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Review

Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research

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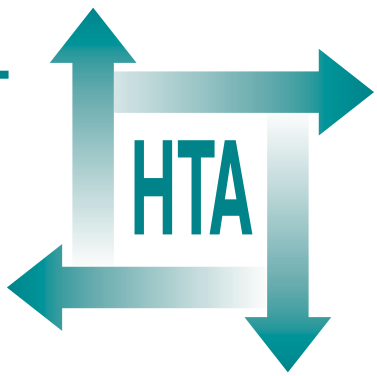
Health Technology Assessment
NHS R&D HTA Programme



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Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research

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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 93/33/03.

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.

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Contents

List of abbreviations

A	adult haemoglobin
AC	haemoglobin C trait
AD	haemoglobin D trait
AE	haemoglobin E trait
AG	citrate agar electrophoresis*
AS	sickle cell trait
BCSH	British Committee for Standards in Haematology
BSCTC	Brent Sickle Cell and Thalassaemia Centre
C	a variant haemoglobin
CA	cellulose acetate electrophoresis*
CA/AG	cellulose acetate electrophoresis followed by citrate agar electrophoresis
CC	haemoglobin C disease; haemoglobin homozygous for C
CI	confidence interval
CMH	Central Middlesex Hospital
D	a variant haemoglobin
E	a variant haemoglobin
EE	haemoglobin E disease; haemoglobin homozygous for E
F	fetal haemoglobin
H	a variant haemoglobin
Hb	haemoglobin
HPLC	high-performance liquid chromatography
IEF	isoelectric focusing
ISC	Indian sub-continent*
LL&S	Lambeth, Lewisham and Southwark
MCH	mean corpuscular haemoglobin*
MCV	mean corpuscular volume*
N/App	not applicable*
N/Av	not available*
NTW	North Thames (West)
PKU	phenylketonuria
PND	prenatal diagnosis
RHA	regional health authority*
RR	relative risk
S	sickle haemoglobin
$S\beta^T$	Sickle β-thalassaemia; haemoglobin heterozygous for S and β^T
SC	Haemoglobin SC disease; haemoglobin heterozygous for S and C
SCD	sickle cell disease
SMAC	Standing Medical Advisory Committee
SS	sickle cell anaemia; haemoglobin homozygous for S
thal	thalassaemia*
TOP	termination of pregnancy*
ZPP	zinc protoporphyrin assay*

* Used only in tables and figures

Executive summary

Introduction

The haemoglobinopathies (thalassaemias and sickle cell disease (SCD)) are inherited disorders of haemoglobin.

In 1993, the UK Standing Medical Advisory Committee made the following recommendations.

- Preconceptual carrier diagnosis for these conditions should be encouraged.
- Antenatal and neonatal screening should be universal in districts where over 15% of the population are from ethnic minorities.
- Specialist counselling should be integral to such programmes.

Although generally welcomed, these recommendations received little attention, possibly because they were not firmly evidence based and were issued as Health Service Guidelines, which did not oblige purchasers or providers to take action.

Objectives

The objectives of this review were:

- to review the literature on haemoglobinopathy screening
- to review the literature on gene prevalence in the various British populations for the sickle and β-thalassaemia genes
- to apply these to Census data in order to develop evidence-based estimates for the prevalence of SCD and β-thalassaemia in England
- to evaluate local data from North West London (Brent) to illuminate debate regarding the outcome of haemoglobinopathy screening programmes and their costs.

Methods

A systematic literature search was undertaken and maintained up to date during preparation of the review. Two or more members of the team reviewed all references. The data relating to the ethnic prevalence of abnormal haemoglobin genes were collected, graded and applied to Census data in order to derive estimates for the prevalence of the haemoglobinopathies in England. These data were validated against all the present English population screening programmes for haemoglobinopathies.

Additional data were collected prospectively from the district of Brent, North West London, on workload and outcomes of antenatal and neonatal screening and follow-up, in order to perform economic analyses.

This approach was then exploited further by combining the prevalence data with an extrapolation of a neonatal haemoglobinopathy screening cost-effectiveness model.

Results: systematic review

The haemoglobinopathies

The haemoglobinopathies are autosomal recessive defects. A distinction is made between carriers (who have only one affected globin locus and remain healthy throughout life, but are at risk of transmitting the disease to their descendants) and people who are homozygous, or doubly heterozygote, for a disorder.

The number of people in the UK who have SCD is rising and is expected to be in excess of 10,000 by the year 2000. Carriers are predominantly Afro-Caribbean and sub-Saharan in origin, but Arab, Mediterranean and Indian peoples are also affected.

There are approximately 600 people with β-thalassaemia major in the UK. It is most common in Mediterranean, Indian, and Pakistani peoples. Alpha-thalassaemia is most common in South-east Asia, Hong Kong and China, with α-thalassaemia major being incompatible with life.

The management of SCD is based on routine prophylactic penicillin for infants and the early use of antibiotics to prevent overwhelming infection.

Thalassaemia treatment is mainly through regular blood transfusions and splenectomy once hypersplenism develops.

Screening
A variety of models of haemoglobinopathy screening exist within Britain, and the service is patchy and often unstructured. Screening programmes may be opportunistic or systematic, targeted or population based. In targeted programmes, consideration needs to be given to the criteria for selection and the population base.

Antenatal screening allows women at risk to make informed decisions about reproduction. It aims to detect carriers, provide genetic counselling, and offer carrier couples the choice of parental diagnosis and selective abortion.

The primary aim of neonatal screening is to identify babies with SCD and commence life-extending prophylactic penicillin and comprehensive care. There is no equivalent reason for the early diagnosis of β-thalassaemia major, and β-thalassaemia trait is not identified by neonatal tests. However, screening does permit genetic counselling for parents with affected or carrier newborns.

In terms of the acceptability of antenatal screening, most British evidence is derived from studies at tertiary prenatal diagnosis centres and termination is more likely for β-thalassaemia major than for SCD, for which the prediction of severity is not feasible.

Cost-effectiveness
Attempts to measure the impact of British neonatal screening programmes have focused on groups of women attending tertiary referral centres for prenatal diagnosis, and the experience of US community-based programmes has shown that these findings may not be generalisable at the population level.

There is no published study reporting the full benefits of neonatal screening for the haemoglobinopathies, although two American studies have examined the cost-effectiveness of neonatal hospital screening.

Laboratory methods
The haemoglobinopathies can be detected by biochemical testing or DNA analysis. Biochemical methods include isoelectric focusing (IEF) and high-performance liquid chromatography (HPLC). Some commentators favour HPLC for large-scale screening programmes. It is recognised, however, that IEF provides more information because of its high resolution.

Results: supplementary research

Prevalence
Prevalence estimates were derived from country rates, and validated and adjusted where necessary for application to the UK. Estimates were derived for β-thalassaemia, and haemoglobin S, C and E traits. The proportions of births with clinically significant disease were calculated using the Hardy–Weinberg equation.

The authors estimate that 17 (0.03/1000) infants are born each year in England with β-thalassaemia major or intermedia, even when allowing for terminations, and 160 (0.25/1000) with SCD.

Outcomes of universal antenatal screening
Using the Central Middlesex Hospital programme for sample data, it was found that unselected women at risk of SCD are significantly less likely to have their partners tested or to accept prenatal diagnosis than tertiary referrals. This was not the case for those at risk of β-thalassaemia; 80% of β-thalassaemia and 16% of sickle cell anaemia births are prevented by universal screening. It is likely therefore that previous British studies have overestimated the impact of universal antenatal screening in preventing SCD births.

Cost-effectiveness of antenatal screening
From the study of Central Middlesex Hospital data, the authors suggest that, in addition to offering genetic choice, a universal antenatal screening and counselling programme is likely to be considered cost-effective at least in areas with haemoglobinopathy traits ≥ 2.5%, especially if a high proportion of these are β-thalassaemia.

Cost-effectiveness of neonatal screening
The results suggest that screening services should aim to cover populations that generate a workload of over 25,000 births per year, and preferably over 40,000. IEF and HPLC are very similar in terms of average cost per test.

At 16 sickle traits/1000 and 0.5 SCD/1000, there is no significant difference in the detection component cost between universal and targeted programmes. Below this prevalence, a targeted programme is cheaper but is likely to miss cases.

The key issue for commissioning organisations is the incremental cost-effectiveness of identifying one extra case of SCD with a universal programme.

These costs are provided at different levels of prevalence.

Cost-effectiveness of neonatal screening follow-up

The integration of nurse specialist follow-up for the purposes of counselling and education within the neonatal screening service resulted in the counselling of 91% of families whose infants had been identified with a clinically significant haemoglobinopathy or trait. Costing information suggests that there may be significant value in the intensive style of follow-up employed by this programme.

Conclusions

Implications for health care

- The evidence supports previous national guidance (Standing Medical Advisory Committee) that commissioners should develop appropriate population-based haemoglobinopathy screening programmes (review).
- Because this study makes no comparison with other programmes, the generalisability of the cost models on which the conclusions are based could usefully be considered in the planning process. Other programmes may have very different structures and therefore costs (study).
- There is currently little cooperation between health authorities and across regions. The evidence suggests that the creation of partnerships when building programmes would ensure efficiencies of scale and expert input, while maintaining closeness to the clinical services (study).
- Commissioners are not currently required to have a quality framework for any implementation plan for their screening programmes. Such a plan would include the linkage to and provision of both counselling and specialist care (review).
- This review suggests a need for all haemoglobinopathy screening programmes to have defined paths of responsibility for every aspect of the work, with agreed service standards for the purpose of audit (review).
- Audit depends on outcome measures (including timetables) being defined for the respective screening processes (study).
- The indications are that there is a need to address the current lack of systematic data collection in this area, particularly:
  - ethnic monitoring (for instance, there is no standard instrument currently used in laboratories to record ethnic group or ethnic origin)
  - ethnic-specific data on screening uptake
  - patient registries to monitor long-term outcomes and mortality (study).

Neonatal screening

- The analyses demonstrate that, for laboratories to be cost-effective, they should be able to screen at least 25,000 births annually (study).
- For areas where there are 16 sickle cell trait and 0.5 SCD cases per 1000 births, the data suggest that universal screening is cost-effective (study).
- In areas where there are fewer births, consideration of value for money and equity is of importance. In those areas where 7–15 per 1000 births have sickle cell trait, universal screening would be justified (study).
- The evidence supports the development of systems to inform parents of their baby's test results and to enter children with major haemoglobinopathies into specialist comprehensive care services (review).
- A national external quality assessment scheme for neonatal haemoglobinopathy screening would be able to address issues of quality assurance (study).

Antenatal screening

- According to the results, universal antenatal screening is cost-effective for all districts having 1% ethnic minorities if 25% of those carry the β-thalassaemia trait (study).
- An important outcome indicator is genetic choice, so some commissioners would purchase services at a lower prevalence in their population (review).

Recommendations for research

The authors' main recommendations for research include:

- study of the disbenefits and potential harms of screening for haemoglobinopathies at any stage
- optimal methods and modes of delivery of counselling for the haemoglobinopathies
- the attitude of the various communities in Britain to risk relating to haemoglobinopathies and how this impacts on the counselling process
- study of the equity and access issues relating to haemoglobinopathy screening, particularly as they relate to race
- the most cost-effective ways of delivering specialist haemoglobinopathy services.

Additional recommendations for research are made within the text of the report.

Chapter 1

Introduction

The haemoglobinopathies (thalassaemias and sickle cell disease (SCD)) are inherited disorders of haemoglobin (Hb). They are found in many populations and parts of the world that are associated with malarial endemicity and, as a result of migration, are among the commonest inherited disorders in north-west Europe.[1,2]

Despite recent improvements, people with these conditions suffer considerable morbidity[3–5] and have a shorter life expectancy than the general population.[6–10]

In 1993, the UK Standing Medical Advisory Committee (SMAC)[11] made the following recommendations.

- Preconceptual carrier diagnosis for these conditions should be encouraged.
- Antenatal and neonatal screening should be universal in districts where over 15% of the population are from ethnic minorities.
- Specialist counselling should be integral to such programmes.
- GPs with "significant numbers of the relevant ethnic groups" should be encouraged to participate.
- Further research should be undertaken to determine more appropriate indicators for universal screening.

The SMAC report, although generally welcomed,[12] received little attention, possibly because its recommendations were not firmly evidence based and it was issued as Health Service Guidelines,[13] which did not oblige purchasers or providers to take action.

Current policy on screening in the UK was outlined by the Chief Medical Officer in 1994[14,15] and indicated that the introduction of future programmes would depend on evidence demonstrating that certain criteria, as described by Wilson and Jungner,[16] were met. The Chief Medical Officer also established a National Screening Committee, which subsequently updated these.[17]

This report aimed to fill gaps in the evidence base relating to screening for the haemoglobinopathies and focused on technical rather than policy issues. The primary objective was to provide (interim) data that health authorities could use to plan future services and which could inform subsequent research studies.

Ethnicity is a dimension of considerable importance in any debate about screening for haemoglobinopathies. There has been great interest in achieving racial equality in health care since the outcome of the Lawrence Inquiry, and we understand that the Department of Health is developing an action plan on racial equality in terms of internal processes (such as employment) and access to health services. This work will be of relevance and will inform debate about the most appropriate means of delivering haemoglobinopathy services.

This report explores technical issues relating to screening for haemoglobinopathies, providing models to assist in decision making. The work demonstrated the lack of current evidence relating to other aspects of haemoglobinopathy screening, which need to be examined to contribute to the policy debate. These issues are:

- access, acceptability and uptake
- economic benefits of screening
- equality, including social equality
- models of follow-up
- risks of litigation.

In the absence of studies of relevance to the UK, it was not feasible to derive evidence solely from a systematic review of published evidence. This report is therefore in two sections. The first summarises existing knowledge about screening as it applies to SCD and thalassaemia. The second presents the results of primary research to fill some of the gaps identified by the earlier review.

SECTION 1

SYSTEMATIC REVIEW

Chapter 2
Methods

Literature review

The research team drew up a study protocol aimed at addressing the research issues raised for population screening in the neonatal period and during pregnancy.

A systematic literature search was undertaken and maintained up to date during the review. Two or more members of the review team reviewed all references.

The MEDLINE electronic reference database was searched using keywords and phrases, each categorised into one of four groups, and then combined with each of the terms in other groups as shown in *Table 1*.

The inclusion criteria were as follows:

- publication date between 1985 and 1996
- article in English or French
- peer-reviewed journals.

In addition, an extensive personal literature collection, spanning over 20 years, of one team member (Professor Davies) was handsearched, as were recent issues of journals in which articles on the subject are most often found, including: *Blood*, *British Journal of Haematology*, *British Medical Journal*, *The Lancet*, *Nature*, *Nature Medicine*, *New England Journal of Medicine* and *Journal of Medical Screening*.

This literature search led to cascade searching of works referenced in articles. In addition, personal contact was established with a number of experts in the field in both England and North America.

The evidence base for screening for haemoglobinopathies is poor and there is little to suggest rapid change. There is a small field of experts in these conditions in the UK and Europe, and we are not aware of further relevant work funded in the UK or Europe. There is, however, a new Cochrane Collaboration Group on Neonatal Screening for the Haemoglobinopathies, which includes researchers from each of the Health Technology Assessment Programme project teams.

Modification of the review

The review team extended their research because of the absence of randomised controlled trials in this field and the paucity of high-quality generalised evidence. Primary research into a variety of aspects of the haemoglobinopathy screening programmes directed by a study member (Professor Davies) from the Department of Haematology, Central Middlesex Hospital (CMH) NHS Trust, was also performed. This is reported here, together with cost modelling using the collected data.

TABLE 1 *MEDLINE search groups*

Group 1	Group 2	Group 3	Group 4
Haemoglobinopathy	Preconception	Screening	Economic
Haemoglobinopathies	Antenatal	Test	Cost
Hemoglobinopathy	Neonatal	Opportunistic	Benefit
Hemoglobinopathies	Population	Targeted	Effective
Thalassaemia	Infant	Universal	Utility
Thalassemia	Paediatric	Selective	Model
Sickle	Pediatric	Diagnosis	
Sickle cell		HPLC	
Traits		IEF	

HPLC, high-performance liquid chromatography; IEF, isoelectric focusing

Chapter 3

The haemoglobinopathies

Genetics

Adult blood contains a mixture of different Hbs. The most common, Hb A, is made of two α- and two β-globin chains ($\alpha_2\beta_2$). These are coded for by four α- and two β-gene loci.

The haemoglobinopathies are autosomal recessive defects of these genes. Over 600 different varieties have been described.[18] They affect either the structure of β-Hb (the variant disorders, e.g. sickle) or reduce the quantity of either α- or β-Hb chains (the thalassaemias).

Sickle Hb (S) is a qualitative defect in which a DNA substitution in the β-chain results in an alteration at position 6 of the amino acid chain, giving rise to a structurally different Hb when the S chains are assembled in the Hb molecule. This variant alters the electric charge of the molecule, thus giving rise to clinical pathology and allowing its easy detection in the laboratory.

The thalassaemias are named after the chain that is deficient (i.e. α- or β-thalassaemia). The former is usually due to gene deletions, the latter to non-deletional alleles, of which over 100 have been described.[19–21] Clinically severe conditions occur when either both β-genes, or three or four α-chains are affected.

Normal adult blood generally contains about 2.6% of Hb A_2 ($\alpha_2\delta_2$), a residual Hb.[18] In the first three months of life, there are also reducing levels of fetal Hb (Hb F, $\alpha_2\gamma_2$). Neither of these two Hb types contain β-chains. Their presence in later life can aid the diagnosis of haemoglobinopathies, while persistent production of Hb F can significantly ameliorate the clinical course of the haemoglobinopathies.

Transmission

A distinction must be made between carriers (who have only one affected globin locus and remain healthy throughout life, but are at risk of transmitting the disease to their descendants) and people who are homozygous, or doubly heterozygote, for a disorder.

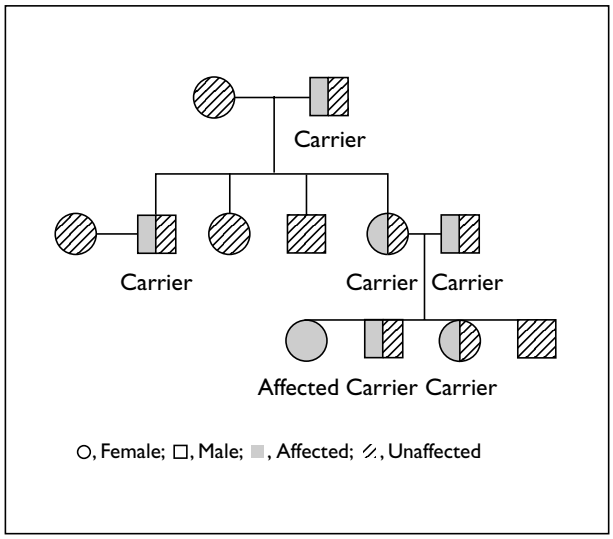


FIGURE 1 *Inheritance of haemoglobinopathies (adapted from reference 11)*

The conditions are recessively transmitted according to Mendelian genetics. Parents have a one in four risk of conceiving an affected child if both are carriers (*Figure 1*).

Prevalence

The haemoglobinopathies originally arose sporadically. Gene prevalence is related to the selective advantage conferred by the genes against malaria.[22,23]

The worldwide distribution of the diseases remains uneven (*Figure 2*), which complicates attempts to predict genetic status in individuals by using broad ethnic group classifications, such as from census data, because these are insensitive to regional variations.

Owing to migration, these conditions are now some of the most common inherited disorders in north-west Europe.[1] Although estimates are available,[11] the strength of evidence supporting them is not clear, nor have they been validated for populations in the UK.

The number of people in the UK who suffer from SCD (sickle cell anaemia (homozygous sickle

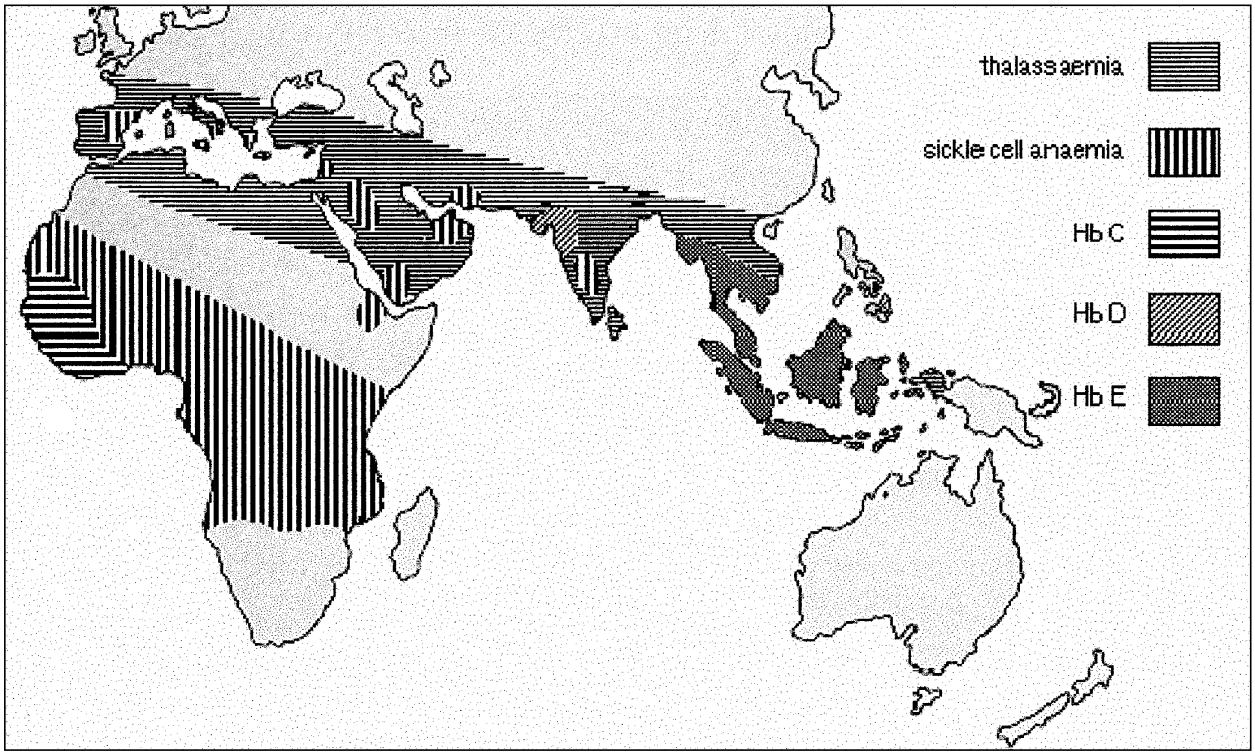


FIGURE 2 *Distribution of the haemoglobinopathies: Europe, Africa, Asia, Australasia*

Hb: SS), or sickle Hb (S) interacting with other β-globin chain gene abnormalities, including Hb SC disease and sickle β-thalassaemia ($S\beta^T$)) is rising and is expected to be in excess of 10,000 by the year 2000.[24] Carriers are predominantly Afro-Caribbean and sub-Saharan in origin, but Arab, Mediterranean and Indian peoples are also affected.

There are approximately 600 people with β-thalassaemia major in the UK. It is most common in Mediterranean (Greek, Cypriot, Turkish and Italian), Indian and Pakistani peoples. Alpha-thalassaemia is most common in south-east Asia, Hong Kong and China; α-thalassaemia major is incompatible with life.

Clinical features

The sickle gene gives rise to clinical pathology when inherited from both parents, or when interacting with other variant β-chains or β-thalassaemias. In addition, genetic expression varies[25] so that some people who are homozygotes producing high Hb F levels may be only mildly affected.

Beta-thalassaemia

Beta-thalassaemia major is characterised by deficient or absent β-chain production and extramedullary erythropoiesis. Raised levels of Hb F compensate partially but death occurs within ten years unless the resultant severe anaemia is reversed and erythropoiesis is suppressed by regular blood transfusions.

Some individuals inherit two β-thalassaemia mutations but require only intermittent transfusions, and their symptoms are not severe. Although significant psychosocial problems have been reported,[26] this clinical syndrome arises as a result of a number of genotypes, including mild β-thalassaemia mutations, which allow some adult Hb (Hb A) production.

Alpha-thalassaemia

Alpha-thalassaemia major (Hb Barts hydrops fetalis), where no α-globin is produced, is associated with intrauterine death (except when intrauterine transfusion has been undertaken) and potentially fatal maternal complications. Hb H disease occurs when three of the four α-genes are non-functional. It is of variable severity, but generally presents a thalassaemia intermedia picture.[27]

Sickle cell disease

The amino acid substitution in S results in polymerisation/crystallisation of the S molecules

within the red blood cell on deoxygenation. This polymerisation produces a change in the cell from a biconcave disc to a crescent or sickle shape. On reoxygenation, the red blood cell initially resumes its biconcave disc shape but, after repeated cycles of "sickling and unsickling", it is damaged permanently, becomes dehydrated and irreversibly sickled, and haemolyses.[8]

The occlusion of small blood vessels occurs, resulting in a painful "crisis" and a variety of potentially fatal clinical presentations due to organ infarction (splenic infarction and sequestration, acute chest syndrome, cerebrovascular thrombosis, etc.). The highest mortality is in children aged one to three years, owing to these problems and overwhelming pneumococcal infection,[9,10] but the natural history of the disease is highly variable at an individual level.

Hb SC is generally less severe.[10]

Management

Over the past four decades, there have been considerable increases in the quality and duration of life for people with β-thalassaemia major[7,28] and those with SCD.[10,29]

The mainstay of treatment for thalassaemia remains regular blood transfusions and also splenectomy after hypersplenism develops.[4,7,28] Transfusion must be accompanied by regular desferrioxamine infusions to prevent iron overload.[7] Newer oral chelating agents remain under trial.[30]

The management of SCD is based on routine prophylaxis with penicillin for infants (which reduces infection rates by 84%[31]) and the early use of antibiotics to prevent overwhelming infection.[9] Patient and carer education is effective in ensuring early treatment for acute complications.[9] Hydroxyurea has been shown to reduce the frequency of sickle crises in adults,[3] probably because it stimulates the production of Hb F.

Bone marrow transplantation offers the chance of a cure for the 25–30% of children with SCD or β-thalassaemia major with a compatible donor,[32] but the procedure is associated with mortality. The remaining majority still experience considerable morbidity[3–5,33,34] and shorter life expectancy[6–10] than the general population.

Chapter 4

Screening

Definition

Screening is:

> "the systematic application of a test or inquiry, to identify individuals at sufficient risk of a specific disorder to warrant further investigation or direct preventative action, amongst persons who have not sought medical attention on account of symptoms of that disorder."[17]

Lappé and colleagues[35] have emphasised three especially important issues for genetic disease. They are that genetic screening should:

- contribute to the health of people suffering from genetic disorders, and/or
- allow carriers for a given abnormal gene to make informed choices regarding reproduction, and/or
- move towards alleviating the anxieties of families and communities who are faced with the prospect of serious genetic disease.

It is also important to recognise that "the incidental harm done by screening and by information [correct or otherwise] that it gives, should be small in relation to the total benefits from the screening–assessment–treatment system."[36]

Models of screening

In theory, because of the inherited nature of the haemoglobinopathies, once a diagnosis has been made, only one definitive test should be necessary during any one person's life, as long as that information is available life-long and whenever that person comes into contact with health services. Strategies that can be adopted include preconception, antenatal, opportunistic and neonatal screening.

A variety of models of haemoglobinopathy screening exist within Britain and the service is patchy and often unstructured. The varied distribution of the "at-risk" population may demand different service models, depending on prevalence, but these should be based on consideration of the benefits and outcomes of screening, the access to health care of those at risk, and issues of equity.

Screening programmes may be opportunistic or systematic, targeted or population based. In selective programmes, attention needs to be given to the criteria for selection and the population base (e.g. community versus hospital).

The SMAC report recommended targeted screening for health authorities with below 15% ethnic minority populations, on the undemonstrated assumption that, in these areas, this was more cost-effective than universal strategies.[11] In contrast, because of the ethical and practical difficulties raised by targeting, the Sickle Cell Disease Guideline Panel convened in the USA recommended that all states should carry out universal screening for sickle cells.[37]

Ethnicity is not always a good predictor of risk. Afro-Caribbeans, Cypriots and Italians frequently marry outside their ethnic group,[11] dissociating risk to a wider population. It has been suggested that mixed parenting in the UK will eventually necessitate universal screening.[38,39]

Selective programmes may also result in higher costs because of the selection process *per se* and because they may not identify all cases or pregnancies at risk. They can attract litigation when those at risk are not selected.[21,40–48]

Organised programmes should raise haemoglobinopathy awareness amongst both the health service staff concerned and the targeted communities at risk.[11] They are best aimed at communities and are most commonly provided in the neonatal period, but models exist for the screening of schoolchildren, which could be developed for adult screening.

Aims

Antenatal screening

Antenatal screening allows women at risk to make informed decisions about reproduction. It aims to

detect carrier parents, provide genetic counselling, and offer carrier couples the choice of prenatal diagnosis (PND) and selective abortion.[49]

In practice, women either choose continuation of, or termination of, affected pregnancies. Other choices (such as choosing a different partner, avoiding pregnancy, or egg or sperm donation from non-carriers) are very uncommon.[50]

Antenatal screening is also known as screening for genetic control of the disease. This is important even where alternative programmes exist because, for couples known to be carriers, their risk of conceiving an affected child is only one in four, yet, historically, without antenatal diagnosis, couples tended to stop reproduction and to terminate (mostly unplanned) pregnancies.[50]

Neonatal screening

The primary aim of neonatal screening is to identify babies with SCD and to commence early prophylactic penicillin[31] and comprehensive care. There is no equivalent reason for the early diagnosis of β-thalassaemia major; the β-thalassaemia trait is not identified by routine neonatal tests. However, it also permits genetic counselling for parents with affected or carrier newborns.[51]

Acceptability of antenatal screening

Prenatal diagnosis and termination

Experience from established screening programmes has shown that most populations with a high prevalence of β-thalassaemia find antenatal screening and the subsequent termination of affected pregnancies to be acceptable.[52] In Britain, reductions in affected birth rates have been less marked, which is ascribed to the limited availability or poor service delivery, rather than unacceptability, of screening programmes.[53]

Worldwide, successful programmes have emphasised community involvement, mass education (including school-based programmes), inter-sectoral collaboration, sensitivity towards cultural and religious values, and the delivery of consistent messages.[54,55]

A number of factors affect the uptake of genetic tests. Some relate to the acceptability of termination; others include the perception of risk, uncertainty about individual risk status, the manner in which an invitation to be tested is made, the extent of information provided prior to testing, and whether effective treatment (or an opportunity to prevent a condition) is available.[56]

The perception that a disease is severe increases attendance rates, partner testing and uptake of PND.[26,57–60] Fewer women accept PND if their partners do not attend initial counselling.[58]

The published British evidence is derived from studies at tertiary PND centres. Nearly 100% of at-risk Cypriots and 60% of Indians request fetal diagnosis, even in the second trimester.[53] Pakistani Muslims have a much lower uptake, although the introduction of first-trimester PND in 1982[61,62] has increased their uptake, as well as that of Indians. Bangladeshis are reported to remain averse.[63]

Termination is more likely for β-thalassaemia major than for SCD, in which the prediction of severity is not feasible.[59,60,64] Termination for SCD appears to be highly sensitive to gestation: 80% of couples request PND in the first trimester compared with 50% later.[57,59,60,64] Afro-Caribbeans are generally less receptive than Africans.[59,60]

Despite these findings, over 50% of first PNDs are carried out in the second trimester.[63] Commentators have argued for improved systems to ensure that delays are minimised.[65]

Cost-effectiveness

Antenatal screening

The aim of antenatal screening is informed choice.[11,21,59,60,66] However, rates of PND and the termination of affected pregnancies are generally used as outcome measures[58,67,68] because, if all women decided to continue with affected pregnancies, it would be difficult to justify the programme on cost grounds, whatever the quality of the decision making.[69,70]

Antenatal diagnosis of the haemoglobinopathies has been possible since the mid-1970s.[71,72] Antenatal screening programmes in countries with a high prevalence of haemoglobinopathy subsequently reduced the birth rate of affected infants by 50–95%.[52] However, given the different cultural and social environment, it is difficult to generalise the outcomes of such programmes to the UK.

Attempts to measure the impact of British programmes have mostly focused on selected groups of women attending tertiary referral centres for

PND. These centres have reported overall PND acceptance rates of 81% for β-thalassaemia,[50] 58% for SS, 47% for $S\beta^T$ and 17% for SC disease,[59,60,64] although, as discussed earlier, uptake is higher amongst certain ethnic groups.

Experience of community-based programmes in the USA has shown that these findings may not be generalisable at a population level.[67,68,73] There, the women involved have usually been shown previously to carry a fetus at risk for a major haemoglobinopathy and have already been informed about the option of PND, with some clinical details of the relevant disease.

Modell and colleagues[63] estimated the impact of antenatal screening by applying recorded PND rates from three perinatal registers to estimates of affected conceptions in each region (using the prevalence estimates presented in this report). However, such an approach does not provide information on the uptake of the component stages of screening, nor does it take account of the variable availability of universal screening countrywide.

An audit of universal screening in North London[65] included the outcomes of only 31 at-risk pregnancies, thus limiting its reliability and generalisability.

Antenatal screening is highly cost-effective at reducing the incidence of β-thalassaemia major[74–76] and remains so even if uptake falls to 50%. There are no comparable studies for SCD.

Neonatal screening

Two American studies have examined the cost-effectiveness of neonatal haemoglobinopathy screening,[77] concluding that screening US black populations was very worth while but, for non-black populations, the cost is high for each case found and life extended. This study has been widely criticised for: comparing screening in black and non-black populations rather than targeted and universal screening; failing to consider the extra costs and reduced effectiveness resulting from selection; and failing to recognise efficiencies inherent in universal screening.[37,40,41,78]

Sprinkle and co-workers[78] studied prevalence and costs of screening in individual states and concluded that universal screening could be provided, at socially acceptable costs, in demographically arranged diverse states, with co-operation on screening between some states. Their results indicated cost-effectiveness of universal screening in US populations in which 5% of births were African–American.

