Ireland, Scotland, or Wales, as well as to the manufacturer. Then, if a pattern of false reactivity emerges, rapid action can be taken.

This incident shook public confidence in HIV testing, which is expected to be virtually 100% sensitive. Vigilance is needed to avoid false negative results.

K Osborne and J McMenamin coordinated the data collection and helped in drafting the report. The retesting exercise relied on the excellent cooperation of many epidemiologists and laboratory scientists throughout England, Wales, Scotland, and Northern Ireland. J Booth, I Chrystie, P Morgan-Capner, E M Ndawula, J Paul, G Underhill, and M Zuckerman kindly provided specimens and results for further analysis. B Davis, D

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Epidemiology and clinical management of meningococcal disease in west Gloucestershire: retrospective, population based study

Philip AL Wylie, David Stevens, William Drake III, James Stuart, Keith Cartwright

See editorial by
Cartwright

Paediatric
Department,
Gloucestershire
Royal Hospital,
Gloucester
GL1 3NN
Philip AL Wylie,
senior registrar
William Drake III,
senior registrar
David Stevens,
consultant
paediatrician

Public Health
Laboratory,
Gloucestershire
Royal Hospital
James Stuart,
regional
epidemiologist
Keith Cartwright,
consultant
microbiologist

Correspondence to:
Dr Cartwright
kcartwright@phls.
co.uk

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Abstract

Objective: To study changes in the epidemiology and management of meningococcal disease in one health district during a period of high local incidence of disease.

Design: Prospective case ascertainment and data collection over 14 years, with retrospective analysis of cases.

Setting: West Gloucestershire (population 320 000).

Subjects: Residents developing meningococcal disease between 1 January 1982 and 31 December 1995.

Results: 252 cases of invasive meningococcal disease were identified, of which 102 (40%) were officially notified and 191 (76%) were confirmed by culture from a deep site. The observed disease incidence of 5.6/100 000/year was about 2.7 times the national incidence (as measured by either statutory notifications or reference laboratory reports). The period 1983-90 was characterised by a prolonged localised outbreak due to serogroup B serotype 15 sulphonamide resistant (B15R) strains. General practitioners gave benzylpenicillin before hospital admission to 18% of patients who presented with meningococcal disease in the first half of the study period and to 40% who presented in the second half. The overall case fatality rate was 6.7% (17/252). Four deaths were directly or indirectly related to lumbar puncture. Of 120 patients whose lumbar puncture yielded meningococci, nine (8%) showed no abnormality on initial examination.

Conclusions: Neither laboratory records nor formal notifications alone can give an accurate estimate of the incidence of meningococcal disease. Because of the dangers of lumbar puncture, the frequency of misleading negative initial findings, and the advent of new diagnostic techniques, the need for samples of cerebrospinal fluid should be critically questioned in each case of suspected meningococcal disease.

Introduction

The two principal sources of data on the incidence of meningococcal disease in England and Wales are notifications of meningococcal meningitis and septicaemia to the Office of National Statistics (formerly the Office of Population Censuses and Surveys) and isolates and samples from clinical cases submitted to the England and Wales Meningococcal Reference Unit at Manchester Public Health Laboratory. After a peak in 1974, the annual incidence of meningococcal disease declined steadily in England and Wales until the mid-1980s, and then rose again.¹ Between 1990 and 1994 the annual incidence of meningococcal disease remained at a higher level of two to three cases per 100 000 population.²

A prolonged outbreak of meningococcal disease caused mainly by B15R (serogroup B serotype 15 sulphonamide resistant) strains began in west Gloucestershire in 1982.³ Gloucester Health Authority and Gloucester Public Health Laboratory coordinated the public health response. An enhanced surveillance scheme was established to ascertain all suspected and confirmed cases. Considerable local efforts were made to inform the public and healthcare providers about meningococcal disease and, from 1986 onwards, to encourage general practitioners to give parenteral benzylpenicillin to all patients suspected of having the disease before hospital admission. This same advice was promulgated to all doctors in the United Kingdom by the chief medical officer in 1988.⁴

We reviewed changes in the epidemiology and clinical management of meningococcal disease in west Gloucestershire during the 14 years to 31 December 1995.

Subjects and methods

Clinical and laboratory definitions

All patients with meningococcal disease were permanent or temporary residents of west Gloucestershire at

the time of onset of their illness; they became ill between 1 January 1982 and 31 December 1995.

