	> 10	0.5
Cardiology outpatient visit[b]	75.79	> 5	0.5
Stress echocardiogram	63.66	> 5	0.5
Respiratory medicine outpatient visit[c]	61.64	> 5	0.5
Ophthalmology outpatient visit	75.79	> 10	1
Nutrition assessment	55.58	> 10	1
Pneumococcal vaccine	10.04	2	1
Hepatitis B vaccine (Engerix B)	38.04	1	1
Influenza vaccine	5.15	1–60	1

Frequency of interventions are based on references 23, 341, 383

[a] *Haematology outpatient visit includes cost of basic tests such as full blood count, serum ferritin, liver function tests, hepatitis B and C tests, creatinine, uric acid and urine analysis*

[b] *Cardiology outpatient visit includes the cost of electrocardiography*

[c] *Respiratory medicine outpatient visit includes cost of pulmonary function tests and chest radiography*

service costs. *Table 32* includes the unit costs of the main components of interventions used in the treatment of sickle cell disorders. The aggregated costs of treating one episode of an acute complication and, in the case of sequelae, the yearly equivalent treatment cost, are presented in *Table 36*. Estimates of age-specific incidence rates of acute complications in patients with sickle cell anaemia and sickle HbC disease are shown in *Tables 37* and *38* respectively. These are discussed below.

The main assumptions for costing of the treatment of acute complications requiring hospitalisation are summarised in *Table 39*.

In addition, the following surgical operations requiring hospitalisation have been assumed to be significantly more frequent in patients with sickle cell disorders than in the normal populations: splenectomy, hip replacement and cholecystectomy.[335]

TABLE 36 *Treatment costs per episode of acute complications, yearly equivalent costs for treatment of sequelae and chronic complications, and extra care during and after pregnancy*

Condition	Episode cost (£)
Acute complication	
Painful crisis	1,450.08
Pneumococcal sepsis	4,112.74
Splenic sequestration	2,119.96
Acute chest syndrome: child	3,128.95
Acute chest syndrome: adult	2,900.86
Stroke	5,082.74
Acute anaemia: child	1,488.08
Acute anaemia: adult	1,526.10
Hip replacement	4,067.26
Cholecystectomy	1,657.22
Splenectomy	1,157.02
Pregnancy care	
Extra antenatal and postnatal care (per pregnancy)	1,664.29
	Annual cost (£)
Sequelae of acute complications	
Hearing loss[a]	515.17
Seizures[a]	1,389.61
Mental retardation[a]	2,526.25
Chronic complications	
Stroke[b]	64,221.32
Retinopathy	295.57
Renal failure	29,163.03
Chronic lung disease: child 6–10 yr	4,051.90
Chronic lung disease: child 11–15 yr	5,207.92
Chronic lung disease: adult	6,852.06
Leg ulcers	2,231.18

[a] Reference 244; US dollars are converted at $1.6:£1; sequelae are considered independently
[b] Reference 384

Treatment of chronic complications

Chronic organ damage due to sickle cell disease can affect almost all organ systems.[336] For costing purposes, we have considered only the most common and severe complications. Unit costs of the main components of interventions for chronic conditions are included in *Table 32*. The aggregated yearly costs of treating a chronic condition are presented in *Table 36*. Estimates of age-specific incidence rates for chronic complications in patients with sickle cell anaemia and sickle HbC disease are shown in *Tables 37* and *38* respectively.

Leg ulcers. The treatment of an acute recurrence of chronic leg ulcers is assumed to last 1 year, mainly provided on an outpatient basis and in the community.[337–339]

Retinopathy. Patients with chronic proliferative retinopathy are assumed to require on average a total of three sessions of laser photocoagulation treatment after diagnosis, followed by three additional ophthalmology outpatient visits.[58,340–342] Regular, once-yearly, ophthalmology outpatient visits are covered under routine interventions.

Renal failure. Patients with chronic renal failure are assumed to receive three sessions of hospital-based haemodialysis per month for the rest of their life. Mean survival after the onset of renal failure has been assumed to be 4 years.[52]

Chronic lung disease. Patients with chronic lung disease are assumed to require lifelong hypertransfusion therapy (including iron chelation and home oxygen therapy for an average of 15 hours per day), 7 days of hospitalisation per year (normal ward) and three additional GP visits per year. Mean survival after the diagnosis of chronic lung disease has been assumed to be 5 years.[53]

Antenatal and postnatal care

Office of Population Censuses and Surveys data on age-specific birth rates of women from African and Caribbean countries were used to estimate the corresponding figures for women with sickle cell disorders,[272] assuming that sickle cell disorders do not significantly alter total birth rates.[343,344]

Pregnant patients with sickle cell disorders have an increased risk of complications during pregnancy compared with the normal population.[345–348] Assumptions for costing take into account

TABLE 37 *Age-specific incidence rates (per 100 person years) of acute and chronic complications associated with sickle cell anaemia*

Age (years)	Painful crisis (refs 351, 352)	Pneumococcal sepsis		Splenic sequestration (ref. 351)	Acute chest syndrome (refs 351, 353)	Acute anaemia (ref. 351)	Leg ulcers (ref. 338)	Hip replacement[b] (ref. 335)	Other operations[c] (ref. 335)	Retinopathy[b] (ref. 356)	Stroke (refs 351, 354)	Renal failure[b] (refs 52, 336, 355, 385)	Chronic lung disease[b] (refs 53, 336, 355, 385)
		Diagnosed[a] (refs 55, 194)	Not diagnosed[a] (refs 55, 194)										
< 1	6.2	2	9	3.25	11.6	3.95	0	0	1.43	0	0.93	0	0
–2	24	2	9	6.2	28	1.7	0	0	1.43	0	0.93	0	0
–3	38.3	2	9	5.3	26.3	3.3	0	0	1.43	0	0.93	0	0
–4	42.4	2	9	2	34.2	5.9	0	0	1.43	0	0.93	0	0
–5	49.6	2	9	1.5	25.5	3.9	0	0	1.43	0	0.93	0	0
–6	40.8	1.6	7.2	1.4	22.2	2	0	0	1.43	0	0.93	0	0
–7	39.2	1.2	5.4	1	28.9	9.3	0	0	1.43	0	0.93	0	0.52
–8	41.6	0.8	3.6	0.5	20.8	3	0	0	1.43	0	0.93	0	0.52
–9	37.9	0.4	1.8	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] Diagnosed on neonatal screening or subsequently; [b] Indirect estimation of age-specific incidence rates; [c] Cholecystectomy or splenectomy

TABLE 38 *Age-specific incidence rates (per 100 person years) of acute and chronic complications associated with sickle HbC disease*

Age (years)	Painful crisis (refs 352, 386)	Pneumococcal sepsis		Splenic sequestration (ref. 351)	Acute chest syndrome (refs 351, 353)	Acute anaemia (ref. 351)	Hip replacement[b] (ref. 335)	Other operations[c] (ref. 335)	Retinopathy[b] (ref. 356)	Stroke[b] (ref. 356)	Renal failure[b] (refs 52, 336, 355, 385)	Chronic lung disease[b] (refs 53, 336, 355, 385)
		Diagnosed[a] (refs 55, 194)	Not diagnosed[a] (refs 55, 194)									
< 1	1.9	0.54	2.7	0	10.9	0	0	0	0	0	0	0
–2	8.5	0.54	2.7	0.5	10.6	0	0	0	0	0	0	0
–3	15.3	0.54	2.7	0	10.4	0	0	0	0	0	0	0
–4	28.5	0.54	2.7	1.5	13.1	1.5	0	0	0	0	0	0
–5	23.3	0.28	1.4	2.9	9.7	0	0	0	0	0	0	0
–6	33.6	0.28	1.4	1.3	5.2	0	0	0	0	0	0	0
–7	29.1	0.28	1.4	1.8	1.8	0	0	0	0	0	0	0
–8	40.3	0.21	0.41	0	5.8	0	0	0.54	0	0	0	0
–9	23	0.14	0.27	0	3.3	0	0	0.54	0	0.25	0	0
–10	40	0.07	0.14	0	3.95	0	0	0.54	4.3	0.25	0	0
–20	40	0	0	0	3.27	0.5	0	0.54	8.3	0.17	0	0
–30	40	0	0	0	3.27	0.5	0.24	0.54	7.4	0.17	0.40	0.08
> 30	40	0	0	0	3.27	0.5	0.24	0.54	3.5	0.17	0.40	0.08

[a] Diagnosed on neonatal screening or subsequently; [b] Indirect estimation of age-specific incidence rates; [c] Cholecystectomy or splenectomy

TABLE 39 *Main assumptions for costing of the treatment of acute complications in patients with sickle cell disorders*

Condition	Treatment assumptions				References
	Length of hospital stay (days)		Special interventions[a]	Sequelae requiring treatment	
	ITU	Normal ward			
Painful crisis	–	7	–	–	48
Pneumococcal sepsis	3	8	–	18% meningitis, of whom 31% die Survivors[c]: 20% deaf, 5% mentally retarded, 8% permanent seizures[b]	244, 387
Splenic sequestration	1	6	Simple transfusion	–	48, 57, 58, 388
Acute chest syndrome	2	5	Exchange transfusion	–	48, 58, 389, 390
Stroke	2	16	CT scan, exchange transfusion, hypertransfusion (lifelong)	20% die < 3 weeks, another 10% < 1 yr Survivors[c]: 25% require temporary rehabilitation for 2 yr, 10% permanent care	354, 384, 391
Acute anaemia	–	7	Simple transfusion	–	48, 58, 348, 388

Assumptions about transfusion requirements are based on references 57, 58, 348, 388

ITU, intensive therapy unit

[a] *Special interventions costed separately because they are not included in the aggregated average costs per hospital day*

[b] *Independent sequelae*

[c] *Survivors of sequelae are assumed to have an average life expectancy similar to other patients with sickle cell disease*

only the additional resources consumed in caring for high-risk pregnancies. It was assumed that pregnant patients require five extra antenatal visits, four extra ultrasound examinations and five extra days of postnatal care per pregnancy compared with a normal woman. In addition, it was assumed that, on average, a pregnant patient will be given 15 units of blood during pregnancy, and require 10 days' hospitalisation on a normal ward and 5 days in an intensive care unit. The rate of caesarean section is 17% higher than in the normal population[344,349,350] (Tuck, S, Royal Free Hospital, London: personal communication, 1997). The average additional costs of antenatal and postnatal care associated with a pregnancy in a patient with sickle cell disease are included in *Table 36*.

Although babies of mothers with sickle cell disease show an increased frequency of neonatal complications, especially of premature births,[345–348] which incur additional health service costs, these have not been included in the calculation of the lifetime treatment costs of patients with sickle cell disorders.

Estimation of incidence rates of acute and chronic conditions associated with sickle cell anaemia and sickle HbC disease

Estimates for age-specific incidence rates of acute and chronic conditions associated with sickle cell disorders are mainly based on published results from: the 'Co-operative Study of Sickle Cell Disease', a prospective study of almost 4000 patients with sickle cell disorders from birth to age 66 years, who were enrolled in various centres throughout the USA;[194,335,338,351–353] studies of a Californian cohort of about 1000 patients;[52,53,336,354,355] the 'Prophylactic Penicillin Study', a randomised controlled trial of over 200 affected children under 3 years of age, who were recruited from multiple centres throughout the USA;[55] and a study based on a Jamaican cohort of over 500 patients.[356] The incidence rates of the various complications have been considered to reflect sickle cell disease-specific events. This assumption may lead to a slight overestimation because complications such as stroke, especially in the older age groups, can be expected to occur also in the normal population, albeit much less commonly, and the distinction between sickle

cell-specific and non-specific events is not always possible. Furthermore, the derived incidence rates might not be fully applicable to the UK population of patients with sickle cell disease because country variations in the expression of the disease are well described, and definitions of various acute and chronic complications might vary. In addition, study results were presented 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 (*Tables 37* and *38*). As a result, the values presented are estimates, which can only indicate the approximate frequency of the complications.

Estimation of survival of screened and unscreened patients with sickle cell disorders

The survival of patients with sickle disorders can be expected to vary between sickle cell anaemia and sickle HbC disease[54,357] as well as between screened and unscreened cohorts.[55]

Recent major studies of mortality in sickle cell disease[54,357] have presented the results from mixed screened and unscreened cohorts. For the purpose of this review it was therefore necessary to reconstruct separate mortality rates from the available data. It was assumed that, whereas screen-detected patients are diagnosed at birth, unscreened individuals with sickle cell anaemia would present gradually, so that all would be recognised by the age of 10 years,[44] and those with sickle HbC disease disease by the age of 20,[46] after which age prophylactic treatment and comprehensive care were assumed to be similar, and to result in the same morbidity and mortality. The mortality experience of early and late diagnosed cohorts of patients with sickle cell anaemia and sickle HbC disease was assumed to differ up to the age of 10 years owing to an increased incidence of pneumococcal sepsis[55] and case fatality of splenic sequestration[45,358] in an ever-decreasing proportion of undiagnosed individuals. Overall mortality was set to be consistent with reports in the current literature, which also informed survival estimates in early and late diagnosed groups after the age of 10 years. The main assumptions underlying the calculation of differential mortality up to age 10 years in affected children who are already diagnosed (neonatally or later), and in those who have not yet been diagnosed, are shown in *Tables 37, 38* and *40*. *Tables 37* and *38* include age-specific incidence rates for pneumococcal sepsis and splenic sequestration. *Table 40* presents the corresponding case fatality rates.

The incidence rates for pneumococcal sepsis and splenic sequestration are of particular importance because they determine the early deaths averted, and severe disability prevented, as a result of early diagnosis. The overall incidence rates of sepsis for sickle cell disease, presented by Gaston *et al.*,[55] were combined with the differential incidence rates for sepsis in sickle cell anaemia and sickle HbC disease in Zarkowsky *et al.*[194] to estimate the early and late diagnosis incidence rates reported in *Tables 37* and *38*. Gill *et al.* followed 694 patients over a 10-year period to establish the incidence rates of splenic sequestration used in these calculations.[351] The age at diagnosis of the unscreened child also plays a critical role in estimates of the clinical benefits of early diagnosis. For sickle HbC disease, data given by Williams *et al.*[46] were used. For sickle cell anaemia, Bainbridge *et al.*[44] give data from a 1985 study based in Jamaica, in which 32% were diagnosed by the end of the first year, 61% by the second, 78% by the third and 86% by the fourth. It was considered that diagnosis at the present time would be likely to be earlier; the distribution given by Bainbridge was therefore shifted forward by 1 year (61% by the first, 78% by the second, and so on).

The estimated survival of current cohorts of patients with sickle cell anaemia and sickle HbC disease, early and late diagnosed, up to 60 years is presented in appendix 3 (*Tables 83–86*). The survival curves (not shown) predict an average life expectancy of

TABLE 40 *Case fatality rates for pneumococcal sepsis and splenic sequestration in early and late diagnosed individuals with sickle cell disease*

Patient category	Condition	Case fatality rate	References
Late diagnosis	Splenic sequestration	0.06	45, 358
Early diagnosis	Splenic sequestration	0.03	45, 358
Early and late diagnosis	Pneumococcal sepsis	0.15	55, 351
Fatality rates have been assumed to be similar for patients with sickle cell anaemia and sickle HbC disease			

45 years for early and late diagnosed patients with sickle cell anaemia, the corresponding figures for patients with sickle HbC disease being 64 years; these are consistent with data from the literature.[54,357] The difference in life expectancy between early and late diagnosed cohorts is less than 6 months.

Calculation of the total lifetime treatment costs

The average lifetime treatment costs over 60 years for patients with sickle cell anaemia have been estimated to be around £173,000 and £162,000 undiscounted, for early and late diagnosed cases respectively, and £52,000 and £49,000 discounted. The corresponding figures for patients with sickle HbC disease are £121,000 and £120,000, and £30,000 and £29,000 respectively. Appendix 3 (*Tables 82–86*) shows the calculations based on the summation of the average annual treatment costs per original cohort member up to a hypothetical age of 60 years.

Consequences of prevention of late diagnoses of sickle cell disorders in terms of early deaths averted, severe disability prevented and treatment costs

Early deaths averted

Deaths up to the age of 10 years were included because, by this age, all sickle cell anaemia was assumed to have been diagnosed in an unscreened cohort. In screened individuals with sickle cell disorders, who are diagnosed early, the introduction of penicillin prophylaxis and comprehensive care has been shown to reduce mortality due to pneumococcal sepsis and splenic sequestration. *Table 41* shows the number of early deaths averted per 100 late diagnoses prevented in patients with sickle cell anaemia and sickle HbC disease. For sickle cell anaemia, the figure is 1.25, for sickle HbC disease 0.57. Calculations are based on the differential survival presented in appendix 3 (*Tables 83–86*), which include assumptions that all children who were identified with sickle cell disorder by a screening programme were given appropriate care, and that patients had a compliance with prophylactic penicillin therapy similar to that achieved by Gaston *et al.*[55] To the extent that low levels of compliance may be achieved in practice, both assumptions may be conservative[205,207] and likely to exaggerate the number of early deaths averted per late diagnosis prevented. The predicted deaths averted are comparable with the earlier work of Gessner *et al.*,[244] which implies 2.4 early deaths averted per 100 early screens. These authors assume that unscreened children are diagnosed later and are therefore exposed to higher mortality rates for a longer period.

Cases of severe disability prevented

In screened individuals with sickle cell disorders, who are diagnosed early, the introduction of penicillin prophylaxis and the subsequent reduction in the incidence of pneumococcal sepsis can be expected to reduce pneumococcal meningitis and its main sequelae, mental retardation, seizures and deafness. The numbers of cases of severe disability prevented per 1000 late diagnoses prevented in patients with sickle cell anaemia and sickle HbC disease are presented in *Table 41*. The main assumptions underlying the calculation of differential morbidity in early and late diagnosed individuals with sickle cell disease up to the age of 10 years can be found in *Tables 37–39*. *Tables 37* and *38* include age-specific incidence rates for pneumococcal sepsis; *Table 39* includes the

TABLE 41 *Number of early deaths, and cases of severe disability, averted per 100 late diagnoses prevented in patients with sickle cell anaemia and sickle HbC disease*

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

assumptions regarding the frequency of pneumococcal meningitis and its sequelae.

Treatment costs

The prevention of late diagnoses in screened individuals with sickle cell disease has a dual effect on treatment costs. While the prevention of early deaths increases treatment costs, the prevention of severe disability reduces the average cost of treatment.

Table 42 shows the differences in treatment costs for early and late diagnosed patients with sickle cell anaemia and sickle HbC disease, discounted and undiscounted, at the ages of 10 and 60 years, to illustrate the short-term and long-term impact of screening on treatment costs. Calculations are based on the average annual treatment costs presented in appendix 3 (*Tables 83–86*). The observed differences after 10 years are small: one late diagnosis prevented leads in all cases to additional treatment costs of about £1000 or less. After the age of 60 years, additional treatment costs associated with the prevention of a late diagnosis of sickle cell anaemia accumulate to over £8000 undiscounted and over £2500 discounted, the corresponding figures for patients with sickle HbC disease being over £1000 and over £800 respectively.

TABLE 42 *Treatment costs for early and late diagnosed patients with sickle cell disorder at the ages of 10 and 60 years*

Patient category	Time of treatment costs (£)			
	10 years (undiscounted)	10 years (discounted [a])	60 years (undiscounted)	60 years (discounted [a])
Sickle cell anaemia, early diagnosis	24,764	18,780	169,222	50,898
Sickle cell anaemia, late diagnosis	23,758	17,801	160,766	48,231
Difference	1,006	979	8,456	2,667
Sickle HbC disease, early diagnosis	12,887	10,072	119,850	29,665
Sickle HbC disease, late diagnosis	12,089	9,249	118,722	28,827
Difference	798	823	1,128	838

[a] *Discount rate 6%*

Chapter 8

Review of incremental cost-effectiveness ratios for haemoglobinopathy screening that are acceptable for policy makers

Purpose of the review

The main results in this study are presented in the form of ICERs, describing the additional costs per additional unit of benefit of changing from a selective to a universal screening strategy. In the case of antenatal screening, these are 'choice' ICERs and 'affected live-birth prevented' ICERs; in the case of neonatal screening, these are 'late diagnosis prevented' ICERs (see chapter 4; p. 35). If ICERs are to be used to inform policy decisions about whether to adopt universal or selective screening strategies, maximum acceptable values need to be agreed.

Maximum acceptable incremental cost-effectiveness ratios

Criteria about what constitutes maximum acceptable ICER values for antenatal and neonatal Hb-pathy screening programmes are empirical and depend on competing healthcare priorities and the political context. Here, various approaches have been taken to arrive at realistic values:

- comparison with other published economic studies of Hb-pathy screening programmes, preferably using similar units of benefit
- comparison with published economic studies of other comparable screening programmes
- consideration of lifetime treatment costs to inform acceptable values for affected live birth prevented ICERs
- consideration of litigation charges for deficient antenatal and neonatal Hb-pathy screening services.

Incremental cost-effectiveness ratios for choice offered

No published studies of antenatal Hb-pathy screening were available directly to inform these ICER values. However, economic studies of other antenatal screening programmes have reported costs comparable with those associated with offering choice over the outcome of a pregnancy with an affected fetus. Although no articles were found that used the specific outcome measure 'choice offered', a number of studies used related measures such as 'high-risk couples detected' or 'affected pregnancies detected'. They are summarised in *Table 43*.

All of the studies present the average cost-effectiveness of the different screening options, which are comparable with incremental values under the assumption that the alternative strategies compared are no screening and screening. The authors of all the studies concluded by recommending the adoption of antenatal screening for the disorder of interest. Although authors are not policy makers, their acceptance of the resulting cost per outcome can be used as an indicator for the potential range of acceptable ICER values for antenatal choice.

Incremental cost-effectiveness ratios for affected live births prevented

The lifetime treatment costs that are averted in cases in which an affected pregnancy has been identified and the parents request genetic termination, can be used as a benchmark figure to indicate affected live birth prevented ICER values at which the expenditure and financial savings of a screening programme are in balance.

The lifetime treatment costs for sickle cell disorders are more important values than the lifetime treatment costs for β-thalassaemia major because changing from a selective to a universal antenatal screening strategy can be expected to result mainly in the prevention of live births affected with sickle cell disorders. Lifetime treatment costs for patients with sickle cell disorders have been estimated to be between £120,000 and £170,000 undiscounted, and between £30,000 and £50,000 discounted (chapter 7; p. 77). For

TABLE 43 *Costs per antenatal screening outcome comparable with 'choice offered'*

Country/year/reference	Disorder	Outcome measure	Cost per outcome (£)[a]
USA/1994/395	Cystic fibrosis	High-risk pregnancy identified	54,000
UK/1995/116	Cystic fibrosis	Carrier couple detected Affected fetus detected	37,875 144,329
UK/1995/115	Cystic fibrosis	Affected fetus detected[b]	40,400–105,040
UK/1995/318	Down's syndrome	Affected fetus detected[b]	22,220–36,360

[a] *All costs are adjusted to 1996 prices, US dollars are converted at $1.6:£1*
[b] *1:4 carrier couples/high-risk pregnancies can be expected to have an affected fetus; costs include those for PND*

TABLE 44 *Grades of recommendation and description of evidence for the adoption of more effective technologies*

Grade	Recommendation	Description of evidence
A	Compelling evidence for adoption	More effective and less costly
B	Strong evidence for adoption	Costs less than c. £10,000 per QALY
C	Moderate evidence for adoption	Costs between c. £10,000 and £50,000 per QALY
D	Weak evidence for adoption	Costs more than c. £50,000 per QALY

Adapted from Laupacis et al.;[258] *costs are uprated to 1996 prices and Canadian dollars are converted at $2.1:£1*

completeness, the corresponding values for β-thalassaemia major were estimated to be over £490,000 undiscounted and about £123,000 discounted (p. 70).

Incremental cost-effectiveness ratios for late diagnosis of sickle cell disease prevented

Laupacis *et al.*[258] relate maximum acceptable ICER values to two components of the available economic evidence. First, the quality of the study is cited as influencing the decision over implementation. Having made the decision maker aware of the quality of the evidence, five grades of recommendation for the adoption of more effective technologies are listed.

Although the data in *Table 44* refer to QALYs, they can be taken as an indicator of the degree of evidence required by a more effective technology with respect to the incremental cost of quality unadjusted life years. The outcomes presented for the neonatal section, late diagnoses prevented, can be converted into the number of life years saved by using appendix 3 (*Tables 83–86*). Up to the age of 60 years, the gain in life years for each late diagnosis of sickle cell anaemia and sickle HbC disease prevented is 0.53 and 0.3 respectively, estimated from the difference in area under the predicted survival curves in screened and unscreened cohorts. As sickle cell anaemia is much more common than sickle HbC disease, a conversion figure of 0.5 life years gained per late diagnosis prevented may be taken as a reasonable estimate.

Naturally, a quality unadjusted life year is not as valuable as a QALY. Therefore, following the logic of Laupacis *et al.*,[258] the incremental cost of an extra late diagnosis prevented must be less than approximately £25,000 for there to be moderate evidence for the adoption of universal screening. Thus, the £20,000 maximum acceptable ICER value chosen in chapter 9 is consistent with the approach taken by Laupacis *et al.*[258]

Neonatal sickle cell screening programmes

Additional comparative evidence is available from Sprinkle *et al.*[243] They calculated the average cost per early diagnosis of sickle cell disease for each state in the USA. Results are presented for both a selective and a universal programme, although an incremental approach is not used (both programmes are compared with a no screening alternative). However, with respect to

the acceptable values for detecting an individual with sickle cell disorder, the presented results are instructive. Within the states listed, the predicted costs per sickle cell disorder case found through universal screening were calculated to range from under £1000 to around £200,000 (all costs uprated to 1997 prices). Amongst the American states that are already screening universally, the costs incurred for detecting an individual with sickle cell disease ranged from £900 to £75,000. The conclusion of these authors was that universal screening should be provided in all states.

Neonatal screening programmes for other disorders

Neonatal screening is undertaken for a range of other genetic disorders. The primary abnormalities are PKU and congenital hypothyroidism, although other disorders may also be identified. Cost-effectiveness ratios for the prevention of late diagnosis of these conditions (comparing a no screening option with universal screening) may provide a basis for comparison with the respective incremental costs associated with neonatal screening for sickle cell disorders, although it has to be considered that the severity of the conditions and the consequences of prevention of late diagnosis in terms of deaths averted and disability prevented are considerably different. *Table 45* lists the corresponding costs per case detected for metabolic and other disorders for which neonatal screening is most commonly offered in the UK. As the primary objectives of metabolic screening are the detection of PKU and congenital hypothyroidism, the costs of sample collection have been attributed exclusively to these disorders. Figures are taken from a recent NHS *Health Technology Assessment* review on the potential for extending neonatal metabolic screening.[306]

TABLE 45 *Cost per case detected for various disorders in a neonatal screening programme*

Disorder	Cost per case detected (£)
PKU	26,827
Congenital hypothyroidism	14,889
Cystic fibrosis	4,746
Tyrosinaemia	36,278
Homocystinuria	29,551
Data from reference 306	

Litigation charges

Litigation charges for deficient antenatal and neonatal Hb-pathy screening services might be used to gauge societal values attached to the objectives of such screening programmes. Two cases published by the press were available. The first concerned a court case in 1989 in which damages of £35,196 (uprated to 1997 value) were awarded for failing to offer antenatal screening to a mother with sickle cell trait who subsequently delivered a baby with sickle cell disease.[14] The second case ended in an out-of court settlement of £217,155 (uprated to 1997 value) for the failure to offer antenatal and neonatal screening to a mother and her subsequently born, affected baby.[15] However, litigation charges are based on the individual circumstances of each case. This might explain the substantial difference in damages paid in these two published cases and limits their use to inform ICERs.

Maximum acceptable incremental cost-effectiveness ratios used for this analysis

The dearth of available information to inform precise ICER values made it necessary to use a range of plausible estimates, intended to serve as indicators of the approximate magnitude of values likely to be acceptable to UK policy makers. For antenatal Hb-pathy screening, we have chosen the following choice ICERs: £50,000, £100,000, £150,000 with a baseline value of £100,000. The range of affected live birth prevented ICERs chosen was from £50,000 to £300,000. For neonatal sickle cell screening, the late diagnosis prevented ICERs used were £10,000, £20,000 and £50,000, with a baseline value of £20,000. The estimates are summarised in *Table 46*.

TABLE 46 *Maximum acceptable incremental cost-effectiveness ratios used in the analysis*

Screening programme	ICER	Baseline value (£)	Range (£)
Antenatal	'Choice offered'	100,000	50,000, 150,000
	'Affected live birth prevented'	–	50,000, 100,000, 150,000, 300,000
Neonatal	'Late diagnosis prevented'	20,000	10,000, 50,000

Chapter 9
Results

Model validation and adjustment

Predicted and observed numbers of fetuses with haemoglobinopathies

The number of fetuses affected by Hb-pathies of each type can be predicted from the assumed ethnic composition, Hb-pathy carrier frequency and inter-ethnic union rates in the antenatal population. *Table 47* compares the predictions for the UK from the current model with those of Hogg and Modell.[228] If the current model is applied to the district health authority data on ethnic composition of antenatal populations used by these authors, it predicts a similar number of fetuses with sickle cell disorders, but only if no inter-ethnic union is assumed. If inter-ethnic union rates are taken into account, the current model predicts fewer fetuses with sickle cell disorders. Hogg and Modell assumed zero inter-ethnic union rates, except that Hb-pathy carrier frequency in Cypriot women was adjusted downwards to account for 10% of unions with north European men.

Ethnic composition data from the 1991 Census, based on births between 1986 and 1991, could be a misleading basis for the analysis of sickle cell disorder prevalence 10 years later. The ethnic composition assumptions underlying earlier research have therefore been reconsidered.

Work undertaken at the London Research Centre[359] suggests that in London there has been a considerable net inward migration of women from Africa since the 1991 Census. This is confirmed by unpublished data from a 1995–1996 survey of women attending for antenatal care in six major inner London maternity units,[133] and also by data on births in the first quarter of 1997 extracted from child health computers in North East Thames.[247] Both these sources show that the proportion of black African women is now considerably in excess of the 1991 Census-based data for equivalent districts by factors of between 1.3 and 2.0.

In the absence of more definitive data, district data on the ethnic composition of antenatal populations were therefore adjusted. The proportion of black African women was increased by an arbitrary factor of 1.6 in the Thames regions and by 1.3 elsewhere; the proportion of north Europeans was reduced in accordance. The resulting ethnic compositions are presented in appendix 3 (*Table 81*). The numbers of affected fetuses predicted in the UK when using these adjusted ethnic composition data, but allowing for inter-ethnic unions, are shown in *Table 47*. This adjustment brings the predicted numbers of affected fetuses more closely into line with earlier projections.[228]

TABLE 47 *Predicted number of fetuses with haemoglobinopathies in the UK per year: comparison of 1997 projections by Hogg and Modell[228] with those of the current model*

Source	Annual number of fetuses with Hb-pathies		
	SCD	**$\beta\beta$, $E\beta$, $\alpha^0\alpha^0$**	**Total**
1997 projections by Hogg and Modell[228]	178.8	38.8	217.6
Current model			
Use of Hogg and Modell's district data on ethnic composition of antenatal poputions:[228] no inter-ethnic unions assumed	176.8	49.0	225.8
Use of Hogg and Modell's district data on ethnic composition of antenatal populations:[228] inter-ethnic unions considered[19]	134.7	43.8	178.5
Adjusted district data on ethnic composition of antenatal populations: inter-ethnic unions considered	171.4	43.9	215.3

SCD, sickle cell disease

*Model predictions under baseline assumptions (*Tables 9 *and* 10*), apart from varying data on ethnic composition of antenatal populations and inter-ethnic unions*

Predictions from the model were also compared with the empirical data that are available from universal neonatal screening programmes in a small number of districts.[7] The adjustment of data on the ethnic composition of antenatal populations leads to a predicted 9.8 cases of Hb-pathies per 10,000 antenatal population in metropolitan North West Thames (a 15% overestimate compared with available empirical data), and 29.8 per 10,000 in South East London (a 16% underestimate. However, North West Thames data cover an earlier period (1990–1994) than the data from South East London (1994–1995), and there has been continuing immigration from sub-Saharan Africa over the last 5 years. When the model was applied to 1996 antenatal ethnic composition data obtained directly from Guy's and Thomas's maternity unit,[133] which serves most of the South East London population, the number of pregnancies with sickle cell disorders predicted by the current model was 37.1 per 10,000 antenatal population, very close to the 36/10,000 observed.

Predicted and observed numbers of prenatal diagnoses for haemoglobinopathies

Table 48 compares the annual number of prenatal diagnoses for Hb-pathies for selective and universal strategies predicted by the model with data from the Oxford PND register[39] collected between 1990 and 1994. The register collects data nationally from districts operating selective, universal or even no screening strategies. Model predictions distinguish between at-risk pregnancies and pregnancies that are not in fact at risk, but are assumed at risk, either because a sample was collected from a partner who is not the biological father or because no partner was available. Predicted and observed numbers are closely comparable.

It should be emphasised that concordance between model and register data does little to validate the model. The rates of uptake of PND being assumed (*Table 17*) were originally calculated in such a way as to make register data compatible with Hogg and Modell's assumptions about Hb-pathy carrier frequency, ethnic composition and inter-ethnic unions in the antenatal population, which are open to question.[360] Moreover, what were originally calculated as overall PND utilisation rates among women with affected fetuses are being used here as PND uptake among women from whom a sample is available for testing. *Table 48* should therefore be inter-preted as no more than a demonstration that the sum total of our baseline assumptions – however flawed their derivation – are in combination compatible with the national data available on the number of PNDs performed.

Antenatal screening results

In order to demonstrate the principal findings, results have been presented for each ethnic group and for three real examples of districts chosen from the UK data set (appendix 3; *Table 81*) with high, medium and low prevalence of ethnic minorities in the antenatal population (referred to as **high-**, **medium-** and **low-prevalence districts**). In addition, summary analyses, including sensitivity analyses, are given for all districts in the UK.

Predicted fetal prevalence of haemoglobinopathies

Tables 49 and *50* describe the fetal prevalence of Hb-pathies by ethnic group and in the three illustrative districts respectively. *Table 50* also characterises the ethnic composition of the three high-, medium- and low-prevalence example districts with regard to the percentage of total ethnic minority women, black groups, total carriers and sickle carriers.

As would be expected from the Hb-pathy carrier frequencies (*Table 13*), β-thalassaemia major occurs

TABLE 48 *Observed and predicted annual numbers of prenatal diagnoses for haemoglobinopathies in the UK*

Source	At-risk conditions of pregnancies undergoing PND				
	SCD	**ββ,Eβ**	**$\alpha^0\alpha^0$**	**No risk**	**Total**
PND register 1990–1994[39]	93.6	76.0	6.0	Not reported	175.6
Current model					
Universal screening	101.3	73.7	4.5	3.2	182.7
Selective screening	97.5	73.6	4.5	2.7	178.3

*Model predictions under baseline assumptions (*Tables 9 *and* 10*) including 5.5% selective and 0.5% universal failure to screen rates*

TABLE 49 *Predicted fetal prevalence of haemoglobinopathies per 10,000 antenatal population by ethnic group*

Ethnic group	Affected fetuses per 10,000 antenatal population				
	SS, Sβ, SD	***SC***	***ββ,Eβ***	***$\alpha^0\alpha^0$***	**Total**
Black Caribbean	28.18	17.41	0.183	0.000	45.77
Black African	99.39	27.33	0.187	0.000	126.91
Black other	17.36	10.61	0.109	0.000	28.07
Indian	2.64	0.00	3.025	0.000	5.67
Pakistani	0.22	0.00	15.076	0.000	15.30
Bangladeshi	0.00	0.00	8.250	0.000	8.25
Chinese	0.01	0.00	1.763	4.850	6.62
Other Asian	0.02	0.00	1.464	0.154	1.63
Other	5.05	0.00	0.150	0.000	5.20
Cypriot	4.37	0.00	44.920	0.700	49.99
Italian	0.09	0.00	2.830	0.000	2.92
North European	0.01	0.00	0.003	0.000	0.01

*Model predictions under baseline assumptions (*Tables 9 *and* 10*)*

For comparison, Hb-pathy carrier frequency by ethnic group is shown in Table 13

TABLE 50 *Predicted fetal prevalence of haemoglobinopathies per 10,000 antenatal population and characterisation of high-, medium- and low-prevalence districts*

Prevalence	Ethnic minority (%)	Black[a] groups (%)	All carriers (%)	Sickle carriers (%)	Affected fetuses per 10,000 women				
					SS, Sβ, SD	**SC**	***ββ, Eβ***	***$\alpha^0\alpha^0$***	**Total**
High	48.7	36.0	8.2	7.1	22.21	7.55	1.15	0.08	30.98
Medium	28.0	6.2	2.4	1.4	2.18	0.96	1.96	0.02	5.12
Low	3.5	0.5	0.5	0.2	0.33	0.09	0.18	0.01	0.62

*Model predictions under baseline assumptions (*Tables 9 *and* 10*)*

[a] *Black Caribbean, black African, black other*

primarily in fetuses of Cypriot, Pakistani and Bangladeshi women, α^0-thalassaemia hydrops fetalis in Chinese, and sickle cell disorders in black ethnic groups. However, because the incidence of disease varies approximately with the square of the carrier frequencies, the distribution of disease is considerably more exaggerated than the distribution of traits. For example, the frequency of sickle cell disorders is approximately four times greater in fetuses conceived by black African compared with other black women, while their carrier frequency is only twice as high. Inter-ethnic union causes the disease frequency to be proportional to somewhat less than the square of the trait frequency.