There is no published study reporting the full benefits of neonatal screening for haemoglobinopathies. Economic evaluation should, optimally, include the enumeration and measurement of all financial and non-financial costs and benefits of a policy for the patient, the family and society.[79]

Sprinkle and Konrad[80] used, without any very clear justification, one half of the price paid for finding phenylketonuria (PKU) as a measure of an acceptable price for identifying SCD. However, this is useful in drawing attention to the comparison between haemoglobinopathies and other diseases for which screening is an option.

Useful comparisons for discussions relating to the equity of programmes can also be made with neonatal screening for congenital hypothyroidism, which has a prevalence of approximately 25 per 100,000 newborns. The UK adopted national, universal screening for this disease in 1981.[81] PKU affects 11 per 100,000 babies screened in the UK, and a universal screening policy was adopted in 1969. SCD, on the other hand, affects about 26 per 100,000 babies in England but there is no national policy, outside the SMAC guidelines, on screening.

Tsevat and colleagues[77] calculated costs per life gained solely as a result of prophylactic penicillin, but did not consider other benefits such as education about splenic sequestration[29,41,82] or the effectiveness of early diagnosis and expectant clinical management, irrespective of penicillin prophylaxis.[83]

A complete assessment of benefits would consider outcomes such as: avoidance of the misdiagnosis of clinical manifestations; opportunity for prophylaxis against infections; prompt treatment of manifestations; screening of siblings; genetic counselling of parents;[83,84] an informed population; informed carriers; and reassurance and parental education about the clinical syndromes, including acute splenic sequestration.[39]

Chapter 5

Screening and diagnostic tests

Specimen collection

Venous anticoagulated samples (using EDTA) are best from the analytical point of view when screening at any age. The options for screening neonates include capillary samples, which are generally spotted on to filter paper and dried, or anticoagulated cord blood samples. However, maternal blood contaminates 1.7% of cord blood samples.[85]

Specimens can be anticoagulated and transported in glass capillary tubes,[46] but these have the disadvantage of fragility and a risk of drying. Therefore, for large-scale screening programmes, collection on to filter paper ('Guthrie' cards) is regarded as the most convenient method because of ease of storage and transport, and their ability to be integrated into existing screening programmes.[43,46,67,84,86,87]

Ideally, anticoagulated samples should be delivered to the laboratory within 24 hours for Hb screening. Samples on filter paper, however, can safely be posted.

Laboratory methods

The haemoglobinopathies can be detected by biochemical testing or DNA analysis. Diagnosis requires a combination of different techniques, including red cell indices, electrophoresis using cellulose acetate followed by citrate agar electrophoresis (CA/AG), or IEF and chromatography (generally using HPLC). These are all considered to be acceptable, except red cell parameters for screening as single techniques, according to recent US clinical guidelines;[37] the appropriate method is dependent on the age of the population to be screened, as well as on the staffing and financial resources available to the laboratory.

In the USA, electrophoresis, usually by IEF, is the most commonly used method of neonatal screening.[37] The California state screening laboratories employ HPLC as the primary screening method for the State's universal programme, covering over 500,000 births per year.[88] The use of HPLC is becoming more widespread. The sample type must be taken into account when considering laboratory methods because those eluted from filter paper can adversely affect resolution if using CA/AG.[87] For this reason, its use is diminishing.

The final choice of technology should take into consideration the sensitivity and specificity of the screening test.[89] All techniques for electrophoresis have high sensitivity and specificity, ranging from 93% for CA/AG to 100% for IEF.[37] The main differences concern the resolution of various Hb bands, the extent of automation, and the cost of the equipment, reagents and manpower (*Table 2*[90,91]).

The US guidelines for neonatal haemoglobinopathy screening addressed sensitivity and specificity, including only studies that reported the testing of a second specimen from an identified infant. Eight studies were found that used CA/AG.[46,84,92–95] These reported an overall sensitivity of 91.3%. The overall specificity was determined from four of the studies as 95.2%.[84,92,93,96] It is well recognised that these techniques may fail to detect β^+-thalassaemia[97] as well as to distinguish between $S\beta^0$, $S\beta^+$, S co-inherited with hereditary persistence of Hb F, and SS. Galacteros and colleagues reported both sensitivity and specificity to be 100% when they evaluated IEF.[96] A recent study across nine US laboratories, using automated HPLC (Bio-Rad) and the same standard operating procedures for the State of California Neonatal Screening Programme, has reported a specificity of 99%,[98] while the same programme has reported, to members of the US Guideline Panel, a sensitivity of over 99.9% for the technique. Present evidence and experience suggest that both IEF and HPLC have acceptable sensitivity and specificity when properly used.

The detection of an abnormality when a variant Hb is present in amounts greater than 5% presents no problems with either technology, and the CMH experience suggests that both are sensitive to lower levels.[99] Diagnostic problems may arise, however, with the thalassaemias and their interactions because they result in variation of the proportions of the different haemoglobins

TABLE 2 *Comparison of laboratory techniques for haemoglobinopathy screening*

Technique	Identifies (Hb)	Disadvantages	Sensitivity	Specificity
Sickle solubility test	S (cannot differentiate SS from S heterozygotes)	Cannot detect AS < 6 months of age		
CA (alkaline pH)	A, F, S/G/D, C/E/O-Arab, H, rare variants Elution and spectrometry needed to quantify A_2	Manual, labour intensive	93.1% (CA followed by AG; pooled data)	95.2% (CA followed by AG, pooled data)
AG (acid pH)	S, D/G, C, E, rare variants not detected by CA	Manual, labour intensive		
Microcolumn chromatography	Quantification of A_2	Another column needed if Hb S present	Not known	Not known
IEF	Varies between systems (e.g. A, F, S, C, D-Punjab, E/A_2/O-Arab) Not validated for A_2 quantification	Visual inspection, prone to human error	100% (unquantified human error)	100% (unquantified human error)
HPLC	Quantifies A_2, F Variant Hb id depends on system (e.g. A, F, S, C, E/A_2, D-Punjab, O-Arab, others)	Hb A_2 level may be inaccurate if Hb S present Less resolution than IEF	99.9% (HPLC confirmed by IEF)	99%

AS, sickle cell trait; CA, cellulose acetate electrophoresis; AG, citrate agar electrophoresis; id, identification

Haemoglobins that can be distinguished from each other are separated by a comma; those that cannot are separated by a forward slash[90,91]

Data are from neonatal studies where second specimen taken from identified infants

No equivalent information is available for antenatal testing because missed variants/disorders may not appear in the fetal/infant genotype

present, be they normal or variant, which can lead to problems of interpretation, particularly in laboratories employing inexperienced staff.

Some commentators favour HPLC for large-scale screening programmes because it provides an automated and quantitative analysis, whereas IEF requires visual inspection and consensus decision making to derive presumptive phenotypes, introducing the potential for human error and judgement.[98] The interpretative nature of IEF means that there are greater requirements for staff and training.[100]

In terms of the level of information provided by each method, IEF can provide more because of its high resolution of Hb variants.[101] However, some authors have reported difficulties in quantifying small amounts of Hb A and S, with the potential for Sβ-thalassaemia being mistaken for sickle cell trait by the inexperienced.[88]

Another shortcoming of using IEF in conjunction with Guthrie samples lies in its reduced ability to detect Hb Barts and, therefore, α-thalassaemia trait.[84,87,101] HPLC probably shares this limitation, which, in both cases, appears to be related to the dried paper samples.

The quantitative data provided by HPLC can be important for distinguishing between homozygote states and the Hb variant interactions with β-thalassaemia (e.g. SS and Sβ-thalassaemia, Hb C disease and Cβ-thalassaemia, and Hb E disease and Eβ-thalassaemia. However, the major disadvantage of HPLC is its inability to detect 'fast-moving' variants.[102] The clinically significant conditions of SCD and β-thalassaemia major should be diagnosed by both technologies. Current investment decisions relating to neonatal haemoglobinopathy screening should therefore be based on the expertise of the laboratory concerned, the depth of knowledge required, and cost calculations.

A second test should be used to confirm any abnormality found and for final diagnosis. It should be borne in mind that the "sickle test" is negative in infants because of the continued presence of Hb F and is, therefore, not indicated. A number of new techniques, some using monoclonal antibody technology, are now coming into use for confirmatory testing.

Although variant haemoglobins should rarely be missed on universal antenatal screening, there are very real problems with the specificity and sensitivity of screening tests for both α-thalassaemia traits, and it does not detect β-thalassaemia traits. More specific testing using DNA technology is not cost-effective. The British Committee for Standards in Haematology has recently published consensus guidelines on these issues.[90]

Whom to treat

All women at risk of carrying a fetus with a clinically significant haemoglobinopathy, as listed in *Table 3*, and female carriers whose partners cannot be tested, should be offered PND.[11]

TABLE 3 *The common clinically significant Hb disorders*

Thalassaemias	Structural Hb disorders
β-Thalassaemia major	Hb SS (sickle cell anaemia)
β-Thalassaemia intermedia	Hb SC disease
Hb Eβ-thalassaemia	Hb SD Punjab disease
β-Thalassaemia hydrops fetalis	Hb Sβ-thalassaemia
Hb H disease	

Based on Modell and Anionwu[21]

Chapter 6

Discussion

Criteria for screening

Revised criteria for British screening programmes were published in 1998,[17] as presented below:

- the health problem
  - important condition
  - natural history understood
  - cost-effective primary prevention implemented.
- screening tests
  - suitable, acceptable tests available to detect the disease early
  - distribution of test values in the target population known
  - agreed policy on further diagnostic investigations.
- treatment
  - effective, acceptable treatment or other interventions available
  - agreed policy on whom to treat
  - optimum management achieved prior to participation in screening.
- screening programmes
  - effectiveness demonstrated in randomised controlled trials
  - acceptable to health professionals and the public
  - benefits outweigh physical and psychological costs
  - opportunity costs balanced against medical expenditure
  - adequate facilities available to offer diagnosis/treatment
  - quality assurance measures in place
  - all other options for managing the condition considered.

Questions addressed by the review

Guided by this framework, this review has identified the following gaps in the evidence base.

- The prevalence and incidence of SCD and β-thalassaemia major across England remains uncertain. Existing point estimates are based on studies conducted in the countries of origin of various ethnic groups within which there is considerable heterogeneity of prevalence. In the UK, the broad classifications of ethnicity include people from different backgrounds so that the application of existing estimates may be inaccurate. Current screening programmes have not collected ethnic group data routinely, or in a systematic fashion, and cannot be used to provide data on ethnic-specific rates. A range of prevalence estimates is required in the absence of more robust data.
- Data for the coverage, uptake and outcomes of antenatal screening services are largely derived from studies of women attending tertiary referral centres for PND, limiting the ability to predict the likely impact of screening amongst unselected populations. This also prevents accurate cost analyses from being undertaken.
- Economic analyses relating to haemoglobinopathy screening programmes in UK settings have not been published. This is needed in order to address a number of issues relating to haemoglobinopathy screening programmes and inform the type of programme that should be established, including:
  - costs and effectiveness of antenatal and neonatal screening programmes
  - the opportunity costs of screening versus not screening
  - the cost-effectiveness of the counselling and follow-up component of a neonatal screening programme.

Of these, the first is addressed by a systematic review-based analysis of available numerator and denominator data (chapters 7 and 8). The others have been addressed through collation and analysis of data derived from actual screening programmes based at the CMH in North-west London (chapters 9–12). The programmes run out of the CMH are among the most developed and comprehensive in the UK and, therefore, provide a source of information that is not available from other centres. These data, therefore, provide for the first time an evidence base and a practical approach from which both commissioners of health services and providers may extrapolate.

SECTION II

SUPPLEMENTARY RESEARCH

Chapter 7
Methods

Objectives

The systematic review demonstrated the paucity of rigorous evidence relating to screening for the haemoglobinopathies worldwide, particularly for the UK. Health care commissioners require further evidence relating to prevalence, uptake, outcomes and costs, in order to ensure that evidence-based decisions are made in this area. Further specific primary research was therefore undertaken using data and programmes directed by one of the team (Professor Sally Davies).

Prevalence

Ethnic-specific births

Ethnic group was defined in accordance with the 1991 UK Census. Cypriots were identified separately from whites because of their high risk of β-thalassaemia.[91]

Birth statistics do not record ethnicity. Therefore, to estimate ethnic-specific births, proxy figures were calculated using the number of children aged 0–4 years recorded in the 1991 Census, adjusted for under-enumeration[103] and divided by five.

Cypriot births were estimated by doubling the reported number of children aged 0–4 years in households where the head of the family was born in Cyprus and subtracting it from the white ethnic group. This was based on the following assumptions.

- Only half the "Cypriot" population of child-bearing age were born abroad because most emigration occurred between 1957 and 1967.
- The geographical distribution of Cypriot parents is similar regardless of whether they were born in the UK or Cyprus (B Modell, University College, London: personal communication, 1996).

Birth rates were mapped to local government (rather than health authority) boundaries because ethnic minority populations tend to be concentrated in city centres, which, outside London, are rarely covered by a single health authority boundary.

Prevalence

Prevalence estimates were derived from country rates provided by the WHO.[2,55,104–107] To validate these estimates and adjust them where necessary for application to the UK, we identified relevant studies carried out in the UK.[38,85,108–112] We supplemented these with others[113–120] from over 2000 compiled by Livingstone.[121] These were carried out in the main countries of origin of ethnic minorities living in the UK, but the majority were unusable because of recruitment bias or small numbers.

The criteria for inclusion were that studies should be based on:

- populations representative of those resident in the UK
- unbiased samples, ideally in a population-based study.

The research papers were graded from A to E (*Table 4*).

TABLE 4 *Key to grading of research papers*

Strength of evidence	Grade
Based on large-scale UK population survey	A
Based on large population survey in country of origin; clear links with UK population	B
Expert advice based on range of studies in country of origin; support from UK studies	C
Expert advice based on unpublished data	D
Assumed to be the same as another ethnic group	E

Estimates were derived for β-thalassaemia and Hb S, C or E traits. The proportion of births with clinically significant disease (β-thalassaemia major or intermedia, Hb SS, Hb SC, Eβ-thalassaemia and Sβ-thalassaemia) were calculated using the Hardy–Weinberg equation:

$$\text{Frequency of homozygous disease} = p^2$$

where p = gene frequency of abnormal trait (≈ carrier frequency/2)

and

$$\text{Frequency of compound heterozygous disease} = (p+q)^2 - (p^2+q^2)$$

where p, q = gene frequencies of different interacting Hb disorders.

Rates were adjusted for customary consanguineous marriage in Pakistanis[122] and for marriage outside the ethnic group for Cypriots.

The weight of evidence for the estimates was graded, following the example of other critical reviews, from being based on a population screening programme (considered analogous to a randomised clinical trial) to expert opinion.[123] Upper and lower estimates were derived if there was insufficient evidence to support a single value for an ethnic group living in the UK.

We did not attempt to determine estimates for α-thalassaemia because: it is relatively uncommon; it is not a clinically significant interaction with other haemoglobinopathies; we could not validate the estimates; and the implications for screening had been dealt with previously.[59,60] Hb D was also excluded, although common among Indians,[118] because its most significant clinical problem (compound heterozygosity with Hb S) is rare in the UK and would be encompassed by the range of estimates for SCD.

Validation

Estimates of the total number of affected births were obtained by combining the ethnic-specific prevalence rates and number of births. These were adjusted for termination using the data derived from studying the outcomes of the CMH service (chapter 9) and other sources.[108] A credible range was calculated from a formula for combining two estimates with upper and lower values.

The estimates were validated against the universal population neonatal screening programmes in North Thames (West) (NTW) and Lambeth, Lewisham and Southwark (LL&S), and against the CMH (South Brent, universal) and Leicester (targeted) hospital antenatal screening programmes.

Central Middlesex Hospital antenatal screening programme

Population

Brent is typical of inner London, with high levels of poverty, unemployment and homelessness. It has a Jarman score[124] of + 27.5 and a population of 243,000: 17% black, 20% Indian subcontinent, 55% white (*Table 5*). Most of the immigration into the borough occurred during the 1950s, and was from the Caribbean and Pakistan.

There are 60,000 women aged 15–44 years in Brent (25% of the total population) (*Figure 3*).

Screening programme description

The CMH programme (*Figure 4*) was the first antenatal screening programme to be established in the UK. Since 1985, all women booking at the antenatal clinic have been screened routinely for the haemoglobinopathy variants, and α- and β-thalassaemia traits. Blood samples are forwarded to the haematology laboratory at this hospital.

TABLE 5 *Population of Brent*

Age group (years)	White	Black	Indian subcontinent	Other Asian	Other	Total
0–4	6423	3654	4455	776	1201	16,509
5–14	11,277	6413	9448	1199	2062	30,399
15–24	20,630	7062	7395	1339	1775	38,201
25–34	24,881	8680	9508	2122	2039	47,230
35–44	16,587	3847	8174	1854	1447	31,909
45–54	15,192	4505	5130	849	823	26,499
55–64	14,205	4181	3556	366	523	22,831
65+	24,961	1793	2160	174	359	29,447
Total	134,156	40,135	49,826	8679	10,229	243,025
%	55	17	20	4	4	100

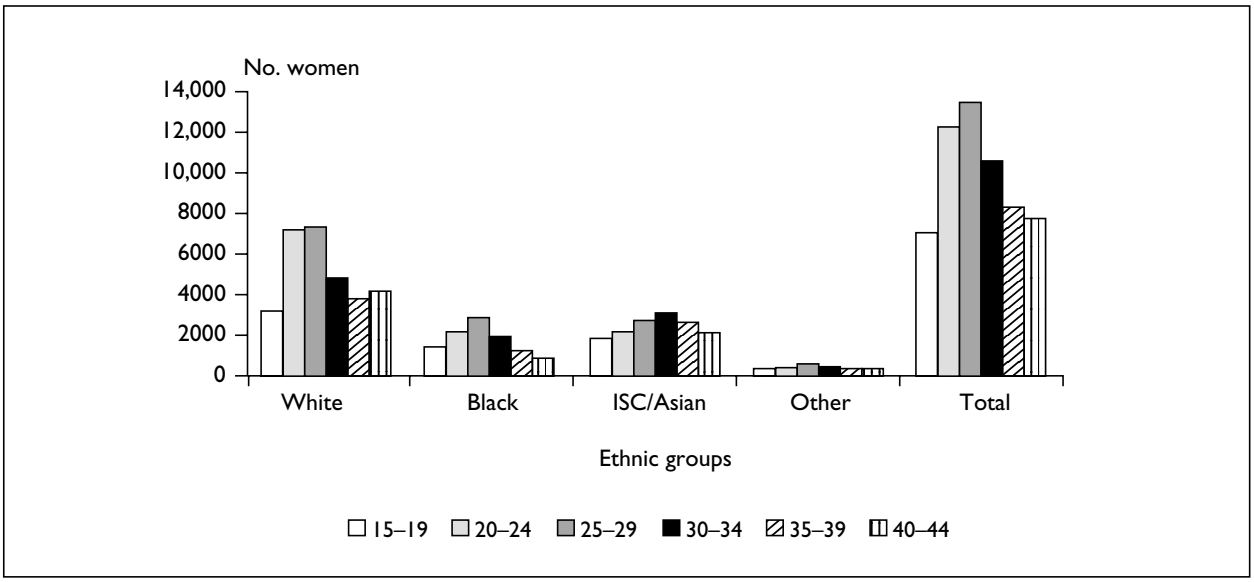


FIGURE 3 *Age breakdown of women living in Brent, aged 15–44 years, by ethnic group (ISC, Indian sub-continent)*

All patients with definite haemoglobinopathy traits or disease, as well as those with putative α-thalassaemia, are referred to the Brent Sickle Cell and Thalassaemia Centre (BSCTC). The Centre was originally on the CMH site, but was moved to a high street location in 1997. Nurse specialists make up to three attempts, by post and telephone, to contact these women. They are informed of their haemoglobinopathy phenotype and both they and their partners are invited for counselling.

The counselling session includes:

- education about inheritance
- the implications of a positive result in the partner and risk to the fetus
- the option of PND.

Arrangements are made for specimen collection from partners. If a partner's result indicates that the fetus is at risk for a clinically significant haemoglobinopathy, PND is offered to the couple (or DNA analysis followed by PND as appropriate if there is a risk of α-thalassaemia major or Hb H disease). Since 1990, any woman with a Hb variant whose partner has not been tested and is from an ethnic minority at risk of carrying a sickle gene has been offered counselling to discuss PND.

Women wishing to proceed to PND are referred to a perinatal medicine centre. If appropriate, they are then counselled by both the nurse specialist and the referring obstetrician for elective termination of an affected pregnancy. The nurse specialist also offers post-termination support.

The nurse specialists ensure that the results of neonatal screening (through the North Thames (West) Neonatal Screening Programme) are given promptly to all women who have been referred, by performing a home visit as soon as the results are available.

In addition to the universal screening of women who are booking for routine antenatal care, the programme accepts tertiary referrals for counselling from other hospitals, using the same facilities, staff and processes.

Data on age, sex, gestation at referral, source of referral, dates of key events (counselling, PND, etc.) and genotypes for all referrals to the BSCTC are recorded manually by nurse counsellors and transferred to a Paradox database after all counselling or other interventions have been completed. Data on ethnicity, partner details and outcomes are also recorded for couples at risk of carrying an affected fetus.

Laboratory methods

These conform to and exceed the specifications laid down by the BCSH General Haematology Task Force.[91,125] Quality control is monitored through participation in the National External Quality Assurance Scheme.

On receipt of the initial sample, the laboratory performs an automated full blood count, including Hb, mean cell volume, and mean corpuscular Hb, using a Coulter STK-S. The laboratory records are checked for each patient to ascertain if the Hb phenotype has been

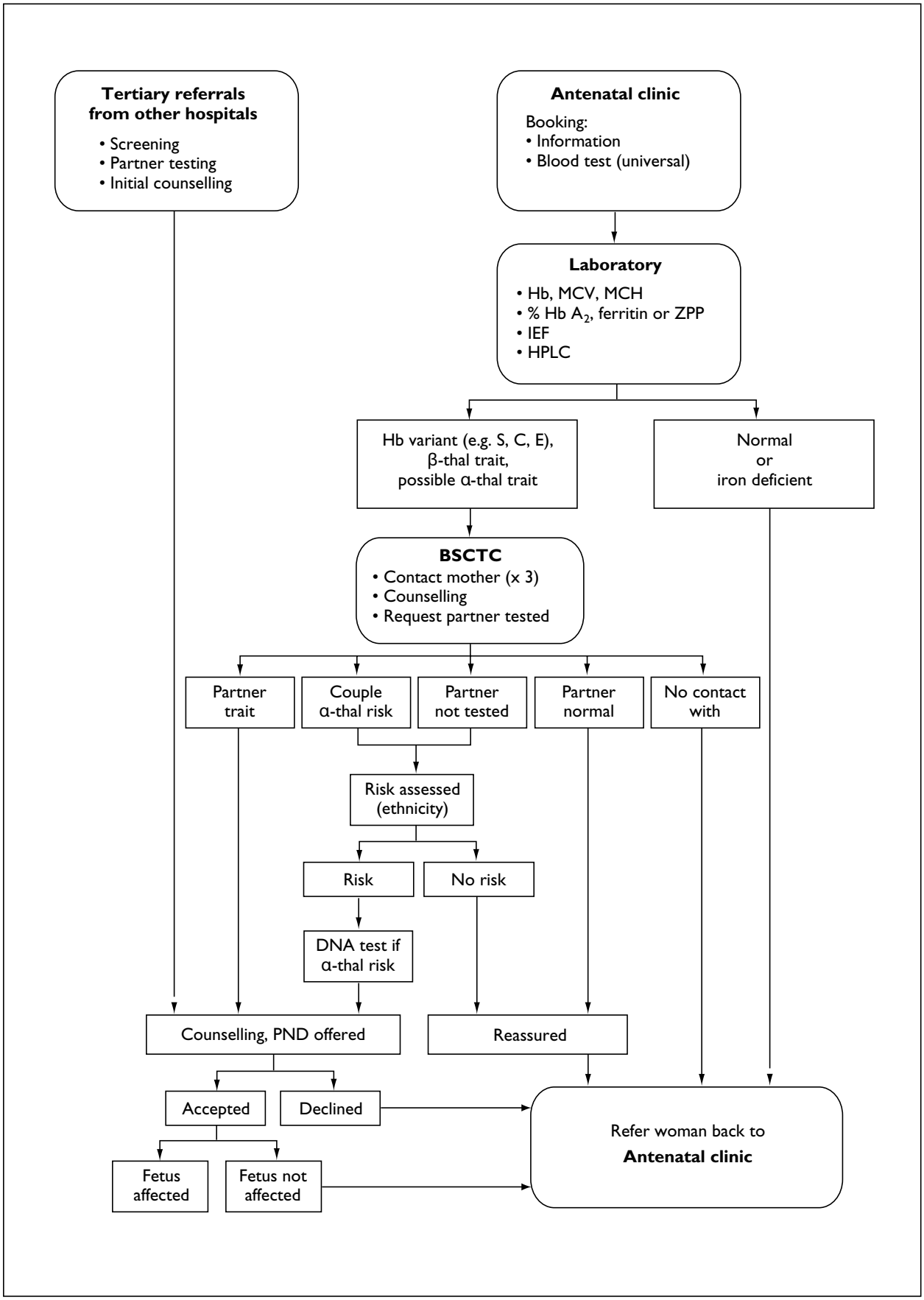


FIGURE 4 *CMH antenatal screening process (MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; ZPP, zinc protoporphyrin assay; thal, thalassaemia)*

performed previously, and, where a prior result is available (approximately 9% of cases), this is provided to the clinic with no further haemoglobinopathy testing being undertaken.

The other samples are subjected to:

- IEF using Isolab neonatal gels to screen for structural Hb abnormalities
- HPLC using a Shimadzu Haemoglobin Analyser for confirmation of variant Hbs
- Hb quantification including Hb A_2.[91,126,127]

The presence of Hb S is confirmed by a solubility test[128] and other variant bands are identified by repeat IEF, with known variants as adjacent controls. This is followed, if required, by acid gel electrophoresis (pH 6.2) or cellulose acetate electrophoresis (pH 8.6) for diagnostic reasons.[129] However, only nine and two, respectively, of these extra tests were performed during the sample year studied for costing purposes.

The β-thalassaemia trait is diagnosed by the finding of Hb A_2 of ≥ 3.5%. All diagnosed and possible thalassaemia trait samples (β and α) are subjected to zinc protoporphyrin assay, using a Protofluor-2 (Helena Laboratories). The large number of women provisionally diagnosed with α-thalassaemia trait reflects the low specificity of the screening test; confirmatory diagnosis requires DNA studies.[54,91]

Data sources and analysis

Information about laboratory methods and counselling was obtained from interviews with haematologists, laboratory technicians and nurse specialists, plus previous reports from the CMH service.[58,130]

Routine data (covering all referrals 1986–1995) were transferred into and analysed with the Statistical Package for Social Sciences. Three descriptive analyses were undertaken:

- to describe (with 95% confidence intervals (CIs)) the performance of universal screening, including: gestation at counselling, percentage counselled, percentage of partners tested, uptake of PND, and percentage terminated; relative risk (RR) and the chi-squared statistic were calculated to compare the β-thalassaemia and sickle cell cohorts
- to describe the performance of screening for tertiary referrals using RR and the chi-squared statistic to compare them with the unselected cohort
- to estimate the percentage of affected births prevented, by comparing the performance of the antenatal programme with the outcomes recorded for screened women, validated by reference to the NTW neonatal screening programme.

Costings

To establish the full costs of the antenatal screening and diagnosis programme, we used workload data from the 1994 calendar year (for which complete data were available) and cost data for 1994–1995 and the calendar year 1995. Adjustments were made to 1994 workload information where there had been changes in screening practice.

Cost information was collected for both the laboratory and follow-up components of the programme. Fixed and variable elements of laboratory costs were determined. Forty-six per cent of annual equivalent costs for HPLC equipment has been allocated to the antenatal programme, compared with only 4% of the annual equivalent costs for the IEF equipment. These figures reflect the overall use of this equipment.

Follow-up cost information was collected by examining the antenatal caseload as a proportion of the total BSCTC activity, and includes fixed costs (support and overheads) and variable costs for salary, which are dependent on the number of referrals (141 during the sample year).

North Thames (West) neonatal screening programme

Population

The area covered by the old North West Thames Regional Health Authority includes eight health authorities (*Table 6*) and 15 local authorities. The total population is 3,406,911, of which 19% are from ethnic minorities (for individual districts the range is 3–61%).

Screening programme description

This programme commenced in 1988 and screens all neonates born in the region for haemoglobinopathies (approximately 50,000 per year). The programme is based at the CMH haematology laboratory. It provides full diagnosis and follow-up of any haemoglobinopathies, in addition to (narrowly defined) screening[131] as shown in *Figure 4*.

From every baby born in the region, additional drops of blood are placed on a separate filter paper (Guthrie card) at the time of screening for PKU and congenital hypothyroidism. This

TABLE 6 *North Thames (West) population*

Population	White (%)	Black (%)	Indian subcontinent (%)	Other Asian (%)	Other (%)	Total (%)
Bedford	472,166 (90)	13,329 (3)	32,212 (6)	1782 (0)	4616 (1)	524,105 (100)
Hillingdon	203,149 (88)	3810 (2)	18,381 (8)	2495 (1)	3767 (2)	231,602 (100)
Kensington, Chelsea and Westminster	254,373 (81)	21,664 (7)	11,775 (4)	8822 (3)	16,940 (5)	313,574 (100)
Barnet	239,909 (82)	10,476 (4)	25,064 (9)	8609 (3)	9895 (3)	293,953 (100)
Brent and Harrow	277,692 (64)	46,972 (11)	83,638 (19)	13,073 (3)	15,411 (4)	436,786 (100)
Ealing, Hammersmith and Fulham	462,682 (74)	40,509 (6)	92,643 (15)	13,186 (2)	19,968 (3)	628,988 (100)
East and North Herts	462,371 (97)	3791 (1)	6461 (1)	1199 (0)	3481 (0)	477,303 (100)
West Herts	475,887 (95)	4581 (1)	12,300 (2)	2465 (0)	5367 (1)	500,600 (100)
Total	2,848,229 (84)	145,132 (4)	282,474 (8)	51,631 (2)	79,445 (2)	3,406,911 (100)

is carried out by a midwife, approximately 7 days after birth.

The screening *and* diagnosis approach is intended to maximise the rate of confirmation of haemoglobinopathies and appropriate follow-up, thereby ensuring maximum benefit from the programme as a result of optimal early clinical management[29,31] and appropriate genetic counselling.

The nurse specialists from the BSCTC, who provide information and non-directive genetic counselling, undertake the follow-up. They also collect specimens where necessary for confirmation of infants' Hb type, including when clinically significant disease is suspected. Ongoing support is provided for families with babies with clinically significant haemoglobinopathies.

In order to maximise the number of haemoglobinopathies confirmed and provide appropriate information and counselling, three nurse specialists are employed. They undertake home visits or see the women in a clinic setting close to their home.

While AS and AC can be confirmed by the laboratory from the initial specimen, other traits require a second specimen. Homozygous states and other clinically significant haemoglobinopathies are also confirmed using a second specimen, collected at term plus 6 weeks. The nurse specialists visit families of babies with AC and AS conditions only once, while those who require confirmatory specimens may require two or more visits.

Once the Hb type has been confirmed, a UK Haemoglobinopathy Card is issued to the family, providing a permanent record of the condition. The result is also sent, by the BSCTC staff, to the general practitioner and, via the local community child health department, to the health visitor.

During 1994, of 26 initial results that indicated clinically significant haemoglobinopathies, only one could not be confirmed; this was because of parental refusal.

Laboratory methods

IEF is used to screen all samples initially. If Hb S and Hb C are indicated, the results are confirmed immediately by monoclonal antibody testing. Follow-up specimens for unidentified traits or confirmation of clinically significant disease are tested with IEF and HPLC.

Costings

Data were collected, as for the antenatal programme, for activity and costs in 1994 and 1995. The costing model presented identifies cost per case detected and cost per extra case detected. There are non-financial costs and costs falling outside health services in all screening programmes, such as stress and costs incurred by the family and society during the screening, notification and follow-up processes, which have not been included.

Items were costed, according to time taken as a proportion of annual productive hours, for the relevant staff salary and other employment costs. Costs of consumables were applied to relevant tasks, as were annual equivalent costs of capital

(which were calculated using a discounted rate of 6% over 7 years).

Hospital overheads were calculated in terms of their fixed and variable elements. Laboratory overheads (supervision, clinical direction, training, stationery, stock control and general clerical costs) were apportioned in the same way.

Medical laboratory scientific officer staff costs are treated as variable, given the interchangeability between laboratory sections. Inputs likely to remain unchanged regardless of the size of the programme (e.g. supervision by a grade 4 medical laboratory scientific officer, a haematologist, stock control and laboratory clerical duties) are fixed elements of the costs.

As the CMH laboratory does not use HPLC for the initial testing of neonatal samples, costs for this method were identified with the assistance of St Thomas' Hospital haematology laboratory, which uses the Bio-Rad Variant analyser for its adult testing programme. The manufacturer provided information on capital and consumable costs.

Chapter 8

Prevalence of sickle cell and β-thalassaemia in England[132]

Summary

A range of estimates for sickle and β-thalassaemia trait and disease were derived for the different ethnic groups living in the UK, which reflected uncertainty over the true population value in certain countries and the heterogeneity within and between countries of origin comprising the same ethnic group. This range correctly predicted the number of affected births observed by the screening programmes.

It is estimated that each year in England:

- 3000 babies (0.47%) carry AS
- 2800 (0.44%) babies carry β-thalassaemia trait
- 43 (0.07 per 1000) conceptions carry β-thalassaemia major or intermedia
- 178 (0.28 per 1000) conceptions carry SCD.

Allowing for terminations (see chapter 9), we estimate that 17 (0.03 per 1000) infants are born with thalassaemia and 160 (0.25 per 1000) with SCD. The geographical patterns of SCD and β-thalassaemia differ, although they correspond with areas of high ethnicity.