A patient was designated as having meningococcal disease if *Neisseria meningitidis* was isolated from blood, cerebrospinal fluid, or other deep tissue; if Gram negative diplococci were seen in cerebrospinal fluid; if clinical signs of meningitis or septicaemia were accompanied by positive serology² or by positive results of a polymerase chain reaction test on cerebrospinal fluid⁵ or blood⁶; or if clinical signs of meningitis or septicaemia were accompanied by a haemorrhagic rash (with or without the presence of meningococci in a throat or pernasal swab).

Specimens of cerebrospinal fluid were designated normal on initial examination if no organisms were seen on a Gram stained film, if the white blood cell count was $<5/\text{mm}^3$, if the glucose concentration was $\geq 3 \text{ mmol/l}$, and if the protein concentration was $<0.4 \text{ g/l}$.

Case finding

Throughout the study period paediatricians and physicians were encouraged to report all suspected cases of meningococcal disease to a member of the Gloucester Public Health Laboratory staff. All suspected cases were investigated and the case notes reviewed by a medical microbiologist. Regular liaison between Gloucester Public Health Laboratory and the Department of Public Health Medicine permitted reconciliation of notified cases with cases ascertained in the laboratory. Cases occurring in residents of west Gloucestershire who were admitted to adjacent hospitals outside the health district were identified by reports to the Gloucestershire consultant in communicable disease control and by periodic inquiry of adjacent microbiologists. Histopathologists notified Gloucester Public Health Laboratory informally of patients suspected of having the disease who died before or immediately after admission to hospital.

Clinical management and microbiological information

Meningococcal isolates from patients were submitted to the Meningococcal Reference Unit for serotyping, serosubtyping, and detailed testing for antibiotic sensitivity. The serotyping reagents available at the unit during the early years of the study period could not differentiate strains of serotype 15. As most serogroup B sulphonamide resistant strains were later shown to belong to serotype 15, the outbreak strain was designated B15R.

At the time of the acute illness, a datasheet was completed by one of us (KC) at Gloucester Public Health Laboratory for each patient suspected or confirmed as having meningococcal disease. Demographic data, presenting symptoms, treatment and outcome were recorded, as well as microbiological information. Hospital records of each patient were examined (by KC) one to three months after discharge from hospital in order to verify information on treatment and outcome. All available hospital records were retrieved and reviewed (by WD and PW) in 1995-6.

Data analysis and statistical tests

We reviewed data on notifications of meningococcal meningitis and meningococcal septicaemia to the Office of Population Censuses and Surveys, and cases confirmed by culture reported by the Meningococcal Reference Unit in England and Wales. The numbers of residents of west Gloucestershire and its three constituent local authorities (Stroud District, Gloucester City, and the Forest of Dean) and of England and Wales were obtained from the 1991 census. All calculations of incidence were based on these figures.

For measuring changes in the epidemiology and management of meningococcal disease, the 14 year study period was arbitrarily divided into two equal portions, 1 January 1982 to 31 December 1988 (the first study period) and 1 January 1989 to 31 December 1995 (the second study period).

Data were analysed using a Microsoft Excel database. The significance of differences was calculated using χ^2 tests with Yates' correction and Mann-Whitney U tests as appropriate.

Results

A total of 252 cases of invasive meningococcal disease (133 in males) were identified in the 14 years to 31 December 1995, a mean annual incidence of 5.6 cases per 100 000 population. Hospital records were available for a second review in 235 cases. In the remaining 17 cases, no hospital notes could be identified, although all cases had a contemporary laboratory datasheet. Five patients (2%) were admitted directly through the accident and emergency department; the remainder were sent to hospital by general practitioners. The clinical case mix represented a continuum of invasive meningococcal disease between meningitis and septicaemia. There were three cases of chronic meningococcal septicaemia, one of septic arthritis, and one of endophthalmitis.

Meningococci were isolated from a deep site, or Gram negative diplococci were seen on microscopy of cerebrospinal fluid, in 209 of the 252 cases (83%). In three cases (1%) the diagnosis was confirmed by methods other than culture, and 40 cases (16%) were diagnosed on clinical grounds. The proportion of cases confirmed by culture from a deep site decreased in the second study period; this was accompanied by a rise in the proportion of clinically diagnosed cases (table 1). Of the 30 clinically diagnosed cases in the second study period, seven yielded meningococci on nasopharyngeal culture.