It is of note that, in the low-prevalence district, 0.62 affected fetuses are predicted per 10,000 antenatal population (*Table 50*), compared with 0.01 among north European women (*Table 49*). This indicates that even in a low-prevalence district most affected fetuses arise from ethnic minority populations.

Predicted frequency of the main screening outcomes of universal and selective antenatal strategies

Tables 51 and *52* show the main screening outcomes for affected and unaffected fetuses by ethnic group, and in the three illustrative districts. Results are given separately for the universal and selective screening programmes. The latter is based

TABLE 51 *Predicted main antenatal screening outcomes for affected and unaffected fetuses per 10,000 antenatal population by ethnic group*

Ethnic group	Prg	Affected fetuses									Unaffected fetuses								Total PNDs
		Live birth		TOP		PND miscarriage		Other pregnancy loss		Total n (= 100%)	Live birth		TOP		PND miscarriage		Other pregnancy loss		Total n (= 100%)	
		n	%	n	%	n	%	n	%		n	%	n	%	n	%	n	%		
Black Caribbean	U	41.27	90.2	3.84	8.4	0.08	0.2	0.59	1.3	45.77	9,814.59	98.6	0.04	0.0	0.24	0.0	139.36	1.4	9,954.23	21.23
	S	41.39	90.4	3.72	8.1	0.08	0.2	0.59	1.3	45.77	9,814.60	98.6	0.04	0.0	0.23	0.0	139.36	1.4	9,954.23	20.54
Black African	U	113.05	89.1	12.00	9.5	0.25	0.2	1.61	1.3	126.91	9,734.03	98.6	0.10	0.0	0.74	0.0	138.21	1.4	9,873.09	66.01
	S	113.45	89.4	11.61	9.1	0.24	0.2	1.61	1.3	126.91	9,734.06	98.6	0.10	0.0	0.72	0.0	138.21	1.4	9,873.09	63.84
Black other	U	25.30	90.1	2.37	8.4	0.05	0.2	0.36	1.3	28.07	9,832.15	98.6	0.02	0.0	0.15	0.0	139.60	1.4	9,971.93	13.16
	S	25.37	90.4	2.29	8.2	0.05	0.2	0.36	1.3	28.07	9,832.16	98.6	0.02	0.0	0.14	0.0	139.60	1.4	9,971.93	12.74
Indian	U	2.27	40.1	3.31	58.3	0.06	1.0	0.03	0.6	5.67	9,854.20	98.6	0.04	0.0	0.17	0.0	139.92	1.4	9,994.33	15.42
	S	2.28	40.3	3.29	58.1	0.06	1.0	0.03	0.6	5.67	9,854.21	98.6	0.04	0.0	0.17	0.0	139.92	1.4	9,994.33	15.35
Pakistani	U	12.12	79.2	2.96	19.4	0.05	0.3	0.17	1.1	15.30	9,844.76	98.6	0.02	0.0	0.14	0.0	139.78	1.4	9,984.70	12.22
	S	12.12	79.2	2.96	19.3	0.05	0.3	0.17	1.1	15.30	9,844.76	98.6	0.02	0.0	0.14	0.0	139.78	1.4	9,984.70	12.22
Bangladeshi	U	7.51	91.0	0.63	7.6	0.01	0.1	0.11	1.3	8.25	9,851.83	98.6	0.01	0.0	0.03	0.0	139.88	1.4	9,991.75	2.60
	S	7.51	91.1	0.62	7.5	0.01	0.1	0.11	1.3	8.25	9,851.83	98.6	0.01	0.0	0.03	0.0	139.88	1.4	9,991.75	2.56
Chinese	U	0.63	9.5	5.54	83.7	0.09	1.3	0.37	5.5	6.62	9,846.09	98.5	0.14	0.0	0.26	0.0	146.88	1.4	9,993.38	23.30
	S	0.63	9.5	5.54	83.7	0.09	1.3	0.37	5.5	6.62	9,846.10	98.5	0.14	0.0	0.26	0.0	146.88	1.4	9,993.38	23.29
Other Asian	U	0.84	51.3	0.73	44.7	0.01	0.7	0.05	3.3	1.63	9,858.11	98.6	0.02	0.0	0.04	0.0	140.20	1.4	9,998.37	3.11
	S	0.84	51.3	0.73	44.7	0.01	0.7	0.05	3.3	1.63	9,858.11	98.6	0.02	0.0	0.04	0.0	140.20	1.4	9,998.37	3.11
Other	U	3.71	71.4	1.41	27.1	0.03	0.5	0.05	1.0	5.20	9,854.77	98.6	0.01	0.0	0.09	0.0	139.93	1.4	9,994.80	7.85
	S	3.76	72.3	1.36	26.1	0.03	0.5	0.05	1.0	5.20	9,854.77	98.6	0.01	0.0	0.09	0.0	139.93	1.4	9,994.80	7.58
Cypriot	U	11.36	22.7	37.81	75.6	0.59	1.2	0.23	0.5	49.99	9,807.33	98.6	0.60	0.0	1.81	0.0	140.27	1.4	9,950.01	159.95
	S	11.40	22.8	37.77	75.6	0.59	1.2	0.23	0.5	49.99	9,807.34	98.6	0.59	0.0	1.81	0.0	140.27	1.4	9,950.01	159.71
Italian	U	0.62	21.3	2.25	77.2	0.03	1.2	0.01	0.3	2.92	9,857.00	98.6	0.02	0.0	0.11	0.0	139.96	1.4	9,997.08	9.38
	S	0.62	21.3	2.25	77.2	0.03	1.2	0.01	0.3	2.92	9,857.00	98.6	0.02	0.0	0.11	0.0	139.96	1.4	9,997.08	9.37
North European	U	0.00	36.1	0.01	62.3	0.00	1.2	0.00	0.5	0.01	9,859.99	98.6	0.00	0.0	0.00	0.0	140.00	1.4	9,999.99	0.05
	S	0.01	56.0	0.01	42.4	0.00	0.8	0.00	0.5	0.01	9,859.99	98.6	0.00	0.0	0.00	0.0	140.00	1.4	9,999.99	0.03

*Model predictions under baseline assumptions (*Tables 9 *and* 10*)*

Prg, programme; U, universal; S, selective

TABLE 52 *Predicted main antenatal screening outcomes for affected and unaffected fetuses per 10,000 antenatal population in high-, medium- and low-prevalence districts*

Ethnic group	Prg	Affected fetuses										Unaffected fetuses										Total PNDs
		Live birth		TOP		PND miscarriage		Other pregnancy loss		Total n (= 100%)		Live birth		TOP		PND miscarriage		Other pregnancy loss		Total n (= 100%)	
		n	%	n	%	n	%	n	%			n	%	n	%	n	%	n	%		
High	U	26.91	86.9	3.61	11.7	0.07	0.2	0.39	1.3	30.98		9,829.09	98.6	0.04	0.0	0.21	0.0	139.67	1.4	9,969.02		18.85
	S	27.00	87.2	3.52	11.4	0.07	0.2	0.39	1.3	30.98		9,829.10	98.6	0.04	0.0	0.21	0.0	139.67	1.4	9,969.02		18.34
Medium	U	4.18	81.6	0.87	16.9	0.02	0.3	0.06	1.2	5.12		9,854.87	98.6	0.01	0.0	0.05	0.0	139.96	1.4	9,994.88		4.09
	S	4.19	81.9	0.85	16.7	0.01	0.3	0.06	1.2	5.12		9,854.87	98.6	0.01	0.0	0.05	0.0	139.96	1.4	9,994.88		4.01
Low	U	0.44	71.3	0.17	27.1	0.00	0.5	0.01	1.2	0.62		9,859.37	98.6	0.00	0.0	0.01	0.0	140.01	1.4	9,999.38		0.78
	S	0.44	72.0	0.16	26.4	0.00	0.5	0.01	1.2	0.62		9,859.37	98.6	0.00	0.0	0.01	0.0	140.01	1.4	9,999.38		0.75

*Model predictions under baseline assumptions (*Tables 9 *and* 10*)*

on carrier testing of women in ethnic minorities and of all women with a low MCH. Among affected fetuses, TOP rates are very low in black and Bangladeshi groups compared with other non-black groups. Consequently, the proportion undergoing TOP increases when moving from the high- to the low-prevalence district and, in the high- and medium-prevalence districts, 80–90% of all affected fetuses result in live births.

Unaffected fetuses might suffer adverse screening-related outcomes, such as PND-induced miscarriage or TOP after a false-positive diagnosis (due either to laboratory error or, in rare instances, the male from whom the sample is taken at partner testing not being the biological father, but a carrier). However, the number of adverse screening outcomes is very small (0.21 PND-induced miscarriages and 0.04 TOPs of unaffected fetuses per 10,000 pregnancies in the high-prevalence district), and scarcely varies between universal and selective programmes. The distribution of adverse events is the reverse of what is seen in many screening programmes, where low-risk groups suffer disproportionately due to false-positive screening results. Instead, most adverse outcomes in Hb-pathy screening occur in the ethnic minority groups with the highest carrier frequencies, namely Cypriot and black African.

Tables 53 and *54* show the number of choices offered over the outcome of pregnancies with affected fetuses, the major outcome by which the performance of antenatal screening has been measured. Results are presented by ethnic group and in the three illustrative districts respectively. In both universal and selective programmes, the proportion of mothers with affected pregnancies for whom the concept of choice offered is not applicable is the same, although it varies between ethnic groups. As expected (because selective screening is based on **ethnicity and low MCH**), universal and selective programmes do not differ in the number of choices offered for women with fetuses affected by **thalassaemias**. The greatest advantage of universal over selective screening with regard to the number of choices offered for women with fetuses affected by **sickle cell disease** is found amongst black ethnic groups, reflecting the differential failure to screen rates of the two programmes. Fetuses of north European women with thalassaemia are detected on selective screening. Those with sickle cell disease, apart from fetuses of women with a low MCH, are missed, but absolute numbers are very small. When comparing the high-, medium- and low-prevalence districts, the differences in the number of choices offered within universal and selective

TABLE 53 *Predicted number of choices offered for women with affected fetuses per 10,000 antenatal population by ethnic group*

Ethnic group	Prg	Number of choices offered for women with fetuses affected by thalassaemia and SCD												
		Thal and SCD	Thalassaemia				Total affected thal n (= 100%)	SCD				Total affected SCD n (= 100%)	No choice affected live births	All affected live births
		Choice not applicable	No choice		Choice			No choice		Choice				
		n	n	%	n	%		n	%	n	%			
Black Caribbean	U	2.09	0.00	0.77	0.17	94.67	0.18	0.35	0.77	43.16	94.67	45.59	0.33	41.27
	S	2.09	0.00	0.94	0.17	94.50	0.18	1.77	3.88	41.74	91.56	45.59	1.73	41.39
Black African	U	10.30	0.00	0.77	0.17	91.11	0.19	0.96	0.76	115.47	91.12	126.72	0.89	113.05
	S	10.30	0.00	0.77	0.17	91.11	0.19	4.80	3.79	111.64	88.09	126.72	4.67	113.45
Black other	U	1.15	0.00	0.78	0.10	95.11	0.11	0.22	0.77	26.60	95.12	27.96	0.20	25.30
	S	1.15	0.00	0.78	0.10	95.11	0.11	1.09	3.90	25.72	91.99	27.96	1.06	25.37
Indian	U	0.44	0.04	1.18	2.75	90.99	3.02	0.03	1.29	2.40	90.88	2.64	0.06	2.27
	S	0.44	0.04	1.20	2.75	90.97	3.02	0.06	2.42	2.37	89.75	2.64	0.09	2.28
Pakistani	U	1.20	0.12	0.79	13.78	91.38	15.08	0.00	0.80	0.21	91.37	0.22	0.12	12.12
	S	1.20	0.12	0.81	13.77	91.36	15.08	0.00	2.06	0.20	90.11	0.22	0.12	12.12
Bangladeshi	U	0.65	0.06	0.70	7.58	91.47	8.25	0.00	2.06	0.00	90.11	0.00	0.06	7.51
	S	0.65	0.16	1.91	7.46	90.26	8.25	0.00	2.06	0.00	90.11	0.00	0.16	7.51
Chinese	U	0.46	0.08	1.28	6.07	91.77	6.61	0.00	1.59	0.01	91.46	0.01	0.05	0.63
	S	0.46	0.08	1.28	6.07	91.77	6.61	0.00	1.66	0.01	91.39	0.01	0.05	0.63
Other Asian	U	0.13	0.02	0.98	1.48	91.19	1.62	0.00	1.15	0.01	91.02	0.01	0.02	0.84
	S	0.13	0.02	1.04	1.47	91.13	1.62	0.00	1.21	0.01	90.96	0.01	0.02	0.84
Other	U	0.32	0.00	1.00	0.14	92.93	0.15	0.05	1.03	4.69	92.90	5.05	0.05	3.71
	S	0.32	0.00	1.00	0.14	92.93	0.15	0.23	4.58	4.51	89.35	5.05	0.22	3.76
Cypriot	U	2.81	0.57	1.24	42.49	93.14	45.62	0.06	1.41	4.06	92.97	4.37	0.61	11.36
	S	2.81	0.57	1.24	42.49	93.14	45.62	0.14	3.13	3.99	91.25	4.37	0.68	11.40
Italian	U	0.16	0.04	1.24	2.64	93.14	2.83	0.00	1.43	0.08	92.95	0.09	0.04	0.62
	S	0.16	0.04	1.24	2.64	93.14	2.83	0.00	3.19	0.08	91.19	0.09	0.04	0.62
North European	U	0.00	0.00	1.32	0.00	94.57	0.00	0.00	1.47	0.01	94.42	0.01	0.00	0.00
	S	0.00	0.00	1.32	0.00	94.57	0.00	0.00	54.63	0.00	41.26	0.01	0.00	0.01

*Model predictions under baseline assumptions (*Tables 9 *and* 10*)*

Thal, thalassaemias $\alpha^0\alpha^0$, ββ, Eβ

TABLE 54 *Predicted number of choices offered for women with affected fetuses per 10,000 antenatal population in high-, medium- and low-prevalence districts*

Ethnic group	Prg	Number of choices offered for women with fetuses affected by thalassaemias and SCDs													
		Thal and SCD	Thalassaemia					SCD						No choice affected live births	All affected live births
		Choice not applicable	No choice		Choice		Total affected thal n (= 100%)	No choice		Choice		Total affected SCD n (= 100%)		
		n	n	%	n	%		n	%	n	%			
High	U	2.22	0.01	1.14	1.14	92.66	1.23	0.23	0.77	27.38	92.03	29.75		0.22	26.91
	S	2.22	0.02	1.23	1.14	92.57	1.23	1.14	3.82	26.47	88.98	29.75		1.22	27.00
Medium	U	0.32	0.02	0.84	1.82	91.47	1.98	0.03	0.80	2.94	93.76	3.14		0.04	4.18
	S	0.32	0.02	0.94	1.81	91.36	1.98	0.12	3.93	2.84	90.63	3.14		0.14	4.19
Low	U	0.04	0.00	1.07	0.18	92.27	0.19	0.00	0.83	0.39	92.18	0.42		0.01	0.44
	S	0.04	0.00	1.17	0.18	92.17	0.19	0.02	4.85	0.37	88.17	0.42		0.02	0.44

*Model predictions under baseline assumptions (*Tables 9 *and* 10)
Thal, thalassaemias $\alpha^0\alpha^0$, ββ, Eβ

programmes are broadly similar, but are generally lower for selective than universal programmes (ranging in universal programmes from 92.0% to 93.8%, and in selective programmes from 88.2% to 90.6% for sickle cell disease and from 92.2% to 92.6% for thalassaemias).

Predicted screening costs of universal and selective antenatal strategies

Tables 55 and *56* describe the total predicted costs and cost components for universal and selective programmes by ethnic group and in the three illustrative districts respectively. The total costs of the screening process incurred by each ethnic group vary. This reflects: different distributions of Hb-pathy carrier states and hence different costs of carrier testing; different prevalences of carrier couples; different levels of uptake of PND; and different laboratory costs for PND. The total costs (figures in brackets are rounded) of screening 10,000 Cypriot women are the greatest (£800,000), followed by Chinese (£425,000), other Asian (£255,000) and black African women (£210,000). The cost difference between selective and universal screening among the ethnic minorities is marginal. Among north Europeans, the selective screening option incurs low, but not zero, costs because women with a low MCH undergo Hb-pathy screening.

When comparing the high-, medium- and low-prevalence districts, a universal programme costs more than a selective one in all three. However, the difference between the two programmes, both in relative and absolute terms, increases as prevalence decreases. The main contribution to total costs is the laboratory screening tests, followed by counselling and PND. TOP costs contribute a very small proportion (< 2%) to overall costs. Differences in total costs per 10,000 antenatal population between selective and universal programmes range from approximately £17,000 in the high-prevalence district to about £29,000 in the low-prevalence district.

Incremental cost-effectiveness ratios for choice offered

The ICER for choice offered (choice ICER) is the additional cost of offering reproductive choice to an additional woman with an affected pregnancy, when moving from a selective to a universal antenatal programme. *Table 57* shows how the ICER is calculated by dividing the difference in costs by the difference in the number of choices offered. Moving from the high- to the low-prevalence district, the cost difference increases by a factor of

TABLE 55 *Predicted total antenatal screening programme costs and cost components per 10,000 antenatal population by ethnic group*

Ethnic group	Prg	Laboratory		Counselling		PND		TOP		Total cost (£) (= 100%)
		£	%	£	%	£	%	£	%	
Black Caribbean	U	50,674	42.5	42,399	35.5	24,528	20.6	1,676	1.4	119,277
	S	48,974	42.5	41,026	35.6	23,742	20.6	1,622	1.4	115,363
African	U	52,629	24.7	78,323	36.8	76,523	36.0	5,230	2.5	212,718
	S	50,860	24.7	75,740	36.8	74,033	36.0	5,059	2.5	205,691
Black other	U	50,411	46.9	40,861	38.0	15,109	14.1	1,033	1.0	107,413
	S	48,718	46.9	39,538	38.1	14,624	14.1	1,000	1.0	103,879
Indian	U	52,231	57.9	14,628	16.2	21,946	24.3	1,444	1.6	90,249
	S	51,357	57.6	14,517	16.3	21,858	24.5	1,438	1.6	89,171
Pakistani	U	50,625	59.1	13,926	16.2	19,866	23.2	1,289	1.5	85,706
	S	49,805	58.7	13,916	16.4	19,860	23.4	1,289	1.5	84,870
Bangladeshi	U	43,955	63.9	20,362	29.6	4,216	6.1	274	0.4	68,807
	S	42,485	63.5	19,944	29.8	4,160	6.2	271	0.4	66,859
Chinese	U	346,130	81.2	45,661	10.7	31,798	7.5	2,456	0.6	426,045
	S	344,563	81.4	44,516	10.5	31,798	7.5	2,454	0.6	423,331
Other Asian	U	216,252	84.7	33,816	13.3	4,808	1.9	326	0.1	255,201
	S	214,659	85.0	32,736	13.0	4,805	1.9	325	0.1	252,525
Other	U	35,882	59.5	14,713	24.4	9,074	15.1	614	1.0	60,284
	S	34,344	59.3	14,171	24.5	8,763	15.1	593	1.0	57,871
Cypriot	U	437,032	54.6	93,816	11.7	252,620	31.6	16,592	2.1	800,060
	S	435,356	54.7	92,048	11.6	252,392	31.7	16,573	2.1	796,369
Italian	U	36,082	58.6	9,435	15.3	15,102	24.5	981	1.6	61,600
	S	34,689	57.6	9,425	15.7	15,097	25.1	980	1.6	60,192
North European	U	33,365	98.5	453	1.3	48	0.1	3	0.0	33,869
	S	4,070	93.4	253	5.8	33	0.8	2	0.1	4,359

*Model predictions under baseline assumptions (*Tables 9 *and* 10*)*

TABLE 56 *Predicted total antenatal screening programme costs and cost components per 10,000 antenatal population in high-, medium- and low-prevalence districts*

Prevalence	Prg	Laboratory		Counselling		PND		TOP		Total cost (£) (= 100%)
		£	%	£	%	£	%	£	%	
High	U	53,802	51.7	25,543	24.5	23,233	22.3	1,577	1.5	104,155
	S	37,957	43.7	24,650	28.4	22,643	26.1	1,537	1.8	86,788
Medium	U	40,679	76.1	6,722	12.6	5,678	10.6	378	0.7	53,457
	S	19,265	60.8	6,440	20.3	5,600	17.7	372	1.2	31,678
Low	U	35,426	93.3	1,376	3.6	1,089	2.9	73	0.2	37,964
	S	7,105	75.6	1,160	12.3	1,064	11.3	71	0.8	9,400

*Model predictions under baseline assumptions (*Tables 9 *and* 10*)*

TABLE 57 *Predicted costs, choices and ICERs for choice offered per 10,000 antenatal population in high-, medium- and low-prevalence districts*

Prevalence	Total programme costs (£)			No. women with affected fetuses: choices offered			Choice ICER (£)
	Universal	Selective	Difference	Universal	Selective	Difference	
High	104,155	86,788	17,367	28.52	27.61	0.91	19,093
Medium	53,457	31,678	21,780	4.76	4.66	0.10	217,201
Low	37,964	9,400	28,563	0.57	0.55	0.02	1,666,891
*Model predictions under baseline assumptions (*Tables 9 *and* 10*)*							

1.6, while the difference in the number of women offered choice decreases by a factor of about 50. As a result, the ICER in the high-prevalence district is 90 times lower and is dominated by the number of choices offered rather than by the costs.

As universal and selective strategies differ only in the number of choices offered to women with fetuses affected by sickle cell disease, and not in those affected by thalassaemias (*Tables 53* and *54*), it is the fetal prevalence of sickle cell disease, rather than the fetal prevalence of Hb-pathies, that affects the incremental cost-effectiveness of selective versus universal screening.

Epidemiological and operational factors influencing the incremental cost-effectiveness of selective versus universal antenatal screening

Epidemiological factors affecting the fetal prevalence of Hb-pathies, such as the ethnic composition of antenatal populations, the Hb-pathy carrier frequency by ethnic group and inter-ethnic union rates, and organisational factors such as the failure to screen rate in selective programmes, combine to determine the incremental cost-effectiveness of selective versus universal screening. Two distinct mechanisms are at play:

- the different coverage of **ethnic minority** women achieved by universal compared with selective screening programmes
- the additional affected fetuses among **north European** women, which can be detected only by a universal programme.

The analyses that follow explore the effect on cost-effectiveness ratios of different assumptions about failure to screen rates, antenatal ethnic composition, carrier frequency and inter-ethnic union rates.

Different coverage of ethnic minority women between universal and selective antenatal screening programmes

In *Table 58,* the failure to screen rate in a universal programme is set at 0.5%, while the selective failure to screen rate is varied through 0.5%, 1.5%, 3.0% and 5.5%. The table shows that, the higher the selective compared with universal failure to screen rates, the more cost-effective it would be to change from a selective to a universal programme.

The case where both selective and universal programmes are equally efficient (i.e. have the same failure to screen rates: *Table 58,* column 1) is instructive. In this case the **only** difference between the two strategies is that the universal programme also screens north European women. The ratio of additional costs to additional benefits remains the same, irrespective of the proportion of north Europeans. Although more women are screened in the low-prevalence district, proportionately more choices are offered.

TABLE 58 *Effect on ICERs for choice offered of differential failure to screen rates between selective and universal programmes*

Prevalence	Choice ICER (£)			
	Selective failure to screen rates			
	0.5%	1.5%	3.0%	5.5%
High	6,341,481	84,823	35,655	19,093
Medium	6,341,481	938,795	415,086	217,201
Low	6,341,481	4,059,390	2,637,648	1,666,891
*Apart from varying failure to screen rates in selective programmes, all other parameters held at baseline level, including universal failure to screen rate 0.5% (*Tables 9 *and* 10*)*				

This example illustrates that there is **no** intrinsic relationship between the prevalence of ethnic minorities in the antenatal population and the relative merit of a universal screening programme. Instead, the advantage of universal screening in a high-prevalence area is a consequence of the higher coverage of those at greater risk. *Table 59* shows that, when there is a differential failure to screen between universal and selective programmes, either an increase in the sickle trait frequency in ethnic minority groups or an increase in the proportion of black African women in the antenatal population would lower choice ICERs, making universal screening relatively more cost-effective.

Screening north European women

It is already evident from the ICERs in the low-prevalence district (*Table 57*) and in the situation where universal and selective strategies have the same failure to screen rate (*Table 58*) that the extra costs of detecting additional cases among north European women through universal screening are extremely high on baseline assumptions. However, the case for universal screening would be enhanced if the prevalence of fetal sickle cell disease in north European women was high enough to justify screening this group in its own right.

Table 60 shows the effects of increasing the assumed carrier frequencies and inter-ethnic union rates on the predicted fetal prevalence of Hb-pathies. Although the predicted prevalence of fetuses affected by sickle cell disease is raised substantially, from 0.01 per 10,000 to 0.214 per 10,000 if carrier frequency and inter-ethnic union rates are set at the maximum, it is still below the 0.42 predicted for the low-prevalence district in *Table 50*. This suggests that the prevalence of affected fetuses in north European women, even under extreme assumptions of high sickle cell trait frequency and inter-ethnic union rates, would **not in itself** merit universal screening, given maximum acceptable ICERs between £50,000 and £150,000.

It is, however, relevant to consider whether a high fetal sickle cell disease prevalence among north Europeans, taken **together** with differential coverage among ethnic minority groups between universal and selective programmes, would justify universal screening. ICERs based on these assumptions are given in *Table 61*.

Areas with a high prevalence of carriers are the areas where higher inter-ethnic union rates might be expected, and where the sickle cell trait frequency among north European women might be higher. These are the districts, however, where the case for universal screening depends almost exclusively on the differential coverage among ethnic minorities.

Summary results of antenatal screening in all districts

This section introduces analyses that have been carried out on all districts in the UK, based on their 1993 boundaries. Although the number of districts has changed since then, the 1993 districts are a convenient basis for modelling because their populations are reasonably close to the catchment areas of maternity units, and their boundaries correspond closely to community provider trusts.

TABLE 59 *Effect on ICERs for choice offered of variation in haemoglobinopathy carrier frequency in ethnic minorities and the proportion of black Africans in the antenatal population*

Prevalence	Choice ICER (£)			
	Hb-pathy carrier frequency in ethnic minority women			
	Baseline value	Baseline value x 1.25	Baseline value	Baseline value x 1.25
	% Black African in antenatal population			
	Baseline value	Baseline value	Baseline value x 1.3	Baseline value x 1.3
High	19,093	12,659	14,576	9,751
Medium	217,201	141,050	204,724	132,888
Low	1,666,891	1,155,587	1,464,894	1,005,530

*Apart from varying Hb-pathy frequency in ethnic minorities and proportion of black Africans in the antenatal population, all other parameters held at baseline levels, including selective failure to screen rate 5.5%, universal failure to screen rate 0.5% (*Tables 9 *and* 10*)*

TABLE 60 *Effect of inter-ethnic union and sickle cell trait frequency on fetal haemoglobinopathy prevalence predicted in north Europeans per 10,000 antenatal population*

Sickle cell trait	Inter-ethnic union (%)	Predicted fetal Hb-pathy prevalence in north Europeans				
		SS, Sβ, SD	*SC*	*ββ, Eβ*	$\alpha^0\alpha^0$	Total
0.050[a]	1.11[a]	0.009	0.000	0.003	0.000	0.012
0.050[a]	5.55	0.025	0.001	0.005	0.000	0.032
0.250	1.11[a]	0.129	0.001	0.065	0.000	0.195
0.250	5.55	0.208	0.006	0.074	0.000	0.288

*Apart from varying sickle cell trait frequency and inter-ethnic union rates among north Europeans, all other parameters held at baseline levels (*Tables 9 *and* 10*)*

[a] *Baseline values*

TABLE 61 *ICERs for choice offered, in relation to sickle cell trait frequency and inter-ethnic union rates in North European women*

Prevalence	Choice ICERs (£)			
	Sickle cell trait frequency in north Europeans			
	0.05%	0.25%	0.05%	0.25%
	Inter-ethnic union rates in north Europeans			
	1.11%	1.11%	5.55%	5.55%
High	19,093	19,023	18,889	18,579
Medium	217,201	205,333	148,132	125,842
Low	1,666,891	1,141,288	349,702	244,116

*Apart from varying sickle cell trait frequency and inter-ethnic union rates among north Europeans, all other parameters held at baseline levels, including selective failure to screen rate 5.5%, universal failure to screen rate 0.5% (*Tables 9 *and* 10*)*

Baseline results

Appendix 3 (*Table 87*) gives a profile of the antenatal population in each district, under baseline assumptions, showing: the estimated percentage of ethnic minorities and percentage of Hb-pathy carriers; the expected fetal prevalence of sickle cell disorders and thalassaemias per 10,000 antenatal population; the costs for universal and selective screening programmes per 10,000 antenatal population; and the corresponding choice ICERs.

Districts differ greatly in the ethnic composition of antenatal populations and percentage of Hb-pathy carriers. Consequently, the expected fetal prevalence of sickle cell disorders shows enormous variation across districts (*Figure 6*), ranging from 29.8 per 10,000 antenatal population in South East London to 0.036 per 10,000 in Western Isles. Fetal thalassaemia (genotypes *ββ*, *Eβ*, $\alpha^0\alpha^0$) prevalence varies from 5.0 in New River to 0.009 per 10,000 in Orkney.

The costs of screening per 10,000 antenatal population in low-prevalence districts are around £5000 to £6000 for selective and £35,000 for universal screening programmes. For high-prevalence districts, universal programmes may cost over £90,000 and selective over £70,000. In one district with particularly large Cypriot and Chinese communities, universal screening is estimated to cost £145,000 and selective screening £128,000. The cost difference between selective and universal programmes narrows as the prevalence of sickle cell disease increases (*Figure 7*).

Choice ICERs vary from less than £20,000 in South East London to over £5,000,000 in Northumberland, Orkney and the Western Isles. In *Figure 8,* the choice ICERs are plotted against the proportion of women from black ethnic minority groups in the antenatal population. Only nine of the 170 districts have proportions

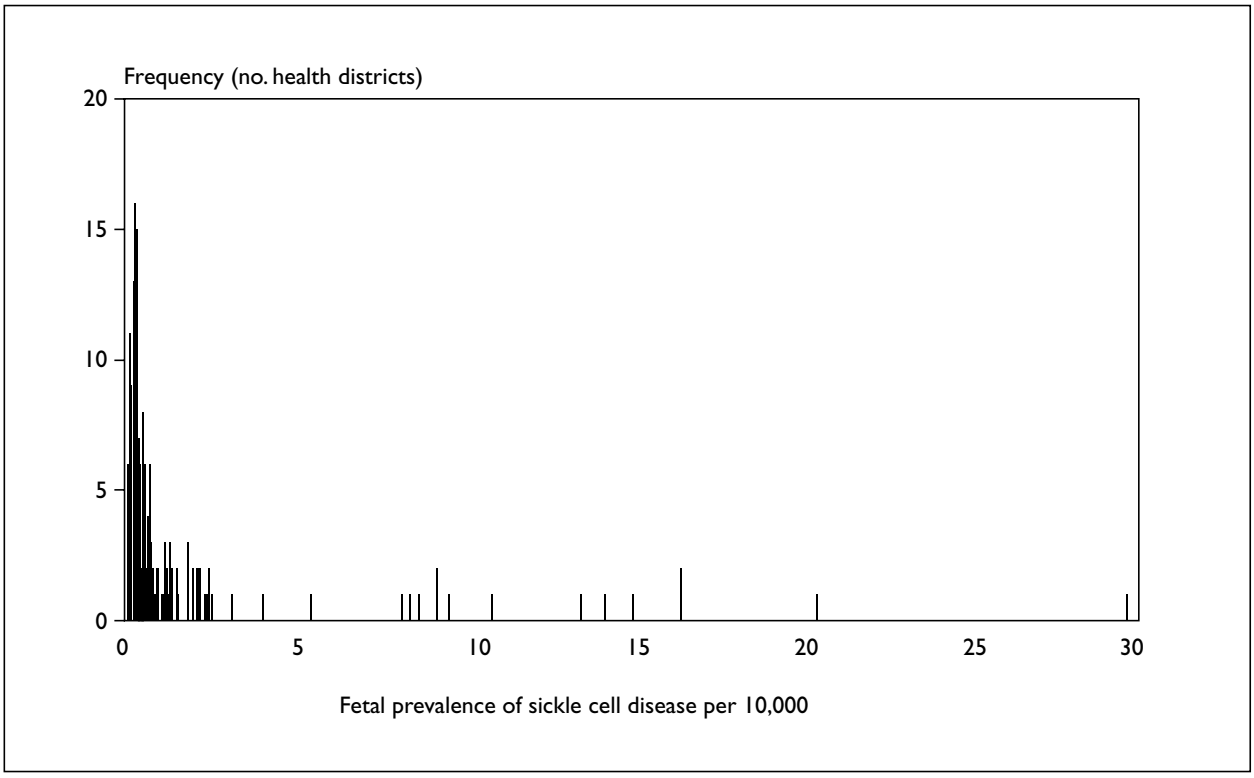

FIGURE 6 *Distribution of expected fetal sickle cell disease prevalence per 10,000 antenatal population in 170 health authorities*

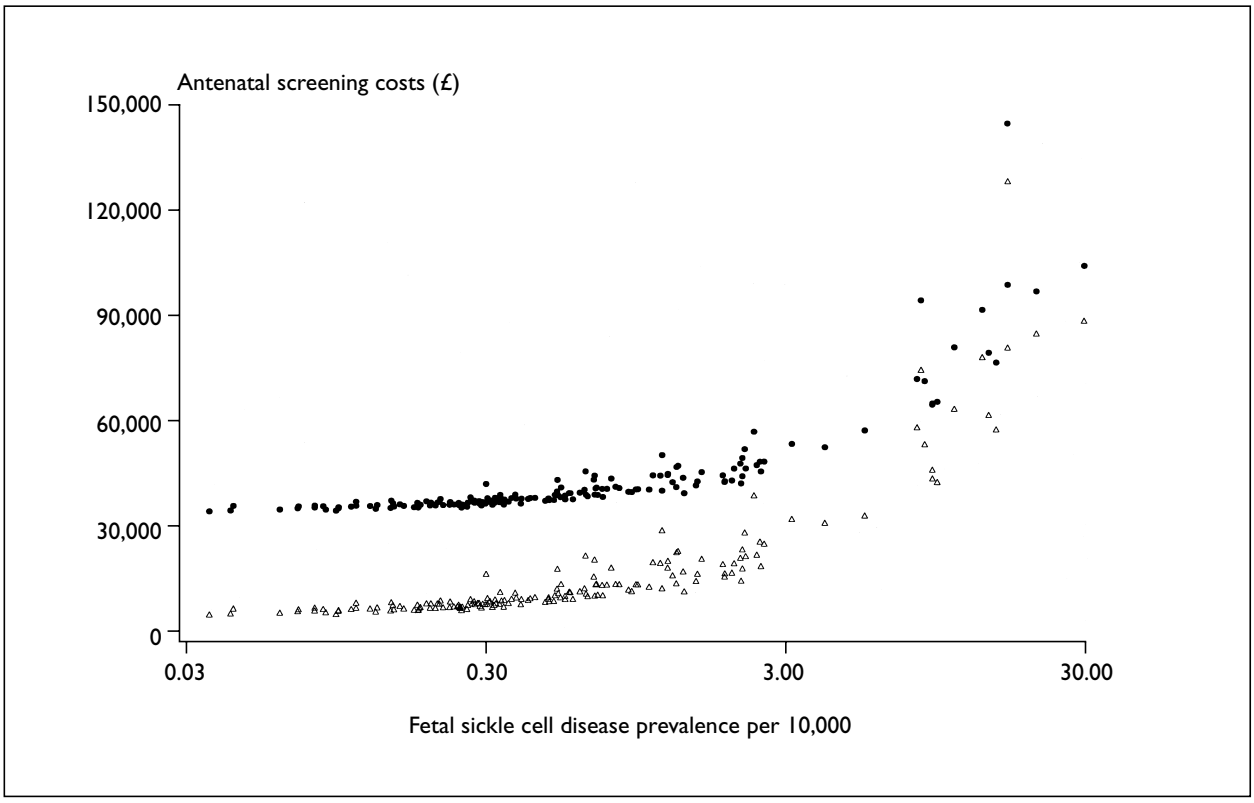

FIGURE 7 *Costs of antenatal screening per 10,000 antenatal population; each symbol represents one health district. Baseline assumptions including universal (●) failure to screen rate 0.5% and selective (△) failure to screen rate 5.5%*

of black women above 15%, 13 above 10%, and 17 above 5%. As already shown in this chapter (p. 92), the proportion of black women in the antenatal population could not provide a rational basis for choosing between selective and universal screening strategies, unless the difference in the failure to screen rates between the two programmes is also considered. However, *Figure 8* suggests that, even when the difference in failure to screen rates are taken into account, there could be a wide variation in the proportion of black women in a district, without a concomitant change in choice ICERs.

Sensitivity analyses

Table 62 summarises the findings of the antenatal sensitivity analysis. It is presented by listing districts that would adopt a universal strategy based on three different acceptable choice ICER values under varying probability and cost parameters. All other districts would screen selectively under all assumptions listed. For ease of presentation, districts have been ranked by decreasing predicted fetal sickle cell disease prevalence and can be identified by numbers given in the footnote.