Findings

Tables 7 and *8* present our estimates of the rates of carrier frequency and clinically significant disease by ethnic group for use in the UK, including the strength of evidence grading and the main sources of information[38,85,109,112–117,119,120,133] (and S Ahmed, University College, London: personal communication, 1997).

The best data were obtained from population screening programmes in Jamaica, which were adopted for the black Caribbean ethnic group, and from Cyprus, although the latter were adjusted for the potential reduction of clinical disease in England owing to unions with non-Cypriots. Data derived from a mixture of sources for most of the other ethnic groups rarely supported a single estimate.

The occurrence of sickle cells is concentrated within black ethnic minorities, with comparatively high carrier rates responsible for high rates of disease: 5.6 per 1000 births among black Caribbeans and 14.7 (7.4–24.8) among black Africans.

TABLE 7 *Prevalence estimates: sickle trait and disease*

Ethnic group	Carrier rate S (low–high)[a]	Carrier rate C (low–high)[a]	Affected fetuses/1000[c] (low–high)[a,d]	Grading	Evidence (references)
White				D	109,112
Black Caribbean	0.11	0.04	5.60	B	38,85
Black African[d]	0.20 (0.10–0.28)	0.03 (0.02–0.08)	14.71 (7.36–4.80)	C	113–115,119
Black other[e]	0.11	0.04	5.60	E	
Indian	0.01 (0.0–0.01)		0.08 (0.00–0.18)	D	111,118
Pakistani[f]				D	110,111
Bangladeshi[g]				D	111
Chinese				D	116,120
Cypriot[h]	0.0075 (0.005–0.10)		0.5 (0.3–0.7)	C	117
Other Asian				E	
Other other[i]				E	

Footnote indicators – see Table 8
Evidence grading as Table 4

TABLE 8 *Prevalence estimates: β-thalassaemia*

Ethnic group	Carrier rate (low–high)[a]	Affected fetuses/ 1000[b] (low–high)[a]	Grading	Evidence (references)
White	0.001	0.0003	D	109,112
Black Caribbean	0.009	0.018	B	38,85
Black African	0.009	0.018	D	113–115,119
Black other[e]	0.009	0.018	E	
Indian	0.035 (0.025–0.045)	0.31 (0.16–0.51)	C	111,118
Pakistani[f]	0.045 (0.035–0.055)	1.01 (0.6–1.51)	C	110,111
Bangladeshi[g]	0.030 (0.020–0.040)	0.83 (0.50–1.20)	C	111
Chinese	0.030 (0.010–0.040)	0.23 (0.03–0.40)	D	116,120
Cypriot[h]	0.160	5.12 (3.84–6.40)	B	117
Other Asian	0.030 (0.010–0.040)	0.23 (0.03–0.40)	E	
Other other[i]	0.001	0.0003	E	

[a] *Lower and upper estimates given if insufficient evidence for a single figure for the UK*
[b] *β-thalassaemia, β-thalassaemia E, but excludes homozygous Hb EE*
[c] *Homozygous Hb SS, SC, Sβ-thalassaemia, but excludes homozygous Hb CC*
[d] *High estimate combines high AS and low AC rates; low estimates combine low AS and high AC rates*
[e] *Black other assumed equal to black Caribbean*
[f] *Allows for consanguineous marriage (half between first cousins) doubling homozygous rate*
[g] *Hb E assumed at 4%, included in rates of compound heterozygous disease Eβ-thalassaemia*
[h] *Estimates assume reduced homozygous rates due to 20% partner exchange (40% lower estimate, 0% higher) with non-Cypriots*
[i] *Other assumed equal to whites*

Evidence grading as Table 4

The upper and lower levels of sickle and Hb C among black Africans reflect differences between countries in Africa. For example, Nigeria has relatively high rates of sickle cells and low rates of Hb C, while Hb C is more prevalent in Ghana.

In contrast, β-thalassaemia is present in all populations living in England, including trace amounts within the indigenous white population, but, except for Cypriots, at lower rates.

The range of estimates for β-thalassaemia amongst Indians, Bangladeshis, Pakistanis and Chinese reflect both uncertainty over the true population value and heterogeneity within their countries of origin, because of the lack of good applicable studies or outcome data from screening programmes performed in their countries of origin.

Tables 9–11 compare district population estimates with the observed annual numbers of carriers and affected births identified by local neonatal and antenatal screening programmes.

Sickle cell disease

About 13% of births affected by SCD were terminated in NTW and LL&S. In NTW and almost all its constituent health authorities, the observed number lies within the expected range, and close to the central estimate. In LL&S, the observed number lies within the expected range but towards the upper estimate (*Tables 9* and *11*).

Beta-thalassaemia

In NTW in 1990–1994, there were 22 cases of β-thalassaemia major or intermedia (64% terminated). This is close to our central estimate of 19 and within the expected range of 12–27 cases over 5 years.

In both Leicester and South Brent, the observed number of β-thalassaemia carriers is close to the central estimate (*Table 12*). In Camberwell, the observed number approaches the upper estimate.

Our validated estimates (*Table 12*) suggest that each year in England about 3000 (0.47%) carrier babies are born with sickle cell trait and 2800 (0.44%) with β-thalassaemia trait. There will be approximately 43 (0.07 per 1000) conceptions affected by β-thalassaemia major or intermedia, and 176 (0.28 per 1000) with SCD.

TABLE 9 *Affected births: universal neonatal screening programmes*

Area	AS		Hb C		SCD (SS, SC, Sβ-thal)	
	Observed mean	Expected no.: mid estimate (low–high)	Observed mean	Expected no.: mid estimate (low–high)	Observed mean	Expected no.: mid estimate (low–high)
NTW 1990–1994	452	457 (337–558)	105	114 (103–163)	25[a]	27 (19–38)
LL&S 1994–1995	N/Av	N/Av	N/Av	N/Av	45[b]	33 (23–47)

N/Av, not available

[a] *Mean 3.3 terminations annually after PND, excluding abortion for other reasons*
[b] *Six (13%) terminations after PND*

TABLE 10 *Validation of prevalence estimates: sickle trait and disease: NTW universal neonatal screening programme*

Area	AS		Hb C		SCD (SS, SC, Sβ-thal)	
	Observed mean 1990–1994	Expected no.: mid estimate (low–high)	Observed mean 1990–1994	Expected no.: mid estimate (low–high)	Observed mean 1990–1994	Expected no.: mid estimate (low–high)
Barnet	52	46 (28–60)	11	9 (7–17)	2.4	3.0 (1.8–4.6)
Brent	134	126 (96–150)	31	33 (30–45)	7.0	7.4 (5.5–10.0)
Ealing	56	66 (50–80)	12	17 (16–23)	2.5	3.7 (2.8–5.0)
Harrow	25	25 (17–32)	4	6 (5–8)	1.0	1.4 (1.0–1.9)
Hillingdon	9	13 (9–16)	4	3 (3–4)	0.5	0.7 (0.5–0.9)
Hounslow	16	22 (14–29)	4	5 (4–7)	1.0	1.3 (0.8–1.9)
H&F, K&C, W[a]	135	136 (103–163)	33	35 (32–51)	7.2	8.4 (6.0–11.7)
Herts	26	24 (20–27)	6	7 (6–8)	0.6	1.3 (1.1–1.6)
PND and TOP[b]	N/App	N/App	N/App	N/App	3.3	N/App
Total	453	458 (337–557)	105	115 (103–163)	25.5	27.2 (19.5–37.6)

TOP, termination of pregnancy; N/App, not applicable

[a] *Hammersmith and Fulham, Kensington and Chelsea, Westminster*
[b] *Excluding spontaneous abortion and abortion for other reasons*

TABLE 11 *Observed and expected births with β-thalassaemia and sickle traits*

Area	Annual no. screened	Trait	Observed mean	Expected no.: mid estimate (low–high)
Leicester (targeted) 1990–1994[a]	1370	β-thalassaemia	51	56 (41–70)
South Brent (universal) 1986–1993[b]	2050	β-thalassaemia	29	31 (24–37)
Camberwell (targeted) 1987–1992[c]	1630	AS, AC, β-thalassaemia	251	216 (171–268)

[a] *Targeted at Asian women (approx. 30% of total births); expected number derived for all births*
[b] *Served by CMH; population estimated from breakdown of births booked at CMH by borough of residence*
[c] *Served by King's College Hospital; expected number derived for all births*

TABLE 12 *Estimated numbers of pregnancies and births affected by β-thalassaemia or sickle cell in England*

	Trait		Disease		TOP (%)	Expected live births	
	Central	Lower–upper	Central	Lower–upper		Central	Lower–upper
β-thalassaemia							
No.	2800	2300–3200	43	30–60	50–70	17	10–25
Rate/1000	4.4	3.6–5.1	0.07	0.05–0.09		0.03	0.02–0.04
Sickle cell							
No.	3000	2400–3600	176	130–240	5–15	160	140–175
Rate/1000	4.7	3.8–5.7	0.28	0.2–0.36		0.25	0.22–0.28

Allowing for the selective termination of 50–70% of fetuses with β-thalassaemia and 5–15% of those with SCD (chapter 9), we estimate that 17 (0.03 per 1000) affected infants are born annually with β-thalassaemia major/intermedia and 160 (0.25 per 1000) with SCD.

Maps 1–4 show the geographical distribution of carriers and disease for β-thalassaemia and sickle cells in England. These highlight the heterogeneity in prevalence, the clustering in inner city areas with high proportions of ethnic minority populations, and the importance of concentrating on cases of disease rather than carrier frequency.

Although the β-thalassaemia trait is more widespread because of its presence in the white population, far fewer county districts are likely to experience a case of β-thalassaemia major or intermedia than SCD. It is estimated that every 2 years 19 county districts (5%) will have a case of β-thalassaemia major or intermedia, compared with 51 (14%) having a case of SCD.

Figure 5 shows the relationship between SCD and the proportion of births among ethnic minorities for individual districts. These range from 0% in the Isles of Scilly to over 60% in Brent, with half of them having less than 3%. This demonstrates that using percentage ethnicity alone, as a decision tool for which screening programme to adopt, may exclude areas with the same or higher rates of haemoglobinopathy than those above a proposed cut-off point.

Similarly, adopting percentage "black" ethnic minority births as an indicator for sickle cell screening would not allow a simple cut-off value for universal screening because the expected prevalence for a district is not a single value but lies within a range of estimates (see appendix 1).

Discussion

Potential biases

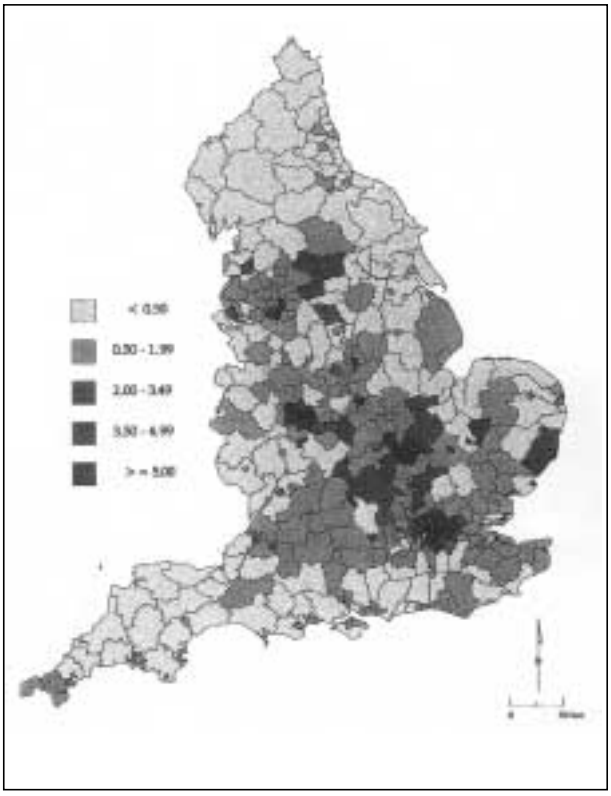
Our estimates simplify the composition and pattern of Hb disorders in the population. First, because data on the ethnic breakdown of births had to be inferred from the 1991 Census, some population groups without routine age-specific data and information on migration, although at greater risk than the autochthonous white British population, were not separately identified (e.g. SCD among southern Italians and other Mediterranean peoples).[134,135] Secondly, some rare Hb disorders have not been included.

Thirdly, apart from Cypriots, no allowance was made for unions between ethnic groups in estimating rates of disease, which may increase or decrease the risk of having an affected fetus. Increasing intermarriage will invalidate these estimates in the future as well as reduce the sensitivity of targeted screening.[38,39,48]

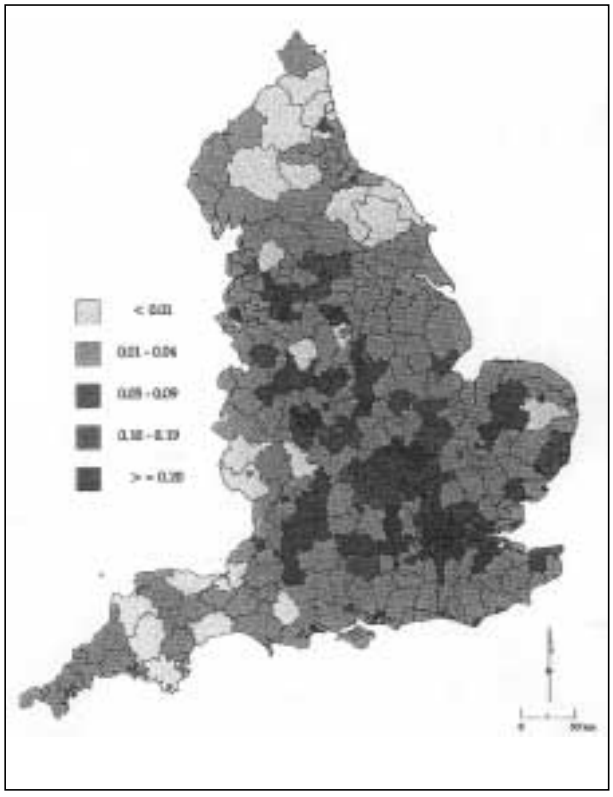
Fourthly, the estimates of disease assume that women having two pregnancies within one calendar year have the same probability of having an affected child as those who only have one baby. This may not be the case for those who undergo a termination after a positive PND, and may slightly underestimate the number of babies affected by thalassaemia, although this was not detected in our validation exercise of NWT.

Conclusions

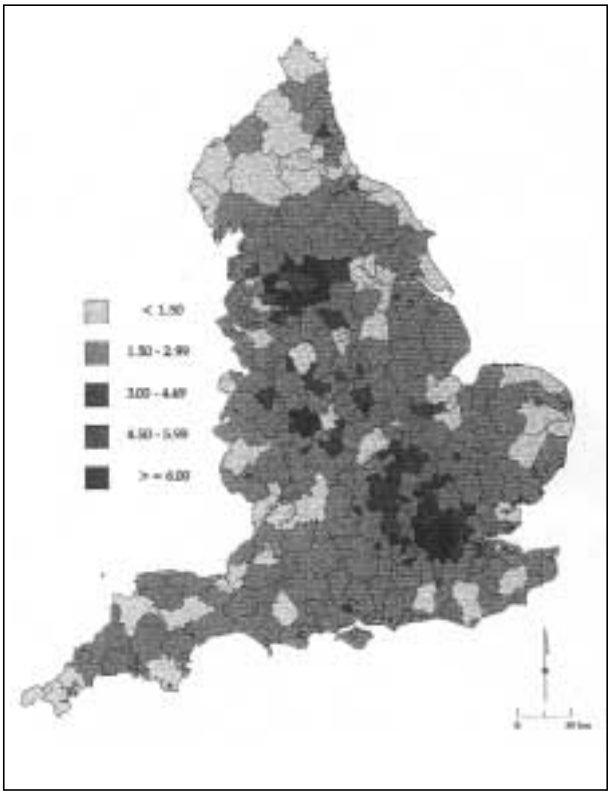
These are the first "evidence-based" rates for sickle cells and β-thalassaemia for use in England, and should underpin the future planning of services for screening and treatment. These figures have already been used to underpin advice from the Health Education Authority to purchasers[136] and modelling undertaken by another London research team.[137] They enable these two haemoglobinopathies to be considered separately and



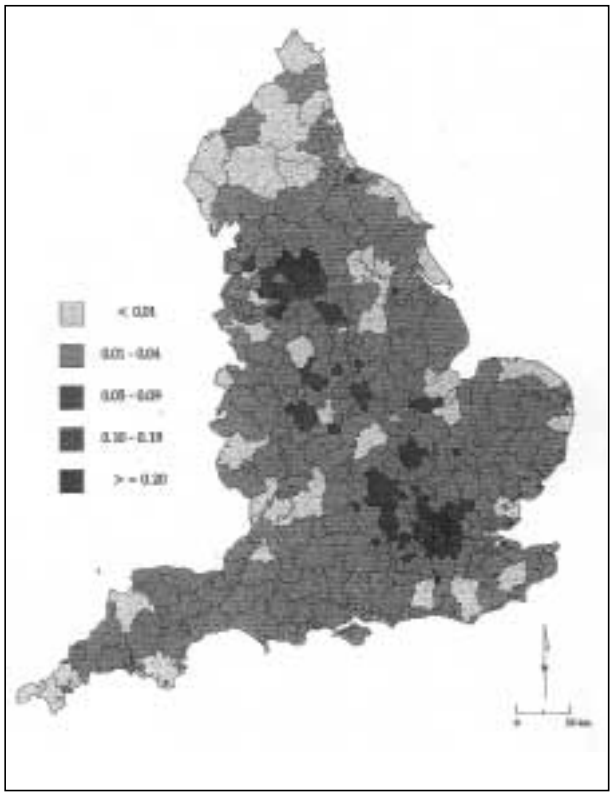
MAP 1 *Sickle cell trait (per 1000 births)*



MAP 2 *Rate of sickle cell disease (per 1000 births)*



MAP 3 *Thalassaemia trait (per 1000 births)*



MAP 4 *Rate of thalassaemia disease (per 1000 births)*

These maps are a pictorial representation of the middle estimates shown in appendix 1, generated using a geographical information system. Reproduction of these maps was difficult. Please contact the corresponding author for more details.

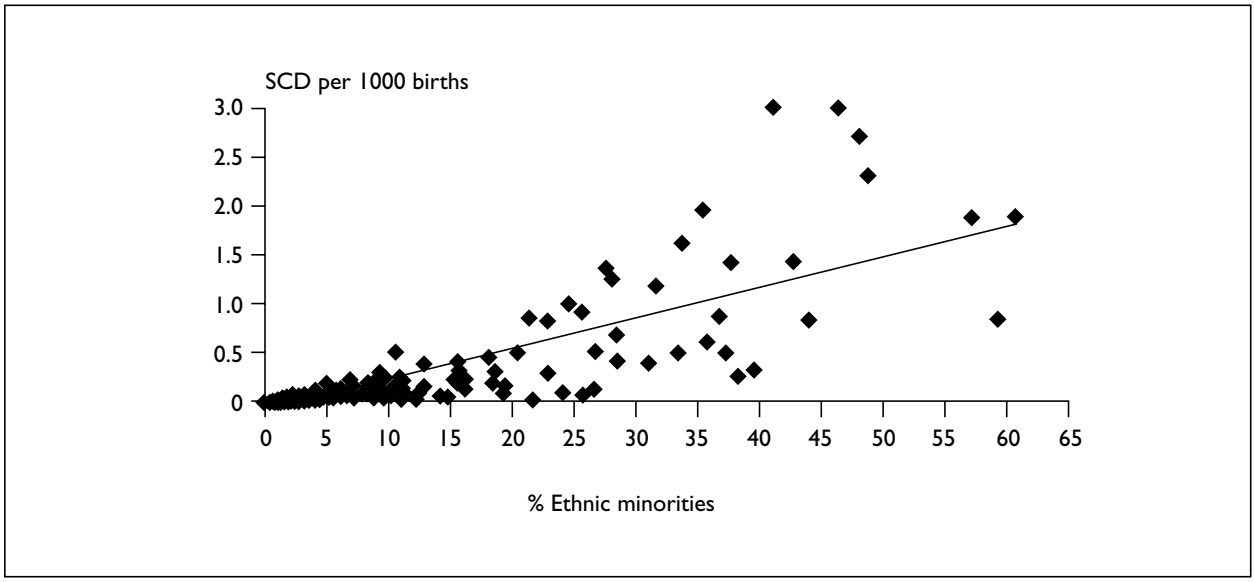


FIGURE 5 *Estimated SCD in county districts by percentage ethnicity (◆, county district; —, forecast)*

allow the cost-effectiveness of testing and case finding to be assessed.

The long-term solution to improving the evidence base (on both the numerator and the denominator) and monitoring changes in the rates of trait and disease in the population is to introduce a standardised instrument for collecting ethnicity data for all community screening programmes. This could be combined with data from existing and future community neonatal and antenatal haemoglobinopathy screening programmes to monitor changes in the rates of carrier frequency and disease in the population.

Chapter 9

Outcomes of universal antenatal screening[138]

Summary

Unselected women at risk of SCD are significantly less likely to have their partner tested or to accept PND than those identified via tertiary referral. This is not the case for those at risk of β-thalassaemia; 80% of β-thalassaemia and 16% of SS births are prevented by universal screening. Previous British studies have overestimated the impact of universal antenatal screening in preventing SCD births.

Women with a fetus at risk for SCD book, on average, 2.7 weeks later in gestation than those at risk for β-thalassaemia. They are less likely to attend counselling (83% versus 93%); their partners are less likely to be tested (77% versus 95%) (*Table 13*); and they are less likely to accept PND (22% versus 90%) (*Table 14*).

Findings

Universal screening (women booking at Central Middlesex Hospital)

Activity

Women were booked at the CMH for over 20,000 pregnancies during the period 1986–1995. They tested positive for haemoglobinopathy trait or disease in 1688 unselected pregnancies (8.3%).

A total of 242 episodes involved women who had previously been screened at the centre during earlier pregnancies. The behaviour of these women and their partners (percentages of those counselled, of whose partners were tested, and those accepting PND) was comparable with first-time attendees throughout the screening process and, therefore, they have been included in the following analysis.

Initial counselling and testing

The initial counselling session was attended by women in 1445 pregnancies (86%) and their partners were tested in 1192 (82%) of these. Eighty-three per cent of women with sickle trait or disease attended, compared with 93% of those with β-thalassaemia trait or disease (RR 0.89; 95% CI 0.85–0.94). Seventy-seven per cent of the partners of those women with sickle trait were tested, compared with 95% of those with β-thalassaemia trait (RR 0.81; 95% CI 0.77–0.83) (*Table 13*).

Many women are reported as putative α-thalassaemia because the basic screen is a reduced mean corpuscular volume, which is common in iron deficiency. Definitive diagnosis requires DNA analysis, which is reserved for cases where both the woman and her partner are from high-risk ethnic groups.

Couples at risk

Both parents were identified as carrying a significant abnormal genotype in 140 pregnancies: 113 (81%) at risk of conceiving a fetus with a clinically significant sickle variant and 22 (16%)

TABLE 13 *Uptake of universal screening programme*

	Maternal phenotype				Total
	Sickle[a]	β-Thal[b]	Other Hb[c]	α-Thal[d]	
(a) No. pregnancies	751	265	272	400	1688
(b) No. women attending counselling	623	246	218	358	1445
% of (a); 95% CI	83; 80–86	93; 89–96	80; 75–85	90; 86–92	86; 84–87
(c) No. partners tested	481	234	164	313	1192
% of (b); 95% CI	77; 74–80	95; 92–97	75; 69–81	87; 84–91	82; 80–84

[a] *Sickle includes the following phenotypes: SS, AS, SC, Sβ-thal*
[b] *β-Thal includes: trait and disease*
[c] *Other Hb includes: AC, AD, AE, AF and other variants*
[d] *α-Thal includes: α-thal trait, Hb H disease and α with variant bands*

of β-thalassaemia major or Eβ-thalassaemia. The women attended follow-up counselling in 135 (96%) of the pregnancies, although on only 67 (48%) occasions did their partners also attend (40% SS compared with 67% β-thalassaemia; RR 0.58; 95% CI 0.38–0.91).

PND was accepted in 35 pregnancies (plus one with a normal result where the partner had not been tested). Eight fetuses were diagnosed as affected and termination was performed for five of these. Two miscarriages of β-thalassaemic fetuses pre-empted the intervention, but both followed requests for termination (*Table 14*).

Gestation at booking

Women with β-thalassaemia booked earlier than those with sickle genotypes (mean 2.7 weeks; 95% CI 0.14–5.1). Thirty-eight per cent of women with sickle genotypes were interviewed before 13 weeks compared with 70% with β-thalassaemia genotypes (RR 0.56; 95% CI 0.38–0.77; chi-squared $p = 0.004$).

The earlier a woman booked, the more likely it was that PND would be accepted (*Table 15*). PND was accepted by proportionately less women at risk of carrying a fetus with SS disease (22%) than for those at risk of β-thalassaemia major (90%) (crude RR 0.26 or 0.37; 95% CI 0.24–0.57 if adjusted for

TABLE 14 *Utilisation of PND and termination: universal programme*

	Potential fetal phenotype						Total
	SS	**SC**	**Other sickle[a]**	**β-Thal**	**Eβ-Thal**	**α-Thal major**	
(a) No. pregnancies	68	39	6	21	1	5	140
(b) No. women attending interview	65	39	6	21	1	3	135
% of (a); 95% CI	96; 88–99	100; 91–100	100; 54–100	100; 84–100	100; 3–100	60; 15–95	96; 92–99
(c) No. partners attending interview	26	21	5	14	1	0	67
% of (a); 95% CI	40; 27–51	54; 37–70	83; 36–100	67; 43–85	100; 3–100	0; 0–52	48; 40–56
(d) No. PNDs accepted	14	1	1	19	0	0	35
% of (b); 95% CI	22; 12–33	3; 0–13	17; 0–64	90; 70–99	0; 0–98	0%; 0–71	26; 19–34
(e) No. fetuses affected	4	0	0	4	N/App	N/App	8
% of (d)	29			21	N/App	N/App	23
(f) No. miscarriages	0	0	0	2	0	0	2
% of (d)				11			6
(g) No. TOPs performed	3	N/App	N/App	2	N/App	N/App	5
% of (e); 95% CI	75; 19–99	N/App	N/App	50; 40–100[b]	N/App	N/App	63; 38–89

[a] *Other sickle includes the following phenotypes: Sβ-thal, SD, SE*
[b] *CI calculated as if four terminations were performed because two miscarriages occurred before termination could be considered, but after the women had indicated it was the preferred option*

TABLE 15 *Relationship between gestation at first interview and accepting PND*

	Potential fetal phenotype			
	SS		**β-Thal**	
	Attending interview	**Accepting PND**	**Attending interview**	**Accepting PND**
No. pregnancies	65	14	21	19
%; 95% CI		22; 13–33		90; 72–98
< 13 weeks gestation	27	11	17	17
%; 95% CI		41; 24–60		100; 84–100
13–22 weeks gestation	30	3	3	2
%; 95% CI		10; 3–25		67; 13–98
> 22 weeks gestation	8	0	1	0
95% CI		0–31		0–95

differences in the time to booking; Mantel–Haenszel summary chi-squared $p = 0.00002$).

Validation

Tertiary referrals (referred for counselling from other hospitals)

Between 1986 and 1995, during 101 pregnancies, 95 women were referred from other hospitals to the BSCTC (75 SCD or trait, 13 β- and two α-thalassaemia trait, 11 other Hb variants). All of those at risk for sickle and β-thalassaemia conceptions and over 99% of their partners were tested. In 88 pregnancies, there was a risk that the fetus would have a clinically significant abnormal Hb phenotype (*Table 16*).

Proportionately more women who were at risk of carrying a fetus with β-thalassaemia major (67%) accepted PND than those at risk for SS (55%) but the difference was not significant (Fisher's exact test $p = 0.7$). Fourteen fetuses were confirmed as having abnormal phenotypes, and ten terminations were performed. PND was more likely to be accepted earlier in gestation (92% acceptance if interviewed before 13 weeks, and 16% if between 13 and 22 weeks gestation).

Women in the universal programme who were at risk of a sickle disease-affected fetus were significantly less likely to have their partner tested (RR 0.65; 95% CI 0.61–0.69; chi-squared $p < 0.00001$) or to accept PND (RR 0.39; 95% CI 0.23–0.66; chi-squared $p = 0.0002$) than those screened as tertiary referrals. There were no significant differences between unselected women and tertiary referrals who were at risk of carrying a β-thalassaemic fetus.

Birth prevalence

From 1986 to 1995, 30 affected live births were recorded for the CMH study population (South Brent): 16 SS, 12 SC, one Sβ-thalassaemia and one β-thalassaemia major (*Table 17*).

After terminated and miscarried fetuses are accounted for, 80% (4/5) of β-thalassaemia and 16% (3/19) of SS births were prevented. One birth (SS) was to a woman who refused termination after a positive PND; all others were to couples who refused PND or left the programme (*Table 17*).

Summary flow charts describing the processes and outcomes are presented in *Figures 6* and *7*.

Discussion

Main findings

Amongst tertiary referrals, the programme achieved comparable rates of PND and termination to elsewhere.[49,59,60,64] Because women within the universal programme undergo the same process, the lower recorded uptake of

TABLE 16 *Utilisation of PND and termination: tertiary referrals*

	Potential fetal phenotype					Total
	SS	**SC**	**Sβ-Thal**	**β-Thal**	**α-Thal**	
No. pregnancies	60	15	3	9	1	88
No. PNDs accepted (%)	33 (55)	2 (13)	0	6 (67)	1 (100)	42 (48)
No. fetuses affected (%)	10 (30)	0	N/App	4 (67)	0	14 (33)
No. TOPs performed (%)	6 (60)	N/App	N/App	4 (100)	N/App	10 (71)

TABLE 17 *Reasons for affected pregnancies coming to term: universal programme*

Reason	**SS**	**SC**	**β-Thal**	**Sβ-Thal**	**Total**
Did not attend/partner not tested	4	1	N/App	N/App	5
Gestation considered too advanced	3	2	N/App	N/App	5
Moral/religious objection to TOP	3	1	1	N/App	5
Not considered severe disease	N/App	5	N/App	1	6
False-negative screen: paternity disputed	N/App	1	N/App	N/App	1
Other/not known	6	2	N/App	N/App	8
Total	16	12	1	1	30

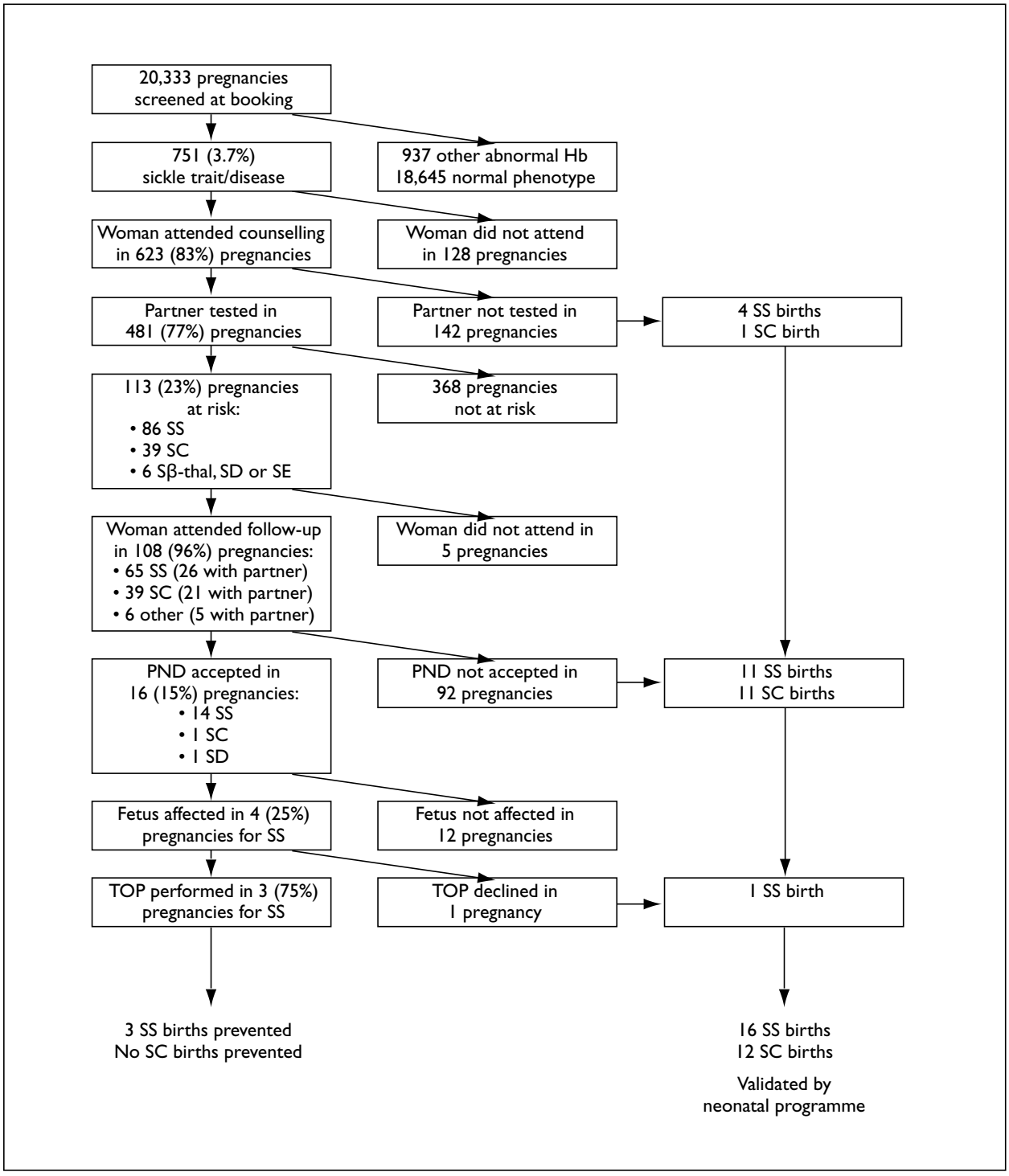


FIGURE 6 *Outcomes of pregnancies with risk of sickle-affected fetuses: CMH universal screening programme 1986–1995*

screening and counselling is likely to be due to patient rather than service factors. The CMH results are compared with published studies in *Table 18*.