The number of cases rose sharply in the study population from 1982. The epidemic curve shows a fluctuating incidence of meningococcal disease thereafter, with an outbreak caused by B15R strains between 1983 and 1990 (fig 1). B15R strains were responsible

Table 1 Diagnostic categories of cases of meningococcal disease, west Gloucestershire, 1982-95. Values are numbers (percentages)

Diagnostic category	1982-8	1989-95	P value
Culture from deep site	103 (84)	88 (68)	
Positive cerebrospinal fluid microscopy, serological or polymerase chain reaction diagnosis	10 (8)	11 (9)	
Clinical diagnosis	10 (8)	30 (23)	0.004
Total	123 (100)	129 (100)	

Table 2 Incidence (per 100 000) of meningococcal disease in west Gloucestershire and nationally

	Official notifications					Culture confirmed cases				
	West Gloucestershire		England and Wales		P value	West Gloucestershire		England and Wales		P value
	No	Rate	No	Rate		No	Rate	No	Rate	
1982-8	51	2.3	5 041	1.4	<0.001	103	4.6	6581	1.8	<0.001
1989-95	51	2.3	10 133	2.8	0.13	88	3.9	9376	2.6	<0.001

Fig 1 Annual incidence of invasive meningococcal disease in west Gloucestershire, 1982-95

for 69 (67%) of 103 cases confirmed by culture in the first study period and 32 (36%) of 88 such cases in the second period. In the second study period a more diverse range of meningococcal serogroups and serotypes was encountered.

A total of 102 cases (40%) were formally notified; the proportion of notified cases was similar in the two study periods. During the first study period, the notification rate in west Gloucestershire was higher than the

national notification rate; in the second study period the rates were similar (table 2). In both study periods the incidence of culture confirmed cases in west Gloucestershire was considerably higher than the equivalent figure for England and Wales (table 2). Incidence of both notified and culture confirmed cases rose substantially in England and Wales in the second study period.

The age distribution of cases also changed significantly over time. A smaller proportion of patients were aged under 5 years in the earlier period (34/123 *v* 63/129; $P < 0.005$). In the first period attack rates were highest in the Stroud district (9.5/100 000) compared with Gloucester City (6.9/100 000) and the Forest of Dean (1.5/100 000); in the second period the highest attack rate was in Gloucester City (9.9/100 000), followed by Stroud (6.5/100 000) and the Forest of Dean (2.2/100 000).

Changes in diagnostic accuracy, clinical management, and outcome between the two study periods are summarised in table 3. The principal differences observed were an increase in the proportion of patients given benzylpenicillin before admission, a decrease in the use of lumbar puncture, an increase in the proportion of patients who had a nasopharyngeal swab, and increases in the proportions of patients treated with dexamethasone and receiving rifampicin before discharge from hospital.

Giving benzylpenicillin before hospital admission significantly reduced the proportion of positive cultures obtained from blood (6% (4/72) *v* 54% (88/164) and cerebrospinal fluid (42% (24/57) *v* 70% (96/138)). In contrast, preadmission benzylpenicillin did

Table 3 Diagnostic accuracy, management and outcome in cases of meningococcal disease, west Gloucestershire. Values are numbers (percentages) unless stated otherwise

	1982-8	1989-95	P value
General practitioner's diagnosis:			
Correct	61/106 (58)	55/108 (51)	
Haemorrhagic rash noted, but diagnosis not made	4/106 (4)	9/108 (8)	
Haemorrhagic rash not noted, diagnosis not made	41/106 (39)*	44/108 (41)*	0.31
Benzylpenicillin before hospital admission:			
Given by general practitioner	22/120 (18)	51/127 (40)	
Not given, yet general practitioner's diagnosis correct or haemorrhagic rash noted, or both	64/120 (53)	31/127 (24)	
Not given; diagnosis not made	34/120 (28)†	45/127 (35)†	<0.0001
Correct diagnosis on hospital admission	86/115 (75)‡	95/120 (79)‡	0.52
Hospital management:			
Lumbar puncture performed	104/123 (85)	94/129 (73)	<0.05
Nasopharyngeal swab taken	58/123 (47)	92/129 (71)	<0.002
Dexamethasone given	16/123 (13)	59/129 (46)	<0.0001
Rifampicin given to index case	18/123 (15)	67/129 (52)	<0.0001
Median (range) of inpatient stay (days)	11 (1-48) (n=115)‡	7 (1-39) (n=120)‡	<0.01
Median (range) stay in intensive therapy unit (days)	2 (<1-95) (n=31)	2 (<1-21) (n=18)	>0.05
No of deaths	9/123 (7)	8/129 (6)	>0.05

*General practitioner's referral letter identified.