The higher the acceptable ICER for changing from a selective to a universal programme, the more districts would adopt universal screening; increasing selective failure to screen rates consistently makes universal programmes more cost-effective. This is illustrated in *Figure 9*. For example, under the baseline assumptions and an acceptable ICER of £100,000, 14 districts would adopt universal screening if the selective failure to screen rate were as high as 5.5%, but only two if the rate could be lowered to 1.5%. All other parameters whose changes over a plausible range of values (*Tables 9* and *10*) influence policy decisions are described in *Table 62,* together with some parameters that have no significant influence. Among the latter are net TOP rate, counselling costs, non-paternity rates, carrier test sensitivity, and the proportion of women who are too late for screening. These have virtually no impact because they affect the costs and/or effects of both universal and selective strategies to a similar extent. Although high levels (30%) of iron deficiency in the antenatal population increase both selective and universal screening costs by between £10,000 in the low-prevalence district and about £16,000 in the high-prevalence district (with ferritin measurement included, the respective costs are £13,000 and £22,000), changes within the range of 5–30% would affect policy choice in only a few districts.

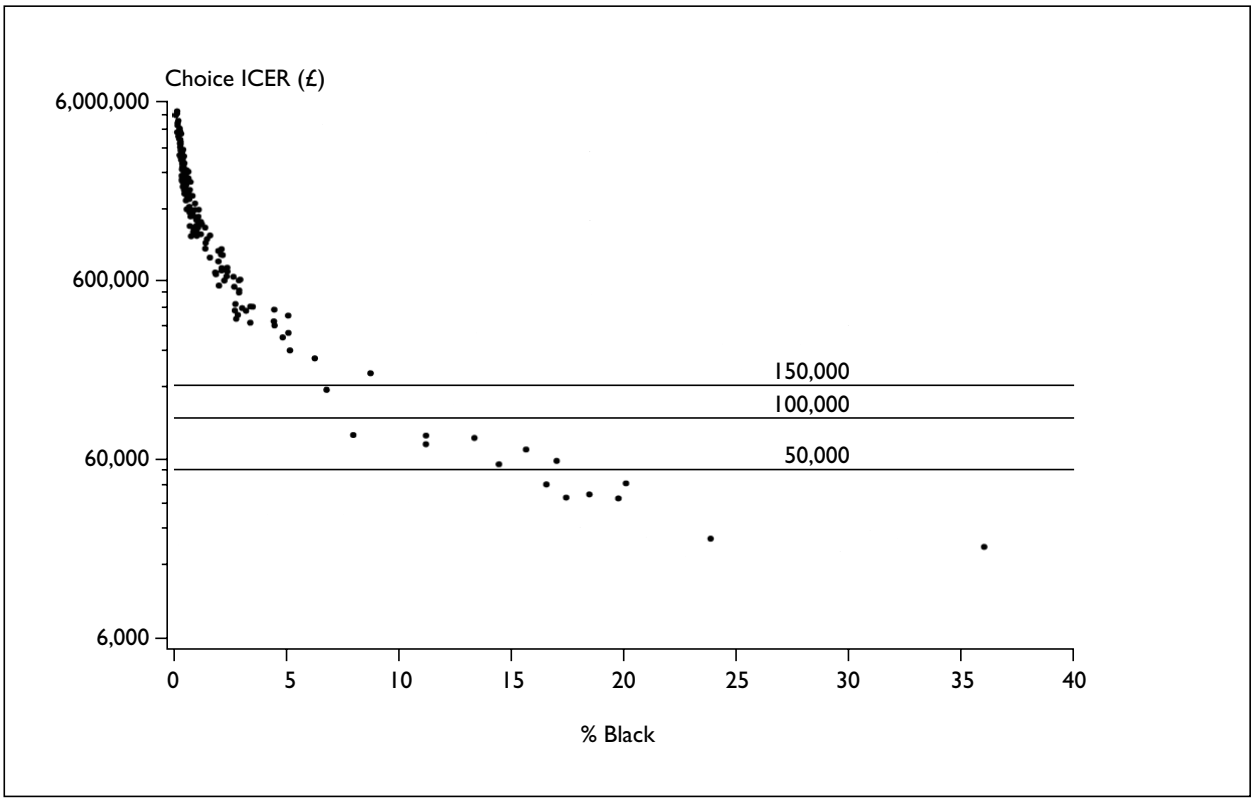

FIGURE 8 *Choice ICER against percentage of black women in the antenatal population; each dot represents one health district Baseline assumptions including failure to screen rates: universal 0.5%, selective 5.5%*

TABLE 62 *Antenatal screening sensitivity analysis: districts (numbered) adopting universal strategy based on choice ICER criteria*

Parameter values	Acceptable choice ICERs (£) to change from selective to universal strategy under different selective failure to screen rates								
	£50,000			£100,000			£150,000		
	5.5%	3.0%	1.5%	5.5%	3.0%	1.5%	5.5%	3.0%	1.5%
Baseline[a]	1–7	1,2	–	1–14	1–7	1,2	1–15	1–8,11,12,14	1,2
North European inter-ethnic union = 5.55% (baseline = 1.11%); sickle trait frequency = 0.25% (baseline = 0.05%)	1–8,14	1,2	–	1–15	1–8,11,12,14	1,2	1–18,20,22	1–15	1–8,14
Hb-pathy carrier frequency x 1.25 in ethnic minorities; % black Africans in antenatal population x 1.3 (compared with baseline)	1–14	1–7	1,2	1–15	1–14	1–4,7	1–17	1–15	1–8
Iron deficiency = 30%, (baseline = 10%)	1–4,6,7	1,2	–	1–14	1–7	1	1–14	1–8,14	1,2
Iron deficiency = 5% (baseline = 10%)	1–7	1,2	–	1–14	1–7	1,2	1–15	1–14	1,2
High net TOP rate[b]	1–7	1,2	–	1–14	1–7	1,2	1–15	1–8,11,12,14	1,2
Low net TOP rate[b]	1–7	1,2	–	1–14	1–7	1,2	1–15	1–8,10–12,14	1,2
Too late for screening ÷ 2 (compared with baseline)	1–7	1,2	–	1–14	1–7	1,2	1–15	1–8,10–12,14	1,2
Non-paternity rate = 1.5% (baseline = 0.5%)	1–7	1,2	–	1–14	1–7	1,2	1–15	1–8,11,12,14	1,2
Carrier test sensitivity = 99.0% (baseline = 99.9%)	1–7	1,2	–	1–14	1–7	1,2	1–15	1–8,11,12,14	1,2
Counselling costs x 2 (compared with baseline)	1–7	1,2	–	1–14	1–7	1,2	1–15	1–8,11,12,14	1,2
Counselling costs ÷ 2 (compared with baseline)	1–7	1,2	–	1–14	1–7	1,2	1–15	1–8,10–12,14	1,2
Laboratory costs x 1.5 (compared with baseline)	1,2	–	–	1–8,11,14	1–3	–	1–14	1–7	1,2
Laboratory costs ÷ 1.5 (compared with baseline)	1–8,11,12,14	1–4,7	–	1–15	1–8,11,12,14	1,2	1–17	1–14	1–7
Time for ethnic ascertainment 1 min; time for pretest information 1 min[c]	1–8,14	1–4,7	–	1–14	1–8,14	1,2	1–16	1–14	1–4,7
Time for ethnic ascertainment 2 min; time for pretest information 2 min	1–8,11,12,14	1–4,6,7	1,2	1–14	1–8,10–14	1–3,7	1–17,22	1–14	1–8,14
'Best plausible case for universal screening'[d]	1–14	1–8,14	1,2	1–17,22	1–15	1–8,14	1–33	1–17,22	1–14

[a] *Baseline parameter values (*Tables 9 *and* 10*), apart from varying selective failure to screen rates;* [b] *High and low net TOP rates are explained in chapter 5 (p. 49);* [c] *1 min midwifery time = £0.39;* [d] *'Best plausible case for universal screening' comprises the following parameter settings (compared with baseline values): inter-ethnic union rates among north Europeans x 3.5; sickle trait frequency in north Europeans x 1.15; carrier frequency in ethnic minorities x 1.15; % black Africans in the antenatal population x 1.2; laboratory costs ÷ 1.5; all other values remain at baseline*

Districts are numbered: 1, South East London; 2, East London and City; 3, New River; 4, Camden and Islington; 5, Wandsworth; 6, Kensington, Chelsea and Westminster; 7, Brent and Harrow; 8, Redbridge and Waltham Forest; 9, Greenwich; 10, Croydon; 11, Central Manchester; 12, Ealing, Hammersmith and Hounslow; 13, Barnet; 14, West Birmingham; 15, Merton and Sutton; 16, Wolverhampton; 17, South Birmingham; 18, South Bedfordshire; 19, Barking and Havering; 20, Sandwell; 21, North Manchester; 22, East Birmingham; 23, South Manchester; 24, Hillingdon; 25, North Birmingham; 26, Kingston and Richmond; 27, Liverpool; 28, Bexley; 29, Bromley; 30, Nottingham; 31, Sheffield; 32, South Glamorgan; 33, North Bedfordshire; all other districts would screen selectively under all assumptions listed

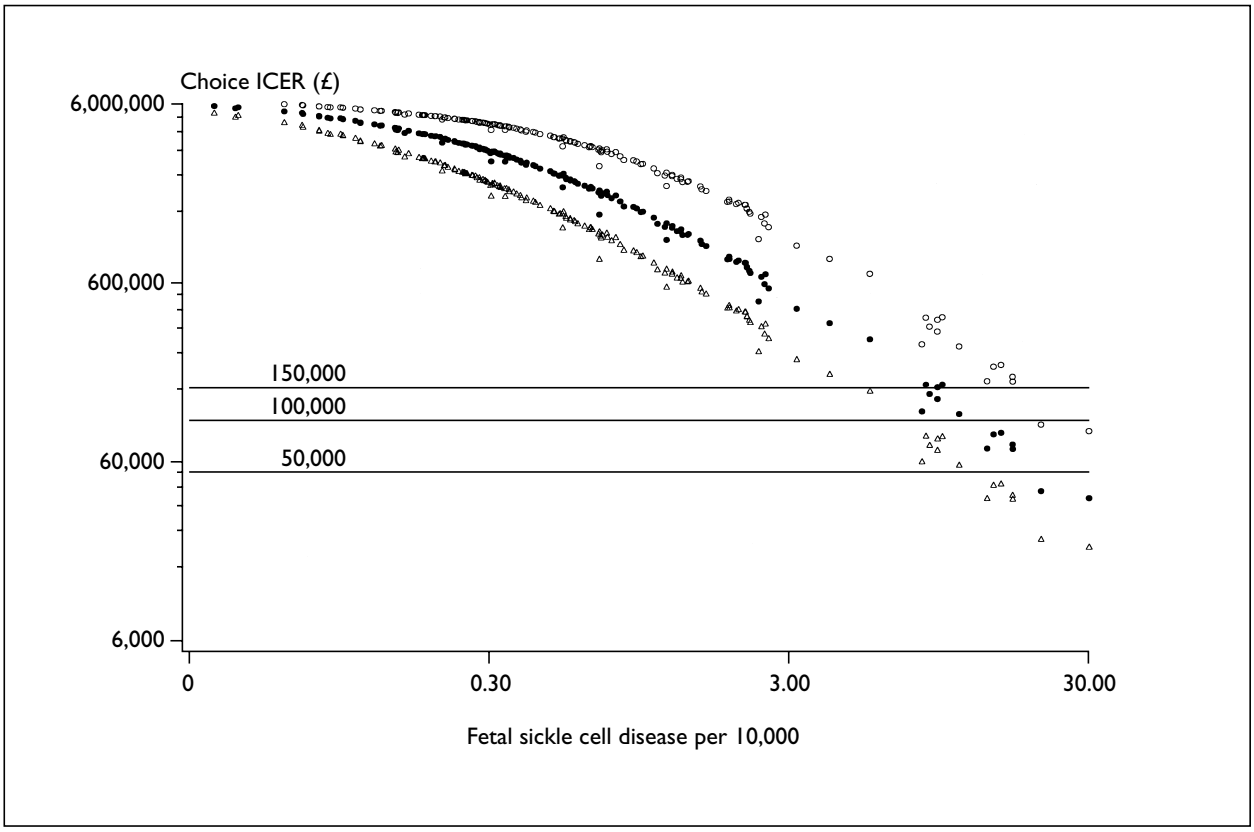

FIGURE 9 *Choice ICER against fetal sickle cell disease prevalence per 10,000 antenatal population; each symbol represents one health district. Failure to screen rates: selective 5.5% (△), 3.0% (●), 1.5% (○); universal 0.5%*

Even parameter changes with moderately large effects on ICERs may affect strategy choice in no more than one or two districts. This is a result of the heavily skewed and uneven distribution of the predicted sickle cell disease prevalence (*Figure 6*), characterised by gaps that separate the districts with the highest two, the highest seven and the highest 14 prevalence estimates from those below. For example, ICERs are sensitive to changes in laboratory test costs but, in spite of this, a 1.5-fold drop in costs would, given a 5.5% selective failure to screen rate and a £100,000 acceptable ICER, result in universal screening in only one extra district (*Table 62*). Similarly, raising the cost by the same amount would result in abandoning universal screening in only two districts.

The effect of including costs for ethnic ascertainment and pretest information was found to favour universal screening, although the changes in ICERs were not dramatic, even if a total of 4 minutes would be spent per woman attending for booking. Even under such extreme assumptions, the screening costs of a selective programme were never higher than those of a universal programme (*Table 63*), preventing universal screening from becoming the dominant strategy on grounds of costs and benefits. However, the cost implications of ethnic ascertainment and pretest information become significant when comparing the cost-effectiveness of selective screening versus no screening (see below; p. 101).

A combined sensitivity analysis was constructed to provide a best plausible case for a universal strategy. In this analysis, a range of factors were set to values that tend to favour universal screening, but at values less extreme than those in the one-way sensitivity analyses. The factors included were:

- inter-ethnic union rate among north Europeans (3.5% compared with baseline 1.1%)
- sickle trait frequency in north Europeans (0.175% compared with baseline 0.05%)
- carrier frequencies in ethnic minorities (1.15 times baseline)
- proportion of black African women in the antenatal population (1.2 times baseline)
- laboratory costs (67% of baseline).

Assuming a £100,000 acceptable ICER and a 5.5% selective failure to screen rate, the best plausible case scenario adds only a further four districts to those that would adopt universal screening on baseline assumptions (*Table 62*).

TABLE 63 *Costs of universal and selective antenatal screening programmes depending on time spent for ethnic ascertainment and pretest information*

Prevalence	Programme	Antenatal screening costs (£)		
		Time for ethnic ascertainment and pretest information each		
		0 min	1 min	2 min
High	Universal	104,155	107,853	111,551
	Selective	86,788	94,183	101,579
Medium	Universal	53,457	57,167	60,877
	Selective	31,678	39,097	46,516
Low	Universal	37,964	41,700	45,436
	Selective	9,400	16,873	24,345

*Apart from varying screening costs, all other parameters held at baseline levels (*Tables 9 *and* 10*)*

1 min midwifery time = £0.39

Subsidiary analyses of antenatal screening

Affected live births prevented as an alternative measure of antenatal screening performance

The number of affected live births prevented as a result of the mother's decision to terminate the pregnancy is another aspect of the programme's performance that can be measured (chapter 2; p. 7). An ICER can be calculated by dividing the cost difference between a selective and a universal programme by the difference in affected live births prevented. *Table 64* illustrates this for the high-, medium- and low-prevalence districts. Affected live birth prevented ICERs are higher than choice ICERs by factors of between four and 10. Although every offer of a PND counts as a 'choice offered', there is no effect on the affected live birth prevented outcome denominator unless the PND is taken up and leads to a TOP. ICERs based on affected live births prevented within each district are presented in appendix 3 (*Table 87*).

Table 65 shows the relationship between TOP rates and affected life birth prevented ICERs. The high net TOP rate (see chapter 5; p. 49), with other parameter values held at baseline levels, would almost double overall programme costs in the high-prevalence district, owing to the increase in the number of PNDs that would be carried out. The affected live birth prevented ICER would be reduced from £186,368 to £33,064. In medium- and low-prevalence districts the effects on the affected live births prevented ICERs are proportionately less than in a high-prevalence district, because the baseline net TOP rates are already higher. As the net TOP rate increases, the number of affected fetuses terminated approaches the number of choices offered, and the affected live birth prevented ICER and choice ICER become closer.

Whereas the net TOP rate is influential only on the affected live birth prevented ICERs, other factors affect both ICERs in the same way. Underlying fetal prevalence of sickle cell disease is again a decisive factor. This is illustrated in *Figure 10,* which plots affected live birth prevented ICERs for each district against fetal sickle cell disease prevalence, otherwise assuming baseline parameter values, including a 5.5% selective and 0.5% universal failure to screen rate. Baseline net TOP rates are designated by 'dots', high rates by 'triangles', and low rates by 'circles'. The graph shows the same form of relationship with fetal sickle cell disorder prevalence as the choice ICERs in *Figure 9,* with lower ICERs for higher TOP uptake. Even assuming a £150,000 acceptable ICER, no district would adopt universal screening at baseline net TOP rates. However, if the high net rates of TOP were assumed, nine

TABLE 64 *Construction of ICERs based on affected live births prevented*

Prevalence	Total programme costs (£)			Affected live births per 10,000			Affected live birth prevented ICER (£)	Choice ICER (£)
	Universal	Selective	Difference	Universal	Selective	Difference		
High	104,155	86,788	17,367	26.91	27.00	0.093	186,368	19,093
Medium	53,457	31,678	21,780	4.18	4.19	0.012	1,773,194	217,201
Low	37,964	9,400	28,563	0.44	0.44	0.004	7,289,446	1,666,891

*Model predictions under baseline assumptions (*Tables 9 *and* 10*)*

TABLE 65 *Affected live birth prevented ICERs based on high, low and baseline net TOP rates per 10,000 antenatal population*

Pre-valence	Net TOP		Costs (£)			No. affected live births			Affected live birth prevented ICER (£)	Choice ICER (£)
	Rate[a]	%	Universal	Selective	Difference	Universal	Selective	Difference		
High	Low	7.9	96,254	79,103	17,151	28.08	28.14	0.058	297,552	18,847
	Baseline	11.7	104,155	86,788	17,367	26.91	27.00	0.093	186,368	19,093
	High	62.1	187,643	167,530	20,114	11.27	11.87	0.608	33,064	22,212
Medium	Low	12.2	51,624	29,869	21,755	4.42	4.43	0.008	2,607,802	216,868
	Baseline	16.9	53,457	31,678	21,780	4.18	4.19	0.012	1,773,194	217,201
	High	65.1	68,151	46,069	22,082	1.71	1.77	0.068	326,108	221,154
Low	Low	22.6	37,674	9,117	28,556	0.47	0.47	0.003	9,620,490	1,665,934
	Baseline	27.1	37,964	9,400	28,563	0.44	0.44	0.004	7,289,446	1,666,891
	High	66.0	39,291	10,678	28,613	0.20	0.21	0.012	2,349,703	1,674,716

*Apart from varying net TOP rates, all other parameter values held at baseline levels (*Tables 9 *and* 10*)*

[a] *Net TOP rates are explained in chapter 5 (p. 49)*

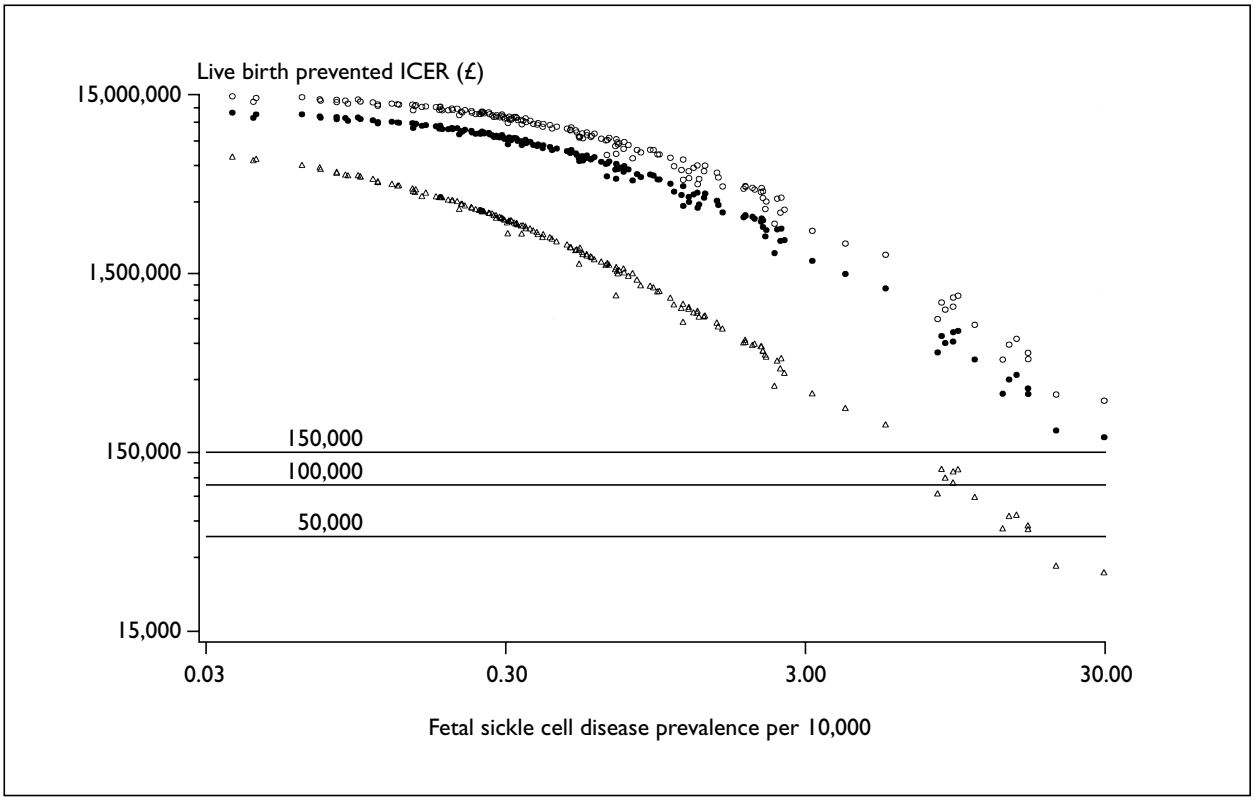

FIGURE 10 *Live birth prevented ICER against fetal sickle cell disease prevalence; each symbol represents one health district. Net TOP rate: high (△), baseline (●), low (○). Other assumptions at baseline including failure to screen rates: universal 0.5%, selective 5.5%*

districts would adopt a universal strategy at the £100,000 choice ICER value and 14 at the £150,000 level. A lower selective failure to screen rate would, of course, weaken the argument for universal screening, even with high TOP rates. The ICERs can be referred to estimates of the lifetime treatment costs for sickle cell disease (chapter 7; pp. 71–76).

Alternative antenatal screening strategies

Cost-effectiveness of lowering failure to screen rates

An alternative to a universal strategy is a selective strategy with a lower failure to screen rate. Under the assumption that reducing the failure to screen rate in a selective programme does not require

TABLE 66 *Incremental cost-effectiveness of moving from a higher to a lower failure to screen rate in selective programmes, for choice ICERs and affected live birth prevented ICERs*

Prevalence	ICER (£) for moving from a higher to a lower selective failure to screen rate	
	Choice ICER	Affected live birth prevented ICER
High	2,945	24,113
Medium	5,644	51,693
Low	6,533	50,456
*Apart from selective failure to screen rates, all other parameters held at baseline levels (*Tables 9 *and* 10*)*		

extra costs, it is possible to calculate the additional cost per additional choice offered upon changing from a selective strategy with a higher failure to screen rate to one with a lower failure to screen rate (*Table 66*). If these ICERs are compared with those for changing from selective to universal screening, it is evident that it is always more cost-effective to reduce the failure to screen rate in a selective programme than to switch to a universal strategy.

The reason for this is that, although costs increase if more ethnic minority women are screened, more women with affected fetuses are offered choice in the same proportion. However, there is presumably a lower limit to the selective failure to screen rate, but it will not be possible to determine what this limit might be until more accurate methods for auditing failure to screen rates are designed and implemented (chapter 12; p. 123).

Selective screening strategy based on ethnicity without regard to mean corpuscular haemoglobin

The selective antenatal screening strategy analysed in this report assumes that all women with a low MCH undergo Hb-pathy carrier testing (for ease of presentation, this strategy is referred to as standard selective strategy in the subsequent section). An alternative selective strategy would be to screen on the basis of ethnic status alone and regardless of the MCH result. Compared with this selective strategy based on ethnicity without regard to MCH, the standard selective strategy offers, in two ways, choice to more women with affected fetuses. First, it identifies all women with thalassaemia traits, whether they are of an ethnic minority group or not, failing only at the 0.5% presumed universal failure to screen rate. Secondly, among those with a low MCH, the standard strategy will identify all but 0.5% of sickle carriers, while the alternative strategy would miss 5.5%, under baseline assumptions. The advantage of carrier testing of those with a low MCH regardless of ethnic status is not so much that it offers choice to north European women with fetuses affected by thalassaemias; instead, the advantage is that it offers choice to those ethnic minority women with affected fetuses, whether with sickle cell disease or thalassaemias, who might have been missed by a selective programme based on ethnic status alone.

The precise cost-effectiveness of the standard selective strategy over the alternative strategy depends on the differential failure to screen rate, and also on the presumed prevalence of iron deficiency in the antenatal population (*Table 67*). On baseline assumptions of 10% iron deficiency, the alternative strategy costs between £3800 and £5200 less than the standard selective strategy per 10,000 pregnancies. Further analyses, not shown here, demonstrate that the choice ICER for changing from selective screening based on ethnicity without regard to MCH to the standard selective strategy is less than £100,000 in 53 districts. Further analyses, not shown here, demonstrate that this should be compared with 14 districts in which the universal versus standard selective ICERs were less than £100,000.

TABLE 67 *Incremental cost-effectiveness for choice offered of moving from a programme of selective screening based on ethnicity without regard to MCH to the standard selective strategy, which allows for haemoglobinopathy carrier testing of all women with low MCH, assuming different levels of iron deficiency*

Prevalence	Choice ICERs (£) for moving from selective screening based on ethnicity without regard to MCH to standard selective screening, under varying iron deficiency levels		
	Iron deficiency 5%	Iron deficiency 10%	Iron deficiency 30%
High	6,057	7,420	12,049
Medium	18,795	26,875	60,019
Low	127,834	200,188	489,559
*Apart from varying levels of iron deficiency, all other parameters held at baseline levels (*Tables 9 *and* 10*)*			

Although the absolute cost of the standard selective strategy compared with selective screening based on ethnicity without regard to MCH is relatively low, and the standard selective strategy is a cost-effective option in many districts, *Table 67* also indicates that ICERs are increasing from the high- to the low-prevalence district and from lower to higher levels of iron deficiency. The economic case for the standard selective strategy to be implemented everywhere is therefore not entirely compelling. However, a full analysis requires a model that includes alternative management of low MCH in north European women. This was beyond the remit of the present review.

No antenatal screening

Although a detailed consideration of a deliberate strategy of no screening is outside the scope of this report, some useful conclusions can be derived by comparing no screening to selective screening. In this context, 'no screening' is taken to mean no carrier testing, regardless of MCH. *Table 68* shows that the ICERs for changing from no screening to selective screening are lower than the ICERs for changing from a selective to a universal strategy. They are also substantially lower than the lowest assumed acceptable ICER values (chapter 8), suggesting a strong economic case for selective screening compared with a no screening policy.

However, this conclusion could be overturned if ethnic ascertainment and the provision of pretest information are included in the costs of selective screening. For every minute spent on ethnic ascertainment and pretest information, about £3800 per 10,000 antenatal population is added to the cost of screening (data not shown). This should be compared with the £9400 cost of the standard selective strategy in the low prevalence district, or £5000 for the selective screening strategy based on ethnicity without regard to MCH. The result is that, as more time is spent on ethnic ascertainment and pretest information, selective screening becomes increasingly less cost-effective in areas of lower prevalence (*Table 69*).

Screening first pregnancies only

If the results of maternal carrier testing in earlier pregnancies could be retained at low additional cost, then there would be a need to test only first pregnancies. While this would have no effect on the incremental cost-effectiveness of universal compared with selective screening, this strategy would make considerable savings (data not shown). In the high-prevalence district, savings of £30,000 per 10,000 pregnancies could be made in a universal programme, assuming that 45% of pregnancies are second pregnancies,[131,132] and £20,000 in a selective programme. In the low-prevalence district, savings of the order of £16,000 and £3500 would be available in universal and selective programmes respectively.

TABLE 68 *Incremental cost-effectiveness of moving from no screening to selective screening, based on choices offered and affected live births prevented*

Prevalence	ICER (£) for moving from no screening to selective screening	
	Choice ICER	Affected live birth prevented ICER
High	3,134	24,746
Medium	6,801	37,367
Low	17,083	59,108

*Model predictions under baseline assumptions (*Tables 9 *and* 10*)*

TABLE 69 *Number of districts (maximum 170) that would adopt a no screening policy in preference to either the standard selective strategy or selective screening based on ethnicity without regard to MCH, in relation to time spent for ethnic ascertainment and/or pretest information*

Choice ICER (£)	No. districts that would adopt no screening in preference to selective screening in relation to time spent each for ethnic ascertainment and/or pretest information					
	Standard selective screening			Selective screening based on ethnicity regardless of MCH		
	0 min	1 min	2 min	0 min	1 min	2 min
50,000	0	40	71	0	17	53
100,000	0	9	20	0	4	17
150,000	0	3	10	0	1	8

*Apart from changing costs for ethnic ascertainment/pretest information, all other parameters held at baseline levels (*Tables 9 *and* 10*)*

However, it has been proposed that a higher uptake of PND and TOP would occur if the mother's carrier status were known before pregnancy (chapter 2; p. 8). As noted earlier, higher PND rates result in substantially higher programme costs (*Table 65*), which would be likely to outweigh the savings available through knowing the mother's carrier status.

Summary of principal findings on antenatal screening

- Selective screening, compared with universal screening, offers choice over the outcome of pregnancy to fewer women with fetuses that are affected by sickle cell disease. The effectiveness of the two programmes in offering choice to women with fetuses affected by the thalassaemias is the same because selective screening is based on ethnicity and low MCH.
- Selective screening is less expensive in all districts, even if resources for up to 2 minutes for ethnic ascertainment are included in the costs.
- Adverse screening outcomes (PND-induced miscarriage, TOP of unaffected fetuses) are very rare in both strategies. Composite measures such as the number of adverse effects per choice offered (not shown separately) do not differ between strategies.
- Screening north European women is not cost-effective on the basis of the criteria used in this review, even under extreme assumptions of high frequency of sickle cell trait and inter-ethnic unions among them.
- A universal policy may be adopted on the presumption that it will result in higher coverage of screening among ethnic minority women than a selective policy.
- Lowering the failure to screen rate in a selective programme is always more cost-effective than changing to a universal policy.
- If the purpose of antenatal screening was the prevention of affected live births rather than reproductive choice, then universal screening would not be cost-effective in any district on the basis of criteria used in this review, given current TOP rates.
- Selective screening is cost-effective compared with no screening, on the basis of the analyses of choices offered and affected live births prevented.
- The inclusion of costs of ethnic ascertainment and/or pretest information slightly strengthens the case for universal compared with selective screening. In moderate- to lower-prevalence districts, the inclusion of these costs could prevent selective screening being cost-effective compared with no screening.

Neonatal screening results

As antenatal screening could have an impact on the relative cost-effectiveness of universal and selective neonatal policies, neonatal screening is not considered in isolation but in conjunction with a preceding selective or universal antenatal programme. As for antenatal screening, principal findings have been presented for three real, example districts with high, medium and low prevalences of ethnic minorities in the antenatal population, referred to as **high-**, **medium-** and **low-prevalence districts** (for characterisation see *Table 50*). In addition, summary analyses, including sensitivity analyses, are given for all districts in the UK.

Population available for neonatal screening

Of the live born infants surviving the perinatal period, a small number whose mothers accepted the offer of PND and who are therefore already definitively diagnosed, are not considered in the neonatal analysis.

From the population of neonates eligible for screening, a small group of infants with at least one parent found to be a carrier and neither known to be a non-carrier can be 'considered at risk' (*Table 70*). A much larger group, with at least one parent known to be a non-carrier, can be 'considered at no risk'. For a third group, whose mothers were not tested, the risk is not known. These include infants of mothers who were not tested owing to failure to screen or late booking, and of north European mothers in selective antenatal programmes.

Table 70 also shows that neither selective nor universal antenatal screening renders neonatal screening redundant at the PND uptake rates assumed here. The need for some form of neonatal screening would remain unless late booking was all but eliminated and the uptake of PND was near 100%.

Predicted frequency of the main screening outcomes and costs of universal and selective neonatal strategies

Table 71 shows how the effects and costs of universal and selective neonatal strategies depend on the antenatal screening option, and on the fetal prevalence of sickle cell disease in the high-, medium- and low-prevalence districts. The predicted number of infants affected with sickle cell disease who are diagnosed late because they have been missed by a combined antenatal/

TABLE 70 *Definition of population qualifying for neonatal screening per 10,000 antenatal population, in the high-prevalence district*

Antenatal programme	No. neonates per 10,000 antenatal population					Total
	Excluded from analysis of neonatal screening		Included in analysis of neonatal screening			
	TOP, other pregnancy loss, perinatal death	Alive, accepted PND	Considered at risk	Considered at no risk	Risk not known	
Universal						
Affected						
SS, Sβ, SD	2.466	0.725	17.212	0.092	1.710	22.206
SC	0.785	0.229	5.964	0.032	0.539	7.547
ββ, Eβ	0.750	0.005	0.315	0.006	0.075	1.151
$\alpha^0\alpha^0$	0.078	0.000	0.000	0.000	0.000	0.078
Unaffected	139.925	13.654	242.704	9,016.997	555.737	9,969.018
Selective						
Affected						
SS, Sβ, SD	2.397	0.702	16.646	0.089	2.372	22.206
SC	0.761	0.221	5.759	0.030	0.776	7.547
ββ, Eβ	0.749	0.005	0.314	0.006	0.076	1.151
$\alpha^0\alpha^0$	0.078	0.000	0.000	0.000	0.003	0.078
Unaffected	139.919	13.218	233.351	4,621.849	4,960.662	9,969.018

*Model predictions under baseline assumptions (*Tables 9–11*)*

TABLE 71 *Predicted main neonatal screening outcomes and costs per 10,000 antenatal population in high-, medium- and low-prevalence districts*

Pre-valence	Fetal SCD pre-valence 10^{-4}	Antenatal/ neonatal programme	SCD diagnosed antenatally	Newborns tested			SCD diagnosed late	Neonatal screening costs (£)				Combined antenatal and neonatal costs (£)
				Total	Carrier	SCD		Laboratory	Counselling		Total	
									SCD	Carrier		
High	29.75	Universal/selective	3.84	4,517	539	24.11	1.430	10,801	639	82	11,523	115,678
		Universal/universal		9,822	576	25.47	0.077	22,133	675	87	22,896	127,051
		Selective/selective	3.72	4,517	539	24.23	1.439	10,803	642	96	11,542	98,330
		Selective/universal		9,822	577	25.59	0.077	22,135	679	108	22,921	109,709
Medium	3.13	Universal/selective	0.48	2,610	102	2.47	0.148	5,769	66	15	5,848	59,305
		Universal/universal		9,836	118	2.61	0.008	21,123	70	17	21,210	74,667
		Selective/selective	0.46	2,610	102	2.48	0.151	5,768	67	17	5,851	37,529
		Selective/universal		9,840	118	2.62	0.008	21,123	71	27	21,221	52,899
Low	0.41	Universal/selective	0.08	324	12	0.31	0.021	714	9	2	724	38,688
		Universal/universal		9,840	26	0.33	0.001	20,918	10	4	20,931	58,895
		Selective/selective	0.07	324	12	0.31	0.024	714	9	2	725	10,125
		Selective/universal		9,840	26	0.34	0.001	20,918	10	14	20,941	30,341

*Model predictions under baseline assumptions (*Tables 9–11*)*

neonatal screening programme do not differ much according to a universal or selective antenatal policy, but are mainly determined by the neonatal component of the screening programme. As expected, the numbers are lower with universal than selective neonatal strategies, but overall figures in both programmes are small, even in the high-prevalence district (0.077 per 10,000 and 1.4 per 10,000 antenatal population respectively). The number of sickle carriers identified through neonatal screening is only marginally higher in a universal compared with a selective programme.

The laboratory screening tests form the major cost component of neonatal screening. Costs occasioned by post-test counselling for infants presumed to have sickle cell disease and counselling for sickle carrier infants contribute only a small additional amount. A universal neonatal programme costs between about £21,000 and £23,000 per 10,000 antenatal population. The cost of a selective programme decreases according to the proportion of ethnic minority women in the antenatal population. It is about £12,000 in the high-prevalence district and only £700 in the low-prevalence district.

Incremental cost-effectiveness ratios for late diagnosis of sickle cell disease prevented

The ICER for late diagnosis of sickle cell disease prevented (late diagnosis prevented ICER) can be constructed by taking the ratio of the difference in neonatal screening costs to the difference in the number of newborns affected with sickle cell disease who have been missed by screening and are thus diagnosed late (*Table 72*).

Table 72 shows the ICERs in the high-prevalence district to be more than 100 times lower than in the low-prevalence district, and dominated by the number of newborns with sickle cell disease diagnosed late rather than by programme costs. The number of cases of late-diagnosed sickle cell disease prevented through universal screening increases with prevalence. The cost difference between the universal and selective strategies, however, decreases as prevalence increases; hence the more favourable ICER in higher prevalence districts. The influence of the preceding antenatal programme on late diagnosis prevented ICERs is minimal in the high-prevalence district but increases in the low-prevalence district.