This study confirms that, when available, there is a high level of demand for PND and termination amongst unselected couples who are at risk of conceiving a fetus with β-thalassaemia (90% and 100% of those at risk respectively) (*Table 14; Figure 7*). The introduction of antenatal screening has led to significant reductions in the birth prevalence of β-thalassaemia,[52] albeit with varying results depending on both the region of residence and ethnic origin.[63] Clearly, monitoring of the residual birth rate is a useful measure of the effectiveness of β-thalassaemia screening programmes.[53]

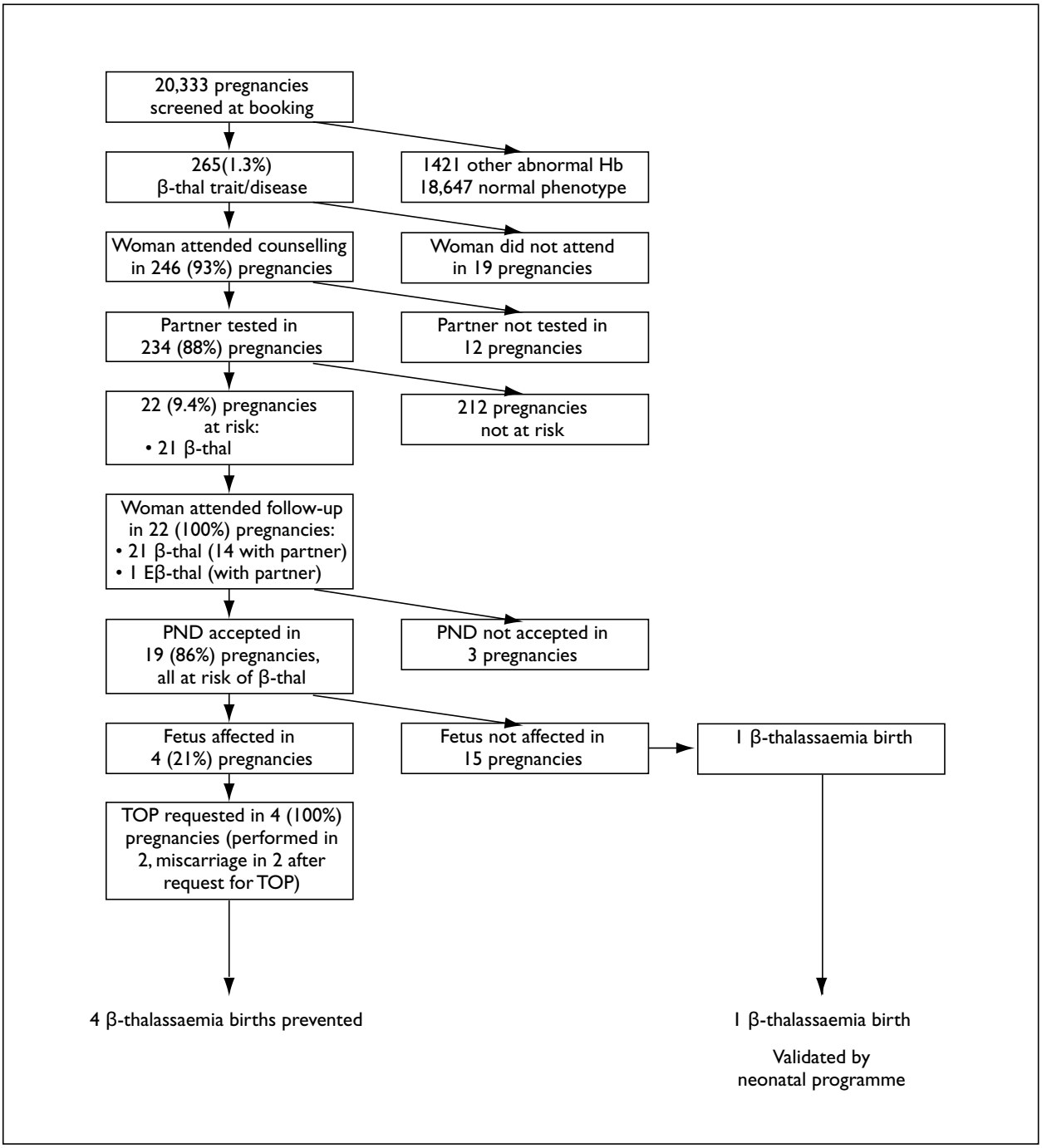


FIGURE 7 *Outcomes of pregnancies with risk of β-thalassaemia-affected fetuses: CMH universal screening programme 1986–1995*

Conversely, although these women who were at risk of conceiving sickle-affected fetuses were receptive to counselling (as evidenced by high levels of attendance), their partners were relatively reluctant to be tested (77% acceptance) or to attend further counselling (39%). A minority of couples accepted PND (22% of 55), which is similar to that reported elsewhere[63,66] and, despite high subsequent rates of termination, there were correspondingly small reductions in the eventual birth rate (16%).

The low rates of PND and termination we report for SCD may be not only realistic but highly appropriate, since rates of attendance, partner testing and uptake of PND are related to the perceived severity of the disease.[26,57–60] The clinical course of SCD remains highly variable and over 50% of individuals now survive beyond the fifth decade.[10]

Nonetheless, higher uptake of counselling and PND have been observed for women booking early in gestation and when their partner is

TABLE 18 *Comparison of reported results from antenatal screening programmes for haemoglobinopathies*

	CMH 1997		London	USA		
	Community	Referral	Referral	Community		
			Petrou *et al.* 1992[59,60]	Schoen *et al.* 1993[67]	Rowley *et al.* 1991[68]	Rowley 1989[73]
Total pregnancies	22,824			54,700	18,907	586,000
Pregnancies with haemoglobinopathy	1688 (7.4%)	101		1019	810	
Pregnant women counselled	1445 (87%)	100			551	
Partners tested	1192[a] (83%)	97		804	315	
"At-risk" pregnancies	140 (12%)	88		81	77	
Acceptance PND						
Risk: SCD	111 (80%)	78	188		[40]	[6563] (1.1%)
PND	16 (14%)	35 (45%)	109 (58%)	[12] (30%)	[12] (14%)	272 (4.1%)
Affected	4	10		3	3	[68]
TOP	3	6		0	0	[24] (35%)
Risk: β-thal	22	9		[16]		
PND	19 (86%)	6 (66%)		[8] (50%)		
Affected	4	4		2		
TOP	4	4		2		
Risk: α-thal				16		
PND				[8]	4	
Affected				2	1	
TOP				2	1	
Other				[9]	12	
Total				(35%)	(47%)	

[ ] calculated from data provided

[a] *69% traits*

tested.[57,60–64] If the observed outcomes of the universal programme for women at risk for SCD are adjusted to match the booking times and partner testing rates of those at risk for β-thalassaemia, an extra eight and seven PNDs, respectively, might have been performed.

Of these 15 PNDs, three extra fetuses affected by SCD might have been terminated (assuming the uptake of termination was the same as for the study population), which would have resulted in an overall 32% reduction in the birth prevalence of SCD. This is similar to the results achieved in Cuba where, despite incomplete coverage due to a lack of reagents, antenatal screening prevented 30% of SS and SC births.[139]

We have not measured the outcomes of counselling; neither can we report ethnic-specific differences in behaviour. More research is required to investigate which components of counselling are essential, at which stage of screening it should be offered and how frequently, as well as further studies of unselected populations to determine ethnic-specific uptake rates. In the meantime, the results presented here should be used for planning antenatal screening programmes and in determining their cost-effectiveness. Efforts should be made to encourage women and their partners to book early in gestation so that PND remains a feasible option if requested.

Limits of the study

This study was based on a service established in a deprived inner London borough with high numbers of people from ethnic minorities. Therefore care must be taken when generalising to other populations. Ethnic details were collected routinely only for couples who were at risk of conceiving an affected child. Thus, we could

not produce ethnic-specific uptake rates, which would have improved generalisability, albeit only to the extent to which ethnic groupings provide accurate information on an individual's origin.

In addition, we do not know whether women book preferentially at the CMH because of the screening programme itself. However, if this is so, those attending this hospital are more likely to participate in screening, thus tending to exaggerate its impact. For planning purposes, especially where the introduction of a programme is likely to stimulate demand, this may not be a concern.

Chapter 10

Cost-effectiveness of antenatal screening

Summary

From our study of CMH data, we suggest that antenatal screening with follow-up counselling can be self-financing at most levels of haemoglobinopathy trait prevalence, with greater savings where a high proportion of the traits is β-thalassaemia.

During 1994, we estimate that the programme saved £62,663 (at 1995 prices) from cases averted. Savings reduce as trait prevalence drops: by 1% there is a small, estimated, net cost of £1140.

For the CMH programme, the cost of identifying an abnormal Hb in the mother is £209. The cost of identifying an at-risk fetus prior to confirmation by PND is £2455. Providing genetic information and counselling costs £109 per mother with abnormal Hb.

Findings

Activity

The haematology laboratory at the CMH undertakes testing for both the antenatal and neonatal programmes: 83% of tests are for neonatal screening and 7% are for antenatal screening, as shown in *Table 19*.

The laboratory tests performed and subsequent progress through the procedure are shown in *Figure 8*.

Costs

Table 20 shows fixed and variable elements of the laboratory costs associated with the antenatal programme during 1994. *Table 21* shows the nurse specialist and other BSCTC costs for the provision of antenatal follow-up, including information collection, education and support. The salary component for the nurse specialist has been deemed to be variable because of the interchangeability of staff between the neonatal, antenatal and other sickle programmes (the number of hours dedicated to antenatal work by the nurse specialist varies according to demand).

Costs of managing high-risk pregnancies

Overall, the cost of identification of at-risk fetuses was £2455 per woman, including the follow-up costs as shown in *Table 22*.

An important outcome of such a community programme is to allow genetic choice. In 1994, 12 women had proven at-risk pregnancies (partner tested), with 37 pregnancies also at risk because the partner's haemoglobinopathy status was unknown. If the main objective is to provide genetic choice to parents, the cost per proven at-risk pregnancy (12 cases) of £2455 is the cost of giving one couple a choice.

Discussion

Main findings

No detailed information relating to the NHS costs for either SCD or β-thalassaemia major have been published. One estimate of hospital costs for SCD is £5000 per annum and for β-thalassaemia major £8150.[21] With optimal care, patients with β-thalassaemia major are now living to over 40 years (assumed to be an average of 41) and the median survival reported for SS patients is 44 years.[10] Therefore, the present value, discounted at 6% (as recommended by the Treasury), of the savings in health service costs per case of SCD, is £77,000, and, for β-thalassaemia major, £123,000.

TABLE 19 *Breakdown of tests, CMH laboratories*

Programme	IEF tests performed (%)	HPLC tests performed (%)	Total (%)
Antenatal	1964 (4)	1987 (46)	3951 (7)
Neonatal	49,973 (89)	154 (4)	50,127 (83)
Other	4103 (7)	2163 (50)	6266 (10)
Total	56,040 (100)	4304 (100)	60,344 (100)

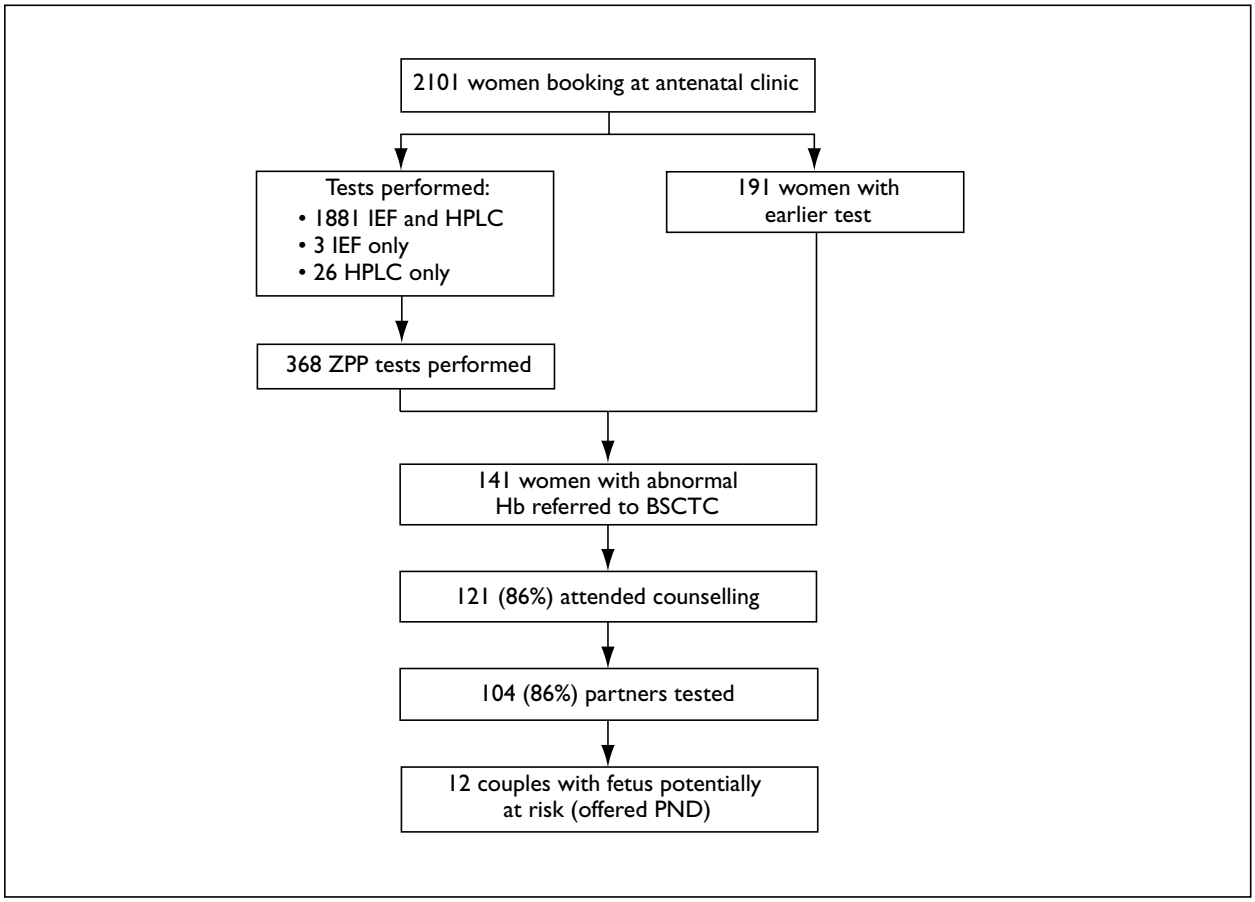


FIGURE 8 *Activity of antenatal screening programme*

TABLE 20 *Fixed and variable elements of laboratory costs*

Screening component	Fixed (£) (1994/95 prices)	Variable (£) (1994/95 prices)
Specimen/information collation	0	3708
Information review/selection/worksheet preparation	0	1507
Specimen preparation	0	1251
IEF testing – women and partners	94	1434
HPLC testing – women and partners	1955	5716
ZPP testing	92.5	120
Programme overheads[a]	3354	3417
Hospital overheads	2707	4100
Subtotal	8202.5	21,253
Total	29,455.5	

[a] *Includes overall clinical direction, laboratory supervision, training and stationery/small replacements*

During the study year, the programme identified 12 pregnancies at risk of a major haemoglobinopathy because both partners had significant traits. As there is a 25% risk of a clinically significant haemoglobinopathy from a conception in which both partners carry a haemoglobinopathy trait, we can expect three of these to result in affected fetuses.

The ratio of SS and S-thalassaemia to β-thalassaemia major in the BSCTC programme is approximately 3:1 (chapter 9). Therefore, 2.25 SCD cases (with total annual treatment costs of £11,250) and 0.75 β-thalassaemia major cases (with treatment costing a total of £6112.50 per year) would have been detected if the parents had pursued PND. If these pregnancies had been

TABLE 21 *Nurse specialist and other BSCTC costs*

Follow-up component	Fixed (£)	Variable (£)
Nurse specialist	0	6824
Secretarial support	0	983
Hospital overheads	836.5	2229.5
Programme overheads[a]	1919	382
Subtotal	2755.5	10,418.5
Total	13,174	

[a] *Includes supervision, overall clinical direction, training, computer equipment and stationery*

TABLE 22 *Follow-up costs*

Outcome	Average cost (£)
Laboratory identification of abnormal Hb in woman	209
Laboratory identification of at-risk fetus (woman and partner with abnormal Hb)	2455
Counselling of woman with abnormal Hb	109

terminated, the net present values (discounted at 6%) for costs averted would have been £173,878 and £92,531 respectively.

The experience in this programme has been that less than one-third of the women with a fetus at risk of a haemoglobinopathy accept PND; these are mainly those with a fetus at risk of β-thalassaemia. The result is that, of all affected pregnancies, 10% with SCD and 95% with β-thalassaemia have been terminated. This equates to 0.225 SCD and 0.7125 β-thalassaemia major cases per year.

The total net present values for costs averted are £17,388 and £87,904 respectively. Since the likely financial savings (£105,292) exceed the programme cost of this service, universal screening and follow-up leads to overall savings in the BSCTC service.

Financial savings to the NHS from such a programme cannot be the sole criterion for introducing a service. However, if a programme has other benefits and also saves on resources then there can be no argument against it, unless another programme saves more or produces even greater benefits or there are other (direct) costs not taken into account (e.g. those met by the user).

When subtracting the annual programme costs (£42,629) from the financial savings, it can be seen that there is likely to be a saving of around £62,663 from a programme in an inner city area like Brent, where there is a high (7.5%) prevalence of haemoglobinopathy traits, of which around three-quarters are sickle cell traits. Based on the CMH costs, *Table 23* shows the likely financial savings or costs at different combinations of trait prevalence and the proportions of these that are β-thalassaemia traits.

At low levels of prevalence of haemoglobinopathy traits, and where most of these are sickle cell traits, the financial savings are smaller than the cost of a universal programme. Financial savings are likely, even at quite low (e.g. 1%) trait prevalences if these are mainly for β-thalassaemia. This suggests that any guidelines on screening policy should take account of the countries of origin of people from ethnic minorities as well as the number of people likely to carry a haemoglobinopathy trait.

The CMH programme shares resources between the antenatal and neonatal programmes. This has major advantages in reducing the cost of maintaining access to the equipment and skills required for an antenatal programme. It includes the sharing of expertise and access to counselling services. When the cost-effectiveness of antenatal screening is being considered it is important to take into account the policy on neonatal screening and treatment.

Based on the limited information available on lifetime costs, we demonstrate that many antenatal screening programmes are likely to

TABLE 23 *Estimated annual NHS savings (cost) of universal screening in £ at 1994/95 prices at different combinations of prevalence and proportions of traits for β-thalassaemia: modelled on CMH data – 2101 women*

% β-thal	Prevalence of trait (%)			
	7.5	5.0	2.5	1.0
25	61,100	37,100	13,100	(1350)
50	142,000	91,000	40,000	9500
100	305,000	199,100	95,000	31,000

be self-financing, and therefore cost-effective, because the savings on service costs are greater than the costs of detection of an affected fetus and termination. Antenatal screening (especially when this is managed alongside a neonatal screening programme) is quite cheap and may be considered to be cost-effective in terms of improved genetic choice. However, two significant uncertainties could change this conclusion. First, on the basis of experience in Brent, it is estimated that the choice to proceed with termination of pregnancy is likely in 95% of occurrences of β-thalassaemia major. However, if this proportion were lower, then the financial savings would be lower and the programmes less cost-effective. Secondly, the costs of lifetime treatment for people with haemoglobinopathies have not been researched in detail.

Sensitivity analyses were carried out on these two estimates. On the basis of a high-prevalence area, with traits carried by 7.5% of the population and 25% of traits being β-thalassaemia major, a programme is likely to "break even" in financial terms even if termination occurs in only 50% of fetuses with thalassaemia. Financial savings are likely at this level of termination for 2.5% of the population with traits, all of which are for thalassaemia, and only a small financial deficit is likely with 2.5% of traits in the community, half of which are for thalassaemia. Given that this calculation makes no allowance for the health and social benefits of screening, choice and better treatment, it is fair to conclude that the cost-effectiveness of antenatal screening is not very sensitive to the estimate of the numbers choosing termination of pregnancy. If the cost of lifetime treatment is overestimated by 50%, then financial savings would occur only for areas where trait prevalence is above 5%, or where the proportion of thalassaemia traits is over 50% and the rate in the population is 2.5%. Again, this suggests that the likely conclusions are not very sensitive to errors in the cost of treatment.

Limits of the study

No attempt has been made to compare the costs and benefits of antenatal universal screening and selective screening. However, it is likely that many of the benefits of universal screening can be achieved with an effective policy of selective screening, although the latter may give rise to its own costs and the risk of litigation when cases are not predicted, and does not take account of the economies of scale. Neither has any attempt been made to estimate the benefits of genetic choice and better management of people affected with significant haemoglobinopathies. Although further work is needed on costing care, possible decisions on termination, and the value of earlier knowledge of significant haemoglobinopathies, these results suggest that antenatal screening is likely to be considered to be cost-effective, at least in areas with haemoglobinopathy traits at or above 2.5%, especially if a high proportion of these are for thalassaemia.

Chapter 11

Neonatal screening: costs and cost-effectiveness[140]

Summary

Screening services should aim to cover populations that generate a workload of over 25,000 births per year, preferably over 40,000. There appears to be little advantage to increasing the workload to over 50,000 births per year. IEF and HPLC then become very similar in terms of average cost per test. At 16 sickle traits/1000 and 0.5 SCD/1000, there is no significant difference in the detection component cost between universal and targeted programmes. Below this prevalence, a targeted programme is cheaper but is likely to miss cases of SCD.

If the detection rate of targeted programmes were at least 90% effective, universal programmes would cease to be good value except at very high prevalence. Greater use of PND resulting in termination and, therefore, fewer affected births, reduces the cost-effectiveness of universal screening.

Findings

Total costs

Table 24 presents laboratory costs that are common to IEF and HPLC technologies. The total costs, and consequently the average costs per baby tested by IEF and HPLC, are similar (*Tables 25–27*).

All costs are quoted in pounds sterling at 1994/1995 prices for the CMH programme, which covers approximately 50,000 neonates. In the data examined, this breakdown is as shown in *Table 28*. This relationship has been built into the cost model.

Average total cost per test is made up of the fixed element and two variable elements: one being population dependent and the other prevalence dependent. The population-dependent component is calculated according to the numbers of women who are screened and reflects scale economies. The prevalence-dependent component was identified because a laboratory situated in a region of low prevalence performs fewer repeat tests than one in a high-prevalence area.

The variable costs for the programme, which screened 47,948 babies, amounted to £132,439.[140] for IEF and £132,395 for HPLC, although these are made up of different components. Consumables (reagent kits and small replacements) for IEF came to £34,630, while the equivalent for HPLC was £59,911. Staff costs for IEF testing were £27,320 and costs for initial HPLC tests £9156. This demonstrates that, if the consumable costs for HPLC should fall, the total costs of screening would be lower by using HPLC.

Average costs per baby tested

Figure 9 shows average costs. There are economies of scale up to a programme size of 25,000. The data also demonstrate little difference between IEF and HPLC in terms of average cost per baby

TABLE 24 *Fixed and variable costs for neonatal haemoglobinopathy screening common to IEF and HPLC technologies*

Programme costs common to both technologies	Fixed (£)	Variable (£)
Processing and audit of birth information	7589	11,310
Reporting of normal results	0	736
Sample delivery	0	856
Sample registration	5680	17,940
Monoclonal antibody test	0	4245
Reporting of abnormal results	0	2448
Laboratory overheads	7518	8605
Total	20,787	46,140

TABLE 25 *Fixed and specific costs for neonatal haemoglobinopathy screening using IEF*

IEF-specific costs	Fixed (£)	Variable (£)
Initial IEF test and immediate repeats	2392	53,841
Interpretation of result	0	11,285
Repeat testing at 6 weeks	163	2307
Hospital overheads	12,675	18,866.5
Subtotal	15,230	86,299.5
Total (including programme costs from *Table 24*)	36,017	132,439.5

TABLE 26 *Fixed and specific costs for neonatal haemoglobinopathy screening using HPLC*

HPLC-specific costs	Fixed (£)	Variable (£)
Initial HPLC test and immediate repeats	18,006	64,485
Results checking/data entry	0	4323.5
Repeat testing at 6 weeks	8	125
Hospital overheads	12,675	17,321.5
Subtotal	30,689	86,255
Total (including programme costs from *Table 24*)	51,476	132,395

TABLE 27 *Outcome costs for neonatal haemoglobinopathy screening*

Outcome costs	IEF (£)	HPLC (£)
Average cost per baby tested (*n* = 47,948)	3.51	3.83
Cost per SCD identified (*n* = 25)	6738	7355
Cost per trait identified (*n* = 721)	234	255

TABLE 28 *Average cost per baby tested*

Components of average cost per baby tested (IEF; CMH programme)	£
Fixed	0.75
Population dependent	2.48
Prevalence dependent	0.28
Total average cost	3.51

tested. The "bumps" on the graph reflect the annual equivalent cost of a new HPLC analyser at intervals of 25,000 tests. The cost of additional IEF equipment occurs at every 100,000 tests.

Figure 10 provides an illustration of the average cost per baby tested by London boroughs, showing clearly the relationship between the number of births and average cost for universal programmes using IEF.

Costs of identifying SCD and trait

Table 29 shows how the average costs of identifying a case of SCD, using IEF, is dependent both on changes in disease prevalence and the number of births screened. The number of births, once it reaches 25,000, appears to make relatively little difference to the identification costs, but these rise sharply below a disease rate of 0.5/1000. As throughout, the technology used makes little difference.

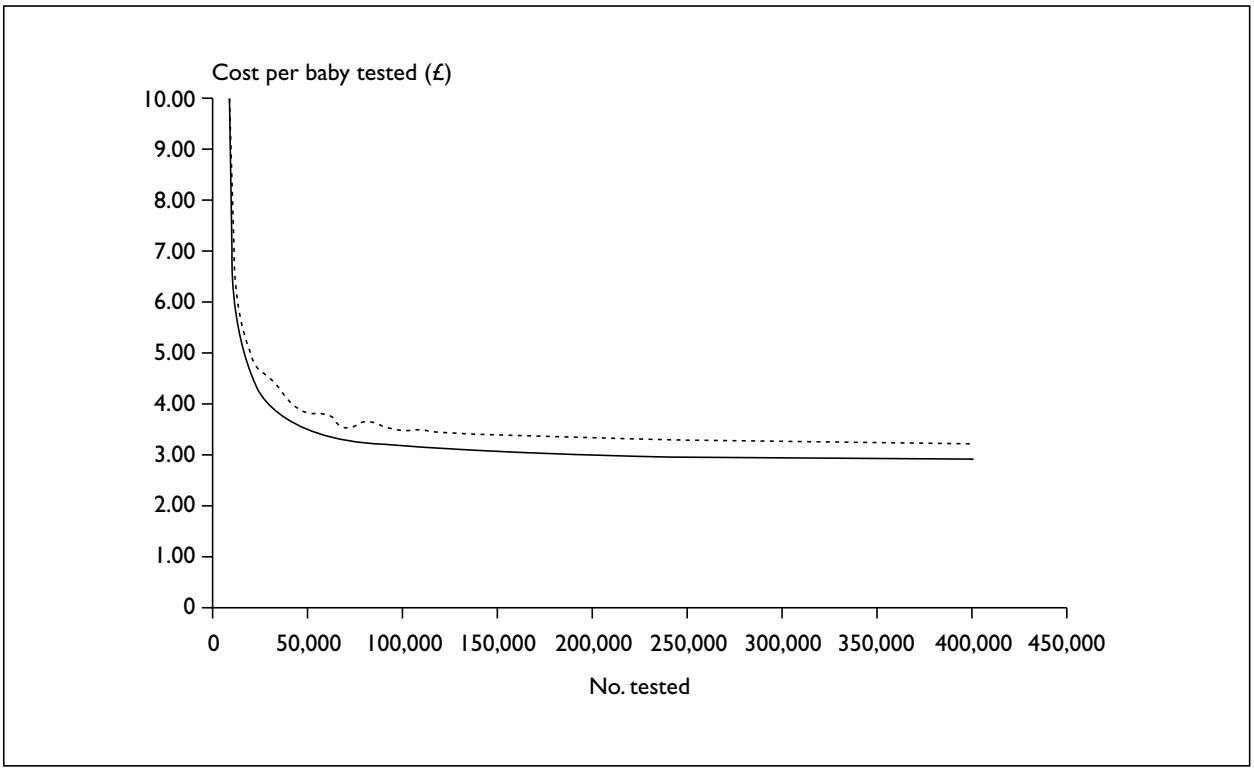


FIGURE 9 *Comparison of average costs per baby tested using IEF (——) and HPLC (- - - -)*

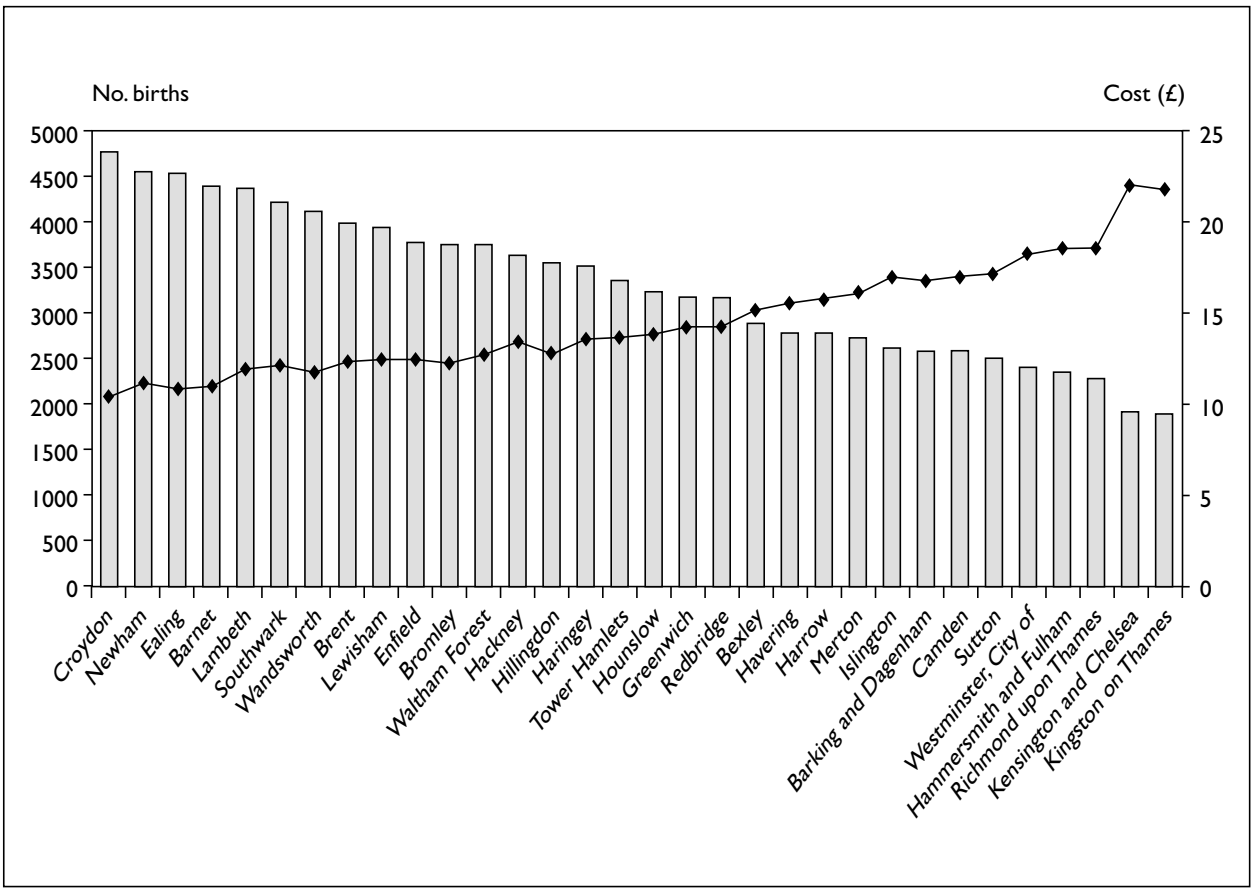


FIGURE 10 *Average cost per baby tested by London borough, using IEF (□, births; ◆, average cost)*

TABLE 29 *Effects of prevalence and number of births on cost (£) of identifying SCD, using IEF*

Disease rate /1000 births	Population				
	5000	**10,000**	**25,000**	**50,000**	**100,000**
0.01	1,078,160	540,599	218,062	110,550	56,793
0.02	540,599	271,818	110,550	56,793	29,915
0.04	271,818	137,428	56,793	29,915	16,476
0.08	137,428	70,232	29,915	16,476	9757
0.16	70,232	36,635	16,476	9757	6397
0.31	37,274	20,475	10,396	7036	5357
0.63	19,676	11,277	6237	4557	3717
1.25	10,477	6278	3758	2918	2498
2.50	5678	3578	2318	1898	1688

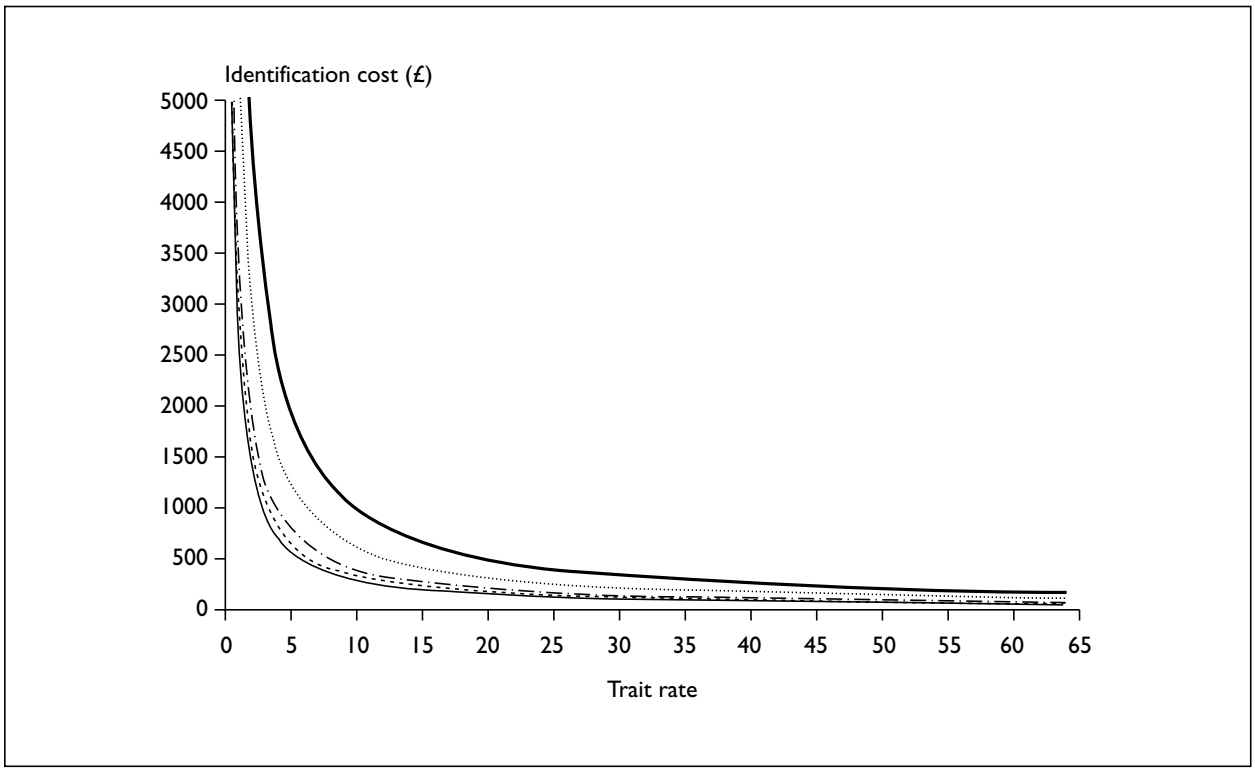


FIGURE 11 *Relationship of prevalence and number of births on cost of sickle trait identification (IEF/universal) (——, 5000; ·····, 10,000; – · – · –, 25,000; - - - -, 50,000; ——, 100,000)*

Figure 11 gives similar information for identifying a baby with trait. These data can be used to model costs for programmes where the gene frequency in the population is either known or has been calculated from census data.[132]

Targeted programme costs

A disease rate of 0.5/1000 is relatively high in England, with half the districts having a prevalence of lower than 0.04/1000 and only 10% (unadjusted for population size) demonstrating a prevalence of > 0.3/1000.