†Excluding admissions directly through accident and emergency.

‡Some hospital notes not available for review.

not reduce the likelihood of isolating meningococci from nasopharyngeal swabs (40% (21/52) *v* 31% (22/71)).

Of 198 patients who had lumbar punctures, 177 gave one or more abnormal results on initial examination; 111 (63%) of the 177 yielded meningococci. Of 21 with apparently normal results on initial examination, nine (43%) subsequently yielded meningococci on culture.

Of the 17 patients who died, 10 were aged under 15 and six were aged under 5 years. Two patients were dead on admission to hospital and no hospital notes could be identified. Of the remaining 15, 11 died within 24 hours of admission to hospital and a further three within the next 24 hours. We reviewed the notes of all 15 patients who died in hospital. In 12, the presentation was consistent with fulminant septicaemia.

Potentially avoidable factors which may have contributed to a fatal outcome were identified in four cases. In two, effective antibiotic therapy was delayed more than 24 hours because results on initial examination of cerebrospinal fluid were normal. In both these patients the cerebrospinal fluid culture subsequently grew meningococci. In two other patients, brain stem herniation was present at postmortem examination. These latter patients had had lumbar puncture, which was followed rapidly by neurological deterioration.

Discussion

Throughout the study period there was heightened local awareness of meningococcal disease among public and professionals in west Gloucestershire, and intensified surveillance. These factors, together with continuous close liaison between microbiologists and clinicians, contributed to a high rate of culture confirmed disease (76%, 191/252). Less than 50% of cases of meningococcal disease in England and Wales were culture confirmed during the winter months of 1995-6 (M Ramsay, personal communication).

Identification of cases

The proportion of notified cases remained low throughout, but within the range of 30-60% reported in other studies.⁷⁻⁹ On diagnosis of meningococcal disease, the practice in Gloucestershire is for the attending clinician or microbiologist to inform the consultant in communicable disease control by telephone so that chemoprophylaxis for close contacts can be arranged urgently. Completion of a notification form for statistical purposes has a lower priority and may be overlooked. The persistently low proportion of notified cases throughout the study period confirms that notifications and cases identified by the laboratory must be reconciled if national ascertainment of meningococcal disease is to approach completeness.

An upward shift in the age of patients at the start of periods of increased meningococcal disease activity has been noted elsewhere.¹⁰ In our series, teenagers predominated in the early years of the outbreak with a low proportion of cases in young children when compared with the disease pattern nationally.¹¹ The age distribution of cases returned to the national norm during the second study period.

The epidemiological characteristics observed in the first study period (a high attack rate caused principally

by a single meningococcal strain in one locality, accompanied by an upward shift in the age distribution of disease) provide clear evidence of an outbreak during these years. The B15R strain has been associated with periods of prolonged high incidence of disease in Norway, Denmark, and the Faroe Islands.¹²⁻¹⁴ In the second study period the local notification rate was close to the expected national figure and there was no predominant serogroup or serotype and no evidence of a continuing outbreak. The relatively high rate of culture confirmed disease in the second study period may have been due to continuing close liaison between clinicians and laboratory and to additional local diagnostic efforts in response to the outbreak. The reasons for the relatively low incidence in the Forest of Dean throughout the 14 year period remain unexplained.

Early treatment

There is much evidence to suggest that early recognition and prompt treatment can influence outcome in meningococcal disease (D Martin, personal communication),¹⁵⁻¹⁷ although this proposition has been questioned.¹⁸ In this study the proportion of patients given benzylpenicillin before admission increased from 18% in the first period to 40% in the second. The latter figure compares favourably with other studies.^{17 19 20}

Recently Riordan et al found that preadmission benzylpenicillin was given to only 17% (22/126) of children with meningococcal disease admitted to Merseyside hospitals.²⁰ In west Gloucestershire, preadmission benzylpenicillin was given in 35% of cases in which the general practitioner mentioned meningococcal disease as a possible diagnosis in the referral letter in the first period, and to 76% of such cases in the second.