Epidemiological and operational factors influencing the incremental cost-effectiveness of selective versus universal neonatal screening

The change in ICERs from high- to low-prevalence districts shows the same pattern that was evident in the analysis of universal versus selective ante-natal screening, and is the result of the same interaction of epidemiological and operational factors. The comparative advantage of universal neonatal screening increases as the difference between universal and selective strategies in their presumed coverage rates increases. This is demonstrated in *Table 73,* which shows late diagnosis prevented ICERs in high-, medium- and low-prevalence districts under different selective failure to screen rates. For a given difference in coverage between the two programmes, the number of newborns with late diagnosed sickle cell disease increases with the proportion of the population in the higher risk, non-north European, groups and with the prevalence of sickle cell trait among them (results not shown).

In parallel with findings from the antenatal section, the neonatal screening of infants born to north European mothers, even under extreme assumptions of high fetal sickle cell disease prevalence, is not cost-effective. It can be seen from the ICERs in the low-prevalence district (*Table 72*) and in the situation where universal and selective strategies have the same failure to screen rate (*Table 73*, column 1) that the extra costs of detecting

TABLE 72 *Predicted costs, numbers of newborns with sickle cell disease diagnosed late, and ICERs for late diagnosis of sickle cell disease prevented per 10,000 antenatal population in high-, medium- and low-prevalence districts*

Antenatal programme	Total neonatal programme costs (£)			No. newborns with SCD diagnosed late despite combined antenatal/ neonatal screening programme			Late diagnosis prevented ICER (£)
	Universal	Selective	Difference	Universal	Selective	Difference	
Antenatal universal							
High	22,896	11,523	11,373	0.077	1.430	1.354	8,401
Medium	21,210	5,848	15,362	0.008	0.148	0.140	109,487
Low	20,931	724	20,207	0.001	0.021	0.020	1,012,118
Antenatal selective							
High	22,921	11,542	11,379	0.077	1.439	1.362	8,355
Medium	21,221	5,851	15,370	0.008	0.151	0.143	107,250
Low	20,941	725	20,216	0.001	0.024	0.023	874,464

*Model predictions under baseline assumptions (*Tables 9–11*)*

TABLE 73 *Effect on ICERs for late diagnosis of sickle cell disease prevented of differential failure to screen rates between selective and universal programmes*

Prevalence	Late diagnosis prevented ICER (£)			
	Selective failure to screen rates			
	0.2%	1.5%	3.0%	5.5%
High	3,846,829	32,520	15,399	8,355
Medium	3,846,829	398,384	196,674	107,250
Low	3,846,829	2,101,262	1,377,960	874,464

*Apart from varying failure to screen rates in selective programmes, all other parameters held at baseline level, including neonatal universal failure to screen rate 0.2% (*Tables 9–11*)*

Preceding antenatal programme assumed to be selective with same failure to screen rates as neonatal programme

additional cases of sickle cell disease in these infants through universal screening on baseline assumptions are extremely high. ICERs based on assumptions of high sickle cell trait and inter-ethnic union rates in north Europeans are shown in *Table 74*. Findings resemble those from antenatal screening (p. 92).

Summary analysis of neonatal screening in all districts

This section introduces analyses that have been carried out on all districts in the UK.

Baseline results

Appendix 3 (*Table 88*) gives: the predicted fetal sickle cell disease prevalence in each district; the number of affected fetuses that would have been diagnosed antenatally; the main neonatal screening outcomes; total programme costs; and late diagnosis prevented ICERs under baseline assumptions.

Sensitivity analyses

Table 75 summarises the results of the neonatal sensitivity analysis. Presentation follows the same format as the antenatal sensitivity analysis (pp. 95–98), listing districts that would adopt a universal strategy based on three different acceptable late diagnosis prevented ICERs under varying parameter values. ICERs for neonatal screening are only marginally influenced by whether a universal or a selective antenatal strategy is assumed (*Table 72*). Neonatal policy choice remains unchanged in virtually all districts under all assumptions tested, irrespective of the preceding antenatal strategy, which is therefore not shown in the table.

Similar to the findings from the antenatal sensitivity analysis, the higher the acceptable late diagnosis prevented ICER for changing from a selective to a universal neonatal programme, the more districts

TABLE 74 *ICERs for late diagnosis of sickle cell disease prevented, in relation to sickle cell trait frequency and inter-ethnic union rates in north European women*

Prevalence	Late diagnosis prevented ICERs (£)			
	Sickle cell trait frequency in north Europeans			
	0.05%	0.25%	0.05%	0.25%
	Inter-ethnic union rates in north Europeans			
	1.11%	1.11%	5.55%	5.55%
High	8,355	8,092	8,346	7,978
Medium	107,250	75,642	102,487	65,176
Low	874,464	200,748	621,906	139,513

*Apart from varying sickle cell trait frequency and inter-ethnic union rates among north Europeans, parameters held at baseline levels, including neonatal selective failure to screen rates 5.5%, neonatal universal failure to screen rate 0.2% (*Tables 9–11*)*

Preceding antenatal programme assumed to be selective with 5.5% failure to screen rate

TABLE 75 *Neonatal screening sensitivity analysis: districts (numbered) adopting universal strategy based on late diagnosis of sickle cell disease prevented ICER criteria*

Parameter values	Acceptable late diagnosis prevented ICERs (£) to change from selective to universal strategy under different selective failure to screen rates								
	£10,000			£20,000			£50,000		
	5.5%	3.0%	1.5%	5.5%	3.0%	1.5%	5.5%	3.0%	1.5%
Baseline[a]	1, 2	–	–	1–7	1, 2	–	1–14	1–8	1, 2
North European inter-ethnic union = 5.55% (baseline = 1.11%); sickle trait frequency = 0.25% (baseline = 0.05%)	1, 2	–	–	1–7	1, 2	–	1–15	1–14	1–4, 7
Hb-pathy carrier frequency x 1.25 in ethnic minorities; % black Africans in antenatal population x 1.3 (compared with baseline)	1–4, 6, 7	1, 2	–	1–14	1–7	1, 2	1–15	1–14	1–7
Iron deficiency = 30% (baseline =10%)	1, 2	–	–	1–7	1, 2	–	1–14	1–8	1, 2
Iron deficiency = 5% (baseline = 10%)	1, 2	–	–	1–7	1, 2	–	1–14	1–8	1, 2
High net TOP rate[b]	–	–	–	–	–	–	1–4, 7	1–2	–
Low net TOP rate[b]	1, 2	–	–	1–7	1, 2	–	1–14	1–8	1, 2
Universal failure to screen rate = 5% (baseline = 0.2%)	1, 2	–	–	1–7	1, 2	–	1–14	1–8	1, 2
Too late for screening ÷ 2 (compared with baseline)	1, 2	–	–	1–7	1, 2	–	1–14	1–8	1, 2
Non-paternity rate = 1.5% (baseline = 0.5%)	1, 2	–	–	1–7	1, 2	–	1–14	1–8	1, 2
Counselling costs x 2 (compared with baseline)	1, 2	–	–	1–7	1, 2	–	1–14	1–8	1, 2
Counselling costs ÷ 2 (compared with baseline)	1, 2	–	–	1–7	1, 2	–	1–14	1–8	1, 2
Laboratory costs x 1.5 (compared with baseline)	–	–	–	1, 2	–	–	1–8, 11, 14	1–4, 7	1
Laboratory costs ÷ 1.5 (compared with baseline)	1, 2	–	–	1–8, 14	1–3	–	1–15	1–14	1–4, 7
Time for ethnic ascertainment 1 min; time for pretest information 1 min[c]	1, 2, 7	2	–	1–8, 14	1, 2, 7	2	1–14	1–8, 11, 12, 14	1–4, 7
Time for ethnic ascertainment 2 min; time for pretest information 2 min	1–4, 6, 7, 14	1–2, 7, 14	1, 2, 7	1–8, 11, 12, 14	1–4, 6, 7, 14	1, 2, 7, 14	1–14	1–8, 10–14	1–8, 14
'Best plausible case for universal screening'[d]	1–7	1, 2	–	1–14	1–8	1, 2	1–17, 22	1–15	1–14

*[a] Baseline parameter values (*Tables 9–11*), apart from varying selective failure to screen rates; [b] High and low net TOP rates are explained in chapter 5 (p. 49); [c] 1 min midwifery time = £0.39; [d] 'Best plausible case for universal screening' comprises the following parameter settings (compared with baseline values): inter-ethnic union rates among north Europeans x 3.5; sickle trait frequency in north Europeans x 1.15; carrier frequency in ethnic minorities ÷ 1.15; % black Africans in the antenatal population x 1.2; laboratory costs ÷ 1.5; all other values remain at baseline*

Districts are numbered: 1, South East London; 2, East London and City; 3, New River; 4, Camden and Islington; 5, Wandsworth; 6, Kensington, Chelsea and Westminster; 7, Brent and Harrow; 8, Redbridge and Waltham Forest; 9, Greenwich; 10, Croydon; 11, Central Manchester; 12, Ealing, Hammersmith and Hounslow; 13, Barnet; 14, West Birmingham; 15, Merton and Sutton; 16, Wolverhampton; 17, South Birmingham; 18, South Bedfordshire; 19, Barking and Havering; 20, Sandwell; 21, North Manchester; 22, East Birmingham; 23, South Manchester; 24, Hillingdon; 25, North Birmingham; 26, Kingston and Richmond; 27, Liverpool; 28, Bexley; 29, Bromley; 30, Nottingham; 31, Sheffield; 32, South Glamorgan; 33, North Bedfordshire; all other districts would screen selectively under all assumptions listed

would adopt universal screening. In addition, increasing selective failure to screen rates consistently makes universal screening more cost-effective. For example, under baseline assumptions and an acceptable ICER of £20,000, universal screening would be adopted by seven districts if the selective failure to screen rate is as high as 5.5%, but by only two districts if the rate was lowered to 3%, and by none if a 1.5% rate could be achieved. Other parameters whose changes over a plausible range of values (*Table 11*) influence policy decisions are described in *Table 75*, together with a list of parameters that have no significant influence. Among the factors that have no effect or negligible effects are: proportion of women too late for antenatal screening; prevalence of iron deficiency in the antenatal population; non-paternity rate; counselling costs; and overall decreased coverage of neonatal screening.

The latter was assessed by comparing a universal programme having a 5% failure to screen rate (baseline assumption 0.2%) with selective programmes that failed to screen 10.3%, 7.8% and 6.3%, in order to preserve the same selective-to-universal differential. This generated almost identical ICERs as the baseline scenario. Among the factors that had a moderate effect on local strategy selection were those relating to epidemiological factors controlling estimated fetal sickle cell disease prevalence, as well as laboratory costs.

Neonatal policy choice is sensitive to changes in the net TOP rate antenatally because higher PND rates, with or without changes in the uptake of TOP, mean that there are fewer affected fetuses in the population that are eligible for neonatal screening. The high net TOP rate assumes a minimum PND rate of 80%, compared with the baseline 13–15% in black women. The high rate is predicted to weaken significantly the case for universal neonatal screening, unless a maximum ICER of £50,000 per additional late diagnosis prevented is employed and the selective failure to screen rate is set to 5.5%.

As was the case for antenatal screening, the inclusion of additional costs for time spent providing pretest information and ethnic ascertainment tended to strengthen the case for universal screening. However, even under extreme assumptions (2 minutes for ethnic ascertainment), the screening costs of a selective programme were never higher than those of a universal programme (*Table 76*). Universal screening would not therefore become the dominant strategy on grounds of costs and benefits.

TABLE 76 *Costs of universal and selective neonatal screening programmes depending on time spent on ethnic ascertainment and pretest information*

Prevalence	Neonatal programme	Neonatal screening costs (£)		
		Time for ethnic ascertainment and pretest information each		
		0 min	1 min	2 min
High	Universal	22,921	24,857	26,793
	Selective	11,542	17,244	22,947
Medium	Universal	21,221	23,778	26,334
	Selective	5,851	10,772	15,693
Low	Universal	20,941	24,242	27,543
	Selective	725	4,704	8,683

*Apart from varying screening costs, all other parameters held at baseline levels (*Tables 9–11*)*

Preceding antenatal programme assumed to be selective

Neonatal screening costs very similar when antenatal programme assumed to be universal

1 min midwifery time = £0.39

A best plausible case for neonatal screening was constructed in a similar fashion as for the antenatal sensitivity analysis by setting epidemiological parameters to values that favour universal screening, but not at the extremes of their ranges, and by assuming laboratory costs at 67% of baseline. The effect of this, assuming a £20,000 acceptable ICER and a 5.5% selective failure to screen rate, is to increase the number of districts that would adopt a universal strategy from seven to 14.

Subsidiary analyses of neonatal screening

Alternative neonatal screening strategies

Targeted neonatal screening

An examination of the population eligible for neonatal screening suggests that, if information on the results of the antenatal programme were available to those responsible for requesting neonatal screening, then a large number of infants would no longer require to be tested. In particular, there would be no need to test infants born to women who are found to be non-carriers, or those born to carrier mothers with non-carrier partners, as such infants would fall into the 'considered at no risk' group (*Table 70*). The neonatal screening strategy

based on this approach has been called targeted screening.

Among the disadvantages of the targeted approach are that the group 'considered at no risk' will include a very small proportion of infants with sickle cell disease. These can arise from false-negative maternal carrier results, false-negative couple assessment, and cases of non-paternity where the true father is a carrier and the male partner from whom the sample is collected is not.

An analysis of the costs of a targeted programme, and the number of infants affected with sickle cell disease who would be diagnosed late, revealed the following main results. First, targeted screening costs a maximum of £2400 per 10,000 antenatal population, and was under £1000 in 157 of the 170 districts. The cost difference between selective and targeted screening was less than £2000 per 10,000 in most districts and less than £5000 per 10,000 in 150. A second finding was that, under most circumstances, it would not be cost-effective to adopt selective screening in preference to targeted screening, because the ICER of moving from a targeted to a universal strategy would be less than the ICER of moving from a targeted to a selective strategy. Selective neonatal screening is thus subject to extended dominance.[361] However, although targeted screening is less expensive, the cost difference is very small and the dominance finding may be of little more than technical interest, except perhaps in the 20 districts where the cost difference exceeds £5000 per 10,000 antenatal population.

In principle, therefore, targeted screening is a cost-effective alternative to selective screening based on *de novo* selection of eligible infants postnatally. Additional analyses suggest that there is little loss of effectiveness over the range of assumptions about false-negative maternal carrier results and non-paternity rates.

No neonatal screening

A comparison of selective and targeted screening versus no neonatal screening produces ICERs based on additional costs of preventing additional late diagnoses of sickle cell disease, which are much lower than the lowest assumed acceptable ICER values (chapter 8), suggesting a strong economic case against no screening (*Table 77*).

However, as was the case for antenatal screening, the inclusion of costs for ethnic ascertainment and the provision of pretest information leads to a different conclusion (*Table 78*). Even 1 minute spent individually on ethnic ascertainment and pretest information would result in

TABLE 77 *Incremental cost-effectiveness of moving from no neonatal screening to a selective and targeted strategy, based on late diagnoses of sickle cell disease prevented*

Prevalence	Late diagnosis prevented ICER (£)	
	Selective neonatal screening	Targeted neonatal screening
High	476	107
Medium	2,354	319
Low	2,274	324

*Model predictions under baseline assumptions (*Tables 9–11*)*

Preceding antenatal programme assumed to be selective

TABLE 78 *Number of districts (maximum 170) that would adopt a no screening policy in preference to either selective or targeted neonatal screening, in relation to time spent for ethnic ascertainment, pretest information, and access to parental antenatal carrier results (for targeted screening only)*

Late diagnosis prevented ICER (£)	No. districts that would adopt no screening in preference to selective or targeted screening in relation to time spent each for ethnic ascertainment, pretest information, and/or access to parental antenatal carrier results (targeted screening only)					
	Selective screening			Targeted screening		
	0 min	1 min	2 min	0 min	1 min	2 min
10,000	2	111	132	0	119	137
20,000	0	62	102	0	84	118
50,000	0	16	41	0	33	78

*Apart from changing costs for ethnic ascertainment, pretest information, access to parental antenatal carrier results, all other parameters held at baseline levels (*Tables 9–11*)*

Preceding antenatal programme assumed selective

the adoption of a no screening policy in 62 districts in preference to selective screening, given a £20,000 acceptable ICER for the prevention of late sickle cell disease diagnoses, and assuming a selective antenatal strategy. In the case of targeted screening, 1 minute spent individually on ethnic ascertainment, pretest information and access to parental antenatal carrier results, would lead to no screening in 84 districts, given the same criteria.

It is important to note that, although a high PND rate would jeopardise the cost-effectiveness of universal screening, it does not affect the argument for selective screening compared with no screening. At the high net TOP rate, 150 districts would adopt selective screening in preference to no screening at the £10,000 ICER criterion, 168 at the £20,000 criterion, and all 170 at £50,000 (data not shown).

Cost-effectiveness of lowering failure to screen rates

Similar to findings from the antenatal screening analysis, it is always more cost-effective to reduce neonatal selective failure to screen rates than to switch to a universal policy, assuming that no extra costs are incurred when selective failure to screen rates are lowered. The relevant incremental cost-effectiveness ratios are precisely the same as those shown in *Table 77* comparing selective screening with a no screening policy. This is because, for any given ethnic composition of the antenatal population, both the costs of a neonatal selective programme and the numbers of late sickle cell disease diagnoses prevented are proportional to the number of infants tested.

Summary of principal findings on neonatal screening

- Screening neonates of north European women is not cost-effective, even under extreme assumptions of high sickle trait frequency and inter-ethnic unions among them.
- A universal strategy may be adopted in preference to a selective strategy on the presumption that it will result in higher coverage among neonates born to ethnic minority women.
- Selective screening is highly cost-effective compared with no screening, on the basis of costs per late diagnosis of sickle cell disease prevented.
- Lowering the failure to screen rate in a selective programme is always more cost-effective than changing to a universal policy.
- Antenatal screening, even if universal, is unlikely to render neonatal screening redundant, unless late antenatal booking is all but eliminated and uptake of PND is near 100%. High PND rates would seriously weaken the case for universal screening, but not the need for selective screening.
- Costs associated with sickle cell carriers identified neonatally are low in relation to total programme costs, and do not affect the comparative cost-effectiveness of universal and selective strategies.
- The inclusion of costs for ethnic ascertainment and pretest information would strengthen the case for universal compared with selective screening, but would considerably weaken the case for selective compared with no screening.
- Targeted screening is a cost-effective alternative to selective screening.

Chapter 10

Discussion

This section reviews the methods used in this review and the results obtained, in the context of previous work on Hb-pathies and antenatal and neonatal screening for other conditions.

The strategy options analysed

The choice of policy options included in the model reflected to some extent those that are currently recommended and most widely practised, but alternative strategies that could be seen as logical extensions or simplifications were also considered. The primary question on which the report focuses is a comparison of universal screening with selective screening based on ethnicity. This was addressed by incorporating maternal ethnic group, partner's ethnic group, ethnic group-specific Hb-pathy carrier frequency, and inter-ethnic union rates into a model of the antenatal and fetal population. A screening model, designed in cooperation with clinicians to ensure face validity, and which reflected the main steps of the screening process, was then applied to this population.

In the case of antenatal screening, the primary analysis compared universal screening with the selective strategy, which is standard in the UK. This comprises selection based on ethnicity, but with carrier testing for all women with a low MCH regardless of ethnicity. Founded on preliminary analyses, it was assumed throughout that carrier testing would be based on HPLC because this concomitantly quantifies HbA_2 and HbF, and gave a lower predicted cost per woman tested. A simpler selective strategy of carrier testing based only on ethnicity regardless of MCH result was also considered. The advantage of the standard strategy is generally understood to be that it identifies north European thalassaemia carriers. These would, however, be exceedingly rare on the carrier frequency assumptions used here. The real advantage of the standard strategy would appear to be that it secures carrier testing for ethnic minority sickle and thalassaemia carriers with a low MCH who might have been missed in a selective programme based on ethnicity without regard to low MCH. A formal comparison of the two selective policies, however, would require a detailed analysis of the alternative management of iron deficiency in pregnancy; this was judged to be outside the scope of this review.

In the case of neonatal screening, the primary analysis was restricted to universal compared with *de-novo* selection based on maternal ethnic status. A subsidiary analysis of targeted screening was also carried out. It was assumed that all three programmes would be operated on neonatal heel prick samples. Cord blood testing was not considered, owing to the higher failure to screen rate and organisational costs. This assessment accords with the earlier recommendations of the SMAC report.[5]

Subsidiary analyses were included that compared selective screening with no screening in both antenatal and neonatal contexts. It is doubtful whether any maternity unit would want to defend an explicit no screening policy; many would regard such a policy as unacceptable. In these circumstances, a comparison of selective screening with no screening reveals a minimum benchmark for economic criteria for screening compared with no screening. By the same token, independently derived economic criteria can be used to confirm or refute the economic basis for a practice that is already widespread: selective screening in preference to no screening.

In the case of neonatal screening, selective screening based on cord blood has been practised in some areas, but a no screening policy is probably the norm in lower-prevalence areas.

Model parameter values

Where possible, probability data used in the model were derived from published evidence. However, most of the information required was particular to certain settings and thus of questionable generalisability. The validity of some data was difficult to assess because they were calculated rather than observed and based on several assumptions. Small numbers limited the reliability of a few estimates. In some cases, the dearth of information made it necessary to use judgement and 'best guesses' to adjust data for use in the model. Such probability estimates carry the risk of bias. Policy decisions,

however, cannot be avoided because of lack of data. This imperfect approach, because it is explicit and evaluated by sensitivity analysis, does not invalidate the technique of decision analysis, but rather the process of exposing uncertainties is one reason for its use.

For one particular model parameter, the failure to screen rate, observed rates appeared to be less relevant than the failure to screen rates that might be achieved if an effort was made to reduce them. The range of values explored, between 1.5% and 5.5%, reflected our subjective assessment of the lowest failure rate that could be reasonably expected and the highest failure rate that could be countenanced. This is not to say that some units may be failing to achieve this minimum standard. A further assumption throughout the report has been that failure to screen rates can be reduced by improved training and organisational factors, without additional cost or staff time implications.

The assumptions made regarding local ethnic composition have particular implications, not so much for the generalisability of the results as for the way they can be interpreted for the purpose of local policy recommendation. First, the district breakdown,[228] which formed a framework for this analysis, was based on health districts as they were in 1993. By 1998, the 170 districts that existed in Great Britain at that time had merged into 120. On the other hand, although the commissioning unit is the health authority, the unit within which the screening policy is implemented is the maternity hospital for antenatal testing and the community provider trust for neonatal testing. Therefore, although 1993 district boundaries are a convenient basis for the analysis of local needs because they correspond more closely with trust catchment populations than do the new districts, local planners would need to consider carefully how to make best use of the district results presented in this review. Secondly, many maternity and community trusts may have more recent ethnic composition data. This can be used in conjunction with *Table 49* to derive new local estimates of fetal sickle cell disease prevalence.

Screening outcomes studied

The screening outcomes were chosen to span the whole spectrum of measurable positive and negative screening consequences. Intangible effects such as reassurance, anxiety and stigmatisation were not included because of a lack of reliable measurement tools.[108–110] Classic decision analysis incorporates the quantification of outcomes in terms of utilities.[362,363] However, the assessment of patients' utilities, which is methodologically difficult and controversial,[248,364–368] was beyond the scope of this project. Because adverse screening outcomes in both strategies compared were minimal, this omission would be unlikely to change policy decisions substantially.

In the primary analysis of antenatal screening, the composite outcome measure of 'choice offered' to women with affected fetuses was defined as the main outcome measure, reflecting the principal objective of the screening programme. This approach takes account of the ethical debate about antenatal screening.[100,222,369,370] A subsidiary analysis using the commonly used outcome measure 'affected live births prevented', was also included.

One criticism of the 'choice offered' analysis is that it accords equal weight to the choice offered to a couple with an affected fetus who wish for PND and then a TOP, and the choice offered to a carrier couple who do not wish to undergo PND. Furthermore, it could be argued that it would be hard to justify screening on the basis of choice in the extreme situation where no couple wanted even a PND.

Although this objection has considerable force, it may not be possible to address it without a full utility analysis. As noted above, this would be methodologically difficult. The model parameters used here assume that only 13–15% of black carrier women with carrier partners wish for PND. It is not known whether the data on which these estimates were based are reliable, or whether they are a reflection of the way in which maternal carriers and carrier couples are counselled and the timing of screening and diagnosis. These are both areas where further research is required before more sophisticated utility modelling is attempted.

For neonatal screening, the model was structured to generate a predicted the number of late diagnoses of sickle cell disease that would be prevented by screening. This is a direct measure of what neonatal screening aims to accomplish.

Cost parameters and the use of incremental cost-effectiveness ratios

The costs of screening not only fall on the health sector but also on other sectors of society, such as social services, the voluntary organisations, patients

and their carers. In this study, only NHS costs were included because decisions about the provision of antenatal and neonatal screening are largely taken by commissioning agencies with respect to a health service budget. The adoption of a societal perspective, although theoretically the superior approach,[246] was not judged to be justified in terms of the additional research time required.

Potential savings resulting from the termination of affected fetuses have not been included in the model because the objective of the programme is reproductive choice and explicitly **not** the prevention of affected births, unless unwanted by the parents. This approach takes account of contemporary theoretical work[109,250,253,321,371] and is in agreement with a number of recent economic evaluations of other antenatal screening programmes.[115,254,318] Lifetime treatment costs have, however, been considered (see chapter 7), and are seen as an adjunct to the decision model but not an integral part of it.

Cost data were assembled by a health economist by adhering to established economic principles.[246] However, the comparability of cost data from different sources is notoriously difficult; this uncertainty was explored in a sensitivity analysis.

An incremental approach was adopted, whereby the difference in costs and the effectiveness between the options were estimated (i.e. ICER). The common use of average cost-effectiveness ratios, whereby the total cost of each programme is divided by the total effectiveness, has been avoided. Average ratios can lead to inefficient decisions because costs and effectiveness of already existing policies are ignored.[246,259,361]

Incremental cost-effectiveness ratios acceptable to policy makers

ICERs were computed for all districts in the UK (appendix 3; *Tables 87* and *88*) to inform policy makers about the costs and effects of moving from a selective to a universal policy. However, to facilitate the formation of specific recommendations, the magnitude of ICER values likely to be acceptable to UK policy makers had to be estimated. Criteria about what constitutes an acceptable value for antenatal and neonatal Hb-pathy screening are empirical and depend on competing healthcare priorities and the political context. For antenatal screening, a search for reports of Hb-pathy screening programmes to compare ICER values was undertaken, but it was unsuccessful. Therefore, studies describing other antenatal screening programmes with outcomes comparable with 'choice offered' were reviewed. The authors of all these studies concluded by recommending the adoption of antenatal screening for the disorder of interest. Although authors are not policy makers and outcomes were not identical, acceptance of the costs per outcome was used as the best available indicator of the potential range of acceptable values for reproductive choice. To gauge societal values that are attached to the objectives of antenatal Hb-pathy screening, examples of litigation charges for deficient screening have been reviewed. However, litigation damages are based on the individual circumstances of each case. This might explain the substantial difference in the damages paid in the two published cases. Little is known about the views of patients or the public concerning the worth of reproductive choice compared with other health-related benefits because methods of obtaining meaningful answers are experimental.[372–374] To take account of the considerable uncertainty about the acceptable values for choice ICERs, a range of values (£50,000, £100,000, £150,0000) was employed, spanning values found in the literature on other antenatal screening programmes.

For the subsidiary analysis of antenatal screening based on the prevention of affected live births rather that reproductive choice, ICERs can be referred to estimates of the lifetime treatment costs associated with sickle cell disease. These were approximately £150,000 undiscounted and £50,000 discounted.

For the neonatal analysis, a range of plausible values attaching to the prevention of the late diagnosis of sickle cell disease was derived from several considerations. First, we estimated that earlier diagnosis resulted in approximately 0.5 additional life years as a result of the estimated 1.25 early deaths prevented for every 100 late diagnoses prevented (chapter 8; p. 80). This can be referred to previous work[258] on benchmark costs per additional life year gained, which were based on a very wide range of different interventions. A second basis for comparison was the cost per case discovered in other neonatal screening programmes. The resulting range (£10,000, £20,000, £50,000) must, like the maximum acceptable ICER values employed for the antenatal analysis, be considered as tentative.

Sensitivity analysis

A wide range of one-way sensitivity analyses were carried out at each failure to screen rate. This allowed the determination of those parameters that are the most influential on policy decisions and an assessment of the degree of uncertainty that is tolerable before calling the policy decision into question.[256,375] The presumed fetal prevalence of sickle cell disease, derived from carrier frequency, ethnic composition and inter-ethnic union rates, is the major determinant of the incremental cost-effectiveness of moving from selective to universal screening. In spite of the adjustment of local ethnic composition data (chapter 9; pp. 83–84), intended to harmonise model predictions with other sources of data and to recognise the fact of recent immigration from Africa, there is uncertainty about the national prevalence of fetal sickle cell disease. However, even if the adjustment is correct at a national level, the implicit assumption that carrier frequencies within the 12 ethnic groups are homogeneous, and that changes since the 1991 Census have affected local ethnic composition in an even way, is not plausible at local level.

A multifactorial sensitivity analysis was therefore constructed to explore the combined effect of all parameters contributing to expected fetal sickle cell disease prevalence. These parameters, the proportion of black African women, carrier frequencies and inter-ethnic union rates, were all set to values that favoured universal screening, although not at the extremes of their range. Low laboratory costs were also assumed. The primary purpose of this analysis was to protect against the underestimation of local sickle cell disease prevalence and to produce a scenario that gave a 'best plausible case' for universal screening.

Model validity

Local empirical data about the number of affected fetuses observed were used to validate the predictions from the model and to adjust ethnic composition assumptions (chapter 9; pp. 83–84). However, they were extremely limited and mostly from the period 1990–1994, since when changes are likely to have occurred. In addition, concordance between model and PND register data should be interpreted as no more than a demonstration that the baseline assumptions in combination are compatible with the national data on the number of PNDs performed. No better formal validation was possible.

Principal findings

There is a widespread belief that universal screening should be carried out in areas of high prevalence and selective screening in areas of low prevalence. The formal incremental analysis reveals that this is not necessarily true. If the failure to screen rates of the strategies are the same, then the case for universal screening depends only on the cost-effectiveness of screening north Europeans, and therefore on the prevalence of sickle cell disease among them.

If, however, the failure to screen rate on universal testing is lower than on selective testing, then universal testing may be justified because it identifies more ethnic minority carriers. The mathematical relationships mean that the higher the prevalence of sickle cell disease among ethnic minorities, or the higher the proportion of ethnic minorities in the population, the more women with affected fetuses will be 'missed' by selective screening, and the narrower the difference in failure to screen rates has to be to justify continued use of a selective strategy.

These are very general results, which could be applied to the comparison of selective and universal screening for any condition. They show that universal screening is justified either by prevalence in the low-risk group or by differential failure to screen rates in the high-risk group, or by both factors combined. We were able to demonstrate that the prevalence of sickle cell disease in north Europeans could not, **by itself**, even under extreme assumptions, be enough to justify screening them, and that the economics of Hb-pathy screening were dominated by differential coverage. Failure to screen rates in a selective policy, ethnic composition and carrier frequencies were therefore the key factors.

Another general result was that the universal versus selective comparison was almost wholly insensitive to costs incurred after the initial screen. ICERs are thus very insensitive to post-test counselling, PND and neonatal carrier counselling costs. There was considerably more sensitivity, however, to costs of items up to and including the initial screen: laboratory costs and costs of pretest information, and ethnic ascertainment.

The inclusion of costs for ethnic ascertainment and for pretest information tended to strengthen the case for universal screening. However, because both costs are applied to the entire population, not only to those towards whom selective screening is

aimed, their inclusion seriously weakens the case for selective screening compared with no screening. The significance of this finding depends on the acceptability of the baseline assumption that the costs of ethnic ascertainment should be absorbed within the costs of general antenatal care, and that the resources required for information-giving could be minimised through the use of posters and leaflets.

The distribution of ethnic minorities within health districts in the UK is very uneven, with the majority living in the larger metropolitan areas. The fact that sickle cell disease requires both parents to be carriers produces a 'number squared' effect, so that the distribution of expected fetal sickle cell disease prevalence among districts is even more skewed. The baseline analyses locate the dividing line between selective and universal screening in the sparsely populated upper end of the fetal sickle cell disease prevalence continuum. As a result, quite large changes in ICER have surprisingly little effect on the number of districts that would adopt one policy or another.

There were two particularly clear and closely related findings. First, a deliberate policy not to screen was shown to be economically unsupportable in comparison with selective screening. This applied equally to antenatal and neonatal screening. A second finding, which is in a sense a corollary because changes in the numbers screened raise costs and benefits in proportion, was that it is always highly cost-effective to reduce the selective failure to screen rate. In fact, lowering the selective failure to screen rate is always more cost-effective than switching to a universal policy. These results follow, again, from the mathematical relationships: there is more benefit per person screened in screening a high-prevalence group than screening a low-prevalence group.

This review may help to dispel some of the concerns that have been expressed about the cost implications of carrier infants within a neonatal programme.[5,201] First, the absolute cost of carrier counselling was small in relation to the total programme costs. Secondly, the difference between universal and selective programmes in the numbers of newborn carriers is too small to have policy implications. A minimum protocol was assumed, but it is clear that the counselling costs could be multiplied several times without appreciable effect on either the ICERs for switching from selective to universal screening or the clear case for selective screening as opposed to no screening.

Another widely held belief is that neonatal screening would not be necessary where a well-run antenatal programme is in place. Our universal and selective strategies both assume that, unless fetal sickle cell disease has been diagnosed or ruled out, all surviving infants will require neonatal testing under a universal neonatal policy, and all those born to ethnic minority women under a selective policy. A sensitivity analysis in which PND uptake rates were increased from 13% to 15% to as much as 80% in black women showed that high PND rates would indeed strongly reduce the number of districts needing to adopt a universal strategy, but they would have no effect on the case for selective screening rather than no screening at all.

A subsidiary analysis suggested that, if information from antenatal screening was used to target those neonates who required screening, then an extremely cost-effective neonatal programme could be constructed because the testing of neonates born to women who are already shown to be non-carriers would be avoided. Targeted screening is an alternative to selective screening, but it needs robust information transfer protocols that would require development and piloting. Selective screening is already an inexpensive option.

Comparison with other studies

There have been no previous formal analyses of antenatal screening. The implications of the analysis presented here can, however, be compared with those of the SMAC report.[5] This recommended universal screening in districts where 15% or more of the antenatal population are at risk of sickle cell disease. This has generally been interpreted as the proportion who are black. There are nine such districts, given our local estimates of ethnic composition. This compares with the 14 districts that would adopt universal screening on the assumption of a £100,000 maximum ICER and a 5.5% failure to screen rate in the present analysis, and the seven that would adopt universal neonatal screening with a £10,000 ICER and a 5.5% failure to screen rate (*Tables 62* and *75*).

Previous studies of neonatal screening in the USA show average costs per case detected by universal testing ranging from £900 to £200,000 in different states.[243] This compares with a range of £900 in a high-prevalence district to £60,000 in a low-prevalence district, and over £200,000 in most parts of Scotland. The incremental

costs for changing from selective to universal programmes cannot be compared because the major articles[242–244] made different assumptions about failure to screen rates, ethnic group-specific sickle cell disease prevalence, and/or the definition of the ethnic groups towards which selective screening would be aimed. However, low screening cost, high sickle cell disease prevalence and high ethnic ascertainment costs were identified as the parameters favouring a universal strategy.

Chapter 11

Conclusions and policy implications

Scope of the review

The analysis is limited to the primary outcome criteria used in modelling: choices offered to women with affected fetuses, and the prevention of late diagnoses of infants with sickle cell disorder. Although the results suggest that adverse outcomes of pregnancy such as PND-induced miscarriage and termination of unaffected pregnancies are very rare, no attempt has been made to incorporate or take account of the psychological effects of screening.

Similarly, no attempt has been made to cover quality assurance issues such as audit of the management of neonatally ascertained carriers or infants with Hb-pathies, or the provision of information about screening. These issues have been regarded as outside the scope of the review because they have no direct bearing on whether screening should be universal or selective.

The need for explicit universal or selective screening policies

The analysis established that a deliberate policy of no antenatal screening or no neonatal screening would be hard to justify economically. In addition, there would be a need for neonatal screening irrespective of the quality or type of antenatal screening service. It is important that, in trusts that have a formal policy stating what type of screening strategy they are operating, staff should be aware of this policy and trained in the necessary procedures.

Laboratory methods for antenatal screening

Our algorithm for antenatal laboratory procedures incorporates the recommendations of the British Society of Haematology. However, there has been concern that these recommendations are not being followed in all districts, and there is some confusion about how they should be implemented. Guidelines endorsing a more precise algorithm for Hb-pathy screening would be helpful.

Sample collection and processing in neonatal screening

The review of neonatal screening options revealed that screening based on cord blood tended to have a poor coverage. The high failure to screen rate could possibly be mitigated by thorough follow-up in the community, but this might be organisationally difficult and require extra expense. Neonatal testing, whether universal, selective or targeted, could therefore usefully be based on the newborn Guthrie card (or other heel prick) samples routinely collected for neonatal metabolic screening.