Cost modelling of targeted screening assumed that targeting would overestimate the size of the at-risk population by 20% but nevertheless fail to test 20% of at-risk babies (based on evidence from Georgia in the USA, although, in

Colorado,[141] risk-group misclassification has been estimated at 30%).

Responsibility for selection of those babies at risk for haemoglobinopathies is likely to lie with the midwife and is associated with extra costs. For the purpose of costing, obtaining a family history has been estimated to take an average of 5 minutes. Most neonatal laboratory screening programmes cover PKU and congenital hypothyroidism. To exclude (and then retrieve and re-file) non-selected cards from haemoglobinopathy testing would incur additional clerical costs; these have been estimated to be for an additional 3 hours per day (£5980 per year) for the CMH programme, based on local information and evidence from Colorado.[141]

Comparing universal and targeted programmes

Programmes may select only babies thought to be at risk because of their ethnicity. The difference between the average cost per baby tested in these targeted programmes and that in universal programmes is shown in *Figure 12* for IEF. Targeted programmes, both IEF and HPLC, have higher average costs per baby tested than universal programmes.

As the fixed costs are quite high, the costs of SCD and trait identification for universal and targeted screening in small programmes are very similar. At 5000 births and at low prevalence, identification costs are slightly lower for universal screening. At low prevalence (less than 0.5/1000 disease rate) and 25,000 or more births, the identification costs of SCD and trait are consistently higher with universal programmes, as shown in *Figure 13*. At high prevalence, regardless of the number of births, identification costs are very similar.

We have modelled a 20% failure rate of targeted programmes to pick up all cases of SCD and, subsequently, calculated the cost of each extra SCD identified by a universal programme (as compared with a targeted programme).

The key issue for commissioning organisations is the incremental cost-effectiveness of identifying one extra case of SCD with a universal programme. *Tables 30* and *31* show cost per extra SCD identified by a universal programme compared with a targeted programme. Commissioners will need to consider whether, for their population and prevalence, they are willing to spend the given amount in order to pick up one case of SCD.

The costing model for neonatal screening has been developed from detailed analysis of the costs of equipment, staffing and other current costs in one major centre. The technology and need for particular technical skills mean that the service has significant scale economies. This justifies ensuring

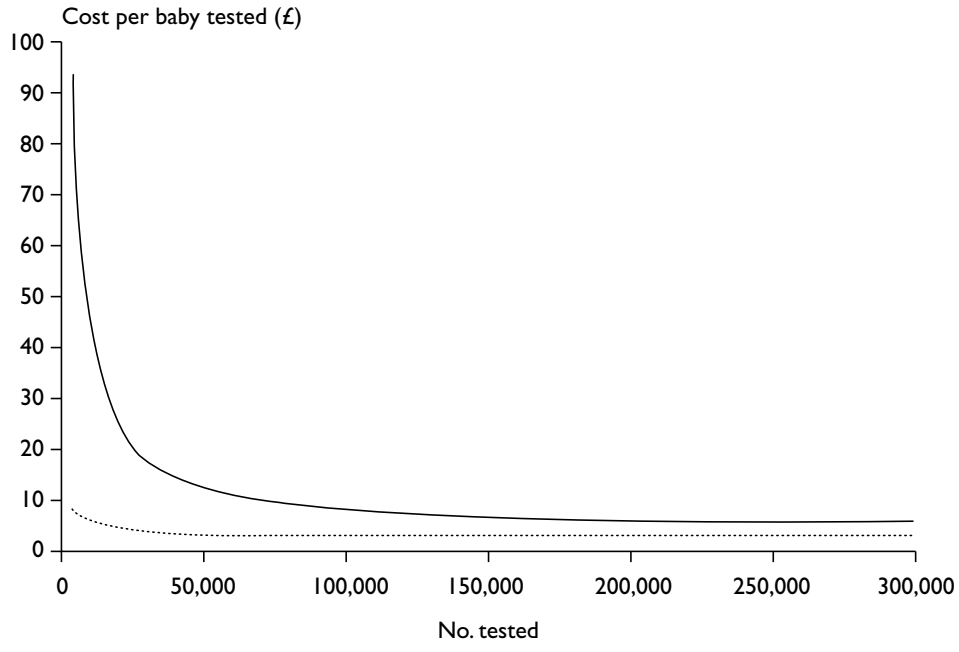


FIGURE 12 *IEF – average cost per baby tested (——, targeted; ·····, universal)*

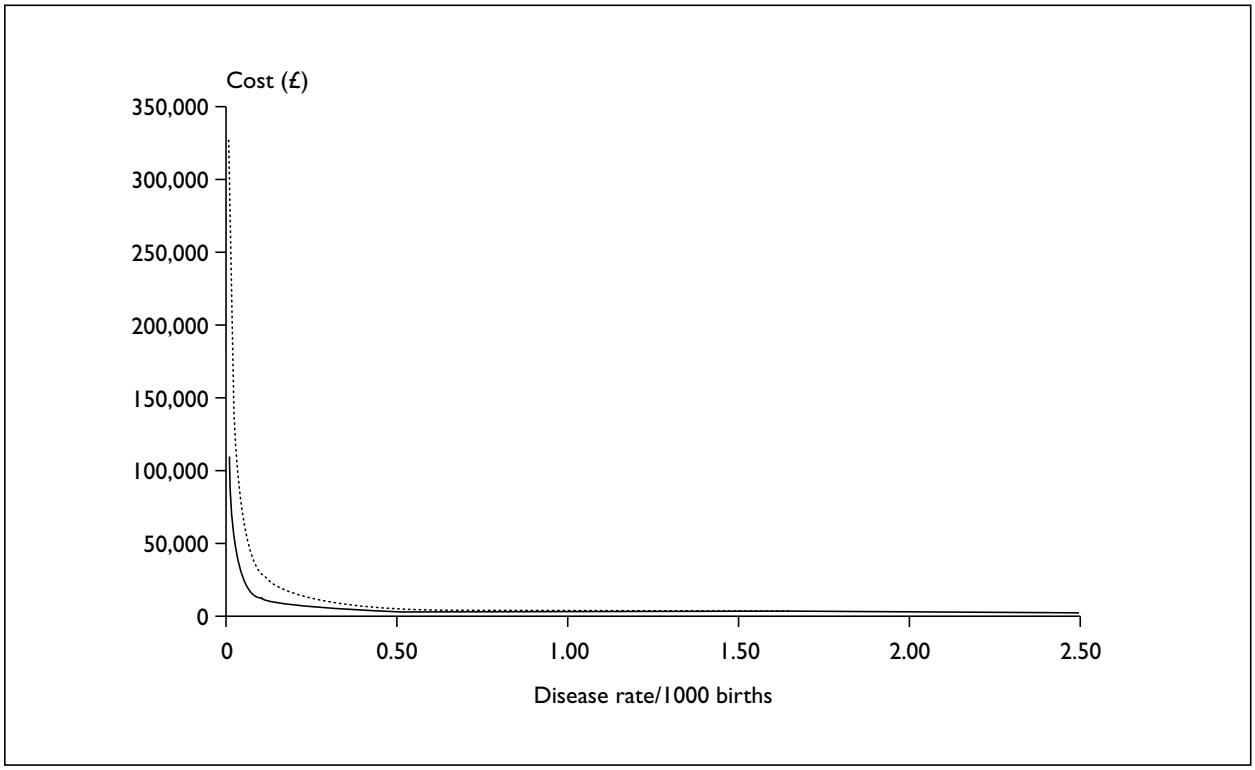


FIGURE 13 *Comparison of identification costs for SCD in universal and targeted programmes (IEF/no. births 50,000) (——, targeted; ·····, universal)*

TABLE 30 *IEF – cost (£) per extra SCD identified by universal programme*

Disease rate /1000 births	No. births				
	5000	**10,000**	**25,000**	**50,000**	**100,000**
0.01	647,981	954,157	1,137,862	1,199,098	1,229,715
0.02	319,114	472,202	564,055	594,673	609,981
0.04	154,681	231,225	277,151	292,460	300,114
0.08	72,464	110,736	133,699	141,354	145,181
0.16	31,356	50,492	61,973	65,801	67,714
0.31	8244	17,812	23,553	25,466	26,423
0.63	1164	5948	8819	9775	10,254
1.25	–777	1615	3050	3529	3768
2.50	–948	248	965	1205	1324

that the programme covers a large population. On the basis of this analysis the pattern of scale economies differs between universal screening and targeted screening. This means that the costs of identifying and following up cases falls as the volume rises, but the cost of targeted screening falls more rapidly. As a result, the difference in cost between the two models increases with volume and the additional costs associated with detecting cases by switching from targeted to universal screening increases with the number of births. This appears strange, but it is a direct consequence of the patterns of costs associated with different scales of provision of targeted and universal screening. It has not been possible to investigate the costs using more sophisticated techniques because that would require information from a large number of screening programmes. It would, in principle, be

TABLE 31 *HPLC – cost (£) per extra SCD identified by universal programme*

Disease rate /1000 births	No. births				
	5000	**10,000**	**25,000**	**50,000**	**100,000**
0.01	702,708	1,008,884	1,192,590	1,253,825	1,284,442
0.02	346,219	4,993,072	591,160	621,778	637,087
0.04	167,975	244,519	290,445	305,754	313,409
0.08	78,853	117,125	140,088	147,743	151,570
0.16	34,292	53,428	64,909	68,737	70,650
0.31	9371	18,939	24,679	26,593	27,550
0.63	1531	6315	9186	10,142	10,621
1.25	–738	1654	3089	3568	3807
2.50	–1047	149	866	1106	1225

TABLE 32 *Sensitivity testing*

Assumption/Varied to	Difference
Targeted programmes will miss 20% of SCDs/Targeted programmes will miss 10% of SCDs	Significant
Targeted programmes will miss 20% of SCDs/Targeted programmes will miss 1% of SCDs	Significant
Hospital overheads as modelled/Hospital overheads doubled	Not significant pop. > 25,000
Current cost of HPLC reagents/Cost of HPLC reagents halved	Significant
SCD births according to prevalence (no PND/TOP)/TOP in 20%	Significant
SCD births according to prevalence (no PND/TOP)/TOP in 10%	Not significant
Midwife selection will take 5 minutes/Midwife selection will take 10 minutes	Not significant
Midwife selection will take 5 minutes/Midwife selection will take 2 minutes	Not significant
Targeted programmes will incur extra clerical costs/Targeted programmes will not incur extra clerical costs	Not significant pop. > 25,000
Fixed costs as modelled/Fixed costs plus 20% and corresponding decrease in variable costs	Not significant
Hospital overheads/Hospital overheads halved	Not significant
Targeted programmes will overestimate at-risk population by 20%/Targeted programmes will overestimate at-risk population by 40%	Not significant
Targeted programmes will overestimate at-risk population by 20%/Targeted programmes will accurately estimate at-risk population	Not significant

useful to test this result in the context of estimates of costs derived from regression techniques to confirm the different scale effects.

Sensitivity analysis

Sensitivity testing of key assumptions has been performed using "cost per extra SCD identified by universal programme" as an indicator. *Table 32* provides a summary of the assumptions varied and the responding sensitivity of the indicator. We have assumed that assumptions are accurate within a range of 20%. The sensitivity analysis, therefore, concludes that indicators must vary beyond 20% of the baseline to demonstrate sensitivity to that assumption.

Discussion

IEF and HPLC are very similar in terms of average cost per test in programmes testing 25,000 neonates or more per year. The choice

of method should depend mainly on the level of expertise and staff mix of the laboratory. If the price of consumables comes down, HPLC will become cheaper than IEF; a choice of IEF would then depend on the benefit from the additional information generated.

At 16 traits/1000 and 0.5 SCD/1000 there is no significant identification cost difference between universal and targeted programmes. Below this prevalence, a targeted programme is cheaper but is likely to miss cases of SCD. The potential for litigation and settlement costs associated with missed cases should not be overlooked.

The sensitivity analysis illustrates that, if targeted programmes were 90–99% effective, universal programmes would cease to be good value except at very high prevalence. If the programme size is > 25,000 then, even when the hospital overheads double, targeted programmes do not become more cost-effective. Greater use of PND resulting in termination and, therefore, fewer affected births, reduces the cost-effectiveness of universal screening.

Given significant economies of scale up to 25,000 births per year (and further up to 40,000–50,000), the organisation of screening services should aim to cover a screened population that will generate this level of work. Districts with lower numbers of babies to be screened could collaborate to achieve scale economies.

Further data

Additional data are presented in *Figures 14* and *15*.

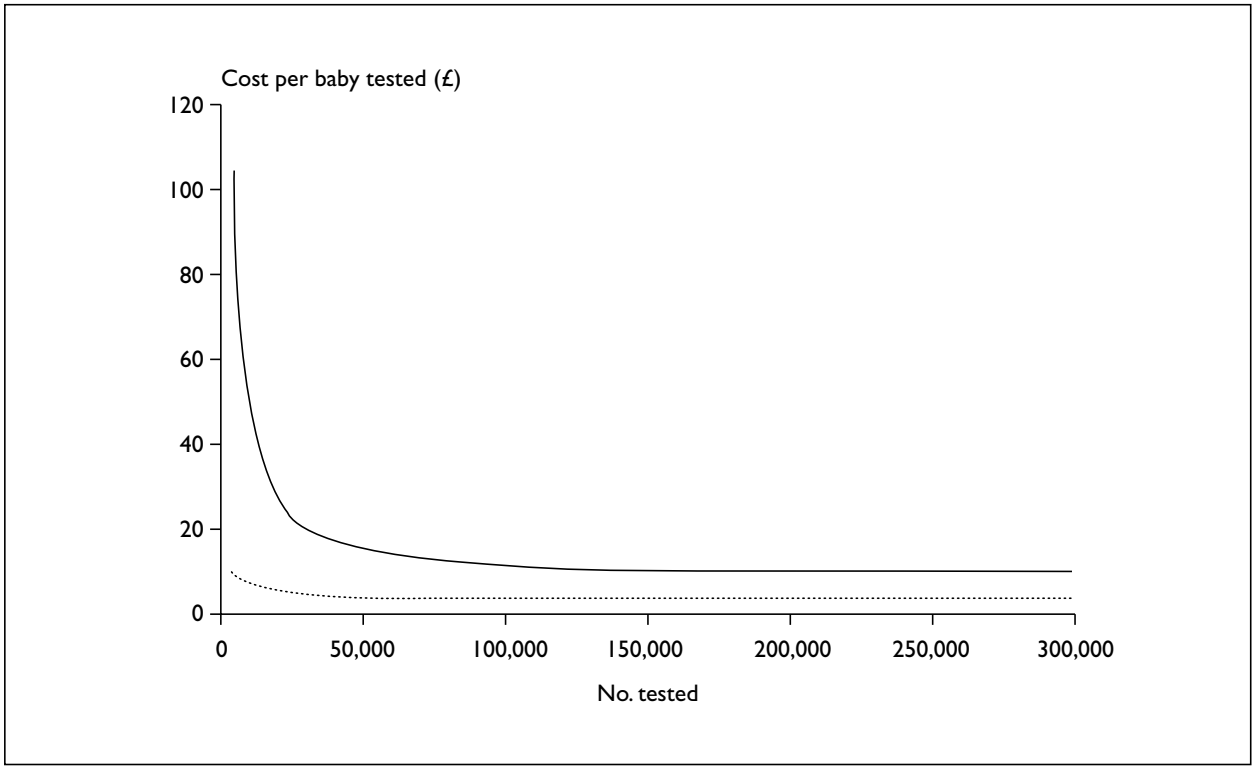


FIGURE 14 *HPLC – average cost per baby tested (——, targeted; ·····, universal)*

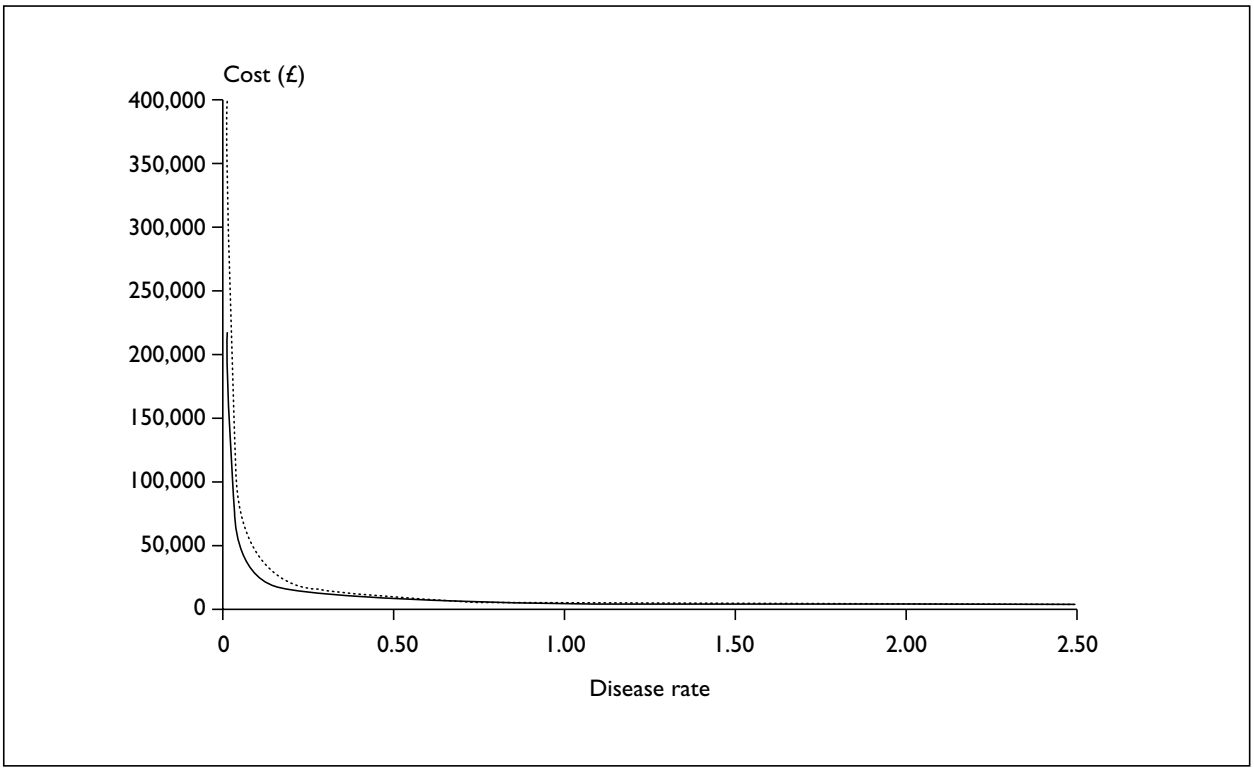


FIGURE 15 *IEF – SCD identification costs – universal/targeted (medium)/population 25,000 (——, targeted; ·····, universal)*

Chapter 12

Neonatal screening: cost-effectiveness of nurse follow-up

Summary

During 1994, the BSCTC nurse specialists counselled, on behalf of the neonatal screening programme, approximately 91% of the families whose infants had been identified with a disease condition or trait.

The cost per referral received was £129.74; cost per woman counselled £142.51; cost per trait confirmed/family counselled £156.28; and cost per SCD confirmed/clinical management facilitated £4400.78.

Findings

Activity

In 1994, of 47,948 babies screened, 25 clinically significant haemoglobinopathies, and 704 haemoglobinopathy traits were confirmed. The results on initial test and at term plus six weeks are shown in *Tables 33* and *34*.

During 1994, it is estimated that the nurse specialists at the BSCTC succeeded in counselling 91% of the families whose infants had been identified with a disease condition or trait. Eighty-one per cent were counselled on first contacting the parents. Eight per cent of the families required two visits and 2% required three, resulting in 91% being counselled (772 of the 848 referred to the BSCTC). Of the 9% of infants whose families were not counselled, only one had probable clinically significant disease. In this instance, the parents were informed of the initial result but refused to have a further specimen collected.

TABLE 33 *Results from initial test*

Initial test	No. infants
Possible SCD	35
AS/AC (no repeat test needed)	618
Possible other trait	195
Referrals to BSCTC for counselling and retest	230
Referrals to BSCTC for counselling only	618
Total referrals to BSCTC	848

Programme costs

Costs are based on those for the 1995–1996 year. *Table 35* provides details of fixed and variable costs, including overheads. Given the limited opportunity for staff to be assigned to other duties, the nurse specialists' salaries have been designated as fixed costs. There is a greater potential for redeployment of the secretarial and administration components and these are therefore considered to be variable costs. The information presented does not include laboratory-related costs.

The outcome costs for the nurse specialists are as shown in *Table 36*.

TABLE 34 *Results at term plus 6 weeks*

Six-week test	No. infants
SCD confirmed	25
AD/AE (or other) trait confirmed	86
Further specimen not available (did not attend)	28
Deceased (one probable SC disease; one A+ band)	2

TABLE 35 *Programme costs*

Item	Fixed (£)	Variable(£)
Nurse specialists	56,869	0
Secretarial support	0	9335
Administration/information support	0	8258.5
Travel	9000	2859
Postage	0	232
Programme overheads[a]	5443	3867
Hospital overheads	4749.5	9406.5
Total	76,061.5	33,958

[a] *Includes supervision, training, equipment*

TABLE 36 *Outcome costs*

Outcome	Cost (£)
Average cost per referral (*n* = 848)	129.74
Average cost per case counselled (*n* = 772)	142.51
Cost per trait confirmed/family counselled (*n* = 704)	156.28
Cost per SCD confirmed/clinical management facilitated (*n* = 25)	4400.78

Discussion

The follow-up model used at the BSCTC has been shown to achieve high levels of acceptance (91% families counselled) and the carrying out of the necessary confirmatory tests. This suggests that it is possible to provide effective follow-up even in a largely mobile population in an urban setting. These data are consistent with the previously reported 92% success rate in trait follow-up in the same programme.[142]

Problems with the attendance of families for follow-up have been commented on extensively elsewhere. For example, Adjaye and colleagues, when reporting on a cord blood screening programme in London, found that follow-up for retesting was unsuccessful in eight out of 20 cases, owing to the families not being traceable or not responding to frequent attempts to make contact.[48]

A study in New York reported that only one-third of families with an infant carrying a trait were reached for follow-up.[143] Suggested reasons for this were: a lack of knowledge about haemoglobinopathies; previous identification of Hb status; high mobility of the population; and suspicion regarding the need for retesting.

An evaluation of trait follow-up in Baltimore[144] found a similar success rate, with only 35% of families attending a counselling session. However, they failed to identify any association between non-compliance and demographic variables, knowledge of SCD, location of health care, birth control decisions, or the desire for future children.

Yang and co-workers[145] identified two additional factors that affected trait follow-up in their evaluation of newborn haemoglobinopathy screening in Alabama. These were the time from birth to when screening results are received by the follow-up service and the distance from the family's home to the counselling service. Several other authors have discussed similar difficulties concerning follow-up.[43,44,83,146–148]

Effective strategies for follow-up and confirmatory testing should provide the following benefits:

- increased numbers of babies who are given optimal care for clinically significant haemoglobinopathies
- better provision of informed genetic choice for people who are identified as carriers and then counselled
- further births with clinically significant disease within a family are averted or pregnancy proceeds in full awareness of the risks and consequences.

Successful follow-up facilitates the early diagnosis of disease and the identification of carriers of traits who can benefit from counselling. The studies cited above suggest that other programmes achieve follow-up of only 50% at best. If we assume, first, that those who are lost to follow-up have, on average, the same disease or trait pattern as those who did attend, and, secondly, that successful follow-up ensures the diagnosis of disease, the commencement of prophylactic penicillin, and the identification of trait carriers, we can estimate the effects of the BSCTC programme in terms of increased diagnosis and counselling.

If the 91% compliance is compared with the 50% reported in other studies, the benefits in each year would be:

- 12 babies given earlier prophylactic penicillin
- 348 couples given informed genetic choice
- one birth averted with clinically significant disease.

The last figure is based on the assumption that 50% of those babies with clinically significant conditions are first babies, and two-thirds of these parents were aware of their haemoglobinopathy status either prior to conception or early in pregnancy. Therefore, approximately two couples are likely to reconsider having further children and we can cautiously estimate that one potential birth is averted as a result. Given our estimate of the increased benefits of a programme with a 91% success rate for follow-up, compared with one with a lower success rate combined with our knowledge of programme costs, we have cautiously placed a financial value on the increased benefit associated with the more successful programme, as shown in *Table 37*. This assumes that programme costs are equal.

Although the costs of nurse follow-up do not appear unreasonable, further work is needed

TABLE 37 *Cost-effectiveness*

Outcome	Cost (£)
Average cost per baby with improved treatment	9168
Cost per couple obtaining genetic choice	334

to demonstrate if the face-to-face home visit approach is the most cost-effective method of confirming trait conditions. For SCD, given the relatively small number per year, and the seriousness of the disease, there is little doubt of the value of supportive one-to-one counselling, and of the usefulness of providing this in the home environment.

On the other hand, the large number of traits identified and the tendency towards non-compliance by these families calls into question the appropriateness of this method for following up trait conditions. Some parents decline counselling because they have received it as part of the antenatal screening programme or because children born earlier were a part of this same programme. We are aware that another follow-up programme based in London provides information on trait conditions by post, in the form of a letter and leaflet, advising that further information and counselling is available on request.

Another important consequence of the trait notification approach used is the impact on the family's psychological well-being. The potential for excessive anxiety in the trait notification process has been observed by several authors.[56,83,149,150]

One American author has suggested that the visiting at home of parents of babies identified as having a trait might indicate that the condition is more serious than it actually is, thus provoking inappropriate levels of anxiety.[46] To balance this, we must take into consideration the advantages of counselling, family screening and genetic advice leading to genetic choice and the prevention of affected births.

We have demonstrated that there may be significant value in the style of follow-up employed by the CMH programme. There is no evidence, however, that the approach described is the most appropriate, suggesting the need for further practice-based research to evaluate such methods of follow-up.[44]

Chapter 13
Discussion

Prevalence

This is the first time that "evidence-based" rates for sickle and β-thalassaemia have been presented for use in the UK. They take forward, and replace, earlier unverified point estimates for the UK produced by the WHO[106] and by the NHS Centre for Reviews and Dissemination.[21] In addition, they have been used as a basis for another Health Technology Assessment programme report on haemoglobinopathy screening.[137]

Through providing a range of values, we are able to reflect the heterogeneity of prevalence within specific ethnic groups and predict the observed prevalence in local districts. For example, both Brent, in North West London (*Table 10*), and LL&S, in South London (*Table 9*), have a high proportion of ethnic minorities but, in Brent, the central estimate was close to the observed data, whereas in LL&S the upper estimate was the nearest to the observed data because proportionally more black Africans living in LL&S originate from countries with high carrier frequencies, such as Nigeria (M Layton, King's College, London: 1998).

Our estimates are the best available data on the prevalence of Hb disorders for the planning of screening and treatment services. While ethnicity is a good proxy measure of the populations at risk from haemoglobinopathies (as long as Cypriots are included), we have shown that previous expert advice to healthcare planners to commission universal or targeted screening on the basis of the proportion of ethnic minorities in the population[11] is over-simplistic and misleading, and cannot be resolved just by lowering the cut-off for universal screening from 15% to 10%, as has been suggested.[21]

This may, in part, explain why universal or targeted screening programmes have not been introduced consistently within the UK.[151] It is clear that the prevalence of clinical disease, the response of mothers to antenatal screening, and the burden in terms of live births is very different between the two haemoglobinopathies. Although both affect β-globin production and involve the same laboratory techniques, the decision on whether to employ targeted or universal screening should be considered separately. Moreover, by providing estimates of the underlying prevalence of disease, the cost-effectiveness of testing and case finding in the UK can be assessed and healthcare planners properly informed.[140]

The best way of improving the evidence base and obtaining better data (both on the numerator and the denominator) to monitor changes in the rates of carrier frequency and disease in the population would be by introducing a standardised instrument for monitoring ethnicity, with screening uptake and outcomes related to this. This could be combined with data from the existing and future community neonatal and antenatal haemoglobinopathy screening programmes.

Antenatal screening

Outcomes

This is the first description of a universal antenatal screening programme for the haemoglobinopathies in the UK that demonstrates its impact on birth prevalence. Among women referred from other hospitals, the programme achieves comparable rates of PND and termination as other tertiary centres[50,59,60,64] as well as with the data from a retrospective audit across England.[63] Because women within the community-based programme are offered the same service, we suggest that the results reported here for universal screening are likely to be equally generalisable.

The high levels of attendance by the women in this programme, at both stages of counselling, probably reflect how they value the opportunity to receive information about their risk status, even if they decline PND.[59,60] This is consistent with the current thinking in screening that recognises the importance of informed decision making, rather than coverage or prevention, as an appropriate screening programme outcome measure.

We have not measured the outcomes of counselling or the more intangible benefits, nor disbenefits, such as anxiety, resulting from

this programme. More research is required to investigate which components are essential, at which stage of screening it should be offered, how frequently, and what form it should take. In the meantime, the results presented here could be used for planning antenatal screening programmes and in determining their cost-effectiveness. Efforts should be made to encourage women and their partners to book early in gestation so that PND remains a feasible option if requested.

Cost-effectiveness

The costs reported are for an area of relatively high prevalence, but the models presented allow costs to be quantified for both targeted and universal screening, in areas of differing prevalence, by extrapolation from these data. It is important to note that, even in a relatively small maternity unit as described (about 2000 births per year) there can still be significant cost savings from screening *per se*, while any selective programme, where the samples are processed by an efficient laboratory with associated counselling, is likely to be considered cost-effective.

No detailed information relating to the NHS costs for either SCD or β-thalassaemia major have been published. Using the estimates available[21] from the CMH programme for the period studied, we have estimated the present value, at 6% of the savings in health service costs per case of SCD averted, as £77,000 and, for β-thalassaemia, £123,000.

We demonstrate that antenatal screening programmes, at most prevalences of haemoglobinopathy traits, are likely to be self-financing and, therefore, cost-effective from an NHS perspective, because the savings in service costs are greater than the costs of the detection of an affected fetus and subsequent termination. Antenatal screening (especially when this is managed alongside a neonatal screening programme) is quite cheap, and may be considered cost-effective in terms of improved genetic choice. Added cost-efficiencies and advantages of expertise can also be gained from centralising work between adjacent districts, as demonstrated in the neonatal costings. Cost-effectiveness is also dependent on the success of the follow-up programme in counselling the maximum number of women and couples.

The SMAC recommended a policy of universal screening for haemoglobinopathies in antenatal clinics when the ethnic minority population exceeds 15%, and of selective screening when this population is lower. However, the results presented here show that the difference in programme cost between universal and selective is small when the haemoglobinopathy trait prevalence is ≥ 1%, with β-thalassaemia trait making up ≥ 25%. In addition, universal programmes have the advantage of a lower likelihood of missing couples at risk and the advantage of offering informed genetic choice to mothers.

Table 38 illustrates the distribution of selected health authorities using the midpoints of the trait ranges as listed in appendix 1. According to these parameters, 15 boroughs fall above this line, all of which are in Greater London, while, of the 15 boroughs with between 0.5% and 1% haemoglobinopathy traits with 75% or more made up of β-thalassaemia trait (the "grey" area), six lie outside Greater London.