Hospital referral patterns in Merseyside and west Gloucestershire were in striking contrast. In Merseyside, 54% (69/126) of patients were referred by the general practitioner compared with 98% (247/252) in west Gloucestershire. The referring general practitioner noted a non-haemorrhagic rash in 35 (14%) of our patients; 22 of these cases were found to have a haemorrhagic rash on admission to hospital, compatible with a rapidly evolving clinical picture. Case fatality rates did not differ significantly between the two time periods in our study, between patients receiving and those not receiving benzylpenicillin before hospital admission, nor between the different age groups; these findings were not unexpected in view of the small numbers of deaths.

Nasopharyngeal swabs

In the second study period the proportion of patients from whom meningococci could be isolated from blood or cerebrospinal fluid declined due to the increasing use of preadmission benzylpenicillin by general practitioners. Giving parenteral antibiotic therapy before hospital admission reduced the yield of positive cultures from blood and cerebrospinal fluid but not the proportion of culture positive nasopharyngeal swabs.¹⁵ A nasopharyngeal swab for meningococcal culture is a useful, safe and relatively non-invasive investigation in meningococcal disease; it is particularly valuable if antibiotics have been given before

admission to hospital.²¹ When meningococcal disease is confirmed by culture, meningococci isolated from nasopharyngeal swabs are indistinguishable from strains obtained from the patient's blood or cerebrospinal fluid.²² Nasopharyngeal swabs were used significantly more in the second study period than the first.

Lumbar puncture

Our review confirmed the dangers of relying on initial cerebrospinal fluid microscopy and chemistry to exclude meningococcal infection. Nine out of 21 apparently normal cerebrospinal fluid samples from patients with suspected meningitis or septicaemia later yielded *N meningitidis* on culture; this affirms that antibiotics should never be withheld when meningococcal disease is suspected but initial cerebrospinal fluid findings are negative. In this series the isolation of meningococci from cerebrospinal fluid that was normal on initial analysis was not uncommon, occurring in 9 (8%) of the 120 cases whose lumbar puncture yielded meningococci. True negative findings are, of course, expected in meningococcal septicaemia unaccompanied by meningitis.

Traditionally, examination of cerebrospinal fluid has been advocated as a benchmark investigation in suspected meningococcal meningitis; it is still likely to clinch the diagnosis and to yield meningococci for sensitivity testing and further identification.^{15 21} However, lumbar puncture is occasionally responsible for brainstem herniation and death.²³ Two of our patients had rapid neurological deterioration after lumbar puncture and died; in two further cases normal findings on initial examination of cerebrospinal fluid in patients with suspected meningococcal meningitis contributed to delay in starting antibiotic treatment. Thus the four deaths in our series which we regarded as potentially avoidable were all related directly or indirectly to lumbar puncture.

In west Gloucestershire the use of lumbar puncture was significantly reduced in the second study period. The likelihood of meningococcal infection in patients

Key messages

- The first doctor to suspect a diagnosis of meningococcal disease should start treatment immediately
- Education and encouragement can increase the proportion of patients with meningococcal disease receiving benzylpenicillin before admission to hospital
- Specimens for polymerase chain reaction testing should be collected from all patients suspected of having meningococcal disease in admission to hospital
- The need for lumbar puncture should be considered carefully in suspected meningococcal meningitis; it is contraindicated in meningococcal septicaemia
- Notifications of meningococcal disease remain incomplete; accurate estimation of numbers of cases requires reconciliation of notifications with laboratory diagnoses and local clinical registers

with a combination of clinical meningitis and a haemorrhagic rash is high. In such patients lumbar puncture is unlikely to change the management and may be hazardous. It should be undertaken in suspected meningococcal meningitis only after careful consideration of the benefit and risk (see box).^{24 25}

Diagnosis and management

New methods of diagnosing meningococcal infections now becoming available include the use of the polymerase chain reaction to amplify meningococcal DNA in cerebrospinal fluid⁵ and blood⁶ as well as improved serology.² The new tests should be particularly useful in the 50% of untreated patients in whom blood cultures have negative results¹⁵ and also for patients who receive parenteral antibiotics before samples are taken. Work is still needed to establish more accurately the sensitivity and specificity of the new diagnostic techniques in larger patient populations. If they prove robust and become widely available, they may lead to a further reduction in the proportion of patients requiring lumbar puncture.

The early use of benzylpenicillin and rapid transfer to hospital remain vital components of the good management of meningococcal disease.²⁵ These factors may have contributed to the low overall case fatality rate in this series. There will always remain a group of patients with fulminant septicaemia for whom even early antibiotics and urgent transfer to hospital are unlikely to alter the course of the disease. The development and successful deployment of effective vaccines for all meningococcal serogroups remains the most important goal in meningococcal research today.