The need for routine information systems to monitor failure to screen rates and other process variables is emphasised as a priority. In view of the complexity of this task, it might be an advantage to locate neonatal screening in the same laboratories that carry out screening for PKU and congenital hypothyroidism, if this avoids duplication of an administrative process. The NHS *Health Technology Assessment* reviews on screening for inborn errors of metabolism[306,376] also have implications for the size and number of neonatal screening laboratories.

Pretest information and ethnic ascertainment

The main analyses here have not counted time spent on pretest information or ethnic ascertainment as part of the screening programme. The comparison of selective screening with no screening showed that time spent on pretest information and ethnic ascertainment could raise the ICER to the point where even selective screening would no longer be economically justifiable. This points to a possible conflict between economic criteria and the principle of informed consent, which needs to be resolved by further research.

Geographical basis of decisions on local screening policy

In districts with substantial cross-boundary flows, maternity units and community provider

trusts cannot be expected to deliver different screening services to residents of different districts. Important factors for the local implementation of policy include the ethnic composition and estimated fetal sickle cell disease prevalence of the hospital's antenatal population, or, in the case of neonatal screening, of the community provider trust area. Where one maternity unit serves several districts, screening requires a consultative process involving the provider
and all commissioners concerned.

Implications for districts adopting a selective strategy

It was shown that the most cost-effective strategy is to minimise selective failure to screen rates. It is important that ethnic minority women and their infants are offered screening to the same high standard in all districts, irrespective of how low their expected fetal sickle cell disease prevalence is. It would not be equitable for higher failure to screen rates to be tolerated in districts with fewer ethnic minority women.

Equity issues in local decisions on selective or universal screening

Even if a standard maximum failure to screen rate is set and adhered to, the equity issue still remains. This is because in higher-prevalence areas ethnic minority women are offered a superior, universal, programme, while in lower-prevalence areas they are offered a lower-quality, selective programme that is more likely to fail them. Like the claim that screening should be of equal benefit to all,[26] this is a form of argument that can be made to point towards universal screening regardless of prevalence or cost.

Another way of recognising the issue is to employ economic criteria, but to bias them in favour of universal screening. For example, rather than use the baseline analysis of which districts would adopt a universal policy under stated ICER and selective failure to screen assumptions, the 'best-plausible case for universal screening' could be used (*Tables 62* and *75*). Whether this constitutes an excessive or an insufficient adjustment for equity issues is a matter of judgement. There appears to be no way of quantifying it within the present framework.

Implications for local decisions on universal or selective testing

The sensitivity analyses indicate that local strategy choice should depend primarily on local costs and on three key factors:

- the maximum acceptable ICER values accorded to choice offered antenatally and late sickle cell disease diagnoses prevented neonatally
- the failure to screen rate that can be achieved in a selective programme
- the presumed local prevalence of fetal sickle cell disease.

The majority of trusts probably do not yet have the means to assess failure to screen rates accurately. In the absence of data, the 5.5% figure would probably be the most appropriate to use. Local fetal prevalence of sickle cell disease could be based on the figures provided in appendix 3 (*Table 87*), bearing in mind boundary changes and the need for the appropriate definition of catchment populations (p. 117). Alternatively, if better local ethnic composition data are available, ethnic group-specific prevalences of fetal sickle cell disease can be used (*Tables 49* or *51*) to derive a district or unit estimate.

To illustrate the effect of failure to screen rate and ICER on policy decision, *Table 79* gives the optimal strategy under a range of economic and failure to screen rate criteria for the 33 districts with the highest prevalence, using the baseline local estimates of fetal sickle cell disease. Districts are accorded either S, indicating selective, U^+ indicating a strong basis for universal testing, or U indicating a reasonable case for universal testing. The U^+ category is derived from the baseline analysis, and the U category from the 'best plausible case' for universal screening. Districts with estimated sickle cell disease prevalence below 1.84 per 10,000 are not included in *Table 79*. Selective policies would be appropriate for them under all scenarios.

This presentation is a way of building in uncertainty, particularly in parameters affecting fetal sickle cell disease prevalence. It also suggests a possible means of giving recognition to equity issues (as just discussed) that cannot be quantified within the present framework.

Use of sickle cell disease prevalence thresholds

It is evident from *Tables 62, 75* and *79* that optimal strategy is strongly related to fetal

TABLE 79 *Antenatal and neonatal screening strategies that might be adopted under different maximum acceptable cost-effectiveness ratios and at specifed selective failure to screen rates*

District health authority (1993 boundaries)	Estimated fetal SCD prevalence per 10,000 antenatal	Antenatal screening: maximum ICERs for choices offered									Neonatal screening: maximum ICERs for late SCD diagnoses prevented								
		£50,000			£100,000			£150,000			£10,000			£20,000			£50,000		
		Selective failure to screen rates									Selective failure to screen rates								
		5.5%	3.0%	1.5%	5.5%	3.0%	1.5%	5.5%	3.0%	1.5%	5.5%	3.0%	1.5%	5.5%	3.0%	1.5%	5.5%	3.0%	1.5%
1. SE London	29.75	U+	U+	U	U+	U+	U+	U+	U+	U+	U+	U	S	U+	U+	U	U+	U+	U+
2. E London and City	20.54	U+	U+	U	U+	U+	U+	U+	U+	U+	U+	U	S	U+	U+	U	U+	U+	U+
3. New River District	16.52	U+	U	S	U+	U+	U	U+	U+	U	U	S	S	U+	U	S	U+	U+	U
4. Camden and Islington	16.49	U+	U	S	U+	U+	U	U+	U+	U	U	S	S	U+	U	S	U+	U+	U
5.Wandsworth	15.10	U+	U	S	U+	U+	U	U+	U+	U	U	S	S	U+	U	S	U+	U+	U
6. Kensington, Chelsea, Westminster	14.25	U+	U	S	U+	U+	U	U+	U+	U	U	S	S	U+	U	S	U+	U+	U
7. Brent and Harrow	13.56	U+	U	S	U+	U+	U	U+	U+	U	U	S	S	U+	U	S	U+	U+	U
8. Redbridge and Waltham Forest	10.92	U	U	S	U+	U	U	U+	U	U	S	S	S	U	U	S	U+	U+	U
9. Greenwich	9.59	U	S	S	U+	U	S	U+	U	U	S	S	S	U	S	S	U+	U	U
10. Croydon	9.24	U	S	S	U+	U	S	U+	U+	U	S	S	S	U	S	S	U+	U	U
11. Central Manchester	9.23	U	S	S	U+	U	S	U+	U+	U	S	S	S	U	S	S	U+	U	U
12. Ealing, Hammersmith, Hounslow	8.70	U	S	S	U+	U	S	U+	U	U	S	S	S	U	S	S	U+	U	U
13. Barnet	8.46	U	S	S	U+	U	S	U+	U+	U	S	S	S	U	S	S	U+	U	U
14.W Birmingham	8.20	U	U	S	U+	U	U	U+	U	U	S	S	S	U	S	S	U+	U	U
15. Merton and Sutton	5.50	S	S	S	U	U	S	U+	U	S	S	S	S	S	S	S	U	U	S
16.Wolverhampton	4.05	S	S	S	U	S	S	U	U	S	S	S	S	S	S	S	U	S	S

U+, universal screening on baseline assumptions; U, universal screening on 'best plausible case' assumptions; S, selective screening

continued

TABLE 79 contd *Antenatal and neonatal screening strategies that might be adopted under different maximum acceptable cost-effectiveness ratios and at specifed selective failure to screen rates*

District health authority (1993 boundaries)	Estimated fetal SCD prevalence per 10,000 antenatal population	Antenatal screening: maximum ICERs for choices offered									Neonatal screening: maximum ICERs for late SCD diagnoses prevented								
		£50,000			£100,000			£150,000			£10,000			£20,000			£50,000		
		Selective failure to screen rates									Selective failure to screen rates								
		5.5%	3.0%	1.5%	5.5%	3.0%	1.5%	5.5%	3.0%	1.5%	5.5%	3.0%	1.5%	5.5%	3.0%	1.5%	5.5%	3.0%	1.5%
17. S Birmingham	3.14	S	S	S	U	S	S	U	U	S	S	S	S	S	S	S	U	S	S
18. S Bedfordshire	2.53	S	S	S	S	S	S	U	S	S	S	S	S	S	S	S	S	S	S
19. Barking and Havering	2.47	S	S	S	S	S	S	U	S	S	S	S	S	S	S	S	S	S	S
20. Sandwell	2.45	S	S	S	S	S	S	U	S	S	S	S	S	S	S	S	S	S	S
21. N Manchester	2.40	S	S	S	S	S	S	U	S	S	S	S	S	S	S	S	S	S	S
22. E Birmingham	2.35	S	S	S	U	S	S	U	U	S	S	S	S	S	S	S	U	S	S
23. S Manchester	2.20	S	S	S	S	S	S	U	S	S	S	S	S	S	S	S	S	S	S
24. Hillingdon	2.18	S	S	S	S	S	S	U	S	S	S	S	S	S	S	S	S	S	S
25. N Birmingham	2.14	S	S	S	S	S	S	U	S	S	S	S	S	S	S	S	S	S	S
26. Kingston and Richmond	2.14	S	S	S	S	S	S	U	S	S	S	S	S	S	S	S	S	S	S
27. Liverpool	2.12	S	S	S	S	S	S	U	S	S	S	S	S	S	S	S	S	S	S
28. Bexley	2.11	S	S	S	S	S	S	U	S	S	S	S	S	S	S	S	S	S	S
29. Bromley	2.01	S	S	S	S	S	S	U	S	S	S	S	S	S	S	S	S	S	S
30. Nottingham	1.98	S	S	S	S	S	S	U	S	S	S	S	S	S	S	S	S	S	S
31. Sheffield	1.87	S	S	S	S	S	S	U	S	S	S	S	S	S	S	S	S	S	S
32. S Glamorgan	1.87	S	S	S	S	S	S	U	S	S	S	S	S	S	S	S	S	S	S
33. N Bedfordshire	1.84	S	S	S	S	S	S	U	S	S	S	S	S	S	S	S	S	S	S

U, universal screening on 'best plausible case' assumptions; S, selective screening

sickle cell disease prevalence, suggesting the possibility of a prevalence 'threshold' for each maximum acceptable ICER and failure to screen rate scenario, above which universal screening would be the preferred option. However, it is not possible in general to calculate a fixed threshold because the ICER depends not only on the sickle cell disease prevalence but also on the precise ethnic composition of each district. This is the cause of the isolated districts marked 'U'.

In spite of this, and in view of both the boundary issues (as mentioned earlier in this chapter) and the uncertainty in the true local prevalence (chapter 10; p. 114), the information in *Table 79* can usefully be translated into approximate thresholds. The thresholds in *Table 80* have been constructed by taking the threshold to be half way between the lowest universal district and the highest selective district. Where there is no single boundary in *Table 79,* an approximate average is given.

These threshold values could be used to assist in policy decisions, should alternative local prevalence estimates be available. Approximate thresholds can also be found for alternative maximum acceptable ICERs, and/or selective failure to screen rates, by interpolation. Finally, alternative degrees of bias away from or towards a universal policy can be introduced, to take account of factors that cannot be included in a formal way, such as equity.

TABLE 80 *Approximate thresholds for fetal sickle cell disease prevalence above which a universal screening strategy would be adopted*

Failure to screen rate in selective programme (%)	Approximate fetal SCD prevalence thresholds per 10,000, above which a universal screening policy would be adopted					
	Maximum acceptable choice ICER in antenatal screening			Maximum acceptable late SCD diagnoses prevented ICER in neonatal screening		
	£50,000	£100,000	£150,000	£10,000	£20,000	£50,000
Baseline analysis						
5.5	12	7	5	18	12	7
3.0	18	12	8	> 30	18	10
1.5	> 30	18	18	> 30	> 30	18
Best plausible case for universal screening						
5.5	7	2.5	1.8	12	7	2.5
3.0	9	5	2.5	18	10	5
1.5	18	8	7	> 30	18	7

Chapter 12

Implications for information systems and recommendations for future research

Information system implications

Local information systems in the antenatal screening process

The coverage that can be achieved in a selective screening programme has emerged as a critical determinant of an economically efficient screening strategy, and also as a key indicator of screening programme performance. The development and use of routinely collected local information on failure to screen rates could therefore be seen as a justifiable priority. The routine systematic monitoring of the delivery of antenatal and neonatal screening services enables providers to detect and remedy shortcomings, renders the quality of service more transparent to managers and health commissioners, and provides data that can inform policy. In contrast, *ad hoc* 'audits' of the coverage of antenatal or neonatal screening are extremely expensive, requiring either additional field staff or more NHS staff time, on every occasion.

Further work is required to define minimal standards for computer systems and to define specifications for routine reports on the screening process. Once implemented, accurate information on most aspects of the screening process, as well as on Hb-pathy carrier frequency within ethnic groups, would be available indefinitely at little further cost.

Although the concepts of collecting and using local data are relatively straightforward, the lack of routinely produced reports indicates that this is difficult in practice. There appear to be two obstacles. The first is that, except in trusts with integrated information systems, data stored on haematology laboratory computers are not linked and merged with the information on maternity patient administration systems. In addition, data on the uptake and timing of PND and TOP may not be entered into maternity systems. These are issues that could be addressed separately within every trust. However, a general definition of what is required needs to be developed and incorporated into specifications for hospital maternity and pathology systems.

A second difficulty is that, even if combined maternity and haematology data were available, trusts tend not to have the software skills required to generate annual reports or analyses that are suitable for monitoring failure to screen rates and other key process indicators. Multidisciplinary research, comprising public health, statistical, epidemiological, haematological and obstetric expertise, is needed to work in collaboration with system programmers, to design a national specification for a routine report on the antenatal screening process and to pilot its implementation on a range of maternity systems in districts with different Hb-pathy prevalences. This should be considered to be an important priority for the implementation of antenatal and neonatal screening policies.

Similar considerations apply to other antenatal screens. Calls for systems for routine audit have been made, for example, for antenatal HIV screening.[377] It should also be noted that investment in greater connectivity between maternity and pathology systems could save midwives from having to re-enter data already on a pathology computer, guaranteeing completeness of the record and eliminating inefficiency and error due to double entry. Eventually, this would allow midwives online access to the screening results on any given patient. With appropriate decision support software, the need for carrier testing, partner recall and other steps in the screening cascade could be flagged for attention, ensuring a much higher quality of service.

Information systems in the neonatal screening process

There is a need to be able to monitor locally the coverage of neonatal screening within ethnic groups. The issue of coverage has been explored recently in the National Audit of Neonatal Screening Programme,[378] which has collected data on process variables from a number of centres, and set standards on several screening parameters, including coverage. Nevertheless, in practice there is enormous difficulty in distinguishing between low coverage and low recording of coverage (chapter 5; pp. 49–51); this is an area that requires further study.

Current arrangements for monitoring failure to screen rates vary from laboratories relying on paper records to those with computer links to local child health computers. Neonatal laboratory computer systems in use in the West Midlands Region[379] and more recently in North Thames[209] include, between them, a number of elements that assist the routine production of statistics on coverage and other process parameters. Among the key features are:

- links between maternity and child health systems, allowing accurate and prompt birth notification
- two-way links between neonatal laboratories and child health systems so that coverage can be assessed against a register of births, and so that neonatal screening results can be reported directly on to the appropriate child health system
- the use of unique identifiers attached to Guthrie cards
- information on mother's ethnic status and Hb-pathy carrier status copied to the neonatal computer.

Although these features are probably prerequisites for the accurate ongoing measurement of failure to screen rates, more research is needed to determine an overall protocol for Guthrie card screening. Experience in West Midlands and North Thames suggests that particular attention must be paid to how the request for a Guthrie test is generated, what identifiers are put on the card, and how laboratory staff match incoming cards against birth records.

Such research has become all the more necessary since two *Health Technology Assessment* reviews have considered the introduction of tandem mass spectrometry to detect a wider range of inborn errors of metabolism in newborn infants.[306,376]

Other initiatives on child health and maternity information systems

It would be appropriate for the recommendations on information systems made here to be reviewed by other groups who are already active in this field. Of particular importance are the Child Health Informatics Consortium and the Royal College of Obstetrics and Gynaecology Audit Committee Subgroup on Maternity Minimum Datasets, which is reviewing data set requirements under the auspices of the Department of Health. The possibility of a national coordinating centre on quality control issues in neonatal screening is also currently under discussion at the Department of Health. The North and South Thames Maternal and Child Health Information Systems Project is expected to make recommendations about links between these systems, and the NHS Executive Information Management Group is also active in this area.

Some of this work is orientated to defining a minimum set of data fields that all systems should have. While this is an important topic, in the context of antenatal and neonatal screening, computer system integration and interconnectivity are perhaps the more important problems to be addressed.

Research recommendations

Uptake of prenatal diagnosis and termination of pregnancy

In the light of the concerns over the uptake of PND and TOP (pp. 49–51), research needs to be commissioned that will determine the relationship between the timing of carrier testing and the uptake of PND and TOP, and whether or not this is dependent on ethnic group.

Uptake in relation to gestational age

Wide variations in reported uptake rates for PND, TOP or both, were noted in chapter 5 (pp. 49–51). To the extent that the objective of antenatal screening is to offer choice over the outcome of pregnancy, variation in uptake across ethnic, cultural or religious groups is not in itself a critical issue. However, evidence that uptake depends on the timing of maternal and paternal carrier testing is of major concern, because it suggests that women who are offered choice later in pregnancy are in effect being offered less of a choice than those tested earlier. Moreover, it must be recognised that what is regarded as limiting or extending choice may well be culturally dependent, and that little is known about what would therefore constitute a real choice in different ethnic groups. Research should, therefore, be commissioned to determine whether earlier carrier testing and couple assessment would affect the uptake of PND and TOP. Furthermore, the need to be able to monitor routinely the process parameters relating to the timing of maternal testing, partner testing, couple assessment, PND and TOP, should be borne in mind when defining requirements for information systems, as noted at the beginning of this chapter.

One simple way of accelerating the screening sequence for the majority of women would be to have test results from earlier pregnancies

available in subsequent pregnancies. This would also reduce the costs of antenatal screening. The facility to transfer specified data fields from earlier pregnancies into the current computer record should be included in specifications of maternity systems.

Effect of counselling on uptake of prenatal diagnosis and termination of pregnancy

Recent studies of the uptake of antenatal HIV testing have demonstrated that a woman's decision about whether to have the test is powerfully influenced by her midwife.[380] Evidence has also been cited that uptake rates may vary from one counsellor to another.[293] While the counsellor's individual character, personality and experience cannot be removed from the counselling process, it is disturbing that women identified as carriers in one hospital may have the natural history of Hb-pathies portrayed as more or less serious than carriers attending another.

It would therefore be useful if a consensus could be arrived at on the management of maternal carriers, with a particular focus on the way in which the paediatric consequences of Hb-pathies are portrayed.

Selective antenatal screening based on ethnic status alone, regardless of mean corpuscular haemoglobin result

The analysis of antenatal screening assumed that all women with a low MCH, including north Europeans, would be screened for Hb-pathy traits, in accordance with guidelines from the British Society of Haematology[6] and the SMAC report.[5] The simpler and less expensive alternative of selective screening based on ethnic status alone, regardless of MCH result, was also examined. Preliminary analyses suggested that the predicted fetal prevalence of thalassaemias in north European women, even among those with a low MCH, would probably not in itself justify screening them for thalassaemia trait. Instead, the economic justification would be that universal screening of those with a low MCH would identify a higher proportion of **ethnic minority women** with fetuses affected by both thalassaemias or sickle cell disease.

The rationale for the current standard approach is that a low MCH result requires that thalassaemia carrier status be excluded. A comparison of the standard strategy with the simpler alternative of selective screening without regard to MCH is valid only if the costs and consequences of the alternative management of low MCH (e.g. iron supplementation on the presumption of iron deficiency) are taken into account. The issue cannot, therefore, be separated from the wider question of the management of iron deficiency in pregnancy. A combined analysis is required, covering both iron deficiency in general and the response to a low MCH.

Fetal prevalence of haemoglobinopathies and late diagnosis of children with sickle cell disease

The district-specific fetal sickle cell disease prevalence rates on which the thresholds for universal screening are based are estimated from ethnic group-specific Hb-pathy carrier frequencies, inter-ethnic union rates and data on ethnic composition. All of these are subject to uncertainty. Although this uncertainty has been allowed for in sensitivity analyses, it would be preferable if the margin of error could be narrowed. A more important reason for research is the lack of information on the numbers of affected fetuses and affected children who are not identified prenatally or neonatally, and the reasons for their being missed. The key questions to be answered are as follows.

- What is the prevalence of sickle cell disease among fetuses/newborns in different parts of the UK?
- What proportion of sickle cell disease among fetuses/newborns in different parts of the UK can be attributed to: (1) ethnic minority women; (2) north European women; (3) north European women with ethnic minority partners; or (4) north European women with ethnic minority ancestry?
- How frequently are children with sickle cell disease diagnosed after 3 months of age?
- How frequently is this a result of failure to screen ethnic minority women and newborns, as opposed to failure to screen north European women and their infants, and could this be avoided by extending the basis for selection to include women who regard themselves as 'white' at antenatal booking but who have non-north European ancestry or non-north European partners?

These questions could be answered by monitoring PNDs, infants diagnosed on newborn screening, and late diagnosed infants, either within an *ad hoc* study or in a nationally coordinated neonatal screening quality control programme. This second option could have the advantage of keeping adverse events after failure to screen under continuing review, as well as auditing management of the affected child.

Pretest information

There is a conflict between the ideal of testing with informed consent, bearing in mind the need to provide information in a range of languages, and the practical difficulties of managing antenatal care without taking undue time to provide pretest information. This is a general problem that has received little attention in the research community.

Legal and ethical research is required to determine how much information needs to be given before informed consent can be considered to have been obtained, and how this information should be given. In particular, it needs to be clarified how much information can be presented passively, via posters, information leaflets or videos, and whether verbal or written confirmation is required that the patient consents to the tests. How information can be given to, and consent obtained from, women whose first language is not English is an additional problem.

A balance must be found between women's right to informed consent and their right to expect that appropriate health care is being provided whether or not they fully understand English, and whether or not they wish to understand the significance of all the screening tests that are routinely carried out. In this context, research on pretest information for Hb-pathies must not be isolated from other screening tests, particularly from those based on the pathological samples collected at antenatal booking.

Acknowledgements

This report was commissioned by the NHS R&D Executive's Health Technology Assessment programme.

We would like to thank Dr Pui-Ling Li for her vital contribution to the project proposal, and project collaborators, Dr R Jones, Professor B Modell and Dr A Yardumian, for their invaluable support and advice. Special thanks also go to the many other specialists consulted and who are listed in appendix 1.

We are also greatly indebted to the referees and editors for reading the report with great diligence and for their helpful advice and constructive criticism.

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Appendix 2

Literature search strategies

Chapter 2: Review of haemoglobinopathy screening strategies
Chapter 5: Parameter probabilities

The following databases were searched electronically from their beginning until August 1997:

MEDLINE
EMBASE
Science Citation Index
Index of Scientific and Technical Proceedings
Cochrane Database of Systematic Reviews
Database of Abstracts of Reviews of Effectiveness

The following search terms were used:

Index terms

hemoglobinopathies, hemoglobins, -abnormal, mass-screening, heterozygote-detection

Free text terms

hemoglobin*, haemoglobin*, sickle*, thalass*, screening, heterozygote testing, heterozygote detection, carrier testing, carrier detection

The following handsearches were conducted:

The *British Journal of Haematology* abstracts of symposia, 1982–1997
The British Library Health Care Information Service MEDLINE updates on Hemoglobinopathies, December 1995–June 1997.

Chapter 3: Rationale for the economic approach

The following databases were searched electronically from their beginning until February 1997:

MEDLINE
HealthSTAR
Health Economics Literature Index
EMBASE
Social Science

The following search terms were used:

Index terms

hemoglobinopathies, hemoglobins, sickle cell trait, mass-screening, cost–benefit analysis, costs and cost analysis, economics

Free text terms

hemoglobin*, haemoglobin*, cost effectiveness, screening, economic evaluation, cost utility, cost minimisation, cost minimization, cost benefit

Chapter 7: Lifetime treatment costs for patients with β-thalassaemia major and sickle cell disorders

The MEDLINE database was searched electronically from the beginning until March 1996.

The following search terms were used:

Index terms

beta-thalassemia in conjunction with chelation-therapy, treatment refusal, patient-compliance, psychotherapy, pregnancy, heart-diseases, endocrine-diseases, endocrine-glands, mortality, survival, survival-analysis, life-expectancy, death

sickle-cell anemia in conjunction with hospitalisation, length of stay, aplastic anemia, chronic kidney-failure, pregnancy, fertility, infertility, splenectomy, osteonecrosis, hip-prosthesis, cerebrovascular-disorder, respiratory insufficiency, eye-diseases, leg-ulcer, cholelithiasis, liver-diseases, cholecystectomy, blood-transfusion, pneumococcal-infections, mortality, survival, survival-analysis, life-expectancy, death

Free text terms

acute chest syndrome, clinical presentation (in conjunction with the index term sickle-cell anemia)

References from our literature searches were managed with the bibliographic software package Reference Manager versions 7 and 8.[396]

Appendix 3

Tables

TABLE 81 *Estimated ethnic composition of antenatal populations of regional and district health authorities in the UK (1993 distribution)*

Regional health authority	**Ethnic composition of antenatal population**											
District health authority	**BC**	**BA**	**BO**	**Ind**	**Pak**	**Ban**	**Chi**	**OA**	**Oth**	**Cyp**	**Ita**	**NE**
E Anglia												
Cambridge	0.3	0.2	0.5	0.5	0.2	0.4	0.3	0.5	1.1	0.3	0.9	94.8
Great Yarmouth and Waveney	0.0	0.2	0.2	0.1	0.0	0.0	0.2	0.2	0.6	0.3	0.2	98.0
Huntingdon	0.3	0.3	1.4	0.4	0.3	0.2	0.1	0.1	1.0	0.4	0.5	95.2
NW Anglia	0.4	0.2	0.8	1.1	2.6	0.1	0.2	0.2	0.9	0.2	1.1	92.1
Norwich	0.0	0.1	0.3	0.2	0.0	0.1	0.1	0.1	0.6	0.2	0.2	97.9
Suffolk	0.4	0.4	2.0	0.2	0.1	0.3	0.2	0.2	1.3	0.2	0.3	94.5
Regional average	**0.3**	**0.2**	**1.0**	**0.4**	**0.6**	**0.2**	**0.2**	**0.2**	**1.0**	**0.2**	**0.5**	**95.2**
Mersey												
Chester	0.0	0.1	0.2	0.2	0.1	0.1	0.2	0.1	0.5	0.1	0.3	98.1
Crewe	0.1	0.0	0.4	0.2	0.0	0.1	0.2	0.1	0.5	0.1	0.1	98.2
Halton	0.0	0.1	0.2	0.0	0.0	0.0	0.1	0.1	0.3	0.0	0.1	98.9
Liverpool	0.4	1.1	1.7	0.3	0.2	0.2	0.8	0.1	1.5	0.1	0.1	93.6
Macclesfield	0.1	0.1	0.2	0.2	0.1	0.0	0.3	0.1	0.5	0.1	0.2	98.0
S Sefton	0.0	0.2	0.2	0.1	0.0	0.0	0.3	0.0	0.5	0.0	0.1	98.5
Southport and Formby	0.0	0.0	0.3	0.1	0.0	0.2	0.3	0.1	0.7	0.2	0.3	97.8
St Helens and Knowsley	0.1	0.1	0.3	0.1	0.1	0.0	0.2	0.0	0.3	0.0	0.1	98.6
Warrington	0.1	0.1	0.2	0.5	0.5	0.1	0.3	0.0	0.6	0.1	0.1	97.4
Wirral	0.0	0.1	0.2	0.1	0.0	0.1	0.4	0.1	0.5	0.1	0.1	98.3
Regional average	**0.1**	**0.3**	**0.5**	**0.2**	**0.1**	**0.1**	**0.4**	**0.1**	**0.7**	**0.1**	**0.1**	**97.3**
NE Thames												
Barking and Havering	1.1	1.2	1.0	1.9	1.0	0.2	0.5	0.3	1.1	0.4	0.2	91.0
Camden and Islington	3.9	10.3	4.2	1.5	0.6	5.8	1.2	2.0	5.2	3.3	2.7	59.3
E London and City	6.4	12.4	5.0	7.5	4.3	16.5	1.0	2.0	3.8	1.3	0.5	39.2
New River District	6.7	9.2	3.8	3.8	0.9	2.1	0.7	1.9	4.2	9.6	2.3	54.7
N Essex	0.1	0.2	0.4	0.5	0.1	0.2	0.3	0.2	0.9	0.2	0.3	96.5
Redbridge and Waltham Forest	5.4	5.4	3.5	9.4	7.5	1.7	0.5	1.7	4.0	1.7	0.6	58.4
S Essex	0.1	0.2	0.4	0.6	0.2	0.2	0.3	0.1	0.9	0.2	0.3	96.4
Regional average	**3.2**	**5.2**	**2.4**	**3.6**	**2.0**	**4.2**	**0.6**	**1.1**	**2.6**	**2.0**	**0.8**	**72.2**
Northern												
E Cumbria	0.0	0.0	0.1	0.0	0.0	0.1	0.1	0.0	0.2	0.1	0.2	98.9
Gateshead	0.0	0.0	0.2	0.3	0.3	0.2	0.2	0.1	0.4	0.0	0.2	98.2
Hartlepool	0.0	0.1	0.1	0.2	0.2	0.2	0.1	0.0	0.2	0.1	0.2	98.8
Newcastle	0.1	0.4	0.2	1.1	2.4	1.1	0.3	0.8	0.9	0.1	0.3	92.4
N Durham	0.0	0.1	0.1	0.1	0.0	0.1	0.1	0.2	0.3	0.0	0.1	98.7
N Tees	0.0	0.1	0.1	0.3	1.3	0.0	0.2	0.2	0.5	0.1	0.1	97.0
N Tyneside	0.0	0.1	0.2	0.4	0.2	0.4	0.3	0.1	0.2	0.0	0.2	97.9
Northumberland	0.0	0.0	0.1	0.2	0.1	0.1	0.2	0.1	0.2	0.1	0.1	98.9
S Cumbria	0.0	0.1	0.1	0.0	0.0	0.0	0.2	0.0	0.3	0.0	0.1	99.0
S Durham	0.1	0.1	0.2	0.2	0.1	0.2	0.1	0.1	0.3	0.1	0.1	98.5
S Tees	0.1	0.2	0.3	0.5	2.5	0.1	0.2	0.1	0.7	0.1	0.1	95.1
S Tyneside	0.0	0.2	0.3	0.5	0.1	0.7	0.1	0.1	0.9	0.0	0.0	97.0
Sunderland	0.0	0.1	0.1	0.3	0.2	0.7	0.2	0.2	0.2	0.0	0.1	97.9
W Cumbria	0.1	0.0	0.1	0.1	0.1	0.1	0.2	0.0	0.2	0.1	0.1	99.2
Regional average	**0.0**	**0.1**	**0.2**	**0.3**	**0.6**	**0.3**	**0.2**	**0.2**	**0.4**	**0.1**	**0.1**	**97.5**

Source: Modified from reference 228

continued

TABLE 81 contd *Estimated ethnic composition of antenatal populations of regional and district health authorities in the UK (1993 distribution)*

Regional health authority	**Ethnic composition of antenatal population**											
District health authority	**BC**	**BA**	**BO**	**Ind**	**Pak**	**Ban**	**Chi**	**OA**	**Oth**	**Cyp**	**Ita**	**NE**
North Western												
Blackpool, Wyre and Fylde	0.0	0.1	0.2	0.2	0.1	0.1	0.2	0.1	0.5	0.1	0.3	98.1
Blackburn, Hyndburn, Ribble Valley	0.0	0.2	0.4	7.0	8.9	0.3	0.1	0.5	1.0	0.0	0.5	81.0
Bolton	0.2	0.2	0.5	7.9	3.5	0.1	0.2	0.4	1.0	0.1	0.2	85.7
Burnley, Pendale, Rossendale	0.0	0.1	0.3	0.2	10.4	1.4	0.1	0.1	0.6	0.1	0.3	86.4
Bury	0.2	0.3	0.6	0.6	3.7	0.1	0.4	0.2	1.0	0.1	0.4	92.3
Central Manchester	6.4	3.4	5.8	1.6	10.9	2.6	0.8	0.8	5.1	0.1	0.3	62.0
Chorley and S Ribble	0.1	0.0	0.4	0.3	0.3	0.0	0.2	0.1	0.6	0.1	0.1	97.9
Lancaster	0.0	0.2	0.1	0.7	0.1	0.1	0.3	0.2	0.6	0.1	0.2	97.4
N Manchester	1.1	0.8	2.5	0.7	4.8	0.1	0.8	0.9	1.8	0.1	0.3	86.1
Oldham	0.4	0.1	1.0	1.0	9.4	5.7	0.1	0.2	1.0	0.1	0.2	80.7
Preston	0.5	0.2	1.3	9.2	2.1	0.3	0.1	0.5	1.7	0.1	0.4	83.6
Rochdale	0.1	0.2	0.6	0.4	9.6	1.7	0.3	0.3	0.9	0.1	0.3	85.5
Salford	0.1	0.2	0.6	0.5	0.5	0.3	0.3	0.2	1.1	0.1	0.2	96.1
S Manchester	1.6	0.5	2.3	1.3	4.9	0.4	0.5	0.4	3.4	0.2	0.3	84.2
Stockport	0.2	0.2	0.5	0.5	1.0	0.1	0.5	0.2	1.0	0.1	0.3	95.4
Tameside and Glossop	0.1	0.1	0.4	1.3	1.5	1.6	0.4	0.1	0.6	0.1	0.5	93.5
Trafford	1.3	0.2	1.4	2.3	1.6	0.1	0.4	0.4	1.7	0.3	0.2	90.2
W Lancashire	0.1	0.1	0.3	0.1	0.0	0.0	0.1	0.0	0.4	0.1	0.2	98.8
Wigan	0.0	0.2	0.2	0.2	0.2	0.0	0.2	0.0	0.4	0.0	0.0	98.4
Regional average	**0.5**	**0.3**	**0.9**	**1.9**	**3.9**	**0.8**	**0.3**	**0.3**	**1.2**	**0.1**	**0.3**	**89.5**
NW Thames												
Barnet	1.1	5.5	1.3	8.7	1.0	0.7	1.4	4.8	4.0	3.3	2.0	66.1
Brent and Harrow	7.0	6.6	3.8	22.0	3.5	0.4	1.0	3.8	5.1	1.1	1.2	44.4
E and N Hertfordshire	0.4	0.2	0.7	1.3	0.2	0.3	0.3	0.2	1.2	0.4	1.3	93.5
Ealing, Hammersmith, Hounslow	4.0	4.2	2.9	14.9	3.5	0.6	0.7	2.3	4.9	0.6	1.2	60.2
Hillingdon	0.9	0.9	0.9	9.9	1.5	0.7	0.5	1.3	2.4	0.4	0.5	80.1
Kensington, Chelsea, Westminster	4.5	8.4	3.6	1.7	1.1	3.9	0.9	2.8	8.6	1.0	4.6	58.9
NW Hertfordshire	0.4	0.3	0.6	0.9	1.0	1.2	0.3	0.4	1.5	0.2	0.7	92.5
N Bedfordshire	1.2	0.5	1.7	3.4	1.3	1.2	0.2	0.4	1.6	0.2	3.1	85.2
SW Hertfordshire	0.5	0.4	0.9	2.2	2.5	0.3	0.4	0.4	2.1	0.4	0.9	89.1
S Bedfordshire	2.1	0.6	2.0	2.8	7.0	2.8	0.3	0.4	2.0	0.2	0.9	78.9
Regional average	**2.6**	**3.0**	**2.0**	**8.2**	**2.5**	**1.1**	**0.6**	**1.8**	**3.4**	**0.8**	**1.5**	**72.7**
Oxford												
Buckinghamshire	1.1	0.3	0.9	1.1	3.5	0.3	0.2	0.3	1.7	0.2	0.7	89.6
E Berkshire	0.9	0.3	1.0	5.9	5.9	0.1	0.3	0.6	1.8	0.2	0.9	82.0
Kettering	0.6	0.1	0.8	1.5	0.1	0.2	0.2	0.1	0.8	0.1	0.8	94.6
Northampton	0.9	0.3	1.4	1.2	0.4	0.8	0.3	0.2	1.3	0.2	0.4	92.6
Oxfordshire	0.5	0.3	1.1	0.6	1.2	0.3	0.2	0.3	1.4	0.2	0.5	93.4
W Berkshire	1.0	0.5	1.1	1.1	1.4	0.1	0.3	0.3	1.5	0.2	0.4	92.0
Regional average	**0.9**	**0.3**	**1.0**	**1.8**	**2.2**	**0.3**	**0.3**	**0.3**	**1.5**	**0.2**	**0.6**	**90.6**
Scotland												
Angus	0.0	0.0	0.3	0.0	0.1	0.0	0.3	0.0	0.3	0.0	0.0	98.9
Borders	0.0	0.1	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.1	99.6
Central (Forth Valley)	0.0	0.0	0.1	0.1	0.5	0.0	0.1	0.1	0.3	0.0	0.0	98.8
Dumfries and Galloway	0.0	0.0	0.1	0.1	0.1	0.0	0.1	0.0	0.1	0.0	0.0	99.4
Dundee City	0.0	0.2	0.2	0.5	1.4	0.1	0.4	0.4	0.7	0.0	0.0	96.1
Fife	0.0	0.1	0.1	0.1	0.4	0.0	0.1	0.1	0.3	0.0	0.0	98.7