We have demonstrated that there are no significant differences in costs between universal and selective programmes where the prevalence is 15 sickle traits/1000 births or 0.5 cases of SCD/1000 births. Again, using the midpoint of the range of estimates, *Figure 16* shows the distribution of boroughs relating to the above cut-off point for sickle trait. This is shown in *Figure 17* for SCD.

It is interesting to note that in a number of boroughs where the two types of programme would appear to be cost neutral by one parameter, they are not quite so by the other. This, again, highlights the minimal dispersion within this model and is shown in *Figure 18*.

A local example

Based on the model and data presented, the example of Greater Manchester demonstrates the issues relating to both prevalence and economies of scale. The Greater Manchester boroughs' total births per year and estimates of the range of prevalence for both AS and SCD births are shown in *Table 39*.

Cost-effectiveness of neonatal screening

The decision whether to use a universal or a targeted strategy should not be based on ethnicity, but on the number of births, the gene prevalence or ethnic mix of the population, and the resulting cost per extra SCD identified with universal screening. The SMAC report cites 15% ethnicity as the point at which universal screening should be introduced, yet universal programmes may be considered good value at a disease prevalence of

TABLE 38 *Boroughs above cut-off point and in "grey" area*

AS rate > 15/1000	AS rate 7–15/1000	SCD rate > 0.5/1000	SCD rate 0.2–0.5/1000
Brent	Barnet	Barnet	Barking and Dagenham
Camden	Ealing	Brent	Bromley
Croydon	Enfield	Camden	Harrow
Hackney	Greenwich	Croydon	Hounslow
Hammersmith and Fulham	Harrow	Ealing	Liverpool
Haringey	Merton	Enfield	Sheffield
Islington	Redbridge	Greenwich	Birmingham
Kensington and Chelsea	Tower Hamlets	Hackney	Sandwell
Lambeth	Manchester	Hammersmith and Fulham	Bristol
Lewisham	Birmingham	Haringey	Luton
Newham	Wolverhampton	Islington	North Bedfordshire
Southwark	Luton	Kensington and Chelsea	Reading
Waltham Forest	Reading	Lambeth	Slough
Wandsworth	Nottingham	Lewisham	Wycombe
Westminster, City of	Forest Heath	Merton	Derby
		Newham	Gloucester
		Redbridge	Leicester
		Southwark	Northampton
		Tower Hamlets	Wellingborough
		Waltham Forest	Nottingham
		Wandsworth	Oxford
		Westminster, City of	Ipswich
		Manchester	
		Wolverhampton	
		Forest Heath	

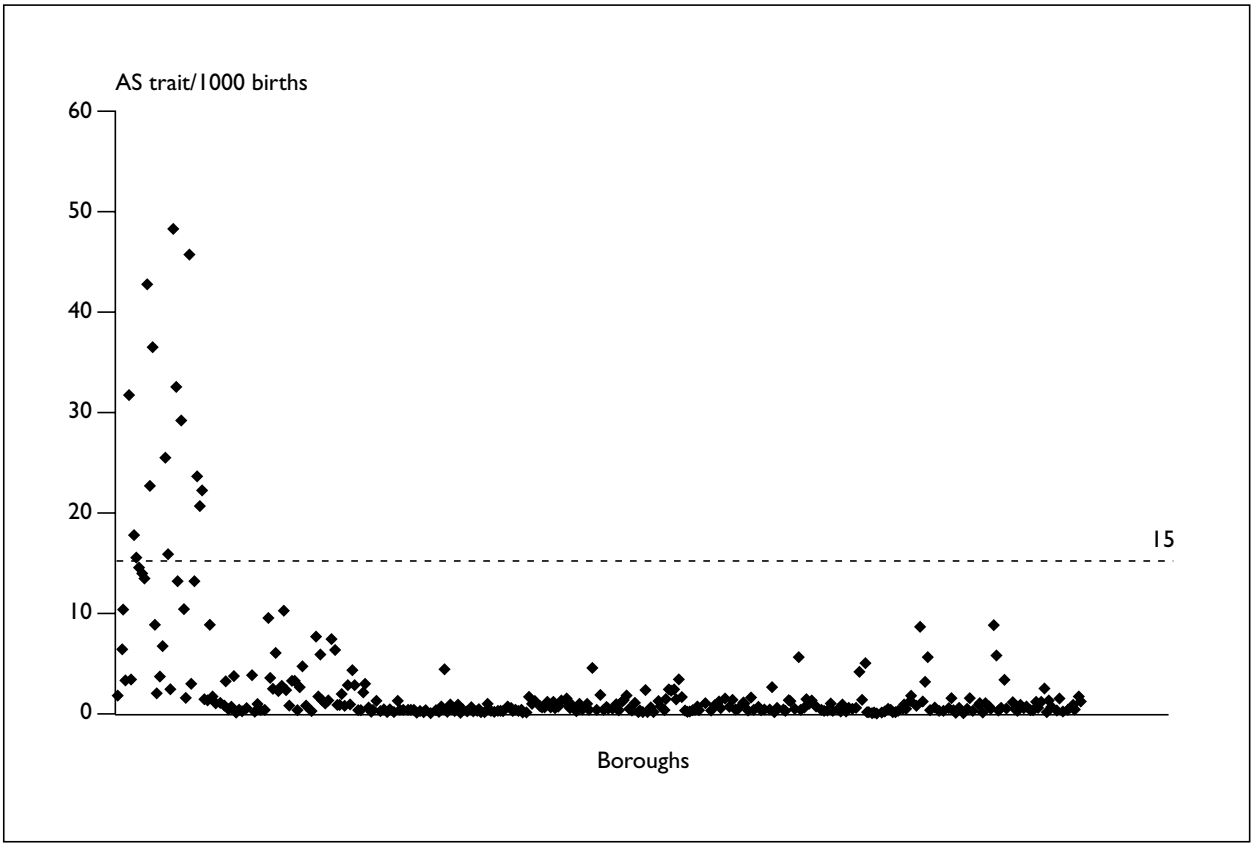


FIGURE 16 *AS trait/1000 births by borough*

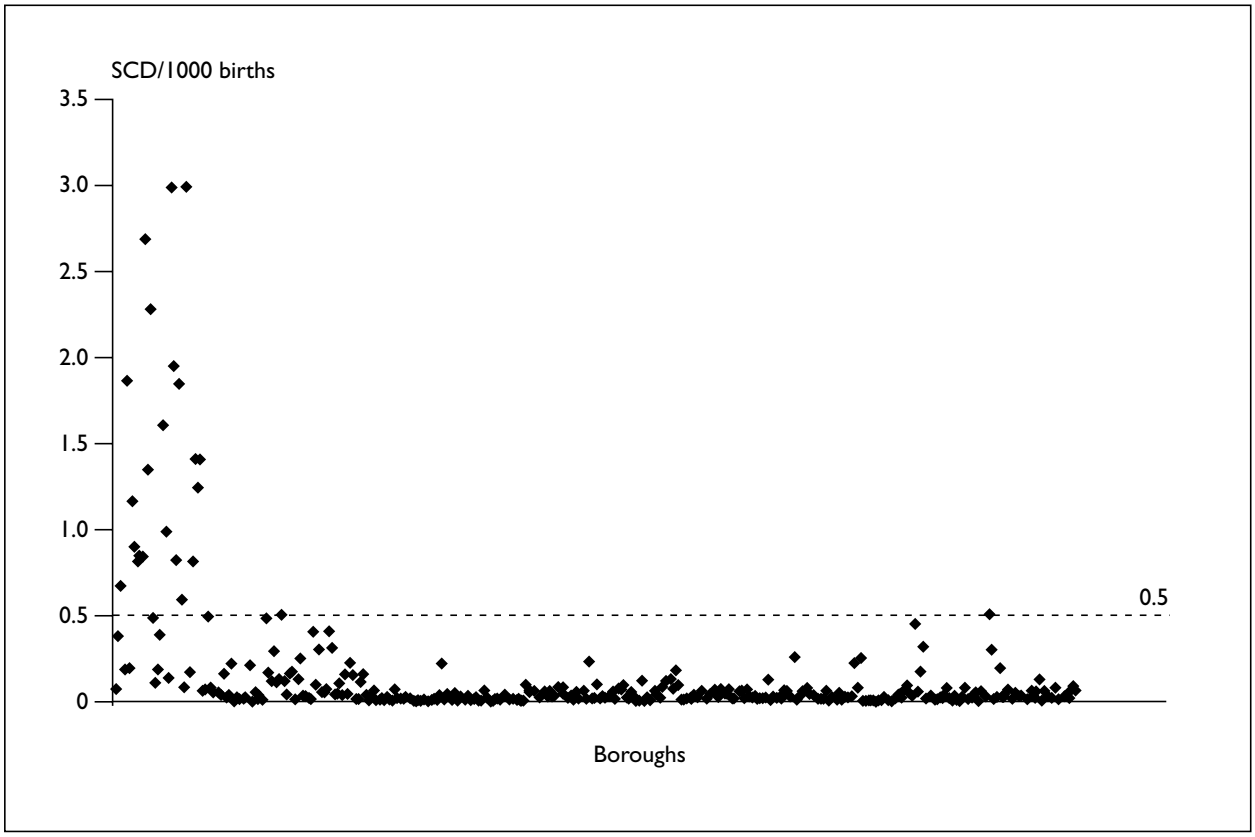


FIGURE 17 *SCD/1000 births by borough*

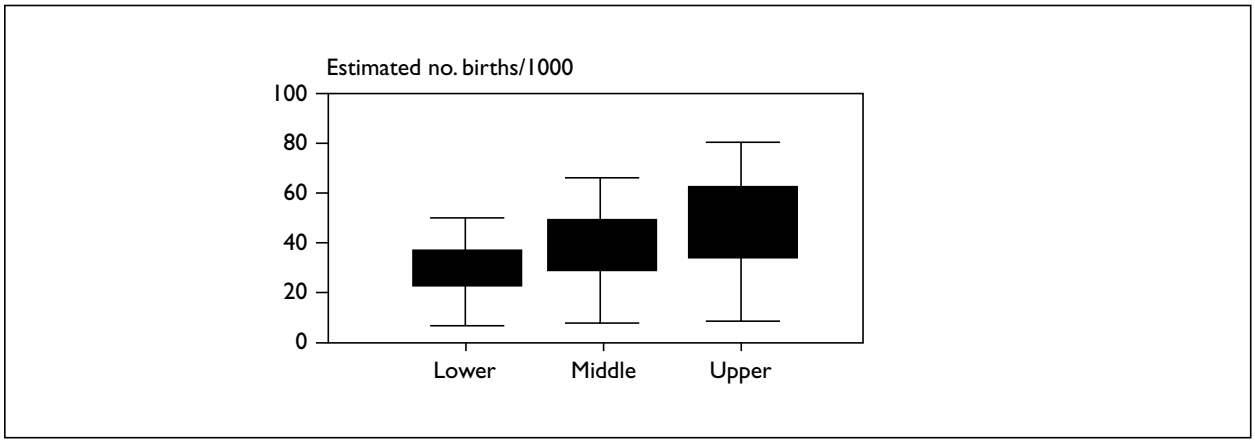


FIGURE 18 *Box plot of range of estimated sickle cell trait births (birth rate ≥ 7 and < 15/1000)*

0.1 or 0.3 per 1000 births, where the cost of an additional case detected is in the range £25,000–100,000. This is likely to be below the figure suggested by the SMAC report and would apply to areas such as NTW, as reported here.

Given significant economies of scale up to 25,000 births per year (and further up to 40,000–50,000), the organisation of screening services should aim to cover a screened population that will generate this level of work. The collaboration of districts with lower numbers of babies to be screened should achieve scale economies.

The true costs of life with a haemoglobinopathy and the advantages of early entry into comprehensive care systems have yet to be addressed, but one must consider both the years of life gained as well as the costs to the family and society as a whole.

TABLE 39 *Greater Manchester boroughs: prevalence of AS and SCD*

District	Births	AS			SCD			AS rate/ 1000	SCD rate/ 1000
		Low	Mid	Upper	Low	Mid	Upper		
Bolton	3500	3.38	5.32	7.15	0.186	0.250	0.332	1.520	0.071
Bury	2370	2.79	3.29	3.70	0.152	0.186	0.230	1.386	0.078
Manchester	6470	50.09	57.85	64.13	2.727	3.275	4.023	8.941	0.506
Oldham	3080	5.08	5.50	5.86	0.266	0.288	0.317	1.785	0.093
Rochdale	3130	3.13	3.51	3.83	0.167	0.191	0.224	1.121	0.061
Salford	3120	3.05	3.59	4.04	0.167	0.202	0.250	1.152	0.065
Stockport	3370	3.08	3.72	4.25	0.170	0.212	0.268	1.103	0.063
Tameside	2970	2.33	2.77	3.16	0.124	0.144	0.170	0.931	0.048
Trafford	2600	7.91	8.59	9.21	0.413	0.447	0.491	3.306	0.172
Wigan	3930	1.46	2.02	2.47	0.086	0.125	0.177	0.513	0.032
Total	34,540	82.30	96.16	107.80	4.458	5.320	6.482	21.758	1.189

Applying the neonatal costing model to populations in England

We applied the costing model, as a simple extrapolation, to our population estimates of AS and SCD to estimate the costs of running a universal programme and the cost per trait and disease found. The costs of a targeted programme were also estimated to provide an estimate of the "cost per extra case" identified by using a universal programme.

Contiguous counties within the current health regions were aggregated to achieve a minimum number of 20,000 births. This is because our model suggests that universal programmes should have > 20,000 births to reduce the average cost per test. For example, in the Northern and Yorkshire Region, Newcastle, Durham, Northumberland and Cumbria were aggregated, giving an annual number of births of nearly 30,000; in the North Thames Region, North London, and Hertfordshire and Essex were aggregated, with annual numbers of births being 65,000 and over 33,000 respectively.

The analysis is summarised in *Table 40*. It provides an illustration of the application of the costing model and an indication of those geographical areas in which universal screening is viable and those in which other screening options may be more appropriate. For purchasers making decisions about the type of programme that is most suitable for their populations, the key indicator is the cost per extra SCD identified by a universal programme. For example, in North London, the estimated cost per extra SCD identified is £7800, whereas, in the West Midlands, it is £30,100. Purchasers need to consider whether they are prepared to incur this amount to identify each case of SCD that would be missed if they were to use a targeted programme.

It should be noted that fixed costs make up a sizeable component of programme costs in both types of programme. In those areas where universal screening is considered too expensive in terms of cost per extra SCD identified, purchasers may want to consider collecting the specimens locally but joining a screening programme elsewhere for testing. Furthermore, by transferring tests to other programmes, county districts with comparatively high rates of AS (on a par with or greater than some parts of London) but located within a regional health authority that has a low sickle cell rate could offer universal screening. For example, Leeds and Kirklees have a sickle cell rate of 3.3/1000 compared with 1.1/1000 in the Regional Health Authority overall; Bristol and Gloucester have a rate of over 4.5/1000 compared with 1.1/1000 overall; and Leicester and Nottingham have rates of 5.8 and 8.8/1000, respectively, compared with 2.3/1000 in Trent overall.

The costs are likely to be lower but further work is required to estimate those (in particular, the additional transport costs) of utilising a programme in another part of the country. The advantages and disadvantages of separating specialist clinical/nursing services from the screening service would also have to be assessed.

Estimates for England, as a whole, have taken into account the need for extra testing equipment for each 100,000 births.

TABLE 40 *Costs of universal neonatal screening using IEF by RHA and counties, and costs per extra trait and extra SCD identified compared with targeting*

Aggregated counties		Births and prevalence			Identification costs		Estimate of missed cases and cost of targeted programme			Comparison of universal versus targeted	
RHAs	**Counties/ county districts**	**Births**	**Trait rate per 1000**	**Disease rate per 1000**	**Per trait (£)**	**Per SCD (£)**	**S and C trait missed (no.)**	**SCD missed (no.)**	**Cost of targeted programme (£)**	**Cost per extra trait identified (£)**	**Cost per extra SCD identified (£)**
Northern and Yorkshire	Newcastle, Durham, Northumberland, Cumbria	29,810	0.5	0.02	7440	156,300	2.96	0.1	42,700	22,800	478,700
	North and West Yorkshire, Humberside, Cleveland	55,010	1.9	0.08	1630	38,900	21.42	0.9	47,000	6000	142,300
Subtotal		**84,820**	**1.4**	**0.06**	**2040**	**48,000**	**24.39**	**1.0**	**47,600**	**8200**	**193,900**
Trent	Leicester, Derby, South Yorkshire	37,750	2.8	0.11	1270	31,700	20.79	0.8	46,800	4100	102,100
	Lincoln, Nottingham	20,130	3.2	0.13	1330	33,300	13.08	0.5	45,000	3200	80,500
Subtotal		**57,880**	**2.9**	**0.12**	**1080**	**27,000**	**33.87**	**1.4**	**49,800**	**3900**	**98,400**
Oxford and Anglia	Bedfordshire, Berkshire, Buckinghamshire, Oxford	35,730	4.3	0.18	830	20,200	30.54	1.3	49,100	2600	62,100
	Cambridge, Northampton, Suffolk, Norfolk	33,730	2.5	0.11	1420	34,100	17.06	0.7	45,900	4400	105,800
Subtotal		**69,460**	**3.4**	**0.14**	**890**	**21,600**	**47.60**	**2.0**	**53,000**	**3,400**	**81,000**
North Thames	North London	65,190	22.9	1.13	150	3100	299.11	14.8	111,200	400	7800
	Hertfordshire and Essex	33,660	1.6	0.07	2280	51,700	10.58	0.5	44,400	7200	163,200
Subtotal		**98,850**	**15.7**	**0.77**	**200**	**4100**	**309.69**	**15.2**	**113,700**	**600**	**12,900**
South Thames	South London	40,430	25.0	1.23	150	3100	201.81	10.0	88,700	300	6700
	Kent, Surrey, Sussex	49,260	1.0	0.05	3080	66,800	10.33	0.5	44,400	11,100	240,700
Subtotal		**89,690**	**11.8**	**0.58**	**260**	**5300**	**212.14**	**10.4**	**91,100**	**900**	**17,900**
South West	Cornwall, Devon, Dorset, Somerset	29,380	0.5	0.03	6810	142,900	3.21	0.2	42,700	20,700	435,000
	Bristol, Gloucester, Hampshire, Wiltshire	48,780	1.9	0.08	1680	40,000	18.95	0.8	46,400	5900	141,400
Subtotal		**78,160**	**1.4**	**0.06**	**2090**	**49,000**	**22.15**	**0.9**	**47,100**	**8300**	**195,100**

continued

TABLE 40 contd *Costs of universal neonatal screening using IEF by RHA and counties, and costs per extra trait and extra SCD identified compared with targeting*

Aggregated counties		Births and prevalence			Identification costs		Estimate of missed cases and cost of targeted programme			Comparison of universal versus targeted	
RHAs	**Counties/ county districts**	**Births**	**Trait rate per 1000**	**Disease rate per 1000**	**Per trait (£)**	**Per SCD (£)**	**S and C trait missed (no.)**	**SCD missed (no.)**	**Cost of targeted programme (£)**	**Cost per extra trait identified (£)**	**Cost per extra SCD identified (£)**
West Midlands	West Midlands	37,190	9.0	0.34	400	10,500	66.78	2.6	57,500	1200	30,100
	Hereford, Shropshire, Staffordshire, Warwickshire	31,940	1.2	0.05	3050	73,900	7.60	0.3	43,800	9500	229,700
Subtotal		**69,130**	**5.4**	**0.21**	**580**	**14,900**	**74.39**	**2.9**	**59,200**	**2100**	**54,100**
North West	Greater Manchester	34,540	3.6	0.15	990	23,300	24.95	1.1	47,800	3100	71,600
	Liverpool, Cheshire, Lancashire	47,770	1.3	0.06	2450	54,700	12.71	0.6	44,900	8700	194,500
Subtotal		**82,310**	**2.3**	**0.10**	**1290**	**29,800**	**37.65**	**1.6**	**50,700**	**5100**	**118,200**
England		630,300	6.0	0.28	490	10,500	761.88	35.5	398,500	1900	41,100

These data should be treated as an indication and starting point for deciding whether to introduce universal screening. The model assumes that 20% of cases are missed under a targeted programme. The evidence for this assumption is, however, weak. Further studies are required to provide better data on the level of missed cases through targeting programmes and on examples of good practice. In addition, the costs of selection involved with targeting were not fully investigated and also require further work. There is also some suggestion that the cost per test may fall over time as consumables become cheaper.

The development of costing models for haemoglobinopathies allowed a number of cost-effectiveness ratios to be calculated, looking at the costs of giving choice and avoiding affected births. In some cases the evidence shows that screening would generate net financial savings. However, it is important to understand that the real objectives should be seen in terms of benefits to families and those who are affected. No attempt has been made in this study to value such gains, but there remains an important research agenda to assess the benefits of choice, better survival and better health.

Cost-effectiveness of nurse follow-up

The costs reviewed and discussed are direct NHS costs, yet the benefits of neonatal screening, as with all screening programmes, depend on there being an available intervention that is more effective when started early. A screening programme with follow-up counselling and access to early treatment is, therefore, likely to realise the maximum potential benefits. Some screening programmes (e.g. some in the USA) have more restricted follow-up, which limits their effectiveness and cost-effectiveness. We have demonstrated an improvement in counselling of over 40% more than previous published results by using the service model described (p. 56).

We have demonstrated that, with dedicated nurse specialists, over 90% of families who have been identified with a major haemoglobinopathy or trait state can be counselled at a cost of £142.51 per case (*Table 36*). This represents a major improvement on other published data for counselling after neonatal screening for haemoglobinopathies and recruitment to comprehensive care. It will be important, in the future, to study both different models of counselling and its effectiveness and impact.

General

A recent report has attempted, by using a questionnaire, to map the screening services for haemoglobinopathies across Greater London.[152] This demonstrated that services are patchy and generally hospital rather than population based. It is essential that neonatal screening programmes are population based and properly linked to other neonatal screening programmes and community child health services. With the focus of antenatal care shifting away from the hospital into the community and primary care, it is becoming increasingly important that antenatal screening programmes should also be organised on a population base. This will be the only way to provide screening and counselling early in pregnancy and, thus, allow women both the maximum time to consider the issues and their decisions and, also, the opportunity of early termination of pregnancy if the mother/couple choose to pursue this.

A recently published national audit of neonatal screening for metabolic disease[153] has demonstrated a need for the overall coordination of screening programmes, at a health authority level, in order to ensure appropriate linkages between patient, sample and laboratory, and the provision of results to the mother, with appropriate counselling, as well as to community child health services, the appropriate clinicians in primary care and specialists. This is essential in order to ensure effective audit in the future for the purposes of clinical governance. Haemoglobinopathy screening programmes in the UK are rarely population based and are not usually subject to stringent audit. It therefore follows that any haemoglobinopathy screening programmes require similar levels of planning and coordination, with defined responsibilities and quality standards.

Commissioners of services could usefully consider the factors and costs that we have demonstrated, but, before deciding on a service model, it is likely that they would wish to replicate our methodology. They could also consider the issues of genetic choice and opportunity costs in coming to their decisions about how to frame their local services and develop suitable collaborative arrangements. It would also be expedient for them to be aware of the prevalence of the haemoglobinopathies compared with other diseases for which screening services are commissioned, as shown in *Table 41*, and the relative costs, as listed in *Table 42*.[154]

TABLE 41 *Some of the diseases tested for in neonatal blood specimens in the UK*

Disease	Prevalence	UK births screened (%)
Hypothyroidism	1:4210	99
PKU	1:12,000	99
Cystic fibrosis	1:2500	16
Haemoglobinopathies	1:2860	9

Based on data from Streetly et al., *1995*[153]

TABLE 42 *Costs per case identified by neonatal screening*

Disease	Cost (£)
Hypothyroidism	14,890
PKU	2150–12,294
Cystic fibrosis	4379–6223

Based on Pollitt et al., *1997*[154]

Although these must also be balanced against the costs of acute interventions for other diseases and the full costs to the NHS, family and society of not screening for haemoglobinopathies, comprehensive care interventions for SCD are cheap: penicillin, vaccination against pneumococcal species, and education to palpate the spleen and manage painful vaso-occlusive crises.

In the USA, 49 of the 50 states mandate neonatal screening for SCD, arranged on a population basis, although there are no state-organised antenatal or community haemoglobinopathy screening programmes.

In the UK, the national charity, the Sickle Cell Society, called for universal neonatal screening over 20 years ago and supports the offer of antenatal screening, thus demonstrating community support for the programme. The patchy provision of service, generally reflecting interested specialists, remains a matter of concern to this organisation and to other charities in the haemoglobinopathy field. This has given rise to questions, within the black press and community, of inequity of access to the services they need as a result of either lack of awareness or, worse, racism.

SECTION III

RECOMMENDATIONS

Chapter 14

Recommendations

Implications for practice

General

- The evidence supports previous national guidance (SMAC) that commissioners should develop appropriate population-based haemoglobinopathy screening programmes.
- Because this study makes no comparison with other programmes, the generalisability of the cost models on which the conclusions are based could usefully be considered in the planning process. Other programmes may have very different structures and therefore costs.
- There is currently little cooperation between health authorities and across regions. The evidence suggests that the creation of partnerships when building programmes would ensure efficiencies of scale and expert input, while maintaining closeness to the clinical services.
- Commissioners are not currently required to have a quality framework for any implementation plan for their screening programmes. Such a plan would include the linkage to and provision of both counselling and specialist care.
- This review suggests a need for all haemoglobinopathy screening programmes to have defined paths of responsibility for every aspect of the work, with agreed service standards for the purpose of audit.
- Audit depends on outcome measures (including timetables) being defined for the respective screening processes.
- The indications are that there is a need to address the current lack of systematic data collection in this area, particularly:
  - ethnic monitoring (for instance, there is no standard instrument currently used in laboratories to record ethnic group or ethnic origin)
  - ethnic-specific data on screening uptake
  - patient registries to monitor long-term outcomes and mortality.

Neonatal screening

- The analyses indicate that, for laboratories to be cost-effective, they should be able to screen at least 25,000 births annually.
- For areas where there are 16 AS and 0.5 SCD cases per 1000 births, the data suggest that universal screening is cost-effective.
- In areas where there are fewer births, consideration of value for money and equity is of importance. In those where 7–15 per 1000 births have AS, universal screening would be justified.
- The evidence supports the development of systems to inform parents of their baby's test results and to enter children with major haemoglobinopathies into specialist comprehensive care services.
- A national external quality assessment scheme for neonatal haemoglobinopathy screening would be able to address issues of quality assurance.

Antenatal screening

- According to this study's results, universal antenatal screening is cost-effective for all districts having 1% ethnic minorities if 25% of those carry the β-thalassaemia trait.
- An important outcome indicator is genetic choice, so some commissioners would purchase services at a lower prevalence in their population.

Recommendations for research

The authors recommend the following research:

- study of the disbenefits and potential harms of screening for haemoglobinopathies at any stage
- study to establish the impact of counselling and the optimal service models for the provision of counselling related to haemoglobinopathy screening programmes
- study comparing the costs and benefits of universal antenatal screening for haemoglobinopathies with those of targeted antenatal screening
- an investigation concerning whether clinical, psychological and social outcomes in patients and families affected by haemoglobinopathies are influenced by the structure and process of services
- the true NHS, family and societal costs of life with major haemoglobinopathies
- optimal methods and modes of delivery of counselling for the haemoglobinopathies

- the attitude of the various communities in the UK to risk relating to haemoglobinopathies and how this impacts on the counselling process
- study of the equity and access issues relating to haemoglobinopathy screening, particularly as they relate to race
- the most cost-effective ways of delivering specialist haemoglobinopathy services
- comparison of the haemoglobinopathy screening service costs in a high-prevalence geographical area with services in areas of lower prevalence and where neonatal and antenatal screening are disconnected
- comparisons of the cost–benefit and effectiveness of targeting screening for haemoglobinopathies compared with universal screening reviewing costs, including litigation
- further consideration of the feasibility of screening services for haemoglobinopathies, with low- and high-prevalence areas combining to reach a critical value to make the service collectively cost-effective
- continuous review of the change process as haemoglobinopathy screening programmes are introduced
- review of the effectiveness of various educational and community awareness initiatives used when developing new haemoglobinopathy screening programmes.

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Appendix 1

Prevalence estimates

This table presents the middle, lower and upper estimates of births (by haemoglobinopathy) for each region in England during 1994. The data show estimates of β-thalassaemia trait, β-thalassaemia disease (β-thalassaemia major and Eβ-thalassaemia), sickle trait, Hb C, and SCD (SS, SC, Sβ-thalassaemia). They are presented in order of county district code and county. Regional health authorities (old boundaries) are also given. Data are given as middle, lower and upper estimates of numbers of births.

Region	County	District code	District name	Births	Thal trait			Thal disease			AS			Hb C	SCD		
					Mid	Lower	Upper	Mid	Lower	Upper	Mid	Lower	Upper	Mid	Mid	Lower	Upper
North Thames	Greater London	H01AA	City of London	50	0.67	0.61	0.73	0.016	0.011	0.020	0.09	0.06	0.13	0.02	0.004	0.003	0.005
North Thames	Greater London	H01AB	Barking and Dagenham	2560	13.99	12.24	15.51	0.248	0.170	0.334	16.59	12.66	19.82	4.26	0.995	0.728	1.359
North Thames	Greater London	H01AC	Barnet	4380	54.05	45.87	60.46	1.089	0.754	1.445	45.76	27.99	60.44	8.81	2.982	1.789	4.602
South Thames	Greater London	H01AD	Bexley	2870	14.99	13.40	16.26	0.285	0.202	0.373	9.59	7.10	11.68	2.33	0.569	0.410	0.782
North Thames	Greater London	H01AE	Brent	3960	59.48	46.02	71.63	0.725	0.434	1.076	125.77	96.20	150.31	32.78	7.410	5.485	10.031
South Thames	Greater London	H01AF	Bromley	3740	14.71	13.32	15.73	0.267	0.190	0.348	13.20	10.89	15.10	3.69	0.761	0.604	0.973
North Thames	Greater London	H01AG	Camden	2560	20.82	16.56	24.36	0.407	0.264	0.563	45.58	30.30	57.87	9.89	2.999	1.888	4.520
South Thames	Greater London	H01AH	Croydon	4750	31.31	26.40	35.50	0.449	0.297	0.620	74.20	60.37	85.53	20.72	4.314	3.370	5.601
North Thames	Greater London	H01AJ	Ealing	4520	56.89	43.23	69.40	0.687	0.403	1.035	66.26	50.16	80.08	17.17	3.738	2.822	4.975
North Thames	Greater London	H01AK	Enfield	3770	116.46	113.01	119.33	3.377	2.505	4.259	53.07	39.74	64.21	12.41	3.249	2.323	4.478
South Thames	Greater London	H01AL	Greenwich	3160	22.79	19.78	25.16	0.405	0.281	0.539	42.82	30.53	52.82	10.12	2.688	1.823	3.869
North Thames	Greater London	H01AM	Hackney	3620	40.73	36.18	44.54	0.752	0.527	0.992	154.68	112.70	188.47	37.66	9.732	6.689	13.894
North Thames	Greater London	H01AN	Hammersmith and Fulham	2330	10.88	9.42	12.04	0.123	0.081	0.171	52.96	42.65	61.24	14.61	3.157	2.409	4.182
North Thames	Greater London	H01AP	Haringey	3510	68.07	63.83	71.55	1.698	1.239	2.170	128.32	94.61	155.56	31.36	8.021	5.583	11.343
North Thames	Greater London	H01AQ	Harrow	2760	34.08	25.94	41.53	0.417	0.250	0.619	24.66	16.85	31.55	5.69	1.366	0.968	1.899
North Thames	Greater London	H01AR	Havering	2770	8.49	7.66	9.12	0.133	0.093	0.174	5.91	4.86	6.79	1.65	0.336	0.269	0.428
North Thames	Greater London	H01AS	Hillingdon	3540	22.28	17.16	26.97	0.256	0.150	0.384	13.12	9.38	16.46	3.21	0.700	0.525	0.932
North Thames	Greater London	H01AT	Hounslow	3220	31.61	23.83	38.85	0.382	0.220	0.583	21.88	13.64	29.00	4.52	1.280	0.824	1.895
North Thames	Greater London	H01AU	Islington	2600	29.34	26.89	31.22	0.678	0.488	0.874	66.27	47.97	81.00	15.89	4.195	2.861	6.017
North Thames	Greater London	H01AW	Kensington and Chelsea	1890	8.82	7.38	9.85	0.120	0.078	0.165	30.18	22.32	36.50	7.50	1.887	1.315	2.670
South Thames	Greater London	H01AX	Kingston on Thames	1880	7.95	6.15	9.19	0.105	0.065	0.149	4.61	3.30	5.70	1.10	0.276	0.193	0.388
South Thames	Greater London	H01AY	Lambeth	4350	33.32	29.92	35.95	0.447	0.312	0.592	209.87	158.81	250.84	53.63	12.987	9.257	18.095
South Thames	Greater London	H01AZ	Lewisham	3920	39.38	36.84	41.05	0.825	0.602	1.049	127.44	101.30	148.48	34.39	7.671	5.763	10.277
South Thames	Greater London	H01BA	Merton	2720	17.48	14.29	19.95	0.267	0.173	0.369	36.22	26.46	44.15	8.86	2.250	1.561	3.191
North Thames	Greater London	H01BB	Newham	4530	73.29	56.62	88.82	1.183	0.725	1.732	132.56	90.24	167.14	29.89	8.397	5.486	12.372
North Thames	Greater London	H01BC	Redbridge	3150	42.79	35.12	49.96	0.755	0.498	1.052	33.08	24.27	40.63	8.15	1.899	1.387	2.589
South Thames	Greater London	H01BD	Richmond upon Thames	2260	7.88	6.80	8.68	0.122	0.083	0.164	3.83	2.89	4.62	0.96	0.222	0.165	0.300
South Thames	Greater London	H01BE	Southwark	4200	37.64	34.83	39.64	0.695	0.503	0.892	191.76	130.03	241.25	42.67	12.558	8.031	18.757
South Thames	Greater London	H01BF	Sutton	2480	8.74	7.46	9.70	0.127	0.085	0.172	7.51	5.69	9.01	1.91	0.448	0.327	0.612
North Thames	Greater London	H01BG	Tower Hamlets	3350	55.75	39.73	71.19	1.386	0.857	1.990	44.36	33.08	53.44	11.11	2.763	1.942	3.887
North Thames	Greater London	H01BH	Waltham Forest	3740	53.01	45.87	59.58	1.115	0.757	1.520	88.55	69.81	103.77	23.66	5.303	3.973	7.115
South Thames	Greater London	H01BJ	Wandsworth	4100	24.74	20.41	28.25	0.317	0.200	0.450	84.97	66.52	99.87	22.66	5.119	3.801	6.923
North Thames	Greater London	H01BK	Westminster, City of	2380	16.41	12.72	19.37	0.253	0.156	0.361	53.01	38.00	65.07	12.68	3.364	2.274	4.856