We thank consultant colleagues at Gloucestershire Royal Hospital and staff at Gloucester Public Health Laboratory and at the Gloucestershire Health Department of Public Health Medicine for their important contributions not only to the immediate management of patients but also in helping with the collection of data for analysis. Ms Rhonwen Morris was instrumental in co-ordinating activities between the Public Health Laboratory and the Department of Public Health Medicine. We also thank

Recommendations for the use of lumbar puncture in suspected cases of meningococcal disease

Contraindications to lumbar puncture in suspected meningococcal infection include:

- Clinical diagnosis of invasive meningococcal infection with typical haemorrhagic rash
- Signs of poor perfusion indicating impending or established septicaemic shock
- Drowsiness or impairment of consciousness manifesting as a Glasgow coma scale score of < 13 or deteriorating Glasgow coma scale scores or signs of raised intracranial pressure
- Signs of raised intracranial pressure
- Focal neurological signs

A normal computed tomography scan does not exclude raised intracranial pressure

If in doubt about the presence of a contraindication, start treatment and omit the lumbar puncture

If lumbar puncture has been omitted and the patient is not improving after 24 hours in spite of treatment, reconsider the need for lumbar puncture

staff of the Public Health Laboratory Service Communicable Disease Surveillance Centre and the Public Health Laboratory Service Meningococcal Reference Unit for data on notifications and on laboratory diagnosed meningococcal infections both in west Gloucestershire and in England and Wales.

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Conflict of interest: None.

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Audit of prenatal diagnosis for haemoglobin disorders in the United Kingdom: the first 20 years

B Modell, M Petrou, M Layton, L Varnavides, C Slater, R H T Ward, C Rodeck, K Nicolaides, S Gibbons, A Fitches, J Old

Abstract

Objectives: To audit services for prenatal diagnosis for haemoglobin disorders in the United Kingdom.

Design: Comparison of the annual number of cases recorded in a United Kingdom register of prenatal diagnoses for haemoglobin disorders, with the annual number of pregnancies at risk of these disorders, by ethnic group and regional health authority. The number of pregnancies at risk was estimated using data on ethnic group from the 1991 census and data from the United Kingdom thalassaemia register, which records the number of babies born with thalassaemia.

Setting: The three national prenatal diagnosis centres for haemoglobin disorders.

Subjects: 2068 cases of prenatal diagnosis for haemoglobin disorders in the United Kingdom from 1974 to 1994.

Main outcome measures: Utilisation of prenatal diagnosis by risk, ethnic group, and regional health authority. Proportion of referrals in the first trimester and before the birth of any affected child.

Results: National utilisation of prenatal diagnosis for haemoglobin disorders was around 20%. During the past 10 years it has remained steady at about 50% for thalassaemias and risen from 7% to 13% for sickle cell disorders. Utilisation for sickle cell disorders varies

regionally from 2% to 20%. Utilisation for thalassaemias varies by ethnic group. It is almost 90% for Cypriots and ranges regionally for British Pakistanis from 0% to over 60%. About 60% of first prenatal diagnoses are done for couples without an affected child. Less than 50% of first referrals are in the first trimester.

Conclusions: National utilisation of prenatal diagnosis for haemoglobin disorders is far lower than expected, and there are wide regional variations. A high proportion of referrals are still in the second trimester and after the birth of an affected child. The findings point to serious shortcomings in present antenatal screening practice and in local screening policies and to inadequate counselling resources, especially for British Pakistanis.

Introduction

Population screening for haemoglobin disorders has been practised for over 20 years and now provides the most extensive available experience of screening for inherited disease.¹ Carriers are reliably detected by a screen that includes measurement of red cell indices (a mean cell haemoglobin concentration <27 pg suggests a thalassaemia) and electrophoresis for abnormal haemoglobins, followed by definitive diagnostic tests.² Therefore, in principle, all couples at risk of having

See p 784

Department of Obstetrics and Gynaecology, University College London Medical School, London WC1E 6HX

B Modell, professor of community genetics

M Petrou, clinical molecular geneticist

C Slater, research assistant

R H T Ward, senior lecturer

C Rodeck, head

Department of Haematological Medicine, King's College Hospital, London SE5 9RS

M Layton, senior lecturer

Lysandros Varnavides, clinical molecular geneticist

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