Source: Modified from reference 228

continued

TABLE 81 contd *Estimated ethnic composition of antenatal populations of regional and district health authorities in the UK (1993 distribution)*

Regional health authority	**Ethnic composition of antenatal population**											
District health authority	**BC**	**BA**	**BO**	**Ind**	**Pak**	**Ban**	**Chi**	**OA**	**Oth**	**Cyp**	**Ita**	**NE**
Scotland contd												
Grampian	0.0	0.2	0.1	0.1	0.1	0.1	0.2	0.2	0.6	0.0	0.0	98.4
Highland	0.0	0.0	0.2	0.0	0.1	0.1	0.1	0.0	0.4	0.0	0.0	99.1
Lothian	0.0	0.2	0.2	0.3	0.9	0.1	0.4	0.3	0.8	0.0	0.0	96.8
Orkney	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.7	0.0	0.0	99.6
Perth and Kinross	0.0	0.0	0.0	0.0	0.1	0.0	0.3	0.0	0.4	0.0	0.0	99.0
Shetland	0.0	0.0	0.2	0.0	0.1	0.1	0.1	0.1	0.6	0.0	0.2	98.8
Argyll and Clyde	0.0	0.1	0.3	0.2	0.2	0.0	0.2	0.1	0.4	0.0	0.0	98.5
Ayreshire and Arran	0.0	0.0	0.0	0.2	0.2	0.0	0.2	0.0	0.2	0.0	0.0	99.1
Greater Glasgow	0.0	0.2	0.2	0.9	2.9	0.0	0.5	0.2	0.7	0.0	0.0	94.4
Lanarkshire	0.0	0.0	0.1	0.1	0.5	0.0	0.2	0.1	0.3	0.0	0.0	98.6
Western Isles	0.0	0.0	0.1	0.0	0.2	0.0	0.0	0.0	0.2	0.0	0.1	99.4
Regional average	**0.0**	**0.1**	**0.1**	**0.3**	**0.9**	**0.0**	**0.3**	**0.2**	**0.5**	**0.0**	**0.0**	**97.6**
SE Thames												
Bexley	0.7	1.1	0.9	2.9	0.2	0.2	0.7	0.5	1.2	0.6	0.4	90.6
Bromley	1.1	0.8	1.1	1.3	0.2	0.4	0.4	0.8	1.8	0.6	0.6	91.1
Canterbury and Thanet	0.1	0.4	0.3	0.3	0.0	0.1	0.2	0.1	0.7	0.3	0.3	97.1
Dartford and Gravesham	0.2	0.3	0.4	4.4	0.2	0.1	0.2	0.3	0.9	0.2	0.4	92.4
E Sussex	0.1	0.4	0.4	0.3	0.1	0.3	0.2	0.2	1.1	0.2	0.5	96.1
Greenwich	2.8	5.7	2.6	4.2	1.0	0.4	1.1	1.4	3.0	0.8	0.3	76.8
Maidstone	0.1	0.2	0.3	0.4	0.1	0.1	0.1	0.2	0.7	0.1	0.3	97.3
Medway	0.2	0.3	0.5	1.7	0.3	0.3	0.2	0.2	0.8	0.2	0.3	95.2
SE Kent	0.1	0.2	0.4	0.3	0.1	0.1	0.1	0.2	0.6	0.2	0.3	97.4
SE London	11.8	17.5	6.7	1.4	0.7	1.0	1.3	1.1	4.3	1.7	1.1	51.3
Tunbridge Wells	0.0	0.2	0.1	0.2	0.0	0.2	0.2	0.0	0.5	0.1	0.3	98.0
Regional average	**3.0**	**4.5**	**2.0**	**1.5**	**0.3**	**0.4**	**0.5**	**0.5**	**1.8**	**0.6**	**0.5**	**84.3**
South Western												
Bristol and District	0.9	0.3	1.1	0.7	0.7	0.2	0.2	0.1	1.3	0.2	0.4	93.9
Cornwall and Scilly	0.0	0.0	0.2	0.0	0.0	0.1	0.1	0.0	0.3	0.1	0.2	98.9
Exeter and N Devon	0.0	0.1	0.1	0.1	0.0	0.1	0.1	0.0	0.5	0.1	0.2	98.5
Gloucestershire	0.4	0.1	0.8	0.8	0.1	0.1	0.2	0.1	0.8	0.2	0.3	96.1
Plymouth and Torbay	0.0	0.1	0.2	0.1	0.0	0.1	0.1	0.1	0.4	0.2	0.2	98.5
Somerset	0.1	0.1	0.1	0.0	0.0	0.1	0.1	0.0	0.3	0.1	0.4	98.6
Regional average	**0.3**	**0.1**	**0.5**	**0.3**	**0.2**	**0.1**	**0.2**	**0.1**	**0.7**	**0.2**	**0.3**	**96.9**
SW Thames												
Chichester	0.0	0.2	0.1	0.1	0.1	0.2	0.2	0.1	0.6	0.2	0.3	98.0
Croydon	5.8	4.2	3.4	5.3	1.6	0.5	0.5	1.7	4.0	0.7	0.7	71.7
East Surrey	0.1	0.2	0.2	0.5	0.3	0.2	0.2	0.3	0.9	0.2	0.5	96.5
Kingston and Richmond	0.7	1.0	1.0	1.9	0.7	0.3	0.6	1.9	2.5	0.5	1.0	87.9
Merton and Sutton	2.0	3.1	1.7	2.8	1.1	0.6	0.7	2.2	2.7	0.5	0.9	81.7
Mid Downs	0.1	0.2	0.3	2.0	1.3	0.2	0.3	0.4	0.9	0.1	0.6	93.6
Mid Surrey	0.2	0.3	0.3	1.2	0.3	0.4	0.4	1.4	1.3	0.3	0.8	93.2
NW Surrey	0.1	0.2	0.3	1.0	1.5	0.3	0.3	0.5	1.2	0.2	1.3	92.9
SW Surrey	0.1	0.2	0.1	0.4	0.1	0.1	0.3	0.2	0.7	0.2	0.6	97.0
Wandsworth Surrey	7.3	8.0	4.8	3.7	2.9	1.0	0.9	2.2	3.6	0.7	1.5	63.4
Worthing	0.0	0.3	0.2	0.2	0.1	0.3	0.3	0.1	0.8	0.1	0.8	96.8
Regional average	**1.6**	**1.7**	**1.2**	**2.0**	**1.0**	**0.4**	**0.4**	**1.1**	**1.9**	**0.4**	**0.9**	**87.5**

Source: Modified from reference 228

continued

TABLE 81 contd *Estimated ethnic composition of antenatal populations of regional and district health authorities in the UK (1993 distribution)*

Regional health authority	**Ethnic composition of antenatal population**											
District health authority	**BC**	**BA**	**BO**	**Ind**	**Pak**	**Ban**	**Chi**	**OA**	**Oth**	**Cyp**	**Ita**	**NE**
Trent												
Barnsley	0.0	0.1	0.2	0.2	0.1	0.0	0.1	0.0	0.2	0.1	0.1	98.7
Doncaster	0.2	0.0	0.4	0.7	0.6	0.0	0.2	0.1	0.5	0.1	0.1	96.9
Leicestershire	0.6	0.3	0.9	12.2	0.7	0.5	0.2	0.6	1.5	0.2	0.4	81.9
N Nottinghamshire	0.1	0.1	0.4	0.3	0.0	0.1	0.1	0.1	0.3	0.1	0.2	98.2
N Derbyshire	0.1	0.1	0.2	0.2	0.1	0.0	0.2	0.0	0.4	0.1	0.3	98.3
N Lincolnshire	0.1	0.1	0.3	0.2	0.1	0.0	0.2	0.1	0.4	0.3	0.2	98.1
Nottingham	1.9	0.2	2.2	1.6	2.2	0.1	0.2	0.2	2.0	0.2	0.5	88.6
Rotherham	0.1	0.1	0.2	0.2	2.8	0.0	0.1	0.1	0.5	0.1	0.2	95.8
Sheffield	1.3	0.6	1.5	0.4	4.0	0.5	0.3	0.3	2.3	0.1	0.2	88.6
S Lincolnshire	0.1	0.1	0.3	0.2	0.1	0.1	0.2	0.1	0.3	0.3	0.3	98.0
Southern Derbyshire	0.8	0.1	1.1	2.5	2.0	0.1	0.2	0.2	1.1	0.1	0.3	91.6
Regional average	**0.6**	**0.2**	**0.9**	**3.1**	**1.3**	**0.2**	**0.2**	**0.2**	**1.1**	**0.1**	**0.3**	**91.7**
Wales												
Clwyd	0.0	0.0	0.2	0.1	0.1	0.1	0.1	0.1	0.3	0.1	0.3	98.7
Dyfed	0.0	0.0	0.1	0.1	0.1	0.1	0.2	0.2	0.4	0.0	0.4	98.3
Gwent	0.1	0.1	0.3	0.2	0.7	0.4	0.2	0.1	0.6	0.0	0.3	97.0
Gwynedd	0.0	0.1	0.2	0.1	0.2	0.1	0.2	0.1	0.6	0.1	0.1	98.2
Mid Glamorgan	0.0	0.0	0.1	0.2	0.1	0.1	0.2	0.1	0.3	0.1	0.2	98.5
Powys	0.0	0.0	0.2	0.0	0.0	0.0	0.1	0.0	0.3	0.1	0.2	99.0
S Glamorgan	0.6	0.9	1.2	1.0	1.2	1.0	0.3	0.5	1.8	0.2	0.4	91.0
W Glamorgan	0.0	0.1	0.2	0.2	0.1	0.8	0.2	0.2	0.8	0.0	0.4	97.0
Regional average	**0.1**	**0.2**	**0.3**	**0.3**	**0.4**	**0.3**	**0.2**	**0.2**	**0.7**	**0.1**	**0.3**	**96.9**
Wessex												
Bath	0.3	0.1	0.6	0.1	0.0	0.1	0.1	0.1	0.6	0.2	0.5	97.2
Basingstoke and N Hampshire	0.2	0.2	0.6	0.4	0.1	0.1	0.2	0.3	0.7	0.2	0.4	96.6
Dorset	0.1	0.2	0.2	0.1	0.0	0.2	0.2	0.1	0.6	0.2	0.4	97.8
Isle of Wight	0.1	0.1	0.2	0.1	0.0	0.1	0.1	0.1	0.4	0.1	0.3	98.4
Portsmth and SE Hampshire	0.1	0.3	0.3	0.3	0.0	0.5	0.2	0.1	0.6	0.1	0.2	97.2
Salisbury	0.1	0.1	0.3	0.1	0.1	0.2	0.1	0.1	0.4	0.3	0.3	98.1
Southampton and SW Hampshire	0.2	0.2	0.6	1.5	0.5	0.4	0.3	0.3	0.9	0.2	0.3	94.8
Swindon	0.3	0.1	0.7	1.1	0.2	0.2	0.2	0.2	1.0	0.2	0.8	94.8
Winchester	0.0	0.0	0.3	0.4	0.0	0.1	0.3	0.1	0.4	0.2	0.3	97.6
Regional average	**0.2**	**0.2**	**0.4**	**0.5**	**0.1**	**0.2**	**0.2**	**0.1**	**0.7**	**0.2**	**0.4**	**96.8**
W Midlands												
Coventry	1.3	0.2	1.3	8.3	2.0	0.9	0.2	0.4	1.6	0.1	0.4	83.4
Dudley	0.9	0.1	1.1	1.8	2.8	0.1	0.2	0.1	1.3	0.1	0.1	91.2
E Birmingham	2.9	0.1	2.1	2.6	24.0	2.9	0.1	0.8	3.1	0.1	0.1	61.1
Herefordshire	0.0	0.1	0.1	0.1	0.0	0.0	0.1	0.0	0.4	0.1	0.2	98.7
Mid Staffordshire	0.2	0.1	0.3	0.5	0.1	0.0	0.2	0.1	0.6	0.1	0.3	97.6
N Birmingham	2.5	0.1	2.4	1.7	1.7	0.1	0.3	0.2	2.0	0.3	0.2	88.6
N Staffordshire	0.2	0.1	0.5	0.4	2.2	0.2	0.1	0.1	0.6	0.1	0.3	95.2
N Worcestershire	0.4	0.1	0.6	0.3	0.9	0.3	0.2	0.1	0.8	0.1	0.3	95.9
SE Staffordshire	0.2	0.1	0.6	0.4	1.9	0.1	0.2	0.1	0.7	0.1	0.2	95.5
Sandwell	3.0	0.1	1.9	10.2	3.7	1.7	0.0	0.2	1.9	0.1	0.3	76.6
Shropshire	0.1	0.1	0.4	0.6	0.5	0.1	0.2	0.3	0.6	0.1	0.2	96.7
Solihull	0.9	0.0	1.1	1.5	0.4	0.0	0.3	0.1	1.1	0.2	0.2	94.1
S Birmingham	3.1	0.5	2.6	4.6	10.4	1.7	0.4	0.8	3.6	0.2	0.3	72.0
Walsall	1.1	0.1	1.2	6.0	4.7	1.3	0.2	0.2	1.2	0.1	0.2	83.9

Source: Modified from reference 228

continued

TABLE 81 contd *Estimated ethnic composition of antenatal populations of regional and district health authorities in the UK (1993 distribution)*

Regional health authority	**Ethnic composition of antenatal population**											
District health authority	**BC**	**BA**	**BO**	**Ind**	**Pak**	**Ban**	**Chi**	**OA**	**Oth**	**Cyp**	**Ita**	**NE**
W Midlands contd												
Warwickshire	0.2	0.1	0.6	3.1	0.2	0.0	0.2	0.1	0.9	0.1	0.4	94.1
W Birmingham	11.9	0.7	4.3	15.9	10.4	5.0	0.5	1.5	3.7	0.1	0.1	45.7
Wolverhampton	5.1	0.2	3.4	13.7	1.4	0.1	0.2	0.4	2.5	0.1	0.5	72.5
Worcester and District	0.1	0.0	0.1	0.2	0.7	0.2	0.1	0.1	0.5	0.2	0.6	97.3
Regional average	**1.8**	**0.2**	**1.3**	**4.0**	**3.8**	**0.8**	**0.2**	**0.3**	**1.5**	**0.1**	**0.3**	**85.6**
Yorkshire												
Bradford	0.7	0.3	1.0	2.9	18.0	1.5	0.1	0.6	1.9	0.1	0.5	72.3
E Riding	0.0	0.1	0.3	0.1	0.1	0.2	0.2	0.2	0.4	0.1	0.1	98.2
Grimsby and Scunthorpe	0.0	0.1	0.2	0.3	0.2	0.5	0.2	0.1	0.3	0.1	0.3	97.7
Leeds	1.0	0.4	1.4	1.8	2.9	0.6	0.4	0.3	1.9	0.1	0.3	88.8
N Yorkshire	0.1	0.1	0.2	0.1	0.1	0.1	0.2	0.1	0.4	0.2	0.2	98.3
Wakefield	0.0	0.1	0.2	0.3	1.6	0.0	0.1	0.0	0.4	0.1	0.1	97.0
W Yorkshire	0.8	0.2	1.1	3.3	8.6	0.2	0.1	0.4	1.5	0.1	0.3	83.5
Regional average	**0.5**	**0.2**	**0.7**	**1.4**	**4.8**	**0.5**	**0.2**	**0.3**	**1.1**	**0.1**	**0.3**	**90.1**

Source: Modified from reference 228

TABLE 82 *Average lifetime treatment costs for patients with β-thalassaemia major and their calculation from annual treatment costs and survival rates*

Year	Annual cost per surviving patient (undiscounted £)	Survival rate (%)	Annual cost per original patient (undiscounted £)	Annual cost per original patient (discounted £)[a]
1	2,111.56	99.85	2,108.39	2,086.48
2	5,350.16	99.69	5,333.57	4,979.39
3	5,301.31	99.54	5,276.93	4,647.64
4	5,293.11	99.39	5,260.82	4,371.19
5	5,306.71	99.24	5,266.38	4,128.12
6	6,131.57	99.09	6,075.78	4,493.00
7	6,123.43	98.94	6,058.52	4,226.64
8	6,123.50	98.79	6,049.40	3,981.39
9	6,131.77	98.64	6,048.38	3,755.39
10	6,123.63	97.93	5,996.87	3,512.65
11	8,063.39	97.24	7,840.84	4,332.79
12	8,060.22	96.58	7,784.56	4,058.20
13	8,273.53	95.94	7,937.63	3,903.77
14	9,469.39	95.33	9,027.17	4,188.31
15	9,387.25	94.38	8,859.68	3,877.93
16	10,966.67	93.47	10,250.54	4,232.75
17	10,971.70	92.60	10,159.79	3,957.81
18	10,644.11	91.78	9,769.17	3,590.22
19	10,320.67	90.99	9,390.78	3,255.82
20	9,580.74	90.21	8,642.79	2,826.87
21	10,697.53	89.47	9,571.08	2,953.30
22	10,701.62	88.78	9,500.90	2,765.70
23	10,707.46	88.13	9,436.49	2,591.46
24	11,793.89	87.51	10,320.83	2,673.89
25	11,444.96	86.93	9,949.10	2,431.68
26	10,855.81	86.37	9,376.16	2,161.93
27	10,727.34	85.85	9,209.42	2,003.29
28	10,732.31	85.36	9,161.10	1,879.98
29	10,732.31	84.89	9,110.65	1,763.80
30	10,724.10	84.42	9,053.29	1,653.48
31	11,938.99	83.97	10,025.17	1,727.35
32	11,451.66	83.54	9,566.72	1,555.05
33	10,724.10	83.14	8,916.02	1,367.25
34	10,724.10	82.75	8,874.19	1,283.80
35	10,681.47	82.38	8,799.39	1,200.93
36	10,681.47	82.02	8,760.94	1,128.00
37	10,681.47	81.68	8,724.62	1,059.74
38	10,681.47	81.35	8,689.38	995.72
39	10,681.47	81.03	8,655.19	935.66
40	10,681.47	80.64	8,613.54	878.45
41	10,681.47	80.26	8,572.95	824.82
42	10,681.47	79.89	8,533.43	774.54
43	10,681.47	79.53	8,494.97	727.41
44	10,681.47	79.18	8,457.59	683.22
45	10,681.47	78.84	8,421.27	641.78
46	10,681.47	78.51	8,386.02	602.91
47	10,681.47	78.18	8,350.77	566.40
48	10,681.47	77.86	8,316.59	532.15
49	10,681.47	77.55	8,283.48	500.03
50	10,681.47	76.97	8,221.53	468.20
51	10,681.47	76.40	8,160.64	438.42
52	10,681.47	75.83	8,099.76	410.52
53	10,681.47	75.27	8,039.94	384.42
54	10,681.47	74.72	7,981.19	360.02
55	10,681.47	74.18	7,923.51	337.18
56	10,681.47	73.64	7,865.83	315.78
57	10,681.47	73.11	7,809.22	295.76
58	10,681.47	72.59	7,753.68	277.04
59	10,681.47	72.07	7,698.13	259.48
60	10,681.47	70.80	7,562.48	240.48
Total	581,408.77		490,385.14	123,057.38

[a] *Discount rate 6%*

TABLE 83 *Average lifetime treatment costs for patients with sickle cell anaemia (diagnosed early), and their calculation from annual treatment costs and survival*

Year	Annual cost per surviving patient (undiscounted £)	Survival rate (%)	Annual cost per original patient (undiscounted £)	Annual cost per original patient (discounted £)[a]
1	1,933.38	99.11	1,936.83	1,936.83
2	2,149.74	98.14	2,132.42	2,011.71
3	2,388.81	97.20	2,346.95	2,088.78
4	2,688.65	96.37	2,619.03	2,198.99
5	2,511.56	95.57	2,426.06	1,921.67
6	2,230.56	94.82	2,137.92	1,597.58
7	2,555.83	94.16	2,432.41	1,714.75
8	2,282.69	93.56	2,158.74	1,435.69
9	2,134.20	93.04	2,007.06	1,259.25
10	5,446.86	92.57	5,096.74	3,016.75
11	3,640.61	92.01	3,385.95	1,890.70
12	3,858.94	91.45	3,567.25	1,879.18
13	3,571.06	90.90	3,281.12	1,630.62
14	3,782.59	90.35	3,454.41	1,619.56
15	4,008.75	89.80	3,638.75	1,609.42
16	4,227.09	89.26	3,813.68	1,591.31
17	4,445.42	88.72	3,986.34	1,569.21
18	4,467.39	88.18	3,981.76	1,478.68
19	4,502.96	87.64	3,989.13	1,397.57
20	4,490.63	86.40	3,921.92	1,296.24
21	4,791.20	85.18	4,125.22	1,286.26
22	4,819.97	83.98	4,091.27	1,203.47
23	4,848.74	82.79	4,057.45	1,125.96
24	4,877.51	81.62	4,023.77	1,053.41
25	5,846.61	80.46	4,754.99	1,174.38
26	4,935.06	79.32	3,956.84	921.94
27	4,963.83	78.20	3,923.59	862.45
28	4,992.60	77.09	3,890.49	806.76
29	5,091.27	76.00	3,911.25	765.16
30	5,050.14	74.31	3,793.09	700.04
31	5,034.17	72.65	3,696.74	643.64
32	5,021.84	71.03	3,605.41	592.21
33	5,009.51	69.44	3,516.32	544.88
34	4,997.18	67.89	3,429.41	501.33
35	4,984.85	66.38	3,344.63	461.26
36	4,972.52	64.90	3,261.92	424.39
37	4,960.19	63.45	3,181.24	390.47
38	4,947.86	62.04	3,102.53	359.25
39	4,935.52	60.65	3,025.75	330.53
40	4,923.19	58.34	2,903.26	299.20
41	4,910.86	56.12	2,785.71	270.83
42	4,898.53	53.98	2,672.90	245.16
43	4,886.20	51.93	2,564.65	221.91
44	4,873.87	49.95	2,460.76	200.87
45	4,861.54	48.05	2,361.07	181.82
46	4,849.21	46.22	2,265.40	164.58
47	4,836.88	44.46	2,173.59	148.97
48	4,824.55	42.77	2,085.49	134.84
49	4,812.22	41.14	2,000.95	122.05
50	4,799.89	38.81	1,882.88	108.35
51	4,787.56	36.61	1,771.76	96.19
52	4,775.23	34.54	1,667.19	85.39
53	4,762.90	32.59	1,568.78	75.80
54	4,750.57	30.74	1,476.18	67.29
55	4,738.24	29.00	1,389.03	59.73
56	4,725.91	27.36	1,307.01	53.02
57	4,713.58	25.81	1,229.83	47.07
58	4,701.25	24.35	1,157.20	41.78
59	4,688.92	22.97	1,088.85	37.09
60	4,676.59	21.67	1,013.59	32.57
Total	263,195.95		172,832.45	51,986.81

[a] *Discount rate 6%*

TABLE 84 *Average lifetime treatment costs for patients with sickle cell anaemia (diagnosed late), and their calculation from annual treatment costs and survival*

Year	Annual cost per surviving patient (undiscounted £)	Survival rate (%)	Annual cost per original patient (undiscounted £)	Annual cost per original patient (discounted £)[a]
1	928.56	98.60	915.54	915.54
2	2,290.01	97.33	2,228.81	2,102.65
3	2,388.81	96.21	2,298.33	2,045.51
4	2,688.65	95.27	2,561.48	2,150.67
5	2,527.08	94.38	2,384.99	1,889.14
6	2,246.08	93.59	2,102.02	1,570.75
7	2,571.35	92.89	2,388.65	1,683.90
8	2,329.81	92.30	2,150.34	1,430.10
9	2,149.73	91.78	1,973.05	1,237.92
10	5,479.75	91.32	5,004.26	2,962.01
11	3,466.57	90.77	3,146.58	1,757.03
12	3,684.91	90.22	3,324.48	1,751.29
13	3,397.02	89.67	3,046.17	1,513.85
14	3,608.55	89.13	3,216.24	1,507.90
15	3,834.72	88.59	3,397.10	1,502.54
16	4,053.05	88.05	3,568.75	1,489.11
17	4,271.38	87.52	3,738.19	1,471.52
18	4,293.35	86.99	3,734.64	1,386.91
19	4,328.92	86.46	3,742.76	1,311.25
20	4,316.59	85.24	3,679.29	1,216.05
21	4,617.16	84.03	3,879.80	1,209.74
22	4,645.93	82.84	3,848.73	1,132.13
23	4,674.70	81.67	3,817.77	1,059.45
24	4,703.48	80.51	3,786.91	991.40
25	5,672.57	79.37	4,502.54	1,112.03
26	4,761.02	78.25	3,725.53	868.04
27	4,789.79	77.14	3,695.01	812.20
28	4,818.56	76.05	3,664.60	759.92
29	4,917.23	74.98	3,686.73	721.24
30	4,876.10	73.30	3,574.33	659.67
31	4,844.61	71.67	3,472.01	604.51
32	4,832.28	70.07	3,385.91	556.15
33	4,819.95	68.51	3,301.93	511.66
34	4,807.62	66.98	3,220.00	470.72
35	4,795.29	65.48	3,140.09	433.06
36	4,782.96	64.02	3,062.14	398.40
37	4,770.63	62.59	2,986.11	366.52
38	4,758.30	61.20	2,911.94	337.18
39	4,745.97	59.83	2,839.60	310.19
40	4,733.63	57.55	2,724.37	280.76
41	4,721.30	55.36	2,613.80	254.12
42	4,708.97	53.25	2,507.70	230.00
43	4,696.64	51.23	2,405.89	208.18
44	4,684.31	49.28	2,308.20	188.42
45	4,671.98	47.40	2,214.46	170.53
46	4,659.65	45.59	2,124.51	154.35
47	4,647.32	43.86	2,038.20	139.69
48	4,634.99	42.19	1,955.38	126.43
49	4,622.66	40.58	1,875.92	114.43
50	4,610.33	38.28	1,765.04	101.57
51	4,598.00	36.12	1,660.70	90.16
52	4,585.67	34.07	1,562.52	80.03
53	4,573.34	32.15	1,470.14	71.03
54	4,561.01	30.33	1,383.20	63.05
55	4,548.68	28.61	1,301.40	55.96
56	4,536.35	26.99	1,224.42	49.67
57	4,524.02	25.46	1,151.99	44.09
58	4,511.69	24.02	1,083.84	39.13
59	4,499.36	22.66	1,019.71	34.73
60	4,487.03	21.38	959.37	30.83
Total	253,305.95		162,454.10	48,737.03

[a] *Discount rate 6%*

TABLE 85 *Average lifetime treatment costs for patients with sickle HbC (diagnosed early), and their calculation from annual treatment costs and survival*

Year	Annual cost per surviving patient (undiscounted £)	Survival rate (%)	Annual cost per original patient (undiscounted £)	Annual cost per original patient (discounted £)[a]
1	1,551.51	99.81	1,548.59	1,548.59
2	1,072.49	99.61	1,068.29	1,007.82
3	1,200.35	99.42	1,193.39	1,062.12
4	1,535.13	99.23	1,523.29	1,278.99
5	1,348.74	99.07	1,336.20	1,058.40
6	1,276.11	98.92	1,262.29	943.26
7	1,141.53	98.74	1,127.20	794.63
8	1,393.42	98.58	1,373.60	913.52
9	1,093.83	98.47	1,077.09	675.78
10	1,537.27	98.36	1,512.08	895.00
11	1,843.12	98.15	1,809.00	1,010.14
12	1,850.76	97.94	1,812.58	954.84
13	1,858.40	97.73	1,816.13	902.56
14	1,866.04	97.51	1,819.66	853.13
15	1,873.68	97.30	1,823.17	806.39
16	1,881.33	97.09	1,826.65	762.20
17	1,888.97	96.88	1,830.11	720.41
18	1,896.61	96.67	1,833.54	680.91
19	1,904.25	96.47	1,836.96	643.57
20	1,971.41	95.95	1,891.57	625.19
21	2,099.53	95.44	2,003.72	624.77
22	2,227.65	94.93	2,114.62	622.03
23	2,355.77	94.42	2,224.27	617.25
24	2,483.89	93.91	2,332.69	610.69
25	3,549.09	93.41	3,315.22	818.79
26	2,722.73	92.91	2,529.71	589.42
27	2,836.69	92.43	2,622.00	576.34
28	2,833.41	91.92	2,604.45	540.08
29	2,900.04	91.43	2,651.43	518.70
30	2,826.86	91.23	2,578.84	475.94
31	2,819.95	91.03	2,566.87	446.92
32	2,816.67	90.83	2,558.25	420.21
33	2,813.40	90.63	2,549.65	395.09
34	2,810.12	90.43	2,541.08	371.47
35	2,806.85	90.23	2,532.54	349.27
36	2,803.57	90.03	2,524.02	328.39
37	2,800.30	89.83	2,515.52	308.76
38	2,797.02	89.63	2,507.05	290.30
39	2,793.74	89.44	2,498.61	272.95
40	2,790.47	87.29	2,435.78	251.02
41	2,787.19	85.19	2,374.53	230.86
42	2,783.92	83.15	2,314.82	212.31
43	2,780.64	81.15	2,256.61	195.26
44	2,777.37	79.21	2,199.86	179.57
45	2,774.09	77.31	2,144.53	165.15
46	2,770.82	75.45	2,090.59	151.88
47	2,767.54	73.64	2,038.00	139.68
48	2,764.27	71.87	1,986.73	128.46
49	2,760.99	70.15	1,936.76	118.14
50	2,757.72	69.63	1,920.14	110.50
51	2,754.44	69.11	1,903.67	103.35
52	2,751.17	68.60	1,887.34	96.66
53	2,747.89	68.09	1,871.14	90.41
54	2,744.62	67.59	1,855.08	84.56
55	2,741.34	67.09	1,839.15	79.09
56	2,738.07	66.59	1,823.36	73.97
57	2,734.79	66.10	1,807.71	69.18
58	2,731.51	65.61	1,792.18	64.71
59	2,728.24	65.13	1,776.78	60.52
60	2,724.96	64.64	1,761.52	56.60
Total	141,994.30		121,108.25	29,976.66

[a] *Discount rate 6%*

TABLE 86 *Average lifetime treatment costs for patients with sickle HbC (diagnosed late), and their calculation from annual treatment costs and survival*

Year	Annual cost per surviving patient (undiscounted £)	Survival rate (%)	Annual cost per original patient (undiscounted £)	Annual cost per original patient (discounted £)[a]
1	546.69	99.63	544.67	544.67
2	1,212.77	99.28	1,204.02	1,135.87
3	1,200.35	98.97	1,188.00	1,057.31
4	1,535.13	98.67	1,514.73	1,271.80
5	1,395.93	98.47	1,374.59	1,088.80
6	1,291.63	98.28	1,269.46	948.62
7	1,157.05	98.13	1,135.45	800.45
8	1,408.94	98.00	1,380.81	918.31
9	1,109.35	97.89	1,085.93	681.32
10	1,552.79	97.79	1,518.48	898.79
11	1,858.64	97.58	1,813.65	1,012.73
12	1,866.28	97.37	1,817.17	957.26
13	1,873.92	97.16	1,820.67	904.82
14	1,881.56	96.95	1,824.15	855.23
15	1,889.21	96.74	1,827.60	808.35
16	1,896.85	96.53	1,831.03	764.03
17	1,904.49	96.32	1,834.44	722.12
18	1,912.13	96.11	1,837.82	682.50
19	1,919.78	95.91	1,841.18	645.05
20	1,986.94	95.39	1,895.40	626.45
21	2,115.05	94.88	2,006.82	625.74
22	2,243.17	94.38	2,117.00	622.73
23	2,371.29	93.87	2,225.94	617.71
24	2,499.41	93.37	2,333.65	610.94
25	3,564.62	92.87	3,310.40	817.60
26	2,738.25	92.37	2,529.37	589.34
27	2,852.21	91.88	2,620.54	576.02
28	2,848.94	91.39	2,603.52	539.89
29	2,915.56	90.90	2,650.15	518.45
30	2,842.38	90.70	2,577.96	475.78
31	2,819.95	90.50	2,551.98	444.33
32	2,816.67	90.30	2,543.41	417.77
33	2,813.40	90.10	2,534.86	392.80
34	2,810.12	89.90	2,526.34	369.32
35	2,806.85	89.70	2,517.84	347.24
36	2,803.57	89.51	2,509.37	326.48
37	2,800.30	89.31	2,500.93	306.97
38	2,797.02	89.11	2,492.51	288.62
39	2,793.74	88.92	2,484.11	271.36
40	2,790.47	86.78	2,421.65	249.56
41	2,787.19	84.70	2,360.76	229.52
42	2,783.92	82.67	2,301.39	211.08
43	2,780.64	80.68	2,243.52	194.13
44	2,777.37	78.75	2,187.09	178.53
45	2,774.09	76.86	2,132.08	164.19
46	2,770.82	75.01	2,078.46	151.00
47	2,767.54	73.21	2,026.18	138.87
48	2,764.27	71.46	1,975.21	127.71
49	2,760.99	69.74	1,925.52	117.45
50	2,757.72	69.22	1,909.00	109.85
51	2,754.44	68.71	1,892.62	102.75
52	2,751.17	68.20	1,876.39	96.10
53	2,747.89	67.70	1,860.28	89.88
54	2,744.62	67.20	1,844.32	84.07
55	2,741.34	66.70	1,828.48	78.63
56	2,738.07	66.21	1,812.78	73.54
57	2,734.79	65.72	1,797.22	68.78
58	2,731.51	65.23	1,781.78	64.33
59	2,728.24	64.75	1,766.47	60.17
60	2,724.96	64.27	1,751.30	56.27
Total	141,564.98		119,968.44	29,129.97

[a] *Discount rate 6%*

TABLE 87 *Antenatal ethnic and carrier composition, affected fetuses expected, and ICERs for choice offered and affected live births prevented, for district health authorities in the UK (1993 distribution): model predictions under baseline assumptions*

Regional health authority District health authority	%				Affected fetuses per 10,000 pregnancies			Programme costs £000 per 10,000 pregnancies		ICER £000	
	Ethnic minorities	Black groups	All carriers	Sickle carriers	Sickle cell disorders	Thalassaemias	Total	Universal	Selective	Choice offered	Affected live births prevented
E Anglia											
Cambridge	5.2	1.0	0.6	0.3	0.64	0.26	0.89	40	12	1,171	6,119
Great Yarmouth and Waveney	2.0	0.4	0.4	0.2	0.34	0.16	0.50	38	9	1,995	8,103
Huntingdon	4.8	1.9	0.7	0.5	0.92	0.26	1.18	40	11	868	5,287
NW Anglia	7.9	1.4	0.8	0.4	0.76	0.58	1.34	41	13	1,013	5,710
Norwich	2.1	0.4	0.4	0.2	0.27	0.13	0.40	37	8	2,296	8,604
Suffolk	5.5	2.9	0.9	0.6	1.37	0.14	1.51	39	11	600	4,202
Mersey											
Chester	1.9	0.3	0.4	0.2	0.18	0.11	0.29	37	8	2,952	9,564
Crewe	1.8	0.6	0.4	0.2	0.25	0.07	0.31	36	7	2,417	9,115
Halton	1.1	0.3	0.3	0.2	0.18	0.05	0.23	35	6	2,958	9,860
Liverpool	6.4	3.1	1.0	0.7	2.12	0.16	2.28	42	14	401	3,055
Macclesfield	2.0	0.4	0.4	0.2	0.30	0.10	0.40	37	8	2,136	8,557
S Sefton	1.5	0.4	0.4	0.2	0.31	0.06	0.37	36	7	2,074	8,498
Southport and Formby	2.2	0.3	0.4	0.2	0.15	0.13	0.27	37	8	3,217	9,642
St Helens and Knowsley	1.4	0.4	0.3	0.2	0.25	0.06	0.30	36	7	2,448	9,219
Warrington	2.6	0.4	0.4	0.2	0.28	0.15	0.44	37	8	2,245	8,547
Wirral	1.7	0.3	0.4	0.2	0.21	0.10	0.31	37	8	2,686	9,284
NE Thames											
Barking and Havering	9.0	3.3	1.2	0.8	2.47	0.46	2.94	46	18	344	2,681
Camden and Islington	40.7	18.4	5.6	4.0	16.49	2.35	18.85	99	80	37	348
E London and City	60.8	23.8	7.3	5.0	20.54	2.98	23.52	97	83	21	203
New River District	45.3	19.7	6.7	4.1	16.52	5.00	21.52	145	127	36	324
N Essex	3.5	0.7	0.5	0.3	0.51	0.19	0.70	39	10	1,441	6,861
Redbridge and Waltham Forest	41.6	14.4	4.6	3.1	10.92	2.45	13.37	81	63	55	504
S Essex	3.6	0.8	0.5	0.3	0.53	0.18	0.71	38	10	1,390	6,755

continued

TABLE 87 contd *Antenatal ethnic and carrier composition, affected fetuses expected, and ICERs for choice offered and affected live births prevented, for district health authorities in the UK (1993 distribution): model predictions under baseline assumptions*