continued

continued

Region	County	District code	District name	Births	Thal trait			Thal disease			AS			Hb C	SCD		
					Mid	Lower	Upper	Mid	Lower	Upper	Mid	Lower	Upper	Mid	Mid	Lower	Upper
North West	Greater Manchester	H02BL	Bolton	3500	20.02	15.47	24.29	0.241	0.138	0.368	5.32	3.38	7.15	1.17	0.250	0.186	0.332
North West	Greater Manchester	H02BM	Bury	2370	8.12	6.67	9.34	0.120	0.073	0.175	3.29	2.79	3.70	0.96	0.186	0.152	0.230
North West	Greater Manchester	H02BN	Manchester	6470	36.92	29.57	43.33	0.576	0.348	0.850	57.85	50.09	64.13	17.41	3.275	2.727	4.023
North West	Greater Manchester	H02BP	Oldham	3080	23.50	18.22	28.59	0.476	0.290	0.701	5.50	5.08	5.86	1.79	0.288	0.266	0.317
North West	Greater Manchester	H02BQ	Rochdale	3130	20.29	16.01	24.31	0.387	0.234	0.574	3.51	3.13	3.83	1.09	0.191	0.167	0.224
North West	Greater Manchester	H02BR	Salford	3120	6.51	5.57	7.17	0.065	0.041	0.092	3.59	3.05	4.04	1.05	0.202	0.167	0.250
North West	Greater Manchester	H02BS	Stockport	3370	8.36	6.75	9.44	0.090	0.053	0.130	3.72	3.08	4.25	1.06	0.212	0.170	0.268
North West	Greater Manchester	H02BT	Tameside	2970	9.67	7.69	11.38	0.133	0.079	0.195	2.77	2.33	3.16	0.81	0.144	0.124	0.170
North West	Greater Manchester	H02BU	Trafford	2600	10.60	8.80	12.00	0.152	0.098	0.212	8.59	7.91	9.21	2.77	0.447	0.413	0.491
North West	Greater Manchester	H02BW	Wigan	3930	5.86	5.22	6.26	0.034	0.020	0.047	2.02	1.46	2.47	0.49	0.125	0.086	0.177
North West	Merseyside	H03BX	Knowsley	2340	3.78	3.29	4.04	0.025	0.015	0.034	1.99	1.76	2.18	0.61	0.111	0.095	0.133
North West	Merseyside	H03BY	Liverpool	6100	13.67	11.10	15.17	0.110	0.064	0.156	23.12	18.15	27.13	6.17	1.398	1.038	1.892
North West	Merseyside	H03BZ	St Helens	2130	3.40	2.95	3.65	0.023	0.014	0.032	0.37	0.30	0.44	0.10	0.021	0.017	0.028
North West	Merseyside	H03CA	Sefton	3190	5.83	4.76	6.40	0.045	0.026	0.063	1.72	1.34	2.02	0.45	0.104	0.077	0.140
North West	Merseyside	H03CB	Wirral	4100	7.66	6.12	8.49	0.057	0.032	0.081	1.40	1.18	1.59	0.40	0.080	0.065	0.100
Trent	South Yorkshire	H04CC	Barnsley	2820	4.75	4.46	4.94	0.049	0.034	0.063	1.08	0.83	1.28	0.27	0.064	0.048	0.085
Trent	South Yorkshire	H04CE	Doncaster	3840	7.82	6.88	8.57	0.077	0.049	0.108	2.96	2.69	3.21	0.94	0.153	0.141	0.168
Trent	South Yorkshire	H04CF	Rotherham	3360	9.27	8.09	10.36	0.138	0.089	0.197	1.51	1.33	1.67	0.45	0.082	0.071	0.096
Trent	South Yorkshire	H04CG	Sheffield	6520	24.17	19.95	27.82	0.359	0.219	0.525	25.51	22.40	28.02	7.80	1.435	1.213	1.738
Northern and Yorkshire	Tyne & Wear	H05CH	Gateshead	2440	3.76	3.37	4.04	0.026	0.016	0.037	0.40	0.36	0.44	0.12	0.019	0.019	0.021
Northern and Yorkshire	Tyne & Wear	H05CJ	Newcastle upon Tyne	3450	11.00	8.87	12.84	0.153	0.092	0.226	3.64	2.29	4.76	0.74	0.232	0.143	0.353
Northern and Yorkshire	Tyne & Wear	H05CK	North Tyneside	2170	3.34	2.91	3.65	0.021	0.012	0.031	0.76	0.57	0.91	0.19	0.044	0.033	0.060
Northern and Yorkshire	Tyne & Wear	H05CL	South Tyneside	1880	2.91	2.58	3.20	0.019	0.011	0.028	1.12	0.84	1.36	0.28	0.067	0.048	0.091
Northern and Yorkshire	Tyne & Wear	H05CM	Sunderland	3640	6.18	5.46	6.74	0.056	0.036	0.079	1.29	0.95	1.57	0.32	0.077	0.055	0.106
West Midlands	West Midlands	H06CN	Birmingham	15,620	161.99	126.66	195.96	2.749	1.653	4.098	150.24	140.05	159.40	49.54	7.746	7.280	8.365
West Midlands	West Midlands	H06CQ	Coventry	4140	23.08	18.11	27.83	0.266	0.156	0.402	15.08	12.55	17.44	4.41	0.749	0.660	0.864
West Midlands	West Midlands	H06CR	Dudley	3910	13.84	11.73	15.83	0.192	0.121	0.277	9.84	9.13	10.48	3.22	0.506	0.475	0.547
West Midlands	West Midlands	H06CS	Sandwell	4160	30.40	23.78	36.95	0.391	0.231	0.590	25.49	22.92	27.98	8.12	1.252	1.183	1.338
West Midlands	West Midlands	H06CT	Solihull	2360	5.42	4.71	6.01	0.048	0.030	0.068	5.51	5.23	5.77	1.85	0.280	0.270	0.294
West Midlands	West Midlands	H06CU	Walsall	3560	22.20	17.75	26.52	0.337	0.206	0.496	10.35	9.15	11.52	3.23	0.499	0.471	0.533
West Midlands	West Midlands	H06CW	Wolverhampton	3440	24.83	19.35	30.17	0.224	0.125	0.350	35.49	32.53	38.32	11.55	1.761	1.677	1.867
Northern and Yorkshire	West Yorkshire	H07CX	Bradford	7490	80.08	62.63	97.08	1.557	0.939	2.324	17.99	15.34	20.32	5.36	0.953	0.820	1.131
Northern and Yorkshire	West Yorkshire	H07CY	Calderdale	2620	12.53	10.28	14.64	0.227	0.140	0.332	2.24	1.95	2.48	0.67	0.125	0.105	0.151
Northern and Yorkshire	West Yorkshire	H07CZ	Kirklees	5120	37.19	29.44	44.69	0.601	0.359	0.902	17.02	15.08	18.81	5.32	0.861	0.787	0.956
Northern and Yorkshire	West Yorkshire	H07DA	Leeds	9070	33.13	27.01	38.57	0.435	0.262	0.644	30.20	26.69	33.17	9.33	1.637	1.425	1.924
Northern and Yorkshire	West Yorkshire	H07DB	Wakefield	4060	8.71	7.68	9.61	0.102	0.065	0.146	1.74	1.41	2.02	0.48	0.098	0.078	0.125

continued

continued

Region	County	District code	District name	Births	Thal trait			Thal disease			AS			Hb C	SCD		
					Mid	Lower	Upper	Mid	Lower	Upper	Mid	Lower	Upper	Mid	Mid	Lower	Upper
South West	Avon	H08UB	Bath	930	2.01	1.89	2.10	0.026	0.018	0.033	2.48	2.40	2.55	0.84	0.130	0.125	0.137
South West	Avon	H08UC	Bristol	5330	15.61	13.59	17.34	0.190	0.123	0.267	25.52	23.45	27.24	8.23	1.377	1.240	1.562
South West	Avon	H08UD	Kingswood	1210	1.75	1.59	1.86	0.008	0.005	0.011	1.05	0.94	1.14	0.33	0.056	0.050	0.065
South West	Avon	H08UE	Northavon	2030	3.56	3.31	3.74	0.034	0.024	0.045	1.54	1.39	1.67	0.48	0.082	0.073	0.093
South West	Avon	H08UF	Wansdyke	920	1.17	1.06	1.23	0.004	0.002	0.005	0.49	0.35	0.61	0.12	0.031	0.021	0.045
South West	Avon	H08UG	Woodspring	1950	4.36	4.06	4.54	0.065	0.047	0.083	0.69	0.55	0.82	0.17	0.040	0.031	0.052
Anglia and Oxford	Bedfordshire	H09UB	Luton	3160	28.91	22.60	35.02	0.522	0.316	0.774	24.50	22.20	26.47	7.80	1.306	1.173	1.487
Anglia and Oxford	Bedfordshire	H09UC	Mid Bedfordshire	1520	2.82	2.53	3.02	0.025	0.016	0.033	2.78	2.34	3.14	0.80	0.159	0.129	0.200
Anglia and Oxford	Bedfordshire	H09UD	North Bedfordshire	1800	10.79	8.62	12.83	0.153	0.094	0.223	10.79	9.64	11.83	3.39	0.560	0.507	0.631
Anglia and Oxford	Bedfordshire	H09UE	South Bedfordshire	1570	2.86	2.58	3.06	0.024	0.016	0.033	1.87	1.58	2.10	0.55	0.104	0.086	0.128
Anglia and Oxford	Berkshire	H10UB	Bracknell Forest	1540	3.43	3.07	3.68	0.042	0.029	0.056	1.65	1.41	1.86	0.48	0.092	0.077	0.113
Anglia and Oxford	Berkshire	H10UC	Newbury	1820	3.36	3.07	3.57	0.032	0.022	0.043	2.58	2.20	2.89	0.76	0.146	0.120	0.181
Anglia and Oxford	Berkshire	H10UD	Reading	2120	9.06	7.46	10.48	0.121	0.073	0.179	15.91	14.06	17.42	4.91	0.884	0.757	1.057
Anglia and Oxford	Berkshire	H10UE	Slough	1850	26.07	20.01	31.93	0.410	0.243	0.619	11.98	9.92	13.91	3.48	0.593	0.522	0.685
Anglia and Oxford	Berkshire	H10UF	Windsor and Maidenhead	1670	6.61	5.30	7.71	0.093	0.057	0.137	1.62	1.20	2.00	0.40	0.088	0.067	0.116
Anglia and Oxford	Berkshire	H10UG	Wokingham	1940	4.83	4.15	5.35	0.053	0.035	0.073	2.05	1.62	2.43	0.55	0.113	0.090	0.144
Anglia and Oxford	Buckinghamshire	H11UB	Aylesbury Vale	2190	7.50	6.42	8.47	0.117	0.075	0.167	4.43	4.01	4.78	1.40	0.241	0.213	0.279
Anglia and Oxford	Buckinghamshire	H11UC	Chiltern	970	2.76	2.30	3.13	0.038	0.023	0.054	0.83	0.73	0.92	0.25	0.045	0.039	0.054
Anglia and Oxford	Buckinghamshire	H11UD	Milton Keynes	2870	9.76	8.27	11.00	0.137	0.089	0.189	8.36	6.92	9.58	2.38	0.471	0.380	0.593
Anglia and Oxford	Buckinghamshire	H11UE	South Bucks	760	2.15	1.86	2.39	0.028	0.018	0.038	0.73	0.61	0.85	0.21	0.037	0.032	0.044
Anglia and Oxford	Buckinghamshire	H11UF	Wycombe	2280	12.96	10.65	15.15	0.226	0.139	0.332	10.05	9.52	10.50	3.36	0.530	0.496	0.575
Anglia and Oxford	Cambridgeshire	H12UB	Cambridge	1140	4.28	3.55	4.80	0.068	0.045	0.092	3.27	2.77	3.68	0.95	0.185	0.152	0.229
Anglia and Oxford	Cambridgeshire	H12UC	East Cambridgeshire	810	1.60	1.59	1.62	0.024	0.018	0.031	0.34	0.32	0.35	0.11	0.018	0.017	0.018
Anglia and Oxford	Cambridgeshire	H12UD	Fenland	1040	1.40	1.31	1.46	0.007	0.004	0.009	0.48	0.42	0.54	0.15	0.026	0.023	0.031
Anglia and Oxford	Cambridgeshire	H12UE	Huntingdonshire	2060	4.47	4.11	4.73	0.054	0.037	0.071	4.47	3.96	4.89	1.37	0.248	0.213	0.296
Anglia and Oxford	Cambridgeshire	H12UF	Peterborough	2450	13.10	10.75	15.30	0.216	0.134	0.314	7.48	6.57	8.27	2.29	0.401	0.350	0.470
Anglia and Oxford	Cambridgeshire	H12UG	South Cambridgeshire	1500	2.61	2.38	2.75	0.025	0.017	0.033	1.07	0.83	1.27	0.28	0.064	0.048	0.087
North West	Cheshire	H13UB	Chester	1390	2.99	2.57	3.24	0.036	0.024	0.047	0.32	0.26	0.38	0.08	0.018	0.014	0.024
North West	Cheshire	H13UC	Congleton	950	1.53	1.37	1.61	0.013	0.008	0.017	0.38	0.30	0.45	0.10	0.023	0.017	0.031
North West	Cheshire	H13UD	Crewe and Nantwich	1420	2.36	2.05	2.55	0.015	0.009	0.022	1.87	1.74	1.97	0.61	0.100	0.092	0.111
North West	Cheshire	H13UE	Ellesmere Port and Neston	990	1.51	1.24	1.65	0.006	0.003	0.010	0.27	0.25	0.29	0.09	0.014	0.013	0.016
North West	Cheshire	H13UF	Halton	1690	2.59	2.29	2.75	0.018	0.011	0.024	0.52	0.48	0.56	0.16	0.028	0.025	0.032
North West	Cheshire	H13UG	Macclesfield	1750	3.31	2.73	3.64	0.026	0.015	0.037	0.96	0.77	1.12	0.26	0.056	0.043	0.073
North West	Cheshire	H13UH	Vale Royal	1410	2.00	1.74	2.15	0.009	0.005	0.013	0.32	0.31	0.33	0.11	0.016	0.016	0.017
North West	Cheshire	H13UJ	Warrington	2460	4.80	4.06	5.29	0.042	0.026	0.060	1.43	1.13	1.69	0.38	0.082	0.063	0.108

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Region	County	District code	District name	Births	Thal trait			Thal disease			AS			Hb C	SCD		
					Mid	Lower	Upper	Mid	Lower	Upper	Mid	Lower	Upper	Mid	Mid	Lower	Upper
Northern and Yorkshire	Cleveland	H14UB	Hartlepool	1260	1.70	1.58	1.79	0.010	0.006	0.014	0.32	0.19	0.42	0.06	0.021	0.012	0.033
Northern and Yorkshire	Cleveland	H14UC	Langbaurgh-on-Tees	1850	2.68	2.51	2.81	0.020	0.013	0.027	0.37	0.27	0.45	0.09	0.022	0.016	0.030
Northern and Yorkshire	Cleveland	H14UD	Middlesbrough	2100	7.66	6.39	8.85	0.119	0.073	0.175	2.85	2.22	3.36	0.76	0.168	0.126	0.224
Northern and Yorkshire	Cleveland	H14UE	Stockton-on-Tees	2260	4.83	4.27	5.29	0.058	0.037	0.081	0.98	0.65	1.26	0.21	0.063	0.040	0.093
South West	Cornwall	H15UB	Caradon	830	1.62	1.57	1.65	0.023	0.017	0.029	0.41	0.40	0.42	0.13	0.021	0.021	0.022
South West	Cornwall	H15UC	Carrick	830	1.04	0.97	1.09	0.003	0.002	0.005	0.30	0.30	0.31	0.11	0.015	0.015	0.016
South West	Cornwall	H15UD	Kerrier	1000	1.29	1.23	1.32	0.007	0.005	0.009	0.53	0.34	0.67	0.11	0.035	0.022	0.053
South West	Cornwall	H15UE	North Cornwall	840	1.31	1.26	1.33	0.013	0.009	0.016	0.37	0.33	0.41	0.11	0.021	0.018	0.025
South West	Cornwall	H15UF	Penwith	600	0.73	0.68	0.77	0.002	0.001	0.003	0.31	0.31	0.31	0.11	0.016	0.016	0.016
South West	Cornwall	H15UG	Restormel	990	1.56	1.49	1.61	0.015	0.011	0.020	0.33	0.32	0.34	0.11	0.017	0.017	0.018
South West	Cornwall	H15UH	Isles of Scilly	30	0.03	0.03	0.03	0.000	0.000	0.000	0.00	0.00	0.00	0.00	0.000	0.000	0.000
Northern and Yorkshire	Cumbria	H16UB	Allerdale	1120	1.59	1.38	1.69	0.007	0.004	0.010	0.34	0.31	0.36	0.11	0.018	0.017	0.020
Northern and Yorkshire	Cumbria	H16UC	Barrow-in-Furness	990	1.54	1.26	1.68	0.008	0.004	0.011	0.16	0.15	0.16	0.05	0.008	0.008	0.008
Northern and Yorkshire	Cumbria	H16UD	Carlisle	1180	1.99	1.82	2.09	0.020	0.014	0.026	0.46	0.43	0.49	0.15	0.025	0.023	0.027
Northern and Yorkshire	Cumbria	H16UE	Copeland	860	1.16	0.98	1.26	0.003	0.001	0.005	0.18	0.16	0.19	0.05	0.010	0.008	0.012
Northern and Yorkshire	Cumbria	H16UF	Eden	510	0.69	0.61	0.73	0.004	0.002	0.005	0.03	0.02	0.03	0.01	0.001	0.001	0.001
Northern and Yorkshire	Cumbria	H16UG	South Lakeland	1020	1.74	1.55	1.84	0.016	0.010	0.021	0.33	0.26	0.39	0.08	0.020	0.015	0.027
Trent	Derbyshire	H17UB	Amber Valley	1350	2.67	2.54	2.76	0.035	0.025	0.045	0.62	0.58	0.66	0.20	0.032	0.030	0.033
Trent	Derbyshire	H17UC	Bolsover	950	1.52	1.46	1.57	0.015	0.011	0.019	0.20	0.18	0.22	0.06	0.010	0.010	0.011
Trent	Derbyshire	H17UD	Chesterfield	1260	1.86	1.70	1.98	0.011	0.007	0.015	1.03	0.90	1.13	0.31	0.057	0.049	0.068
Trent	Derbyshire	H17UE	Derby	3150	16.31	13.09	19.31	0.217	0.130	0.325	14.11	12.88	15.23	4.55	0.720	0.670	0.785
Trent	Derbyshire	H17UF	Derbyshire Dales	680	1.06	0.98	1.10	0.009	0.006	0.012	0.17	0.15	0.19	0.05	0.010	0.008	0.012
Trent	Derbyshire	H17UG	Erewash	1370	2.56	2.31	2.75	0.022	0.015	0.030	1.36	1.29	1.43	0.46	0.068	0.066	0.070
Trent	Derbyshire	H17UH	High Peak	1090	1.73	1.55	1.82	0.014	0.009	0.018	0.41	0.36	0.45	0.12	0.023	0.020	0.027
Trent	Derbyshire	H17UJ	North East Derbyshire	1100	1.63	1.51	1.70	0.012	0.008	0.016	0.19	0.18	0.21	0.06	0.010	0.009	0.010
Trent	Derbyshire	H17UK	South Derbyshire	910	1.91	1.67	2.12	0.016	0.010	0.023	0.87	0.57	1.13	0.19	0.052	0.034	0.077
South West	Devon	H18UB	East Devon	1070	1.71	1.60	1.76	0.017	0.012	0.022	0.13	0.12	0.14	0.04	0.007	0.006	0.007
South West	Devon	H18UC	Exeter	1190	2.15	1.99	2.27	0.023	0.016	0.030	0.69	0.44	0.89	0.14	0.044	0.028	0.067
South West	Devon	H18UD	Mid Devon	790	1.12	1.07	1.15	0.009	0.006	0.011	0.28	0.24	0.32	0.08	0.016	0.013	0.021
South West	Devon	H18UE	North Devon	1010	1.55	1.40	1.64	0.011	0.007	0.015	0.25	0.16	0.33	0.05	0.016	0.010	0.025
South West	Devon	H18UF	Plymouth	3190	5.82	5.51	6.01	0.070	0.051	0.090	2.23	1.72	2.64	0.56	0.135	0.099	0.184
South West	Devon	H18UG	South Hams	810	1.06	0.99	1.10	0.005	0.004	0.007	0.13	0.10	0.15	0.03	0.007	0.006	0.009
South West	Devon	H18UH	Teignbridge	1200	1.85	1.77	1.90	0.018	0.013	0.023	0.30	0.25	0.34	0.08	0.017	0.014	0.022
South West	Devon	H18UJ	Torbay	1270	2.49	2.35	2.57	0.033	0.024	0.043	0.66	0.54	0.76	0.18	0.039	0.030	0.050
South West	Devon	H18UK	Torridge	590	0.78	0.74	0.80	0.005	0.003	0.006	0.09	0.09	0.10	0.03	0.005	0.005	0.005

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Region	County	District code	District name	Births	Thal trait			Thal disease			AS			Hb C	SCD		
					Mid	Lower	Upper	Mid	Lower	Upper	Mid	Lower	Upper	Mid	Mid	Lower	Upper
South West	Devon	H18UL	West Devon	480	0.72	0.69	0.75	0.006	0.005	0.008	0.09	0.09	0.10	0.03	0.005	0.005	0.005
South West	Dorset	H19UB	Bournemouth	1690	3.80	3.44	4.02	0.053	0.037	0.069	1.72	1.17	2.17	0.37	0.112	0.072	0.165
South West	Dorset	H19UC	Christchurch	410	0.87	0.82	0.90	0.013	0.009	0.016	0.23	0.20	0.26	0.07	0.013	0.011	0.016
South West	Dorset	H19UD	East Dorset	670	1.03	0.93	1.10	0.008	0.005	0.011	0.14	0.12	0.16	0.04	0.008	0.006	0.010
South West	Dorset	H19UE	North Dorset	560	0.79	0.73	0.83	0.006	0.004	0.008	0.02	0.02	0.03	0.01	0.001	0.001	0.001
South West	Dorset	H19UF	Poole	1680	2.66	2.45	2.79	0.023	0.016	0.031	0.64	0.51	0.74	0.17	0.037	0.029	0.048
South West	Dorset	H19UG	Purbeck	510	0.85	0.82	0.86	0.009	0.007	0.012	0.22	0.17	0.26	0.06	0.013	0.010	0.018
South West	Dorset	H19UH	West Dorset	910	1.52	1.42	1.57	0.016	0.011	0.021	0.21	0.19	0.24	0.06	0.012	0.010	0.015
South West	Dorset	H19UJ	Weymouth and Portland	730	1.44	1.34	1.49	0.019	0.014	0.025	0.36	0.26	0.45	0.08	0.023	0.015	0.033
Northern and Yorkshire	Durham	H20UB	Chester-le-Street	680	1.07	1.02	1.11	0.010	0.007	0.013	0.53	0.42	0.62	0.14	0.032	0.024	0.043
Northern and Yorkshire	Durham	H20UC	Darlington	1270	2.96	2.65	3.19	0.041	0.028	0.054	0.85	0.80	0.90	0.27	0.043	0.041	0.044
Northern and Yorkshire	Durham	H20UD	Derwentside	990	1.39	1.35	1.42	0.011	0.008	0.014	0.26	0.19	0.31	0.06	0.016	0.011	0.022
Northern and Yorkshire	Durham	H20UE	Durham	850	1.42	1.27	1.50	0.013	0.009	0.017	0.29	0.19	0.38	0.06	0.019	0.012	0.029
Northern and Yorkshire	Durham	H20UF	Easington	1250	1.48	1.37	1.55	0.003	0.001	0.004	0.32	0.26	0.37	0.09	0.018	0.014	0.024
Northern and Yorkshire	Durham	H20UG	Sedgefield	1100	1.61	1.56	1.64	0.014	0.010	0.018	0.44	0.28	0.57	0.09	0.029	0.018	0.045
Northern and Yorkshire	Durham	H20UH	Teesdale	240	0.26	0.25	0.26	0.000	0.000	0.000	0.00	0.00	0.00	0.00	0.000	0.000	0.000
Northern and Yorkshire	Durham	H20UJ	Wear Valley	740	0.87	0.84	0.88	0.003	0.002	0.004	0.15	0.13	0.17	0.04	0.008	0.007	0.010
South West	East Sussex	H21UB	Brighton	1830	3.76	3.24	4.12	0.037	0.023	0.051	3.02	2.16	3.72	0.72	0.189	0.129	0.271
South West	East Sussex	H21UC	Eastbourne	950	2.03	1.83	2.16	0.026	0.018	0.034	0.88	0.68	1.05	0.23	0.053	0.039	0.071
South West	East Sussex	H21UD	Hastings	1140	2.78	2.70	2.84	0.047	0.035	0.059	1.41	1.18	1.59	0.40	0.081	0.065	0.101
South West	East Sussex	H21UE	Hove	1070	2.67	2.27	2.94	0.035	0.023	0.047	1.23	0.96	1.45	0.32	0.073	0.054	0.097
South West	East Sussex	H21UF	Lewes	990	1.74	1.61	1.82	0.018	0.012	0.023	0.86	0.73	0.98	0.25	0.049	0.040	0.062
South West	East Sussex	H21UG	Rother	800	1.30	1.14	1.40	0.010	0.006	0.013	0.36	0.29	0.42	0.10	0.021	0.016	0.027
South West	East Sussex	H21UH	Wealden	1470	2.16	1.95	2.27	0.014	0.009	0.019	0.88	0.63	1.07	0.21	0.056	0.038	0.080
North Thames	Essex	H22UB	Basildon	2310	4.10	3.67	4.42	0.033	0.021	0.045	2.74	2.34	3.06	0.81	0.152	0.127	0.186
North Thames	Essex	H22UC	Braintree	1520	2.39	2.22	2.50	0.019	0.013	0.025	0.93	0.74	1.09	0.25	0.055	0.042	0.073
North Thames	Essex	H22UD	Brentwood	820	1.83	1.64	1.96	0.023	0.016	0.030	0.98	0.78	1.14	0.26	0.057	0.044	0.074
North Thames	Essex	H22UE	Castle Point	990	1.71	1.60	1.80	0.018	0.012	0.023	0.46	0.34	0.57	0.11	0.028	0.020	0.038
North Thames	Essex	H22UF	Chelmsford	2030	3.67	3.28	3.96	0.033	0.022	0.045	1.63	1.33	1.89	0.45	0.093	0.074	0.118
North Thames	Essex	H22UG	Colchester	1880	3.97	3.56	4.24	0.047	0.032	0.062	2.59	1.86	3.19	0.61	0.162	0.111	0.232
North Thames	Essex	H22UH	Epping Forest	1450	5.05	4.66	5.34	0.092	0.066	0.119	1.56	1.17	1.90	0.37	0.090	0.067	0.120
North Thames	Essex	H22UJ	Harlow	1050	2.68	2.22	3.00	0.031	0.019	0.043	1.64	1.38	1.85	0.47	0.092	0.076	0.115
North Thames	Essex	H22UK	Maldon	610	0.82	0.74	0.88	0.003	0.002	0.004	0.44	0.41	0.46	0.15	0.023	0.022	0.025
North Thames	Essex	H22UL	Rochford	880	1.41	1.30	1.49	0.011	0.008	0.015	0.38	0.30	0.46	0.10	0.022	0.017	0.028
North Thames	Essex	H22UM	Southend-on-Sea	2260	4.72	4.12	5.19	0.052	0.033	0.072	1.69	1.35	1.98	0.46	0.097	0.075	0.127
North Thames	Essex	H22UN	Tendring	1350	2.24	2.12	2.33	0.023	0.016	0.030	0.35	0.32	0.37	0.11	0.018	0.017	0.019
North Thames	Essex	H22UP	Thurrock	2030	4.41	3.89	4.80	0.048	0.032	0.064	2.01	1.34	2.58	0.43	0.125	0.081	0.184
North Thames	Essex	H22UQ	Uttlesford	840	1.41	1.28	1.50	0.013	0.009	0.017	0.32	0.28	0.35	0.10	0.017	0.015	0.020

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continued

Region	County	District code	District name	Births	Thal trait			Thal disease			AS			Hb C	SCD		
					Mid	Lower	Upper	Mid	Lower	Upper	Mid	Lower	Upper	Mid	Mid	Lower	Upper
South West	Gloucestershire	H23UB	Cheltenham	1270	3.73	3.40	3.97	0.062	0.044	0.080	1.14	0.93	1.32	0.31	0.063	0.051	0.078
South West	Gloucestershire	H23UC	Cotswold	910	1.26	1.13	1.34	0.005	0.003	0.007	1.02	0.80	1.20	0.27	0.062	0.046	0.083
South West	Gloucestershire	H23UD	Forest of Dean	910	1.16	1.09	1.19	0.005	0.003	0.007	0.26	0.22	0.30	0.08	0.015	0.012	0.020
South West	Gloucestershire	H23UE	Gloucester	1610	4.11	3.50	4.63	0.030	0.018	0.044	7.42	6.98	7.80	2.47	0.385	0.363	0.414
South West	Gloucestershire	H23UF	Stroud	1250	1.69	1.60	1.74	0.010	0.007	0.013	0.51	0.50	0.52	0.18	0.026	0.026	0.026
South West	Gloucestershire	H23UG	Tewkesbury	870	1.73	1.61	1.80	0.023	0.016	0.029	0.37	0.29	0.44	0.09	0.022	0.017	0.029
South West	Hampshire	H24UB	Basingstoke and Deane	2100	4.48	4.10	4.75	0.052	0.036	0.068	3.98	3.52	4.36	1.22	0.220	0.189	0.261
South West	Hampshire	H24UC	East Hampshire	1290	2.14	1.97	2.24	0.021	0.014	0.027	0.43	0.32	0.52	0.10	0.026	0.019	0.037
South West	Hampshire	H24UD	Eastleigh	1410	3.16	2.83	3.40	0.040	0.028	0.053	1.03	0.87	1.17	0.29	0.056	0.047	0.068
South West	Hampshire	H24UE	Fareham	1090	2.32	2.10	2.44	0.030	0.021	0.039	0.54	0.39	0.67	0.12	0.033	0.023	0.047
South West	Hampshire	H24UF	Gosport	1110	1.95	1.79	2.05	0.020	0.014	0.026	0.63	0.49	0.74	0.16	0.037	0.028	0.050
South West	Hampshire	H24UG	Hart	990	2.17	1.99	2.27	0.030	0.022	0.039	0.50	0.39	0.58	0.13	0.029	0.022	0.038
South West	Hampshire	H24UH	Havant	1370	3.10	2.92	3.21	0.048	0.035	0.061	1.38	0.91	1.76	0.28	0.091	0.057	0.137
South West	Hampshire	H24UJ	New Forest	1820	2.91	2.70	3.03	0.027	0.019	0.035	0.62	0.49	0.72	0.16	0.036	0.028	0.047
South West	Hampshire	H24UK	Portsmouth	2530	5.26	4.49	5.89	0.057	0.036	0.081	3.04	2.23	3.70	0.75	0.185	0.130	0.260
South West	Hampshire	H24UL	Rushmoor	1360	3.04	2.82	3.21	0.042	0.029	0.055	1.77	1.64	1.89	0.57	0.095	0.086	0.107
South West	Hampshire	H24UM	Southampton	2770	9.41	7.76	10.81	0.117	0.074	0.167	5.25	4.37	6.03	1.51	0.278	0.235	0.335
South West	Hampshire	H24UN	Test Valley	1240	2.38	2.20	2.50	0.027	0.019	0.036	0.64	0.56	0.71	0.19	0.034	0.030	0.039
South West	Hampshire	H24UP	Winchester	1120	1.74	1.60	1.82	0.015	0.010	0.019	0.31	0.23	0.37	0.08	0.019	0.014	0.025
West Midlands	Hereford & Worcester	H25UB	Bromsgrove	1050	1.93	1.77	2.04	0.018	0.013	0.024	1.21	1.04	1.36	0.36	0.068	0.057	0.082
West Midlands	Hereford & Worcester	H25UC	Hereford	640	1.04	0.94	1.11	0.008	0.005	0.011	0.40	0.32	0.48	0.11	0.024	0.018	0.031
West Midlands	Hereford & Worcester	H25UD	Leominster	450	0.52	0.47	0.55	0.001	0.000	0.001	0.02	0.02	0.02	0.01	0.001	0.001	0.001
West Midlands	Hereford & Worcester	H25UE	Malvern Hills	840	1.53	1.47	1.57	0.019	0.014	0.025	0.22	0.17	0.27	0.05	0.013	0.010	0.018
West Midlands	Hereford & Worcester	H25UF	Redditch	1130	3.45	3.02	3.84	0.051	0.033	0.072	2.64	2.45	2.79	0.86	0.141	0.129	0.157
West Midlands	Hereford & Worcester	H25UG	South Herefordshire	600	1.18	1.15	1.19	0.018	0.013	0.022	0.07	0.06	0.08	0.01	0.004	0.003	0.004
West Midlands	Hereford & Worcester	H25UH	Worcester	1220	3.32	2.88	3.69	0.051	0.033	0.071	0.76	0.70	0.82	0.24	0.041	0.037	0.046
West Midlands	Hereford & Worcester	H25UJ	Wychavon	1190	1.85	1.74	1.92	0.017	0.012	0.022	0.22	0.21	0.24	0.07	0.011	0.011	0.012
West Midlands	Hereford & Worcester	H25UK	Wyre Forest	1160	1.76	1.55	1.93	0.012	0.007	0.017	0.51	0.45	0.55	0.16	0.027	0.024	0.032
North Thames	Hertfordshire	H26UB	Broxbourne	1100	4.32	4.19	4.42	0.096	0.071	0.121	1.32	1.08	1.51	0.34	0.076	0.060	0.096
North Thames	Hertfordshire	H26UC	Dacorum	1830	4.18	3.60	4.65	0.046	0.029	0.066	1.49	1.28	1.67	0.44	0.079	0.069	0.094
North Thames	Hertfordshire	H26UD	East Hertfordshire	1610	2.82	2.55	3.00	0.028	0.019	0.037	0.73	0.60	0.85	0.20	0.042	0.033	0.054
North Thames	Hertfordshire	H26UE	Hertsmere	1210	5.59	5.07	5.99	0.110	0.079	0.143	1.80	1.23	2.29	0.38	0.107	0.073	0.153
North Thames	Hertfordshire	H26UF	North Hertfordshire	1570	4.94	4.06	5.72	0.049	0.030	0.072	3.84	3.38	4.26	1.19	0.195	0.177	0.218
North Thames	Hertfordshire	H26UG	St Albans	1730	6.52	5.37	7.46	0.109	0.071	0.151	3.94	3.35	4.43	1.15	0.221	0.182	0.272
North Thames	Hertfordshire	H26UH	Stevenage	1230	2.92	2.56	3.20	0.033	0.022	0.045	3.05	2.70	3.34	0.94	0.167	0.145	0.198
North Thames	Hertfordshire	H26UJ	Three Rivers	950	3.26	2.81	3.64	0.045	0.030	0.062	1.40	1.03	1.72	0.34	0.077	0.058	0.103
North Thames	Hertfordshire	H26UK	Watford	1180	7.03	5.78	8.20	0.123	0.077	0.179	4.05	3.63	4.41	1.27	0.216	0.192	0.249
North Thames	Hertfordshire	H26UL	Welwyn Hatfield	1230	3.82	3.39	4.14	0.058	0.041	0.077	2.08	1.65	2.45	0.55	0.120	0.092	0.157

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Region	County	District code	District name	Births	Thal trait			Thal disease			AS			Hb C	SCD		
					Mid	Lower	Upper	Mid	Lower	Upper	Mid	Lower	Upper	Mid	Mid	Lower	Upper
Northern and Yorkshire	Humberside	H27UB	Boothferry	780	0.99	0.96	1.01	0.005	0.004	0.006	0.25	0.24	0.26	0.09	0.013	0.013	0.013
Northern and Yorkshire	Humberside	H27UC	Cleethorpes	830	1.25	1.17	1.30	0.010	0.007	0.013	0.20	0.15	0.24	0.05	0.012	0.008	0.016
Northern and Yorkshire	Humberside	H27UD	East Yorkshire	940	1.52	1.42	1.58	0.015	0.011	0.020	0.27	0.20	0.33	0.07	0.017	0.012	0.023
Northern and Yorkshire	Humberside	H27UE	East Yorks. Borough of Beverley	1160	2.06	1.89	2.17	0.021	0.015	0.028	0.52	0.40	0.62	0.13	0.031	0.023	0.041
Northern and Yorkshire	Humberside	H27UF	Glanford	830	1.47	1.37	1.53	0.016	0.011	0.021	0.22	0.16	0.26	0.05	0.013	0.009	0.017
Northern and Yorkshire	Humberside	H27UG	Great Grimsby	1290	1.87	1.74	1.95	0.013	0.009	0.017	0.92	0.58	1.19	0.19	0.061	0.037	0.094
Northern and Yorkshire	Humberside	H27UH	Holderness	490	0.67	0.62	0.69	0.004	0.003	0.005	0.19	0.14	0.23	0.05	0.012	0.008	0.017
Northern and Yorkshire	Humberside	H27UJ	Kingston-upon-Hull	3780	6.27	5.74	6.64	0.058	0.039	0.078	2.72	2.08	3.25	0.69	0.167	0.120	0.230
Northern and Yorkshire	Humberside	H27UK	Scunthorpe	860	2.86	2.46	3.24	0.049	0.032	0.067	0.97	0.73	1.18	0.24	0.057	0.042	0.077
South West	Isle of Wight	H28UB	Medina	860	1.33	1.25	1.38	0.011	0.008	0.015	0.54	0.43	0.64	0.14	0.032	0.024	0.043
South West	Isle of Wight	H28UC	South Wight	490	0.80	0.76	0.83	0.008	0.006	0.011	0.18	0.17	0.18	0.06	0.009	0.009	0.009
South Thames	Kent	H29UB	Ashford	1260	1.78	1.58	1.91	0.007	0.004	0.010	1.07	0.84	1.25	0.29	0.063	0.048	0.084
South Thames	Kent	H29UC	Canterbury	1400	3.01	2.79	3.15	0.041	0.029	0.054	1.36	1.00	1.66	0.33	0.084	0.059	0.118
South Thames	Kent	H29UD	Dartford	1220	2.80	2.38	3.14	0.024	0.015	0.035	1.55	1.09	1.95	0.37	0.091	0.064	0.127
South Thames	Kent	H29UE	Dover	1280	2.01	1.83	2.13	0.015	0.010	0.020	0.66	0.52	0.78	0.17	0.039	0.029	0.051
South Thames	Kent	H29UF	Gillingham	1320	3.85	3.44	4.21	0.054	0.037	0.072	2.04	1.74	2.30	0.60	0.108	0.093	0.129
South Thames	Kent	H29UG	Gravesham	1290	5.96	4.73	7.14	0.058	0.034	0.087	1.87	1.20	2.52	0.41	0.082	0.064	0.105
South Thames	Kent	H29UH	Maidstone	1780	3.05	2.79	3.24	0.028	0.019	0.037	1.25	0.96	1.49	0.32	0.074	0.055	0.100
South Thames	Kent	H29UJ	Rochester upon Medway	2230	6.16	5.19	7.02	0.065	0.041	0.093	3.14	2.42	3.78	0.83	0.170	0.133	0.220
South Thames	Kent	H29UK	Sevenoaks	1330	2.19	2.01	2.31	0.019	0.013	0.026	0.65	0.52	0.76	0.18	0.037	0.029	0.048
South Thames	Kent	H29UL	Shepway	1120	2.45	2.29	2.56	0.035	0.025	0.045	0.54	0.44	0.62	0.14	0.030	0.024	0.038
South Thames	Kent	H29UM	Swale	1570	2.42	2.28	2.52	0.021	0.015	0.028	0.92	0.61	1.17	0.19	0.060	0.038	0.090
South Thames	Kent	H29UN	Thanet	1480	3.20	3.05	3.30	0.046	0.034	0.059	1.56	1.21	1.84	0.40	0.093	0.069	0.125
South Thames	Kent	H29UP	Tonbridge and Malling	1380	2.47	2.29	2.60	0.026	0.018	0.034	1.42	0.93	1.83	0.30	0.093	0.058	0.141
South Thames	Kent	H29UQ	Tunbridge Wells	1330	2.27	2.11	2.38	0.024	0.017	0.031	0.40	0.28	0.50	0.09	0.024	0.017	0.034
North West	Lancashire	H30UB	Blackburn	2300	23.34	17.82	28.71	0.348	0.203	0.531	3.83	1.96	5.60	0.67	0.169	0.111	0.244
North West	Lancashire	H30UC	Blackpool	1830	3.38	2.70	3.77	0.024	0.013	0.035	0.86	0.70	1.00	0.24	0.051	0.039	0.066
North West	Lancashire	H30UD	Burnley	1250	6.46	5.17	7.70	0.122	0.075	0.179	0.66	0.45	0.84	0.15	0.041	0.027	0.061
North West	Lancashire	H30UE	Chorley	1150	1.90	1.67	2.06	0.013	0.008	0.019	0.83	0.74	0.91	0.26	0.045	0.040	0.053
North West	Lancashire	H30UF	Fylde	680	1.41	1.15	1.55	0.014	0.008	0.019	0.20	0.17	0.22	0.06	0.011	0.009	0.013
North West	Lancashire	H30UG	Hyndburn	1200	7.21	5.78	8.56	0.135	0.082	0.201	0.58	0.41	0.72	0.13	0.036	0.024	0.051
North West	Lancashire	H30UH	Lancaster	1440	2.64	2.21	2.92	0.019	0.011	0.027	0.65	0.38	0.87	0.12	0.041	0.024	0.063
North West	Lancashire	H30UJ	Pendle	1210	12.83	10.34	15.25	0.273	0.169	0.400	0.61	0.55	0.66	0.18	0.033	0.029	0.039
North West	Lancashire	H30UK	Preston	1870	10.74	8.28	13.04	0.116	0.066	0.178	5.10	3.95	6.19	1.39	0.244	0.209	0.289
North West	Lancashire	H30UL	Ribble Valley	500	1.02	0.87	1.12	0.011	0.007	0.015	0.07	0.06	0.09	0.02	0.004	0.003	0.004
North West	Lancashire	H30UM	Rossendale	900	2.62	2.13	3.04	0.040	0.024	0.058	0.57	0.48	0.63	0.17	0.032	0.027	0.040
North West	Lancashire	H30UN	South Ribble	1190	1.77	1.52	1.93	0.008	0.004	0.012	0.52	0.48	0.55	0.17	0.027	0.025	0.029
North West	Lancashire	H30UP	West Lancashire	1320	2.23	1.95	2.37	0.019	0.012	0.025	0.71	0.57	0.82	0.19	0.042	0.032	0.056
North West	Lancashire	H30UQ	Wyre	1010	1.75	1.41	1.92	0.011	0.006	0.016	0.32	0.25	0.39	0.08	0.020	0.014	0.027

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continued

Region	County	District code	District name	Births	Thal trait			Thal disease			AS			Hb C	SCD		
					Mid	Lower	Upper	Mid	Lower	Upper	Mid	Lower	Upper	Mid	Mid	Lower	Upper
Trent	Leicestershire	H31UB	Blaby	1030	2.80	2.34	3.19	0.024	0.015	0.035	1.40	1.11	1.67	0.39	0.071	0.060	0.087
Trent	Leicestershire	H31UC	Charnwood	1820	7.95	6.29	9.42	0.098	0.060	0.141	2.37	1.49	3.18	0.50	0.120	0.085	0.167
Trent	Leicestershire	H31UD	Harborough	840	1.88	1.76	1.96	0.026	0.019	0.034	0.48	0.38	0.57	0.12	0.027	0.021	0.034
Trent	Leicestershire	H31UE	Hinckley and Bosworth	1120	1.96	1.74	2.14	0.014	0.009	0.020	0.56	0.42	0.68	0.14	0.030	0.023	0.039
Trent	Leicestershire	H31UF	Leicester	4540	55.98	41.30	70.25	0.551	0.299	0.875	26.12	18.17	33.75	6.37	1.184	0.965	1.462
Trent	Leicestershire	H31UG	Melton	570	1.08	0.96	1.16	0.011	0.007	0.014	0.20	0.18	0.22	0.06	0.010	0.009	0.010
Trent	Leicestershire	H31UH	North West Leicestershire	920	1.47	1.36	1.55	0.012	0.008	0.015	0.50	0.42	0.57	0.14	0.028	0.023	0.034
Trent	Leicestershire	H31UJ	Oadby and Wigston	640	3.70	2.90	4.45	0.042	0.025	0.062	0.96	0.55	1.35	0.19	0.042	0.030	0.056
Trent	Leicestershire	H31UK	Rutland	320	0.56	0.52	0.58	0.006	0.004	0.008	0.30	0.21	0.37	0.07	0.019	0.013	0.028
Trent	Lincolnshire	H32UB	Boston	620	1.03	0.95	1.08	0.009	0.006	0.011	0.80	0.55	1.00	0.18	0.052	0.034	0.076
Trent	Lincolnshire	H32UC	East Lindsey	1280	2.39	2.25	2.47	0.029	0.021	0.037	1.00	0.86	1.12	0.29	0.057	0.047	0.070
Trent	Lincolnshire	H32UD	Lincoln	1280	3.26	3.07	3.38	0.055	0.040	0.070	1.00	0.90	1.08	0.30	0.054	0.048	0.063
Trent	Lincolnshire	H32UE	North Kesteven	890	1.76	1.62	1.85	0.021	0.015	0.028	0.40	0.31	0.47	0.10	0.023	0.017	0.030
Trent	Lincolnshire	H32UF	South Holland	710	0.89	0.84	0.93	0.003	0.002	0.005	0.26	0.26	0.26	0.09	0.013	0.013	0.013
Trent	Lincolnshire	H32UG	South Kesteven	1430	2.94	2.73	3.07	0.040	0.028	0.051	0.58	0.42	0.72	0.13	0.035	0.025	0.050
Trent	Lincolnshire	H32UH	West Lindsey	820	1.68	1.63	1.70	0.025	0.019	0.032	0.22	0.21	0.24	0.06	0.012	0.011	0.013
Anglia and Oxford	Norfolk	H33UB	Breckland	1370	2.13	2.03	2.19	0.018	0.013	0.023	1.50	1.30	1.67	0.45	0.085	0.071	0.105
Anglia and Oxford	Norfolk	H33UC	Broadland	1170	1.94	1.75	2.06	0.016	0.011	0.021	0.23	0.16	0.29	0.05	0.013	0.010	0.018
Anglia and Oxford	Norfolk	H33UD	Great Yarmouth	1100	2.15	1.99	2.25	0.026	0.019	0.034	0.64	0.47	0.78	0.15	0.039	0.027	0.054
Anglia and Oxford	Norfolk	H33UE	King's Lynn and West Norfolk	1510	2.84	2.67	2.95	0.034	0.024	0.044	0.74	0.68	0.79	0.23	0.038	0.036	0.042
Anglia and Oxford	Norfolk	H33UF	North Norfolk	890	1.02	0.94	1.06	0.001	0.000	0.002	0.19	0.15	0.22	0.05	0.011	0.008	0.015
Anglia and Oxford	Norfolk	H33UG	Norwich	1560	2.78	2.53	2.98	0.025	0.017	0.034	1.52	1.25	1.75	0.43	0.087	0.069	0.110
Anglia and Oxford	Norfolk	H33UH	South Norfolk	1170	1.66	1.58	1.71	0.013	0.009	0.017	0.17	0.12	0.22	0.04	0.011	0.007	0.016
Anglia and Oxford	Northamptonshire	H34UB	Corby	740	1.04	0.93	1.10	0.005	0.003	0.007	0.49	0.47	0.52	0.16	0.026	0.024	0.028
Anglia and Oxford	Northamptonshire	H34UC	Daventry	810	1.16	1.05	1.24	0.005	0.003	0.007	0.52	0.46	0.57	0.16	0.028	0.024	0.032
Anglia and Oxford	Northamptonshire	H34UD	East Northamptonshire	880	1.48	1.37	1.55	0.013	0.009	0.018	0.50	0.48	0.52	0.17	0.025	0.024	0.026
Anglia and Oxford	Northamptonshire	H34UE	Kettering	1040	1.92	1.63	2.14	0.011	0.006	0.017	0.71	0.53	0.87	0.18	0.039	0.030	0.050
Anglia and Oxford	Northamptonshire	H34UF	Northampton	2720	8.93	7.53	10.13	0.115	0.074	0.162	11.48	10.48	12.34	3.67	0.612	0.553	0.692
Anglia and Oxford	Northamptonshire	H34UG	South Northamptonshire	830	1.57	1.47	1.63	0.018	0.012	0.023	1.14	0.92	1.32	0.31	0.067	0.052	0.088
Anglia and Oxford	Northamptonshire	H34UH	Wellingborough	920	2.96	2.47	3.42	0.025	0.015	0.037	4.60	4.32	4.86	1.53	0.234	0.223	0.247
Northern and Yorkshire	Northumberland	H35UB	Alnwick	330	0.59	0.55	0.61	0.007	0.005	0.009	0.05	0.05	0.06	0.02	0.003	0.003	0.003
Northern and Yorkshire	Northumberland	H35UC	Berwick-upon-Tweed	250	0.32	0.31	0.32	0.002	0.001	0.002	0.04	0.02	0.05	0.01	0.003	0.001	0.004
Northern and Yorkshire	Northumberland	H35UD	Blyth Valley	1020	1.76	1.65	1.83	0.020	0.014	0.026	0.09	0.06	0.11	0.01	0.006	0.004	0.008
Northern and Yorkshire	Northumberland	H35UE	Castle Morpeth	490	0.73	0.64	0.79	0.004	0.003	0.006	0.05	0.04	0.06	0.02	0.002	0.002	0.003

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continued

Region	County	District code	District name	Births	Thal trait			Thal disease			AS			Hb C	SCD		
					Mid	Lower	Upper	Mid	Lower	Upper	Mid	Lower	Upper	Mid	Mid	Lower	Upper
Northern and Yorkshire	Northumberland	H35UF	Tynedale	600	0.67	0.63	0.69	0.001	0.000	0.001	0.02	0.02	0.02	0.01	0.001	0.001	0.001
Northern and Yorkshire	Northumberland	H35UG	Wansbeck	740	1.12	1.01	1.19	0.007	0.005	0.010	0.08	0.07	0.10	0.02	0.004	0.004	0.004
Northern and Yorkshire	North Yorkshire	H36UB	Craven	550	0.99	0.86	1.10	0.009	0.005	0.014	0.13	0.11	0.15	0.04	0.008	0.006	0.010
Northern and Yorkshire	North Yorkshire	H36UC	Hambleton	890	1.71	1.60	1.78	0.022	0.016	0.029	0.16	0.15	0.16	0.05	0.008	0.008	0.009
Northern and Yorkshire	North Yorkshire	H36UD	Harrogate	1690	3.42	3.08	3.61	0.042	0.029	0.055	0.91	0.76	1.03	0.25	0.053	0.042	0.067
Northern and Yorkshire	North Yorkshire	H36UE	Richmondshire	620	1.35	1.25	1.41	0.019	0.014	0.025	0.29	0.28	0.30	0.09	0.015	0.014	0.016
Northern and Yorkshire	North Yorkshire	H36UF	Ryedale	1070	1.63	1.50	1.71	0.014	0.009	0.018	0.13	0.10	0.16	0.03	0.008	0.006	0.010
Northern and Yorkshire	North Yorkshire	H36UG	Scarborough	1050	1.43	1.30	1.51	0.007	0.004	0.010	0.16	0.15	0.17	0.05	0.008	0.008	0.008
Northern and Yorkshire	North Yorkshire	H36UH	Selby	1100	1.45	1.35	1.50	0.007	0.005	0.010	0.27	0.15	0.36	0.04	0.019	0.010	0.031
Northern and Yorkshire	North Yorkshire	H36UJ	York	1250	2.44	2.20	2.60	0.029	0.020	0.038	0.58	0.48	0.67	0.16	0.033	0.027	0.042
Trent	Nottinghamshire	H37UB	Ashfield	1400	2.22	2.08	2.32	0.018	0.013	0.024	1.28	1.06	1.46	0.36	0.074	0.059	0.094
Trent	Nottinghamshire	H37UC	Bassetlaw	1320	1.75	1.64	1.82	0.009	0.006	0.012	0.63	0.52	0.72	0.18	0.037	0.029	0.047
Trent	Nottinghamshire	H37UD	Broxtowe	1330	3.44	3.07	3.73	0.046	0.032	0.062	1.75	1.47	1.99	0.50	0.097	0.080	0.119
Trent	Nottinghamshire	H37UE	Gedling	1350	2.98	2.74	3.16	0.036	0.025	0.048	2.49	2.24	2.70	0.78	0.136	0.119	0.158
Trent	Nottinghamshire	H37UF	Mansfield	1340	2.17	2.05	2.27	0.018	0.013	0.024	1.31	1.22	1.39	0.43	0.069	0.064	0.076
Trent	Nottinghamshire	H37UG	Newark and Sherwood	1250	2.27	2.16	2.34	0.026	0.019	0.034	0.94	0.86	1.01	0.29	0.051	0.046	0.058
Trent	Nottinghamshire	H37UH	Nottingham	4010	18.32	15.21	21.15	0.238	0.145	0.351	35.33	33.86	36.60	11.99	1.838	1.755	1.949
Trent	Nottinghamshire	H37UJ	Rushcliffe	1100	3.10	2.72	3.40	0.041	0.028	0.056	1.32	1.18	1.45	0.41	0.067	0.062	0.073
Anglia and Oxford	Oxfordshire	H38UB	Cherwell	1830	4.95	4.40	5.42	0.065	0.043	0.090	5.82	5.07	6.44	1.76	0.327	0.275	0.398
Anglia and Oxford	Oxfordshire	H38UC	Oxford	1480	6.62	5.30	7.75	0.095	0.057	0.140	8.56	7.43	9.48	2.59	0.479	0.403	0.584
Anglia and Oxford	Oxfordshire	H38UD	South Oxfordshire	1620	2.50	2.27	2.64	0.018	0.012	0.024	0.72	0.68	0.76	0.24	0.038	0.035	0.040
Anglia and Oxford	Oxfordshire	H38UE	Vale of White Horse	1430	2.64	2.39	2.81	0.028	0.019	0.037	0.85	0.76	0.92	0.26	0.046	0.041	0.053
Anglia and Oxford	Oxfordshire	H38UF	West Oxfordshire	1310	2.24	2.09	2.34	0.023	0.016	0.030	0.84	0.71	0.94	0.24	0.048	0.039	0.060
West Midlands	Shropshire	H39UB	Bridgnorth	530	1.05	0.96	1.10	0.013	0.009	0.017	0.18	0.15	0.20	0.05	0.010	0.008	0.012
West Midlands	Shropshire	H39UC	North Shropshire	620	1.44	1.33	1.51	0.022	0.015	0.028	0.17	0.15	0.19	0.05	0.009	0.008	0.009
West Midlands	Shropshire	H39UD	Oswestry	440	0.64	0.56	0.68	0.004	0.002	0.005	0.15	0.09	0.20	0.03	0.010	0.006	0.017
West Midlands	Shropshire	H39UE	Shrewsbury and Atcham	1160	2.15	1.97	2.26	0.025	0.017	0.032	0.42	0.32	0.50	0.10	0.025	0.018	0.034
West Midlands	Shropshire	H39UF	South Shropshire	380	0.64	0.57	0.69	0.005	0.003	0.007	0.25	0.14	0.34	0.04	0.017	0.010	0.028
West Midlands	Shropshire	H39UG	The Wrekin	2160	6.71	5.81	7.46	0.095	0.063	0.131	3.50	3.14	3.83	1.09	0.183	0.165	0.207
South West	Somerset	H40UB	Mendip	1200	1.99	1.91	2.04	0.022	0.016	0.028	0.55	0.46	0.63	0.15	0.032	0.026	0.041
South West	Somerset	H40UC	Sedgemoor	1160	1.66	1.54	1.72	0.012	0.008	0.016	0.20	0.17	0.22	0.06	0.011	0.009	0.013
South West	Somerset	H40UD	South Somerset	1740	3.05	2.92	3.12	0.036	0.027	0.046	1.10	0.78	1.35	0.25	0.070	0.047	0.101
South West	Somerset	H40UE	Taunton Deane	1100	2.11	1.95	2.21	0.027	0.019	0.035	0.22	0.19	0.25	0.06	0.013	0.011	0.016
South West	Somerset	H40UF	West Somerset	300	0.54	0.50	0.56	0.006	0.004	0.008	0.03	0.03	0.03	0.01	0.002	0.001	0.002
West Midlands	Staffordshire	H41UB	Cannock Chase	1210	2.06	1.93	2.16	0.020	0.014	0.026	0.71	0.61	0.81	0.21	0.039	0.033	0.048
West Midlands	Staffordshire	H41UC	East Staffordshire	1260	4.98	4.20	5.71	0.084	0.053	0.122	2.07	1.93	2.19	0.67	0.111	0.101	0.123
West Midlands	Staffordshire	H41UD	Lichfield	1000	2.25	2.06	2.37	0.031	0.022	0.041	0.43	0.39	0.47	0.13	0.022	0.020	0.023

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continued

Region	County	District code	District name	Births	Thal trait			Thal disease			AS			Hb C	SCD		
					Mid	Lower	Upper	Mid	Lower	Upper	Mid	Lower	Upper	Mid	Mid	Lower	Upper
West Midlands	Staffordshire	H41UE	Newcastle-under-Lyme	1250	2.01	1.81	2.14	0.015	0.010	0.020	0.59	0.53	0.65	0.18	0.031	0.028	0.036
West Midlands	Staffordshire	H41UF	South Staffordshire	1120	2.08	1.92	2.20	0.021	0.015	0.028	0.91	0.71	1.08	0.24	0.053	0.040	0.069
West Midlands	Staffordshire	H41UG	Stafford	1220	2.72	2.49	2.87	0.036	0.026	0.047	1.31	1.17	1.43	0.40	0.071	0.062	0.083
West Midlands	Staffordshire	H41UH	Staffordshire Moorlands	940	1.12	1.07	1.16	0.003	0.002	0.005	0.16	0.13	0.17	0.05	0.009	0.007	0.011
West Midlands	Staffordshire	H41UJ	Stoke-on-Trent	3380	10.96	9.20	12.61	0.163	0.100	0.239	4.09	3.74	4.40	1.31	0.218	0.197	0.246
West Midlands	Staffordshire	H41UK	Tamworth	1050	2.02	1.93	2.09	0.025	0.018	0.032	0.94	0.76	1.08	0.25	0.054	0.042	0.070
Anglia and Oxford	Suffolk	H42UB	Babergh	860	1.37	1.29	1.42	0.013	0.009	0.017	0.46	0.44	0.48	0.15	0.025	0.023	0.027
Anglia and Oxford	Suffolk	H42UC	Forest Heath	860	1.80	1.70	1.86	0.013	0.010	0.017	7.66	6.54	8.56	2.26	0.442	0.360	0.555
Anglia and Oxford	Suffolk	H42UD	Ipswich	1660	3.96	3.55	4.31	0.041	0.027	0.056	9.70	9.45	9.92	3.35	0.504	0.488	0.526
Anglia and Oxford	Suffolk	H42UE	Mid Suffolk	980	1.44	1.37	1.48	0.012	0.008	0.015	0.31	0.24	0.37	0.08	0.019	0.014	0.025
Anglia and Oxford	Suffolk	H42UF	St Edmundsbury	1180	2.40	2.28	2.47	0.034	0.025	0.043	0.75	0.65	0.83	0.21	0.042	0.035	0.052
Anglia and Oxford	Suffolk	H42UG	Suffolk Coastal	1210	2.16	1.96	2.28	0.016	0.011	0.021	4.14	3.51	4.65	1.21	0.240	0.194	0.303
Anglia and Oxford	Suffolk	H42UH	Waveney	1270	1.62	1.50	1.69	0.006	0.004	0.008	0.56	0.46	0.64	0.16	0.033	0.026	0.043
South Thames	Surrey	H43UB	Elmbridge	1500	4.19	3.57	4.61	0.058	0.039	0.078	1.29	0.92	1.60	0.30	0.076	0.054	0.107
South Thames	Surrey	H43UC	Epsom and Ewell	730	3.05	2.53	3.43	0.049	0.033	0.067	0.97	0.70	1.20	0.23	0.056	0.040	0.076
South Thames	Surrey	H43UD	Guildford	1530	2.78	2.44	3.00	0.025	0.016	0.033	0.83	0.69	0.96	0.23	0.046	0.038	0.058
South Thames	Surrey	H43UE	Mole Valley	910	1.46	1.33	1.55	0.012	0.008	0.016	0.25	0.17	0.31	0.05	0.015	0.010	0.022
South Thames	Surrey	H43UF	Reigate and Banstead	1490	3.23	2.82	3.56	0.036	0.023	0.050	1.41	0.99	1.75	0.33	0.086	0.059	0.123
South Thames	Surrey	H43UG	Runnymede	940	2.06	1.79	2.26	0.024	0.016	0.033	0.45	0.41	0.50	0.14	0.022	0.021	0.024
South Thames	Surrey	H43UH	Spelthorne	1170	3.29	2.86	3.66	0.042	0.028	0.057	1.00	0.81	1.18	0.27	0.051	0.043	0.060
South Thames	Surrey	H43UJ	Surrey Heath	1030	2.31	2.00	2.52	0.027	0.018	0.037	0.48	0.37	0.57	0.12	0.026	0.020	0.034
South Thames	Surrey	H43UK	Tandridge	870	1.73	1.53	1.86	0.018	0.012	0.024	0.34	0.26	0.41	0.09	0.018	0.014	0.023
South Thames	Surrey	H43UL	Waverley	1290	2.11	1.84	2.30	0.015	0.009	0.022	0.47	0.33	0.60	0.11	0.029	0.019	0.042
South Thames	Surrey	H43UM	Woking	1230	5.43	4.43	6.31	0.093	0.057	0.135	1.43	1.03	1.77	0.34	0.088	0.061	0.125
West Midlands	Warwickshire	H44UB	North Warwickshire	770	1.10	1.02	1.16	0.006	0.004	0.008	0.48	0.40	0.54	0.14	0.026	0.022	0.033
West Midlands	Warwickshire	H44UC	Nuneaton and Bedworth	1600	4.98	4.19	5.73	0.050	0.031	0.072	1.95	1.30	2.54	0.44	0.103	0.074	0.141
West Midlands	Warwickshire	H44UD	Rugby	1090	3.24	2.66	3.75	0.026	0.015	0.040	2.83	2.53	3.12	0.89	0.143	0.132	0.158
West Midlands	Warwickshire	H44UE	Stratford-on-Avon	1160	1.77	1.63	1.85	0.013	0.009	0.018	0.25	0.21	0.28	0.07	0.014	0.011	0.016
West Midlands	Warwickshire	H44UF	Warwick	1320	5.00	4.08	5.82	0.054	0.033	0.077	1.88	1.40	2.34	0.48	0.091	0.075	0.111
South Thames	West Sussex	H45UB	Adur	700	1.33	1.24	1.41	0.016	0.011	0.021	0.55	0.47	0.62	0.16	0.031	0.026	0.038
South Thames	West Sussex	H45UC	Arun	1330	2.32	2.10	2.46	0.023	0.016	0.031	0.60	0.38	0.77	0.12	0.039	0.024	0.060
South Thames	West Sussex	H45UD	Chichester	1070	1.92	1.78	2.00	0.022	0.016	0.029	0.43	0.32	0.52	0.10	0.027	0.019	0.038
South Thames	West Sussex	H45UE	Crawley	1370	6.80	5.31	8.14	0.087	0.051	0.132	2.21	1.55	2.81	0.53	0.115	0.086	0.153
South Thames	West Sussex	H45UF	Horsham	1370	2.03	1.81	2.17	0.012	0.008	0.017	0.47	0.39	0.53	0.13	0.026	0.021	0.033
South Thames	West Sussex	H45UG	Mid Sussex	1420	2.97	2.68	3.17	0.038	0.027	0.051	0.51	0.43	0.58	0.14	0.028	0.023	0.033
South Thames	West Sussex	H45UH	Worthing	1070	2.10	1.80	2.30	0.022	0.014	0.031	0.55	0.39	0.68	0.13	0.034	0.023	0.049
South West	Wiltshire	H46UB	Kennet	1070	1.61	1.51	1.66	0.013	0.009	0.017	0.54	0.51	0.56	0.18	0.029	0.027	0.032
South West	Wiltshire	H46UC	North Wiltshire	1730	4.10	3.89	4.25	0.065	0.047	0.083	1.78	1.57	1.96	0.53	0.099	0.085	0.118
South West	Wiltshire	H46UD	Salisbury	1280	2.10	1.92	2.21	0.019	0.013	0.025	0.61	0.54	0.68	0.18	0.034	0.029	0.041
South West	Wiltshire	H46UE	Thamesdown	2530	6.60	5.80	7.27	0.081	0.054	0.111	4.50	3.86	5.06	1.33	0.245	0.208	0.294
South West	Wiltshire	H46UF	West Wiltshire	1430	2.63	2.49	2.71	0.031	0.022	0.039	1.82	1.70	1.92	0.59	0.098	0.090	0.109
			England	632,500	2780	2338	3166	43	28	60	3013	2352	3560	799	178	133	238

Screening for haemoglobinopathies

In 1993, the HTA programme decided to commission research to provide an overview of screening for haemoglobinopathies, to review current evidence on the costs and benefits of screening for haemoglobinopathies and to review current NHS practice in order to develop a structured framework for decision making about policy and research.

Two complementary projects were commissioned (project numbers 93/33/01 and 93/33/03).

1. The team at the Institute of Child Health conducted a systematic review of current models of screening practice for haemoglobinopathies in the NHS. Published and unpublished data sources were used to assess the costs and effectiveness of existing and alternative available screening models in: (a) identifying carrier couples; (b) identifying affected newborns; and (c) delivering appropriate education and counselling to affected families.

   The review process led to the development of a decision analytical framework, the identification of its key parameters, and estimation of parameter values and typical ranges in different demographic settings. This model was used: (a) to identify measures to monitor screening programme performance; (b) to develop a strategy for the selection of appropriate screening models at a local level; and (c) to highlight future research priorities.

2. The team based at Brent conducted a systematic review of the evidence relating to screening for the haemoglobinopathies. This was accompanied by primary research addressing uptake, costs, benefits and outcomes.

   As a result of this work, a report was produced that included implications for practice and recommendations for future research and development.

The HTA monographs resulting from these two projects are 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).

Davies SC, Cronin E, Gill M, Greengross P, Hickman M, Normand C. Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research. *Health Technol Assess* 2000;**4**(3).

The Editors

Health Technology Assessment panel membership

This report was identified as a priority by the Population Screening Panel.

Acute Sector Panel

Current members

Chair:
Professor Francis H Creed
University of Manchester

Professor Clifford Bailey
University of Leeds

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We look forward to hearing from you.

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