Regional health authority District health authority	%				Affected fetuses per 10,000 pregnancies			Programme costs £000 per 10,000 pregnancies		ICER £000	
	Ethnic minorities	Black groups	All carriers	Sickle carriers	Sickle cell disorders	Thalassaemias	Total	Universal	Selective	Choice offered	Affected live births prevented
Northern											
E Cumbria	1.1	0.2	0.3	0.1	0.09	0.08	0.17	36	6	4,083	10,950
Gateshead	1.8	0.2	0.3	0.1	0.08	0.11	0.19	36	7	4,191	10,789
Hartlepool	1.2	0.2	0.3	0.1	0.17	0.09	0.27	35	6	2,993	9,864
Newcastle	7.6	0.7	0.7	0.3	0.70	0.57	1.27	41	14	1,050	5,732
N Durham	1.3	0.2	0.3	0.2	0.20	0.06	0.26	36	7	2,823	9,654
N Tees	3.0	0.3	0.4	0.2	0.27	0.28	0.56	37	9	2,296	8,605
N Tyneside	2.1	0.2	0.4	0.2	0.15	0.12	0.27	36	8	3,188	10,049
Northumberland	1.1	0.1	0.3	0.1	0.04	0.08	0.13	36	6	5,160	11,471
S Cumbria	1.0	0.2	0.3	0.2	0.15	0.05	0.20	35	6	3,290	10,188
S Durham	1.5	0.3	0.3	0.2	0.22	0.10	0.31	36	7	2,636	9,432
S Tees	4.9	0.7	0.5	0.3	0.49	0.45	0.94	38	10	1,481	7,082
S Tyneside	3.0	0.5	0.5	0.2	0.39	0.13	0.52	36	8	1,705	7,464
Sunderland	2.1	0.2	0.4	0.2	0.16	0.13	0.29	36	7	3,015	9,918
W Cumbria	0.8	0.2	0.3	0.1	0.08	0.06	0.14	35	6	4,243	11,089
North Western											
Blackpool, Wyre and Fylde	1.9	0.3	0.4	0.2	0.24	0.11	0.36	37	8	2,463	8,948
Blackburn, Hyndburn, Ribble Valley	19.0	0.6	1.3	0.4	0.64	1.64	2.28	46	21	1,197	5,219
Bolton	14.3	0.9	1.1	0.5	0.79	0.84	1.62	44	18	1,055	4,960
Burnley, Pendale, Rossendale	13.6	0.4	0.9	0.2	0.30	1.75	2.05	42	16	1,811	7,836
Bury	7.7	1.1	0.7	0.4	0.70	0.69	1.39	41	13	1,078	5,919
Central Manchester	38.0	15.6	4.1	3.0	9.23	2.07	11.30	65	45	67	634
Chorley and S Ribble	2.1	0.5	0.4	0.2	0.24	0.10	0.34	36	7	2,468	9,010
Lancaster	2.6	0.3	0.4	0.2	0.31	0.11	0.42	37	8	2,139	8,249
N Manchester	13.9	4.4	1.5	0.9	2.40	0.88	3.27	47	22	332	2,653
Oldham	19.3	1.5	1.4	0.4	0.69	1.97	2.66	44	20	797	5,064
Preston	16.4	2.1	1.4	0.7	1.21	0.69	1.90	45	20	674	3,769
Rochdale	14.5	0.9	1.0	0.3	0.52	1.67	2.19	43	18	1,197	6,338
Salford	3.9	0.9	0.5	0.3	0.55	0.17	0.72	38	9	1,327	6,595
S Manchester	15.8	4.4	1.6	1.0	2.20	0.96	3.16	46	21	351	2,630
Stockport	4.6	0.9	0.6	0.3	0.57	0.28	0.86	39	11	1,296	6,536
Tameside and Glossop	6.5	0.6	0.6	0.3	0.33	0.46	0.79	39	11	1,803	7,760
Trafford	9.8	2.8	1.1	0.7	1.36	0.51	1.87	44	17	594	3,982
W Lancashire	1.2	0.4	0.3	0.2	0.25	0.05	0.30	35	6	2,435	9,136
Wigan	1.6	0.4	0.4	0.2	0.34	0.08	0.42	36	7	1,967	8,301

continued

TABLE 87 contd *Antenatal ethnic and carrier composition, affected fetuses expected, and ICERs for choice offered and affected live births prevented, for district health authorities in the UK (1993 distribution): model predictions under baseline assumptions*

Regional health authority District health authority	%				Affected fetuses per 10,000 pregnancies			Programme costs £000 per 10,000 pregnancies		ICER £000	
	Ethnic minorities	Black groups	All carriers	Sickle carriers	Sickle cell disorders	Thalassaemias	Total	Universal	Selective	Choice offered	Affected live births prevented
NW Thames											
Barnet	33.9	7.9	3.7	2.2	8.46	2.24	10.69	94	74	80	680
Brent and Harrow	55.6	17.4	5.7	4.0	13.56	1.94	15.50	92	77	36	325
E and N Hertfordshire	6.5	1.3	0.8	0.4	0.81	0.33	1.14	41	13	964	5,375
Ealing, Hammersmith, Hounslow	39.8	11.2	4.0	2.7	8.70	1.45	10.14	71	53	71	622
Hillingdon	19.9	2.7	1.7	0.9	2.18	0.84	3.02	52	28	362	2,427
Kensington, Chelsea, Westminster	41.1	16.5	4.9	3.7	14.25	1.28	15.53	79	61	43	390
NW Hertfordshire	7.5	1.3	0.8	0.4	0.83	0.41	1.25	41	13	895	5,181
N Bedfordshire	14.8	3.4	1.4	0.8	1.84	0.61	2.45	44	19	423	3,101
SW Hertfordshire	10.9	1.8	1.0	0.6	1.21	0.71	1.92	45	18	657	4,022
S Bedfordshire	21.1	4.8	1.9	1.0	2.53	1.51	4.05	48	25	285	2,313
Oxford											
Buckinghamshire	10.4	2.3	1.0	0.6	1.25	0.73	1.99	43	16	626	4,149
E Berkshire	18.0	2.2	1.4	0.7	1.31	1.24	2.55	47	23	593	3,654
Kettering	5.4	1.5	0.7	0.4	0.74	0.17	0.90	38	10	1,060	5,958
Northampton	7.4	2.6	0.9	0.6	1.29	0.29	1.58	41	14	622	4,249
Oxfordshire	6.6	1.9	0.8	0.5	1.05	0.35	1.40	40	13	759	4,759
W Berkshire	8.0	2.6	1.0	0.6	1.50	0.38	1.88	42	14	547	3,835
Scotland											
Angus	1.1	0.4	0.3	0.2	0.18	0.04	0.22	35	6	2,954	9,941
Argyll and Clyde	1.5	0.4	0.3	0.2	0.26	0.06	0.31	35	6	2,371	9,079
Ayreshire and Arran	0.9	0.1	0.3	0.1	0.07	0.05	0.12	35	6	4,530	11,182
Borders	0.4	0.1	0.2	0.1	0.10	0.02	0.12	34	5	4,038	11,033
Central (Forth Valley)	1.2	0.1	0.3	0.1	0.10	0.09	0.19	35	6	3,984	10,801
Dumfries and Galloway	0.6	0.1	0.2	0.1	0.06	0.03	0.09	35	5	4,689	11,496
Dundee City	3.9	0.3	0.5	0.2	0.30	0.28	0.58	38	9	2,108	8,260
Fife	1.3	0.2	0.3	0.2	0.14	0.09	0.23	35	6	3,335	10,259
Grampian	1.6	0.3	0.3	0.2	0.29	0.05	0.34	36	7	2,184	8,565
Greater Glasgow	5.6	0.4	0.5	0.2	0.38	0.50	0.88	39	11	1,823	7,670
Highland	0.9	0.2	0.3	0.2	0.13	0.04	0.17	35	6	3,471	10,352
Lanarkshire	1.4	0.1	0.3	0.1	0.11	0.11	0.21	35	6	3,832	10,644
Lothian	3.2	0.4	0.4	0.2	0.35	0.19	0.54	38	9	1,917	7,948
Orkney	0.4	0.0	0.2	0.1	0.04	0.01	0.05	34	5	5,043	10,966
Perth and Kinross	1.0	0.1	0.3	0.1	0.07	0.05	0.12	36	6	4,420	10,996
Shetland	1.2	0.2	0.3	0.2	0.09	0.03	0.12	35	5	4,024	10,578
Western Isles	0.6	0.1	0.2	0.1	0.04	0.04	0.07	34	5	5,314	11,722

continued

TABLE 87 contd *Antenatal ethnic and carrier composition, affected fetuses expected, and ICERs for choice offered and affected live births prevented, for district health authorities in the UK (1993 distribution): model predictions under baseline assumptions*

Regional health authority District health authority	%				Affected fetuses per 10,000 pregnancies			Programme costs £000 per 10,000 pregnancies		ICER £000	
	Ethnic minorities	Black groups	All carriers	Sickle carriers	Sickle cell disorders	Thalassaemias	Total	Universal	Selective	Choice offered	Affected live births prevented
SE Thames											
Bexley	9.4	2.6	1.2	0.7	2.11	0.49	2.61	48	21	402	2,932
Bromley	8.9	3.0	1.1	0.7	2.01	0.43	2.44	46	19	415	3,041
Canterbury and Thanet	2.9	0.8	0.5	0.3	0.69	0.20	0.89	39	10	1,138	6,128
Dartford and Gravesham	7.6	0.9	0.8	0.4	0.73	0.28	1.01	41	13	1,118	5,539
E Sussex	3.9	0.9	0.6	0.3	0.71	0.20	0.91	39	10	1,093	5,860
Greenwich	23.2	11.2	3.2	2.5	9.59	0.79	10.37	65	42	80	726
Maidstone	2.7	0.6	0.4	0.3	0.47	0.13	0.60	37	8	1,537	7,196
Medway	4.8	0.9	0.6	0.3	0.65	0.24	0.89	39	11	1,202	6,161
SE Kent	2.6	0.6	0.4	0.2	0.42	0.16	0.58	38	9	1,697	7,583
SE London	48.7	36.0	8.2	7.1	29.75	1.23	30.98	104	87	19	186
Tunbridge Wells	2.0	0.3	0.4	0.2	0.33	0.11	0.44	37	8	1,992	8,162
South Western											
Bristol and District	6.1	2.3	0.8	0.5	1.16	0.28	1.43	40	12	700	4,614
Cornwall and Scilly	1.1	0.3	0.3	0.2	0.16	0.08	0.24	36	6	3,145	10,008
Exeter and N Devon	1.5	0.2	0.3	0.2	0.18	0.09	0.28	36	7	2,943	9,510
Gloucestershire	3.9	1.3	0.6	0.4	0.65	0.17	0.83	38	10	1,173	6,314
Plymouth and Torbay	1.5	0.4	0.4	0.2	0.26	0.12	0.38	37	8	2,364	8,889
Somerset	1.4	0.3	0.3	0.2	0.23	0.10	0.32	36	7	2,576	9,306
SW Thames											
Chichester	2.0	0.3	0.4	0.2	0.29	0.13	0.42	37	8	2,161	8,377
Croydon	28.3	13.3	3.5	2.8	9.24	0.86	10.10	65	43	78	714
E Surrey	3.5	0.5	0.5	0.2	0.42	0.19	0.62	38	9	1,667	7,289
Kingston and Richmond	12.1	2.8	1.3	0.8	2.14	0.50	2.64	49	23	380	2,738
Merton and Sutton	18.3	6.7	2.2	1.6	5.50	0.67	6.17	57	33	144	1,249
Mid Downs	6.4	0.6	0.6	0.3	0.52	0.38	0.90	40	12	1,435	6,567
Mid Surrey	6.8	0.8	0.7	0.3	0.69	0.32	1.01	43	16	1,106	5,696
NW Surrey	7.1	0.7	0.7	0.3	0.53	0.47	1.01	41	13	1,355	6,386
SW Surrey	3.0	0.4	0.4	0.2	0.36	0.17	0.53	38	9	1,861	7,777
Wandsworth Surrey	36.6	20.0	5.0	4.0	15.10	1.11	16.21	77	57	43	414
Worthing	3.2	0.5	0.5	0.2	0.48	0.16	0.65	38	9	1,487	7,022

continued

TABLE 87 contd *Antenatal ethnic and carrier composition, affected fetuses expected, and ICERs for choice offered and affected live births prevented, for district health authorities in the UK (1993 distribution): model predictions under baseline assumptions*

Regional health authority District health authority	%				Affected fetuses per 10,000 pregnancies			Programme costs £000 per 10,000 pregnancies		ICER £000	
	Ethnic minorities	Black groups	All carriers	Sickle carriers	Sickle cell disorders	Thalassaemias	Total	Universal	Selective	Choice offered	Affected live births prevented
Trent											
Barnsley	1.3	0.3	0.3	0.2	0.20	0.09	0.29	36	7	2,788	9,619
Doncaster	3.1	0.7	0.5	0.2	0.31	0.21	0.52	37	9	2,121	8,440
Leicestershire	18.1	1.8	1.5	0.8	1.29	0.63	1.92	47	22	643	3,500
N Nottinghamshire	1.8	0.6	0.4	0.2	0.29	0.09	0.38	36	7	2,221	8,822
N Derbyshire	1.7	0.4	0.3	0.2	0.24	0.07	0.32	36	7	2,462	9,115
N Lincolnshire	1.9	0.5	0.4	0.2	0.27	0.20	0.46	38	9	2,353	8,792
Nottingham	11.4	4.4	1.3	0.9	1.98	0.51	2.48	43	16	408	3,122
Rotherham	4.2	0.4	0.5	0.2	0.23	0.46	0.69	37	8	2,546	9,126
Sheffield	11.4	3.3	1.2	0.8	1.87	0.73	2.60	43	17	424	3,157
S Lincolnshire	2.0	0.5	0.4	0.2	0.32	0.18	0.51	38	9	2,066	8,395
S Derbyshire	8.4	2.0	0.9	0.5	0.96	0.46	1.42	40	13	829	5,025
Wales											
Clwyd	1.3	0.2	0.3	0.2	0.12	0.08	0.20	36	6	3,569	10,443
Dyfed	1.7	0.1	0.3	0.1	0.11	0.08	0.19	36	7	3,704	10,395
Gwent	3.0	0.5	0.4	0.2	0.30	0.19	0.49	36	8	2,079	8,390
Gwynedd	1.8	0.3	0.3	0.2	0.23	0.10	0.33	36	7	2,496	8,961
Mid Glamorgan	1.5	0.2	0.3	0.2	0.13	0.08	0.21	36	7	3,492	10,306
Powys	1.0	0.2	0.3	0.2	0.10	0.06	0.15	35	6	3,954	10,804
S Glamorgan	9.0	2.7	1.1	0.7	1.87	0.43	2.30	43	15	438	3,186
W Glamorgan	3.0	0.3	0.4	0.2	0.21	0.14	0.35	37	8	2,514	8,906
Wessex											
Bath	2.8	1.0	0.5	0.3	0.49	0.14	0.63	37	9	1,479	7,302
Basingstoke and N Hampshire	3.4	1.0	0.5	0.3	0.55	0.19	0.74	39	10	1,352	6,813
Dorset	2.2	0.4	0.4	0.2	0.32	0.13	0.45	37	8	2,021	8,178
Isle of Wight	1.6	0.4	0.4	0.2	0.25	0.09	0.34	36	7	2,424	9,001
Portsmouth and SE Hampshire	2.8	0.6	0.5	0.3	0.51	0.15	0.65	37	9	1,429	6,996
Salisbury	1.9	0.5	0.4	0.2	0.28	0.17	0.45	37	8	2,210	8,683
Southampton and SW Hampshire	5.2	1.0	0.6	0.3	0.57	0.26	0.83	39	11	1,315	6,470
Swindon	5.2	1.2	0.6	0.4	0.62	0.25	0.87	39	11	1,225	6,290
Winchester	2.4	0.4	0.4	0.2	0.21	0.16	0.37	38	9	2,701	9,214

continued

TABLE 87 contd *Antenatal ethnic and carrier composition, affected fetuses expected, and ICERs for choice offered and affected live births prevented, for district health authorities in the UK (1993 distribution): model predictions under baseline assumptions*

Regional health authority District health authority	%				Affected fetuses per 10,000 pregnancies			Programme costs £000 per 10,000 pregnancies		ICER £000	
	Ethnic minorities	Black groups	All carriers	Sickle carriers	Sickle cell disorders	Thalassaemias	Total	Universal	Selective	Choice offered	Affected live births prevented
W Midlands											
Coventry	16.6	2.8	1.5	0.8	1.57	0.72	2.28	45	20	508	3,298
Dudley	8.8	2.1	0.9	0.5	0.95	0.58	1.53	40	13	824	5,029
E Birmingham	38.9	5.1	2.7	1.1	2.35	4.03	6.37	57	38	241	1,958
Herefordshire	1.3	0.3	0.3	0.2	0.18	0.09	0.27	36	7	2,959	9,636
Mid Staffordshire	2.4	0.6	0.4	0.2	0.36	0.12	0.48	37	8	1,910	8,089
N Birmingham	11.4	5.0	1.4	1.0	2.14	0.49	2.63	44	18	377	2,978
N Staffordshire	4.8	0.7	0.5	0.3	0.38	0.43	0.81	38	10	1,769	7,825
N Worcestershire	4.1	1.1	0.6	0.3	0.58	0.25	0.84	38	9	1,263	6,671
SE Staffordshire	4.5	0.9	0.5	0.3	0.44	0.38	0.82	38	10	1,603	7,429
Sandwell	23.4	5.0	2.0	1.2	2.45	1.09	3.54	48	25	302	2,290
Shropshire	3.3	0.7	0.5	0.3	0.39	0.20	0.59	38	9	1,767	7,742
Solihull	5.9	2.0	0.8	0.5	0.90	0.23	1.13	40	12	888	5,352
S Birmingham	28.0	6.2	2.4	1.4	3.14	1.98	5.12	53	32	217	1,773
Walsall	16.1	2.3	1.3	0.7	1.14	1.07	2.21	44	19	666	4,121
Warwickshire	5.9	0.9	0.6	0.4	0.52	0.21	0.73	39	11	1,477	6,590
W Birmingham	54.3	17.0	5.0	3.3	8.20	2.63	10.83	72	57	58	551
Wolverhampton	27.5	8.7	2.7	1.9	4.05	0.73	4.77	53	31	179	1501
Worcester and District	2.7	0.2	0.4	0.2	0.11	0.23	0.34	37	8	3,667	10,231
Yorkshire											
Bradford	27.7	1.9	1.8	0.6	1.16	3.00	4.16	50	29	555	3,583
E Riding	1.8	0.5	0.4	0.2	0.32	0.11	0.43	37	8	2,043	8,475
Grimsby and Scunthorpe	2.3	0.4	0.4	0.2	0.27	0.16	0.43	37	8	2,226	8,737
Leeds	11.2	2.8	1.1	0.7	1.52	0.64	2.15	43	16	521	3,629
N Yorkshire	1.7	0.3	0.4	0.2	0.19	0.15	0.34	37	8	2,856	9,498
Wakefield	3.0	0.3	0.4	0.2	0.20	0.30	0.50	37	8	2,830	9,501
W Yorkshire	16.5	2.1	1.3	0.6	1.08	1.48	2.56	44	20	696	4,301

TABLE 88 *Main neonatal screening outcomes, costs and ICERs for late diagnosis of sickle cell disease prevented for district health authorities in Great Britain (1993 distribution): model predictions under baseline assumptions, per 10,000 antenatal population*

Regional health authority District health authority	**Fetal SCD prevalence 10^{-4}**	**Antenatal/ neonatal programme combination**	**SCD identified antenatally 10^{-4}**	**Newborns tested**		**SCD diagnosed late 10^{-4}**	**Neonatal screening costs (£)**	**Late diagnosis prevented ICER (£000)**
				SCD identified neonatally 10^{-4}	**Sickle carriers identified neonatally 10^{-4}**			
E Anglia								
Cambridge	0.64	Universal/selective	0.11	0.49	19	0.031	1,081	670
		Universal/universal		0.52	34	0.002	20,953	
		Selective/selective	0.10	0.49	19	0.034	1,082	606
		Selective/universal		0.53	34	0.002	20,964	
Great Yarmouth and Waveney	0.34	Universal/selective	0.06	0.25	8	0.017	411	1,247
		Universal/universal		0.27	23	0.001	20,921	
		Selective/selective	0.06	0.25	8	0.020	411	1,045
		Selective/universal		0.27	23	0.001	20,931	
Huntingdon	0.92	Universal/selective	0.14	0.72	26	0.045	1,020	468
		Universal/universal		0.76	42	0.002	20,977	
		Selective/selective	0.13	0.73	26	0.048	1,021	435
		Selective/universal		0.77	42	0.002	20,988	
NW Anglia	0.76	Universal/selective	0.13	0.59	23	0.037	1,630	552
		Universal/universal		0.62	38	0.002	20,965	
		Selective/selective	0.12	0.59	23	0.040	1,631	508
		Selective/universal		0.63	38	0.002	20,975	
Norwich	0.27	Universal/selective	0.05	0.20	8	0.014	431	1,531
		Universal/universal		0.21	23	0.001	20,919	
		Selective/selective	0.05	0.20	8	0.017	432	1,239
		Selective/universal		0.22	23	0.001	20,930	
Suffolk	1.37	Universal/selective	0.19	1.09	39	0.067	1,200	312
		Universal/universal		1.16	55	0.003	21,018	
		Selective/selective	0.18	1.10	39	0.070	1,202	297
		Selective/universal		1.17	55	0.004	21,029	
Mersey								
Chester	0.18	Universal/selective	0.04	0.13	6	0.010	386	2,190
		Universal/universal		0.14	20	0.000	20,912	
		Selective/selective	0.03	0.13	6	0.013	387	1,641
		Selective/universal		0.14	21	0.000	20,922	
Crewe	0.25	Universal/selective	0.04	0.19	8	0.013	378	1,616
		Universal/universal		0.20	23	0.001	20,920	
		Selective/selective	0.04	0.19	8	0.016	378	1,295
		Selective/universal		0.20	23	0.001	20,930	
Halton	0.18	Universal/selective	0.03	0.13	5	0.010	228	2,127
		Universal/universal		0.14	20	0.000	20,910	
		Selective/selective	0.03	0.13	5	0.013	229	1,606
		Selective/universal		0.15	20	0.000	20,921	
Liverpool	2.12	Universal/selective	0.29	1.70	47	0.103	1,429	201
		Universal/universal		1.80	64	0.005	21,057	
		Selective/selective	0.28	1.71	47	0.106	1,431	194
		Selective/universal		1.81	64	0.005	21,068	
Macclesfield	0.3	Universal/selective	0.05	0.23	8	0.016	424	1,354
		Universal/universal		0.25	23	0.001	20,920	
		Selective/selective	0.05	0.23	8	0.019	424	1,120
		Selective/universal		0.25	23	0.001	20,930	

continued

TABLE 88 contd *Main neonatal screening outcomes, costs and ICERs for late diagnosis of sickle cell disease prevented for district health authorities in Great Britain (1993 distribution): model predictions under baseline assumptions, per 10,000 antenatal population*

Regional health authority District health authority	**Fetal SCD prevalence 10^{-4}**	**Antenatal/ neonatal programme combination**	**SCD identified antenatally 10^{-4}**	**Newborns tested**		**SCD diagnosed late 10^{-4}**	**Neonatal screening costs (£)**	**Late diagnosis prevented ICER (£000)**
				SCD identified neonatally 10^{-4}	**Sickle carriers identified neonatally 10^{-4}**			
Mersey contd								
S Sefton	0.31	Universal/selective	0.05	0.24	8	0.017	326	1,299
		Universal/universal		0.26	22	0.001	20,920	
		Selective/selective	0.05	0.24	8	0.020	327	1,083
		Selective/universal		0.26	22	0.001	20,930	
Southport and Formby	0.15	Universal/selective	0.04	0.10	7	0.008	448	2,624
		Universal/universal		0.11	21	0.000	20,913	
		Selective/selective	0.03	0.10	7	0.011	448	1,874
		Selective/universal		0.11	21	0.000	20,923	
St Helens and Knowsley	0.25	Universal/selective	0.04	0.19	7	0.013	298	1,613
		Universal/universal		0.20	22	0.001	20,916	
		Selective/selective	0.04	0.19	7	0.017	299	1,294
		Selective/universal		0.20	22	0.001	20,927	
Warrington	0.28	Universal/selective	0.06	0.21	9	0.015	535	1,465
		Universal/universal		0.22	23	0.001	20,921	
		Selective/selective	0.05	0.21	9	0.018	535	1,195
		Selective/universal		0.23	23	0.001	20,931	
Wirral	0.21	Universal/selective	0.04	0.15	6	0.011	357	1,886
		Universal/universal		0.17	21	0.000	20,913	
		Selective/selective	0.04	0.16	6	0.015	357	1,464
		Selective/universal		0.17	21	0.001	20,924	
NE Thames								
Barking and Havering	2.47	Universal/selective	0.36	1.97	54	0.119	1,961	170
		Universal/universal		2.08	70	0.006	21,081	
		Selective/selective	0.34	1.98	54	0.122	1,962	165
		Selective/universal		2.09	70	0.006	21,092	
Camden and Islington	16.49	Universal/selective	2.25	13.26	316	0.787	9,134	17
		Universal/universal		14.00	343	0.042	22,041	
		Selective/selective	2.18	13.33	317	0.793	9,145	17
		Selective/universal		14.08	343	0.042	22,059	
E London and City	20.54	Universal/selective	2.76	16.56	438	0.982	13,505	10
		Universal/universal		17.49	468	0.053	22,455	
		Selective/selective	2.67	16.64	438	0.988	13,520	10
		Selective/universal		17.57	468	0.053	22,475	
New River District	16.52	Universal/selective	2.41	13.14	317	0.780	10,017	16
		Universal/universal		13.88	342	0.042	22,010	
		Selective/selective	2.33	13.21	317	0.786	10,028	16
		Selective/universal		13.95	342	0.042	22,028	
N Essex	0.51	Universal/selective	0.09	0.39	14	0.025	726	843
		Universal/universal		0.41	29	0.001	20,939	
		Selective/selective	0.09	0.39	14	0.028	726	745
		Selective/universal		0.42	29	0.001	20,949	
Redbridge and Waltham Forest	10.92	Universal/selective	1.57	8.70	239	0.517	9,016	26
		Universal/universal		9.19	261	0.028	21,721	
		Selective/selective	1.52	8.75	239	0.522	9,024	26
		Selective/universal		9.24	261	0.028	21,736	
South Essex	0.53	Universal/selective	0.09	0.41	15	0.026	756	807
		Universal/universal		0.43	30	0.001	20,942	
		Selective/selective	0.09	0.41	15	0.029	756	717
		Selective/universal		0.44	30	0.001	20,952	

continued

TABLE 88 contd *Main neonatal screening outcomes, costs and ICERs for late diagnosis of sickle cell disease prevented for district health authorities in Great Britain (1993 distribution): model predictions under baseline assumptions, per 10,000 antenatal population*

Regional health authority District health authority	**Fetal SCD prevalence 10^{-4}**	**Antenatal/ neonatal programme combination**	**SCD identified antenatally 10^{-4}**	**Newborns tested**		**SCD diagnosed late 10^{-4}**	**Neonatal screening costs (£)**	**Late diagnosis prevented ICER (£000)**
				SCD identified neonatally 10^{-4}	**Sickle carriers identified neonatally 10^{-4}**			
Northern								
E Cumbria	0.09	Universal/selective	0.02	0.06	3	0.006	224	3,718
		Universal/universal		0.06	18	0.000	20,904	
		Selective/selective	0.02	0.06	3	0.009	224	2,378
		Selective/universal		0.07	18	0.000	20,915	
Gateshead	0.08	Universal/selective	0.02	0.05	4	0.005	363	4,024
		Universal/universal		0.06	19	0.000	20,906	
		Selective/selective	0.02	0.05	4	0.008	363	2,500
		Selective/universal		0.06	19	0.000	20,917	
Hartlepool	0.17	Universal/selective	0.03	0.13	5	0.010	256	2,197
		Universal/universal		0.14	19	0.000	20,909	
		Selective/selective	0.03	0.13	5	0.013	257	1,646
		Selective/universal		0.14	19	0.000	20,920	
Newcastle	0.70	Universal/selective	0.12	0.54	20	0.034	1,561	600
		Universal/universal		0.57	35	0.002	20,960	
		Selective/selective	0.11	0.54	20	0.037	1,562	548
		Selective/universal		0.58	35	0.002	20,971	
N Durham	0.20	Universal/selective	0.04	0.15	5	0.011	279	1,978
		Universal/universal		0.16	20	0.000	20,911	
		Selective/selective	0.03	0.15	5	0.014	279	1,520
		Selective/universal		0.16	20	0.000	20,921	
N Tees	0.27	Universal/selective	0.05	0.20	7	0.014	612	1,489
		Universal/universal		0.22	21	0.001	20,916	
		Selective/selective	0.05	0.20	7	0.017	613	1,212
		Selective/universal		0.22	21	0.001	20,926	
N Tyneside	0.15	Universal/selective	0.03	0.10	6	0.008	431	2,530
		Universal/universal		0.11	21	0.000	20,913	
		Selective/selective	0.03	0.11	6	0.012	431	1,827
		Selective/universal		0.12	21	0.000	20,923	
Northumberland	0.04	Universal/selective	0.02	0.02	2	0.004	222	5,932
		Universal/universal		0.03	17	0.000	20,900	
		Selective/selective	0.01	0.02	2	0.007	222	3,127
		Selective/universal		0.03	17	0.000	20,910	
S Cumbria	0.15	Universal/selective	0.03	0.11	4	0.009	207	2,477
		Universal/universal		0.12	18	0.000	20,907	
		Selective/selective	0.03	0.11	4	0.012	207	1,798
		Selective/universal		0.12	19	0.000	20,917	
S Durham	0.22	Universal/selective	0.04	0.16	7	0.012	315	1,829
		Universal/universal		0.17	21	0.001	20,915	
		Selective/selective	0.04	0.16	7	0.015	316	1,429
		Selective/universal		0.18	21	0.001	20,925	
S Tees	0.49	Universal/selective	0.08	0.37	13	0.024	1,009	860
		Universal/universal		0.40	28	0.001	20,936	
		Selective/selective	0.08	0.38	13	0.027	1,009	759
		Selective/universal		0.40	28	0.001	20,947	
S Tyneside	0.39	Universal/selective	0.07	0.30	13	0.02	640	1,080
		Universal/universal		0.31	28	0.001	20,936	
		Selective/selective	0.07	0.30	13	0.023	640	925
		Selective/universal		0.32	28	0.001	20,946	

continued

TABLE 88 contd *Main neonatal screening outcomes, costs and ICERs for late diagnosis of sickle cell disease prevented for district health authorities in Great Britain (1993 distribution): model predictions under baseline assumptions, per 10,000 antenatal population*

Regional health authority District health authority	**Fetal SCD prevalence 10^{-4}**	**Antenatal/ neonatal programme combination**	**SCD identified antenatally 10^{-4}**	**Newborns tested**		**SCD diagnosed late 10^{-4}**	**Neonatal screening costs (£)**	**Late diagnosis prevented ICER (£000)**
				SCD identified neonatally 10^{-4}	**Sickle carriers identified neonatally 10^{-4}**			
Northern contd								
Sunderland	0.16	Universal/selective	0.03	0.11	7	0.009	432	2,401
		Universal/universal		0.12	21	0.000	20,915	
		Selective/selective	0.03	0.11	7	0.012	432	1,758
		Selective/universal		0.12	21	0.000	20,925	
W Cumbria	0.08	Universal/selective	0.02	0.05	3	0.006	173	3,883
		Universal/universal		0.06	18	0.000	20,903	
		Selective/selective	0.02	0.06	3	0.009	174	2,445
		Selective/universal		0.06	18	0.000	20,914	
North Western								
Blackpool, Wyre and Fylde	0.24	Universal/selective	0.05	0.18	7	0.013	386	1,662
		Universal/universal		0.19	21	0.001	20,915	
		Selective/selective	0.04	0.18	7	0.016	386	1,324
		Selective/universal		0.20	21	0.001	20,926	
Blackburn, Hyndburn, Ribble Valley	0.64	Universal/selective	0.19	0.42	30	0.027	3,845	668
		Universal/universal		0.45	44	0.001	20,980	
		Selective/selective	0.18	0.43	30	0.030	3,846	604
		Selective/universal		0.46	44	0.001	20,989	
Bolton	0.79	Universal/selective	0.21	0.53	34	0.033	2,930	570
		Universal/universal		0.56	48	0.002	20,993	
		Selective/selective	0.21	0.53	34	0.036	2,931	522
		Selective/universal		0.57	48	0.002	21,003	
Burnley, Pendale, Rossendale	0.30	Universal/selective	0.05	0.23	14	0.015	2,723	1,239
		Universal/universal		0.24	28	0.001	20,935	
		Selective/selective	0.05	0.23	14	0.018	2,724	1,041
		Selective/universal		0.25	28	0.001	20,945	
Bury	0.70	Universal/selective	0.11	0.54	20	0.034	1,579	596
		Universal/universal		0.57	34	0.002	20,956	
		Selective/selective	0.11	0.55	20	0.037	1,579	545
		Selective/universal		0.58	34	0.002	20,966	
Central Manchester	0.23	Universal/selective	1.21	7.46	226	0.444	8,229	32
		Universal/universal		7.88	248	0.024	21,653	
		Selective/selective	1.17	7.50	226	0.448	8,236	32
		Selective/universal		7.92	248	0.024	21,667	
Chorley and S Ribble	0.24	Universal/selective	0.05	0.18	8	0.013	430	1,667
		Universal/universal		0.19	23	0.001	20,919	
		Selective/selective	0.04	0.18	8	0.016	431	1,328
		Selective/universal		0.20	23	0.001	20,929	
Lancaster	0.31	Universal/selective	0.06	0.23	8	0.016	536	1,366
		Universal/universal		0.24	23	0.001	20,921	
		Selective/selective	0.06	0.23	8	0.019	536	1,128
		Selective/universal		0.25	23	0.001	20,932	
N Manchester	2.40	Universal/selective	0.33	1.92	61	0.116	2,940	165
		Universal/universal		2.03	78	0.006	21,095	
		Selective/selective	0.32	1.93	62	0.119	2,942	161
		Selective/universal		2.04	78	0.006	21,106	

continued

TABLE 88 contd *Main neonatal screening outcomes, costs and ICERs for late diagnosis of sickle cell disease prevented for district health authorities in Great Britain (1993 distribution): model predictions under baseline assumptions, per 10,000 antenatal population*

Regional health authority District health authority	**Fetal SCD prevalence 10^{-4}**	**Antenatal/ neonatal programme combination**	**SCD identified antenatally 10^{-4}**	**Newborns tested**		**SCD diagnosed late 10^{-4}**	**Neonatal screening costs (£)**	**Late diagnosis prevented ICER (£000)**
				SCD identified neonatally 10^{-4}	**Sickle carriers identified neonatally 10^{-4}**			
North Western contd								
Oldham	0.69	Universal/selective	0.11	0.54	45	0.034	3,943	535
		Universal/universal		0.57	59	0.002	21,023	
		Selective/selective	0.11	0.54	45	0.036	3,944	493
		Selective/universal		0.57	59	0.002	21,033	
Preston	1.21	Universal/selective	0.29	0.86	51	0.053	3,385	354
		Universal/universal		0.91	66	0.003	21,044	
		Selective/selective	0.28	0.86	51	0.056	3,387	334
		Selective/universal		0.91	66	0.003	21,054	
Rochdale	0.52	Universal/selective	0.09	0.40	22	0.026	2,929	735
		Universal/universal		0.43	36	0.001	20,960	
		Selective/selective	0.08	0.40	22	0.029	2,929	660
		Selective/universal		0.43	36	0.001	20,969	
Salford	0.55	Universal/selective	0.09	0.42	17	0.027	823	774
		Universal/universal		0.45	32	0.001	20,947	
		Selective/selective	0.09	0.43	17	0.031	823	690
		Selective/universal		0.46	32	0.001	20,958	
S Manchester	2.20	Universal/selective	0.33	1.74	67	0.105	3,316	179
		Universal/universal		1.84	83	0.006	21,103	
		Selective/selective	0.32	1.75	67	0.108	3,318	173
		Selective/universal		1.85	83	0.006	21,114	
Stockport	0.57	Universal/selective	0.10	0.44	16	0.028	963	742
		Universal/universal		0.47	31	0.001	20,946	
		Selective/selective	0.09	0.44	16	0.032	963	665
		Selective/universal		0.47	31	0.001	20,956	
Tameside and Glossop	0.33	Universal/selective	0.07	0.24	18	0.017	1,341	1,243
		Universal/universal		0.26	32	0.001	20,946	
		Selective/selective	0.07	0.24	18	0.020	1,342	1,043
		Selective/universal		0.26	32	0.001	20,956	
Trafford	1.36	Universal/selective	0.22	1.06	44	0.065	2,074	309
		Universal/universal		1.12	59	0.003	21,028	
		Selective/selective	0.21	1.06	44	0.068	2,075	294
		Selective/universal		1.13	59	0.003	21,039	
W Lancashire	0.25	Universal/selective	0.04	0.19	7	0.013	261	1,606
		Universal/universal		0.20	21	0.001	20,916	
		Selective/selective	0.04	0.19	7	0.017	261	1,289
		Selective/universal		0.21	21	0.001	20,926	
Wigan	0.34	Universal/selective	0.06	0.26	8	0.018	351	1,205
		Universal/universal		0.28	23	0.001	20,921	
		Selective/selective	0.05	0.27	8	0.021	351	1,016
		Selective/universal		0.29	23	0.001	20,932	
NW Thames								
Barnet	8.46	Universal/selective	1.32	6.64	163	0.395	7,249	38
		Universal/universal		7.02	182	0.021	21,472	
		Selective/selective	1.28	6.68	163	0.399	7,254	38
		Selective/universal		7.06	182	0.021	21,485	
Brent and Harrow	13.56	Universal/selective	2.05	10.71	307	0.636	11,989	17
		Universal/universal		11.31	331	0.034	21,949	
		Selective/selective	1.99	10.77	308	0.640	11,999	16
		Selective/universal		11.37	331	0.034	21,964	

continued

TABLE 88 contd *Main neonatal screening outcomes, costs and ICERs for late diagnosis of sickle cell disease prevented for district health authorities in Great Britain (1993 distribution): model predictions under baseline assumptions, per 10,000 antenatal population*

Regional health authority District health authority	**Fetal SCD prevalence 10^{-4}**	**Antenatal/ neonatal programme combination**	**SCD identified antenatally 10^{-4}**	**Newborns tested**		**SCD diagnosed late 10^{-4}**	**Neonatal screening costs (£)**	**Late diagnosis prevented ICER (£000)**
				SCD identified neonatally 10^{-4}	**Sickle carriers identified neonatally 10^{-4}**			
NW Thames contd								
E and N Hertfordshire	0.81	Universal/selective	0.15	0.62	25	0.039	1,367	532
		Universal/universal		0.66	40	0.002	20,970	
		Selective/selective	0.14	0.62	25	0.042	1,368	490
		Selective/universal		0.66	40	0.002	20,981	
Ealing, Hammersmith, Hounslow	8.70	Universal/selective	1.34	6.84	205	0.407	8,538	34
		Universal/universal		7.23	226	0.022	21,589	
		Selective/selective	1.30	6.88	205	0.411	8,545	34
		Selective/universal		7.27	226	0.022	21,602	
Hillingdon	2.18	Universal/selective	0.44	1.62	69	0.098	4,144	183
		Universal/universal		1.72	85	0.005	21,110	
		Selective/selective	0.42	1.63	69	0.101	4,146	177
		Selective/universal		1.73	85	0.005	21,120	
Kensington, Chelsea, Westminster	14.25	Universal/selective	1.94	11.45	288	0.680	9,110	20
		Universal/universal		12.10	313	0.036	21,920	
		Selective/selective	1.88	11.51	288	0.685	9,120	20
		Selective/universal		12.16	313	0.037	21,937	
NW Hertfordshire	0.83	Universal/selective	0.14	0.64	28	0.040	1,570	507
		Universal/universal		0.68	43	0.002	20,980	
		Selective/selective	0.13	0.65	28	0.043	1,571	469
		Selective/universal		0.69	43	0.002	20,991	
N Bedfordshire	1.84	Universal/selective	0.29	1.44	58	0.087	3,095	217
		Universal/universal		1.52	74	0.005	21,075	
		Selective/selective	0.28	1.45	58	0.090	3,096	210
		Selective/universal		1.53	74	0.005	21,086	
SW Hertfordshire	1.21	Universal/selective	0.22	0.92	36	0.057	2,258	349
		Universal/universal		0.97	51	0.003	21,006	
		Selective/selective	0.21	0.93	36	0.060	2,259	330
		Selective/universal		0.98	51	0.003	21,016	
S Bedfordshire	2.53	Universal/selective	0.37	2.01	81	0.121	4,411	146
		Universal/universal		2.13	97	0.006	21,148	
		Selective/selective	0.36	2.02	81	0.124	4,414	142
		Selective/universal		2.14	97	0.006	21,159	
Oxford								
Buckinghamshire	1.25	Universal/selective	0.20	0.98	37	0.060	2,170	329
		Universal/universal		1.04	52	0.003	21,011	
		Selective/selective	0.19	0.99	37	0.063	2,171	312
		Selective/universal		1.05	52	0.003	21,021	
E Berkshire	1.31	Universal/selective	0.26	0.97	46	0.059	3,690	308
		Universal/universal		1.03	61	0.003	21,033	
		Selective/selective	0.25	0.98	46	0.062	3,691	293
		Selective/universal		1.04	61	0.003	21,043	
Kettering	0.74	Universal/selective	0.12	0.57	24	0.036	1,136	584
		Universal/universal		0.60	39	0.002	20,969	
		Selective/selective	0.12	0.57	24	0.039	1,136	534
		Selective/universal		0.61	39	0.002	20,979	

continued

TABLE 88 contd *Main neonatal screening outcomes, costs and ICERs for late diagnosis of sickle cell disease prevented for district health authorities in Great Britain (1993 distribution): model predictions under baseline assumptions, per 10,000 antenatal population*

Regional health authority District health authority	**Fetal SCD prevalence 10^{-4}**	**Antenatal/ neonatal programme combination**	**SCD identified antenatally 10^{-4}**	**Newborns tested**		**SCD diagnosed late 10^{-4}**	**Neonatal screening costs (£)**	**Late diagnosis prevented ICER (£000)**
				SCD identified neonatally 10^{-4}	**Sickle carriers identified neonatally 10^{-4}**			
Oxford contd								
Northampton	1.29	Universal/selective	0.19	1.02	40	0.062	1,575	328
		Universal/universal		1.08	56	0.003	21,019	
		Selective/selective	0.19	1.02	40	0.066	1,577	312
		Selective/universal		1.09	56	0.003	21,030	
Oxfordshire	1.05	Universal/selective	0.16	0.82	30	0.051	1,395	406
		Universal/universal		0.87	45	0.003	20,989	
		Selective/selective	0.15	0.83	30	0.054	1,396	381
		Selective/universal		0.88	45	0.003	21,000	
W Berkshire	1.50	Universal/selective	0.22	1.19	40	0.073	1,698	281
		Universal/universal		1.26	56	0.004	21,024	
		Selective/selective	0.21	1.19	40	0.076	1,700	269
		Selective/universal		1.27	56	0.004	21,035	
Scotland								
Angus	0.18	Universal/selective	0.03	0.14	5	0.010	242	2,103
		Universal/universal		0.14	20	0.000	20,911	
		Selective/selective	0.03	0.14	5	0.013	242	1,592
		Selective/universal		0.15	20	0.000	20,921	
Argyll and Clyde	0.26	Universal/selective	0.04	0.20	7	0.014	309	1,541
		Universal/universal		0.21	22	0.001	20,917	
		Selective/selective	0.04	0.20	7	0.017	309	1,246
		Selective/universal		0.22	22	0.001	20,927	
Ayreshire and Arran	0.07	Universal/selective	0.02	0.05	2	0.005	192	4,298
		Universal/universal		0.05	17	0.000	20,902	
		Selective/selective	0.02	0.05	2	0.008	192	2,604
		Selective/universal		0.05	17	0.000	20,912	
Borders	0.10	Universal/selective	0.02	0.07	2	0.006	88	3,396
		Universal/universal		0.07	16	0.000	20,901	
		Selective/selective	0.02	0.07	2	0.010	88	2,242
		Selective/universal		0.08	16	0.000	20,911	
Central (Forth Valley)	0.10	Universal/selective	0.02	0.07	3	0.006	244	3,417
		Universal/universal		0.07	17	0.000	20,903	
		Selective/selective	0.02	0.07	3	0.009	244	2,251
		Selective/universal		0.08	17	0.000	20,914	
Dumfries and Galloway	0.06	Universal/selective	0.02	0.04	2	0.005	125	4,545
		Universal/universal		0.05	17	0.000	20,900	
		Selective/selective	0.01	0.04	2	0.008	126	2,694
		Selective/universal		0.05	17	0.000	20,911	
Dundee City	0.30	Universal/selective	0.06	0.23	9	0.016	795	1,352
		Universal/universal		0.24	23	0.001	20,922	
		Selective/selective	0.05	0.23	9	0.019	795	1,119
		Selective/universal		0.25	23	0.001	20,932	
Fife	0.14	Universal/selective	0.03	0.11	4	0.009	265	2,518
		Universal/universal		0.11	19	0.000	20,907	
		Selective/selective	0.02	0.11	4	0.012	265	1,821
		Selective/universal		0.12	19	0.000	20,917	

continued

TABLE 88 contd *Main neonatal screening outcomes, costs and ICERs for late diagnosis of sickle cell disease prevented for district health authorities in Great Britain (1993 distribution): model predictions under baseline assumptions, per 10,000 antenatal population*

Regional health authority District health authority	**Fetal SCD prevalence 10^{-4}**	**Antenatal/ neonatal programme combination**	**SCD identified antenatally 10^{-4}**	**Newborns tested**		**SCD diagnosed late 10^{-4}**	**Neonatal screening costs (£)**	**Late diagnosis prevented ICER (£000)**
				SCD identified neonatally 10^{-4}	**Sickle carriers identified neonatally 10^{-4}**			
Scotland contd								
Grampian	0.29	Universal/selective	0.05	0.22	7	0.015	338	1,407
		Universal/universal		0.24	22	0.001	20,918	
		Selective/selective	0.05	0.22	7	0.019	338	1,156
		Selective/universal		0.24	22	0.001	20,928	
Greater Glasgow	0.38	Universal/selective	0.07	0.28	11	0.019	1,136	1,106
		Universal/universal		0.30	25	0.001	20,928	
		Selective/selective	0.07	0.28	11	0.022	1,136	944
		Selective/universal		0.30	25	0.001	20,938	
Highland	0.13	Universal/selective	0.03	0.09	4	0.008	200	2,755
		Universal/universal		0.10	19	0.000	20,907	
		Selective/selective	0.02	0.09	4	0.011	200	1,942
		Selective/universal		0.10	19	0.000	20,918	
Lanarkshire	0.11	Universal/selective	0.02	0.08	3	0.007	286	3,188
		Universal/universal		0.08	18	0.000	20,904	
		Selective/selective	0.02	0.08	3	0.010	287	2,148
		Selective/universal		0.09	18	0.000	20,914	
Lothian	0.35	Universal/selective	0.06	0.26	9	0.018	651	1,199
		Universal/universal		0.28	24	0.001	20,924	
		Selective/selective	0.06	0.26	9	0.021	651	1,011
		Selective/universal		0.28	24	0.001	20,934	
Orkney	0.04	Universal/selective	0.02	0.02	2	0.003	153	6,121
		Universal/universal		0.02	17	0.000	20,901	
		Selective/selective	0.01	0.02	2	0.007	153	3,174
		Selective/universal		0.03	17	0.000	20,911	
Perth and Kinross	0.07	Universal/selective	0.02	0.05	2	0.005	206	4,243
		Universal/universal		0.05	17	0.000	20,902	
		Selective/selective	0.02	0.05	2	0.008	207	2,582
		Selective/universal		0.06	17	0.000	20,912	
Shetland	0.09	Universal/selective	0.02	0.06	4	0.006	247	3,725
		Universal/universal		0.06	19	0.000	20,906	
		Selective/selective	0.02	0.06	4	0.009	247	2,379
		Selective/universal		0.07	19	0.000	20,916	
Western Isles	0.04	Universal/selective	0.01	0.02	1	0.003	113	6,137
		Universal/universal		0.02	16	0.000	20,899	
		Selective/selective	0.01	0.02	1	0.007	113	3,185
		Selective/universal		0.03	16	0.000	20,909	
SE Thames								
Bexley	2.11	Universal/selective	0.33	1.65	48	0.100	2,011	201
		Universal/universal		1.75	64	0.005	21,057	
		Selective/selective	0.32	1.66	48	0.103	2,013	194
		Selective/universal		1.76	64	0.005	21,068	
Bromley	2.01	Universal/selective	0.30	1.59	49	0.096	1,910	210
		Universal/universal		1.68	65	0.005	21,056	
		Selective/selective	0.29	1.59	49	0.099	1,912	203
		Selective/universal		1.69	65	0.005	21,067	

continued

TABLE 88 contd *Main neonatal screening outcomes, costs and ICERs for late diagnosis of sickle cell disease prevented for district health authorities in Great Britain (1993 distribution): model predictions under baseline assumptions, per 10,000 antenatal population*

Regional health authority District health authority	**Fetal SCD prevalence 10^{-4}**	**Antenatal/ neonatal programme combination**	**SCD identified antenatally 10^{-4}**	**Newborns tested**		**SCD diagnosed late 10^{-4}**	**Neonatal screening costs (£)**	**Late diagnosis prevented ICER (£000)**
				SCD identified neonatally 10^{-4}	**Sickle carriers identified neonatally 10^{-4}**			
SE Thames contd								
Canterbury and Thanet	0.69	Universal/selective	0.11	0.54	15	0.034	612	628
		Universal/universal		0.57	30	0.002	20,945	
		Selective/selective	0.11	0.54	15	0.037	613	571
		Selective/universal		0.58	30	0.002	20,955	
Dartford and Gravesham	0.73	Universal/selective	0.17	0.53	25	0.033	1,575	614
		Universal/universal		0.56	40	0.002	20,972	
		Selective/selective	0.16	0.53	25	0.036	1,576	560
		Selective/universal		0.56	40	0.002	20,982	
E Sussex	0.71	Universal/selective	0.12	0.55	18	0.035	830	612
		Universal/universal		0.58	33	0.002	20,952	
		Selective/selective	0.11	0.55	18	0.038	830	558
		Selective/universal		0.59	33	0.002	20,963	
Greenwich	9.59	Universal/selective	1.32	7.70	183	0.458	5,220	38
		Universal/universal		8.13	204	0.024	21,559	
		Selective/selective	1.27	7.74	183	0.463	5,226	37
		Selective/universal		8.17	205	0.025	21,574	
Maidstone	0.47	Universal/selective	0.08	0.36	12	0.024	562	901
		Universal/universal		0.39	27	0.001	20,933	
		Selective/selective	0.08	0.37	12	0.027	562	791
		Selective/universal		0.39	27	0.001	20,944	
Medway	0.65	Universal/selective	0.12	0.49	19	0.031	1,011	676
		Universal/universal		0.52	34	0.002	20,955	
		Selective/selective	0.11	0.49	19	0.034	1,012	611
		Selective/universal		0.52	34	0.002	20,966	
SE London	29.75	Universal/selective	3.84	24.12	539	1.430	11,523	8
		Universal/universal		25.47	576	0.077	22,896	
		Selective/selective	3.72	24.23	539	1.439	11,542	8
		Selective/universal		25.60	577	0.077	22,921	
SE Kent	0.42	Universal/selective	0.07	0.32	11	0.021	556	1,021
		Universal/universal		0.34	26	0.001	20,930	
		Selective/selective	0.07	0.32	11	0.024	556	881
		Selective/universal		0.34	26	0.001	20,940	
Tunbridge Wells	0.33	Universal/selective	0.06	0.25	8	0.017	430	1,255
		Universal/universal		0.27	23	0.001	20,921	
		Selective/selective	0.06	0.25	8	0.020	430	1,051
		Selective/universal		0.27	23	0.001	20,932	
South Western								
Bristol and District	0.16	Universal/selective	0.17	0.91	33	0.056	1,301	369
		Universal/universal		0.97	49	0.003	21,000	
		Selective/selective	0.16	0.92	33	0.060	1,302	348
		Selective/universal		0.98	49	0.003	21,011	
Cornwall and Scilly	0.16	Universal/selective	0.03	0.12	5	0.009	239	2,348
		Universal/universal		0.13	19	0.000	20,909	
		Selective/selective	0.03	0.12	5	0.012	240	1,729
		Selective/universal		0.13	19	0.000	20,919	

continued

TABLE 88 contd *Main neonatal screening outcomes, costs and ICERs for late diagnosis of sickle cell disease prevented for district health authorities in Great Britain (1993 distribution): model predictions under baseline assumptions, per 10,000 antenatal population*

Regional health authority District health authority	**Fetal SCD prevalence 10^{-4}**	**Antenatal/ neonatal programme combination**	**SCD identified antenatally 10^{-4}**	**Newborns tested**		**SCD diagnosed late 10^{-4}**	**Neonatal screening costs (£)**	**Late diagnosis prevented ICER (£000)**
				SCD identified neonatally 10^{-4}	**Sickle carriers identified neonatally 10^{-4}**			
South Western contd								
Exeter and N Devon	0.18	Universal/selective	0.04	0.13	5	0.010	302	2,157
		Universal/universal		0.14	20	0.000	20,910	
		Selective/selective	0.03	0.13	5	0.013	302	1,622
		Selective/universal		0.14	20	0.000	20,921	
Gloucestershire	0.65	Universal/selective	0.11	0.51	20	0.032	839	657
		Universal/universal		0.54	35	0.002	20,956	
		Selective/selective	0.10	0.51	20	0.035	840	596
		Selective/universal		0.54	35	0.002	20,967	
Plymouth and Torbay	0.26	Universal/selective	0.05	0.20	7	0.014	318	1,558
		Universal/universal		0.21	21	0.001	20,916	
		Selective/selective	0.04	0.20	7	0.017	319	1,257
		Selective/universal		0.21	21	0.001	20,926	
Somerset	0.23	Universal/selective	0.04	0.17	5	0.012	301	1,744
		Universal/universal		0.18	20	0.001	20,912	
		Selective/selective	0.04	0.17	5	0.016	301	1,377
		Selective/universal		0.19	20	0.001	20,923	
SW Thames								
Chichester	0.29	Universal/selective	0.06	0.22	7	0.015	418	1,414
		Universal/universal		0.23	22	0.001	20,918	
		Selective/selective	0.05	0.22	7	0.018	419	1,161
		Selective/universal		0.24	22	0.001	20,929	
Croydon	9.24	Universal/selective	1.27	7.41	203	0.441	6,255	37
		Universal/universal		7.83	225	0.024	21,597	
		Selective/selective	1.23	7.45	203	0.446	6,262	36
		Selective/universal		7.87	225	0.024	21,612	
E Surrey	0.42	Universal/selective	0.08	0.32	12	0.021	724	1,012
		Universal/universal		0.34	26	0.001	20,931	
		Selective/selective	0.07	0.32	12	0.024	725	874
		Selective/universal		0.34	26	0.001	20,941	
Kingston and Richmond	2.14	Universal/selective	0.34	1.68	52	0.102	2,558	192
		Universal/universal		1.78	68	0.005	21,066	
		Selective/selective	0.32	1.69	52	0.105	2,560	186
		Selective/universal		1.79	68	0.005	21,077	
Merton and Sutton	5.50	Universal/selective	0.77	4.40	113	0.263	4,000	70
		Universal/universal		4.65	132	0.014	21,294	
		Selective/selective	0.75	4.42	113	0.266	4,003	69
		Selective/universal		4.67	132	0.014	21,306	
Mid Downs	0.52	Universal/selective	0.11	0.38	17	0.025	1,324	839
		Universal/universal		0.40	32	0.001	20,947	
		Selective/selective	0.10	0.38	17	0.028	1,324	741
		Selective/universal		0.41	32	0.001	20,957	
Mid Surrey	0.69	Universal/selective	0.13	0.52	20	0.033	1,403	628
		Universal/universal		0.55	34	0.002	20,956	
		Selective/selective	0.12	0.52	20	0.036	1,403	571
		Selective/universal		0.56	34	0.002	20,966	

continued

TABLE 88 contd *Main neonatal screening outcomes, costs and ICERs for late diagnosis of sickle cell disease prevented for district health authorities in Great Britain (1993 distribution): model predictions under baseline assumptions, per 10,000 antenatal population*

Regional health authority District health authority	**Fetal SCD prevalence 10^{-4}**	**Antenatal/ neonatal programme combination**	**SCD identified antenatally 10^{-4}**	**Newborns tested**		**SCD diagnosed late 10^{-4}**	**Neonatal screening costs (£)**	**Late diagnosis prevented ICER (£000)**
				SCD identified neonatally 10^{-4}	**Sickle carriers identified neonatally 10^{-4}**			
SW Thames contd								
NW Surrey	0.53	Universal/selective	0.10	0.40	17	0.026	1,444	797
		Universal/universal		0.42	31	0.001	20,945	
		Selective/selective	0.10	0.40	17	0.029	1,445	709
		Selective/universal		0.43	31	0.001	20,955	
SW Surrey	0.36	Universal/selective	0.07	0.27	10	0.018	631	1,156
		Universal/universal		0.29	25	0.001	20,925	
		Selective/selective	0.06	0.28	10	0.022	631	981
		Selective/universal		0.30	25	0.001	20,936	
Wandsworth Surrey	15.1	Universal/selective	1.99	12.20	300	0.725	8,256	20
		Universal/universal		12.89	326	0.039	21,972	
		Selective/selective	1.92	12.26	300	0.730	8,266	20
		Selective/universal		12.95	326	0.039	21,989	
Worthing	0.48	Universal/selective	0.08	0.37	12	0.024	679	877
		Universal/universal		0.40	27	0.001	20,933	
		Selective/selective	0.08	0.37	12	0.027	679	772
		Selective/universal		0.40	27	0.001	20,944	
Trent								
Barnsley	0.20	Universal/selective	0.04	0.15	5	0.011	264	1,925
		Universal/universal		0.16	20	0.000	20,911	
		Selective/selective	0.03	0.15	5	0.014	264	1,487
		Selective/universal		0.17	20	0.000	20,922	
Doncaster	0.31	Universal/selective	0.06	0.23	11	0.016	647	1,347
		Universal/universal		0.24	26	0.001	20,927	
		Selective/selective	0.06	0.23	11	0.019	647	1,116
		Selective/universal		0.25	26	0.001	20,937	
Leicestershire	1.29	Universal/selective	0.34	0.89	56	0.055	3,737	335
		Universal/universal		0.94	71	0.003	21,059	
		Selective/selective	0.33	0.90	56	0.058	3,738	317
		Selective/universal		0.95	71	0.003	21,069	
N Nottingham	0.29	Universal/selective	0.05	0.22	8	0.015	380	1,421
		Universal/universal		0.23	23	0.001	20,921	
		Selective/selective	0.05	0.22	8	0.018	380	1,167
		Selective/universal		0.24	23	0.001	20,931	
N Derbyshire	0.24	Universal/selective	0.04	0.18	7	0.013	350	1,635
		Universal/universal		0.20	22	0.001	20,916	
		Selective/selective	0.04	0.19	7	0.016	351	1,308
		Selective/universal		0.20	22	0.001	20,926	
N Lincolnshire	0.27	Universal/selective	0.05	0.20	7	0.014	404	1,551
		Universal/universal		0.21	22	0.001	20,917	
		Selective/selective	0.05	0.20	7	0.017	404	1,253
		Selective/universal		0.21	22	0.001	20,927	
Nottingham	1.98	Universal/selective	0.29	1.57	60	0.095	2,442	207
		Universal/universal		1.66	77	0.005	21,083	
		Selective/selective	0.27	1.58	60	0.098	2,443	200
		Selective/universal		1.67	77	0.005	21,094	

continued

TABLE 88 contd *Main neonatal screening outcomes, costs and ICERs for late diagnosis of sickle cell disease prevented for district health authorities in Great Britain (1993 distribution): model predictions under baseline assumptions, per 10,000 antenatal population*

Regional health authority District health authority	**Fetal SCD prevalence 10^{-4}**	**Antenatal/ neonatal programme combination**	**SCD identified antenatally 10^{-4}**	**Newborns tested**		**SCD diagnosed late 10^{-4}**	**Neonatal screening costs (£)**	**Late diagnosis prevented ICER (£000)**
				SCD identified neonatally 10^{-4}	**Sickle carriers identified neonatally 10^{-4}**			
Trent contd								
Rotherham	0.23	Universal/selective	0.04	0.17	7	0.012	849	1,714
		Universal/universal		0.18	21	0.001	20,915	
		Selective/selective	0.04	0.17	7	0.015	849	1,358
		Selective/universal		0.19	21	0.001	20,926	
Sheffield	1.87	Universal/selective	0.27	1.49	51	0.091	2,406	217
		Universal/universal		1.58	67	0.005	21,059	
		Selective/selective	0.25	1.50	51	0.094	2,408	209
		Selective/universal		1.59	67	0.005	21,070	
S Lincolnshire	0.32	Universal/selective	0.06	0.24	8	0.017	418	1,297
		Universal/universal		0.26	23	0.001	20,920	
		Selective/selective	0.05	0.24	8	0.020	418	1,081
		Selective/universal		0.26	23	0.001	20,930	
S Derbyshire	0.96	Universal/selective	0.17	0.74	32	0.046	1,764	441
		Universal/universal		0.78	48	0.002	20,993	
		Selective/selective	0.16	0.74	32	0.049	1,765	412
		Selective/universal		0.79	48	0.002	21,004	
Wales								
Clwyd	0.12	Universal/selective	0.03	0.09	4	0.007	274	2,876
		Universal/universal		0.09	19	0.000	20,906	
		Selective/selective	0.02	0.09	4	0.011	274	2,001
		Selective/universal		0.10	19	0.000	20,917	
Dyfed	0.11	Universal/selective	0.03	0.08	4	0.007	345	3,154
		Universal/universal		0.08	19	0.000	20,906	
		Selective/selective	0.02	0.08	4	0.010	346	2,132
		Selective/universal		0.09	19	0.000	20,917	
Gwent	0.30	Universal/selective	0.05	0.23	10	0.016	621	1,364
		Universal/universal		0.24	25	0.001	20,925	
		Selective/selective	0.05	0.23	10	0.019	622	1,127
		Selective/universal		0.25	25	0.001	20,936	
Gwynedd	0.23	Universal/selective	0.04	0.17	7	0.013	379	1,709
		Universal/universal		0.19	21	0.001	20,915	
		Selective/selective	0.04	0.18	7	0.016	379	1,354
		Selective/universal		0.19	21	0.001	20,926	
Mid Glamorgan	0.13	Universal/selective	0.03	0.09	4	0.008	305	2,775
		Universal/universal		0.10	19	0.000	20,907	
		Selective/selective	0.03	0.09	4	0.011	305	1,952
		Selective/universal		0.10	19	0.000	20,917	
Powys	0.10	Universal/selective	0.02	0.07	4	0.006	217	3,429
		Universal/universal		0.07	18	0.000	20,905	
		Selective/selective	0.02	0.07	4	0.009	217	2,256
		Selective/universal		0.08	18	0.000	20,915	
S Glamorgan	1.87	Universal/selective	0.28	1.48	47	0.090	1,930	225
		Universal/universal		1.57	63	0.005	21,051	
		Selective/selective	0.26	1.49	47	0.093	1,931	216
		Selective/universal		1.58	63	0.005	21,062	
W Glamorgan	0.21	Universal/selective	0.04	0.15	10	0.011	628	1,912
		Universal/universal		0.16	24	0.000	20,922	
		Selective/selective	0.04	0.15	10	0.014	628	1,479
		Selective/universal		0.16	24	0.000	20,933	

continued

TABLE 88 contd *Main neonatal screening outcomes, costs and ICERs for late diagnosis of sickle cell disease prevented for district health authorities in Great Britain (1993 distribution): model predictions under baseline assumptions, per 10,000 antenatal population*

Regional health authority District health authority	**Fetal SCD prevalence 10^{-4}**	**Antenatal/ neonatal programme combination**	**SCD identified antenatally 10^{-4}**	**Newborns tested**		**SCD diagnosed late 10^{-4}**	**Neonatal screening costs (£)**	**Late diagnosis prevented ICER (£000)**
				SCD identified neonatally 10^{-4}	**Sickle carriers identified neonatally 10^{-4}**			
Wessex								
Bath	0.49	Universal/selective	0.08	0.38	14	0.025	589	864
		Universal/universal		0.40	30	0.001	20,939	
		Selective/selective	0.07	0.38	14	0.028	589	761
		Selective/universal		0.41	30	0.001	20,950	
Basingstoke and N Hampshire	0.55	Universal/selective	0.09	0.43	16	0.027	724	775
		Universal/universal		0.45	31	0.001	20,943	
		Selective/selective	0.09	0.43	16	0.031	724	692
		Selective/universal		0.46	31	0.001	20,954	
Dorset	0.32	Universal/selective	0.06	0.24	8	0.017	451	1,287
		Universal/universal		0.26	23	0.001	20,921	
		Selective/selective	0.05	0.25	8	0.020	451	1,074
		Selective/universal		0.26	23	0.001	20,932	
Isle of Wight	0.25	Universal/selective	0.05	0.19	7	0.013	334	1,614
		Universal/universal		0.20	22	0.001	20,916	
		Selective/selective	0.04	0.19	7	0.017	334	1,294
		Selective/universal		0.20	22	0.001	20,926	
Portsmouth and SE Hampshire	0.51	Universal/selective	0.08	0.39	13	0.025	590	843
		Universal/universal		0.42	28	0.001	20,938	
		Selective/selective	0.08	0.39	13	0.029	591	745
		Selective/universal		0.42	28	0.001	20,949	
Salisbury	0.28	Universal/selective	0.05	0.21	8	0.015	403	1,443
		Universal/universal		0.23	23	0.001	20,920	
		Selective/selective	0.05	0.21	8	0.018	403	1,181
		Selective/universal		0.23	23	0.001	20,930	
Southampton and SW Hampshire	0.57	Universal/selective	0.11	0.43	19	0.027	1,088	762
		Universal/universal		0.45	34	0.001	20,953	
		Selective/selective	0.10	0.43	19	0.031	1,088	680
		Selective/universal		0.46	34	0.001	20,963	
Swindon	0.62	Universal/selective	0.11	0.47	20	0.030	1,085	698
		Universal/universal		0.5	35	0.001	20,955	
		Selective/selective	0.11	0.47	20	0.033	1,085	629
		Selective/universal		0.50	35	0.002	20,966	
Winchester	0.21	Universal/selective	0.05	0.15	7	0.011	486	1,913
		Universal/universal		0.16	22	0.000	20,916	
		Selective/selective	0.04	0.15	7	0.014	486	1,480
		Selective/universal		0.17	22	0.000	20,926	
W Midlands								
Coventry	1.57	Universal/selective	0.32	1.16	60	0.071	3,457	263
		Universal/universal		1.23	75	0.004	21,074	
		Selective/selective	0.31	1.17	60	0.074	3,459	252
		Selective/universal		1.24	75	0.004	21,085	
Dudley	0.95	Universal/selective	0.16	0.73	33	0.046	1,830	443
		Universal/universal		0.78	48	0.002	20,993	
		Selective/selective	0.15	0.74	33	0.049	1,832	413
		Selective/universal		0.79	48	0.002	21,004	

continued

TABLE 88 contd *Main neonatal screening outcomes, costs and ICERs for late diagnosis of sickle cell disease prevented for district health authorities in Great Britain (1993 distribution): model predictions under baseline assumptions, per 10,000 antenatal population*

Regional health authority District health authority	**Fetal SCD prevalence 10^{-4}**	**Antenatal/ neonatal programme combination**	**SCD identified antenatally 10^{-4}**	**Newborns tested**		**SCD diagnosed late 10^{-4}**	**Neonatal screening costs (£)**	**Late diagnosis prevented ICER (£000)**
				SCD identified neonatally 10^{-4}	**Sickle carriers identified neonatally 10^{-4}**			
W Midlands								
E Birmingham	2.35	Universal/selective	0.35	1.85	88	0.111	7,947	125
		Universal/universal		1.96	102	0.006	21,158	
		Selective/selective	0.34	1.86	88	0.114	7,949	123
		Selective/universal		1.97	102	0.006	21,167	
Herefordshire	0.18	Universal/selective	0.04	0.13	5	0.010	272	2,158
		Universal/universal		0.14	20	0.000	20,910	
		Selective/selective	0.03	0.13	5	0.013	272	1,623
		Selective/universal		0.14	20	0.000	20,921	
Mid Staffordshire	0.36	Universal/selective	0.06	0.27	11	0.018	510	1,177
		Universal/universal		0.29	25	0.001	20,927	
		Selective/selective	0.06	0.27	11	0.021	511	996
		Selective/universal		0.29	25	0.001	20,938	
N Birmingham	2.14	Universal/selective	0.31	1.71	67	0.103	2,458	190
		Universal/universal		1.81	83	0.005	21,101	
		Selective/selective	0.29	1.72	67	0.107	2,460	184
		Selective/universal		1.82	83	0.005	21,113	
N Staffordshire	0.38	Universal/selective	0.07	0.29	13	0.019	992	1,084
		Universal/universal		0.31	27	0.001	20,933	
		Selective/selective	0.06	0.29	13	0.022	993	929
		Selective/universal		0.31	27	0.001	20,943	
N Worcestershire	0.58	Universal/selective	0.09	0.46	18	0.029	868	722
		Universal/universal		0.48	33	0.001	20,950	
		Selective/selective	0.09	0.46	18	0.032	869	648
		Selective/universal		0.49	33	0.001	20,960	
SE Staffordshire	0.44	Universal/selective	0.07	0.34	14	0.022	922	953
		Universal/universal		0.36	28	0.001	20,936	
		Selective/selective	0.07	0.34	14	0.025	923	830
		Selective/universal		0.36	29	0.001	20,947	
Sandwell	2.45	Universal/selective	0.44	1.87	93	0.113	4,885	153
		Universal/universal		1.98	109	0.006	21,175	
		Selective/selective	0.43	1.88	93	0.116	4,888	149
		Selective/universal		1.99	109	0.006	21,186	
Shropshire	0.39	Universal/selective	0.07	0.30	12	0.020	686	1,070
		Universal/universal		0.32	27	0.001	20,932	
		Selective/selective	0.07	0.30	12	0.023	686	918
		Selective/universal		0.32	27	0.001	20,942	
Solihull	0.90	Universal/selective	0.15	0.70	30	0.043	1,257	479
		Universal/universal		0.74	45	0.002	20,985	
		Selective/selective	0.14	0.70	30	0.047	1,258	445
		Selective/universal		0.74	45	0.002	20,996	
S Birmingham	3.14	Universal/selective	0.48	2.47	102	0.148	5,848	109
		Universal/universal		2.61	118	0.008	21,210	
		Selective/selective	0.46	2.49	102	0.151	5,851	107
		Selective/universal		2.63	118	0.008	21,221	
Walsall	0.14	Universal/selective	0.23	0.85	48	0.052	3,326	359
		Universal/universal		0.90	63	0.003	21,038	
		Selective/selective	0.22	0.85	48	0.055	3,328	339
		Selective/universal		0.90	64	0.003	21,048	

continued

TABLE 88 contd *Main neonatal screening outcomes, costs and ICERs for late diagnosis of sickle cell disease prevented for district health authorities in Great Britain (1993 distribution): model predictions under baseline assumptions, per 10,000 antenatal population*

Regional health authority District health authority	**Fetal SCD prevalence 10^{-4}**	**Antenatal/ neonatal programme combination**	**SCD identified antenatally 10^{-4}**	**Newborns tested**		**SCD diagnosed late 10^{-4}**	**Neonatal screening costs (£)**	**Late diagnosis prevented ICER (£000)**
				SCD identified neonatally 10^{-4}	**Sickle carriers identified neonatally 10^{-4}**			
W Midlands contd								
Warwickshire	0.52	Universal/selective	0.12	0.37	20	0.024	1,228	855
		Universal/universal		0.40	35	0.001	20,954	
		Selective/selective	0.11	0.38	20	0.027	1,229	754
		Selective/universal		0.40	35	0.001	20,964	
W Birmingham	8.20	Universal/selective	1.21	6.51	263	0.387	11,517	28
		Universal/universal		6.88	285	0.021	21,721	
		Selective/selective	1.17	6.54	263	0.390	11,525	28
		Selective/universal		6.91	285	0.021	21,734	
Wolverhampton	4.05	Universal/selective	0.68	3.13	137	0.187	5,841	87
		Universal/universal		3.31	155	0.010	21,315	
		Selective/selective	0.66	3.15	137	0.191	5,845	86
		Selective/universal		3.33	155	0.010	21,327	
Worcester and District	0.11	Universal/selective	0.03	0.07	5	0.007	552	3,225
		Universal/universal		0.08	20	0.000	20,908	
		Selective/selective	0.03	0.07	5	0.010	552	2,164
		Selective/universal		0.08	20	0.000	20,919	
Yorkshire								
Bradford	1.16	Universal/selective	0.21	0.88	45	0.054	5,608	301
		Universal/universal		0.93	58	0.003	21,026	
		Selective/selective	0.20	0.89	45	0.057	5,609	287
		Selective/universal		0.94	58	0.003	21,035	
E Riding	0.32	Universal/selective	0.05	0.25	8	0.017	382	1,284
		Universal/universal		0.26	23	0.001	20,921	
		Selective/selective	0.05	0.25	8	0.020	382	1,072
		Selective/universal		0.27	23	0.001	20,932	
Grimsby and Scunthorpe	0.27	Universal/selective	0.05	0.21	8	0.014	489	1,480
		Universal/universal		0.22	23	0.001	20,921	
		Selective/selective	0.05	0.21	8	0.018	489	1,206
		Selective/universal		0.22	23	0.001	20,931	
Leeds	1.52	Universal/selective	0.24	1.19	47	0.073	2,350	272
		Universal/universal		1.26	62	0.004	21,040	
		Selective/selective	0.23	1.20	47	0.076	2,351	260
		Selective/universal		1.27	62	0.004	21,051	
N Yorkshire	0.19	Universal/selective	0.04	0.14	6	0.010	353	2,065
		Universal/universal		0.15	20	0.000	20,911	
		Selective/selective	0.04	0.14	6	0.014	353	1,570
		Selective/universal		0.15	20	0.000	20,922	
Wakefield	0.20	Universal/selective	0.04	0.14	6	0.011	601	1,984
		Universal/universal		0.15	21	0.000	20,913	
		Selective/selective	0.04	0.14	6	0.014	601	1,523
		Selective/universal		0.16	21	0.000	20,923	
W Yorkshire	1.08	Universal/selective	0.19	0.82	38	0.051	3,373	368
		Universal/universal		0.87	52	0.003	21,009	
		Selective/selective	0.19	0.83	38	0.053	3,374	347
		Selective/universal		0.88	53	0.003	21,018	

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This report was identified as a priority by the Population Screening Panel.

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ISSN 1366-5278