Public Health Reviews

Inherited haemoglobin disorders: an increasing global health problem

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Abstract Despite major advances in our understanding of the molecular pathology, pathophysiology, and control and management of the inherited disorders of haemoglobin, thousands of infants and children with these diseases are dying through lack of appropriate medical care. This problem will undoubtedly increase over the next 20 years because, as the result of a reduction in childhood mortality due to infection and malnutrition, more babies with haemoglobin disorders will survive to present for treatment. Although WHO and various voluntary agencies have tried to disseminate information about these diseases, they are rarely mentioned as being sufficiently important to be included in setting health care priorities for the future. It takes considerable time to establish expertise in developing programmes for the control and management of these conditions, and the lessons learned in developed countries will need to be transmitted to those countries in which they occur at a high frequency.

Keywords Hemoglobinopathies/mortality/therapy/epidemiology; Anemia, Sickle cell/mortality/therapy/epidemiology; Thalassemia/mortality/therapy/epidemiology; Malaria/complications/blood; Genetic techniques; Child; Cost of illness; Forecasting (*source: MeSH*).

Mots clés Hémoglobinopathie/mortalité/thérapeutique/épidémiologie; Anémie cellule falciforme/mortalité/thérapeutique/épidémiologie; Thalassémie/mortalité/thérapeutique/épidémiologie; Paludisme/complication/sang; Technique génétique; Enfant; Coût maladie; Prévision (*source: INSERM*).

Palabras clave Hemoglobinopatías/mortalidad/terapia/epidemiología; Anemia de células falciformes/mortalidad/terapia/epidemiología; Talasemia/mortalidad/terapia/epidemiología; Paludismo/complicaciones/sangre; Técnicas genéticas; Niño; Costo de la enfermedad; Predicción (*fuente: BIREME*).

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Voir page 711 le résumé en français. En la página 712 figura un resumen en español.

Introduction

As a result of heterozygote advantage against malaria, the inherited haemoglobin disorders are the commonest monogenic disease (*1*, *2*). It has been estimated that approximately 7% of the world population are carriers of such disorders and that 300 000–400 000 babies with severe forms of these diseases are born each year (*3*). Although these conditions occur at their highest frequency in tropical regions, population migrations have ensured that they are now encountered in most countries.

Because some of these inherited haemoglobin disorders, if left untreated, result in death in the first few years of life, their effect on the burden of health care is only now being appreciated in many parts of the world; it is only when improvements in hygiene, nutrition, and the control of infection reduce childhood mortality rates that babies with severe haemoglobin disorders survive long enough to present for diagnosis and treatment. As a result of such demographic changes, the impact of these diseases is now being felt all over the Indian subcontinent and in many parts of Asia, and this will undoubtedly be the case in sub-Saharan Africa as it undergoes a similar transition.

It is therefore vital that international health agencies and governments of countries where the haemoglobin disorders occur at a high frequency become aware of the future extent of this problem and develop programmes for their control and management.

Inherited haemoglobin disorders

Normal human haemoglobin

The structure of human haemoglobin (Hb) changes during embryonic, fetal and adult life (*1*). All the

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normal haemoglobins are tetramers of two pairs of unlike globin chains. Adult and fetal haemoglobin have α chains combined with β(Hb A, $\alpha_2\beta_2$), δ(Hb A_2, $\alpha_2\delta_2$) or γ chains (Hb F, $\alpha_2\gamma_2$), whereas in the embryo α-like chains (termed ζ chains) combine with γ (Hb Portland, $\zeta_2\gamma_2$) or ε chains (Hb Gower 1, $\zeta_2\varepsilon_2$), and α and ε chains form Hb Gower 2 ($\alpha_2\varepsilon_2$) (Fig. 1). Embryonic haemoglobin production is continued to the yolk sac stage of development and thereafter is replaced by fetal haemoglobin up to shortly before birth. After birth, Hb F is replaced by Hbs A and A_2 over the first year of life.

The genes for the α-like globin chains are found in a cluster at the tip of the short arm of chromosome 16, while those for the β-like chains are also found in a cluster, in this case on chromosome 11. The complete nucleotide sequence of these regions has been determined and the molecular pathology of most of the haemoglobin disorders is well defined.

Spectrum of inherited haemoglobin disorders

Inherited haemoglobin disorders fall into two main groups: the structural haemoglobin variants and the thalassaemias. The structural haemoglobin variants mostly result from single amino-acid substitutions in the α or β chains (*1*). In many cases these are innocuous but in others they may alter the stability or functional properties of the haemoglobin and lead to a clinical disorder.

The thalassaemias are classified according to the particular globin chains that are ineffectively synthesized into the α, β, δβ, and εδβ thalassaemias (*2*). From a public health view point only the α and β thalassaemias are sufficiently common to be of importance.

Clinical features of the important haemoglobin disorders

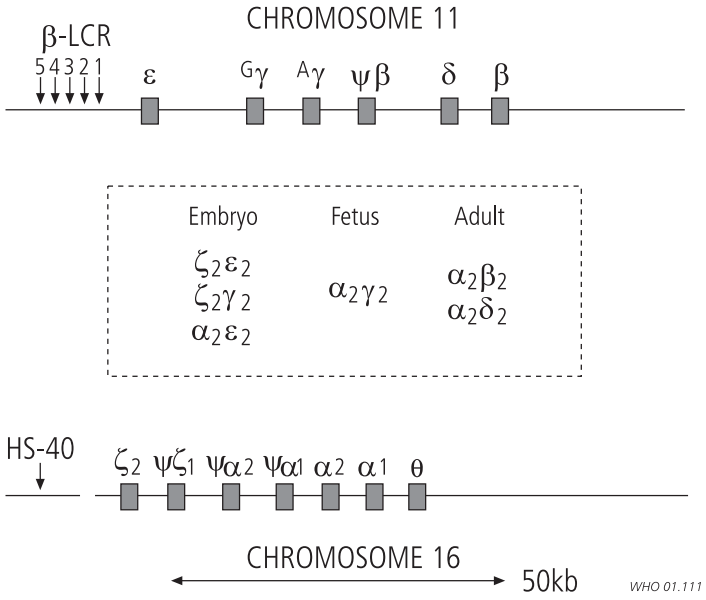
Structural haemoglobin variants

Although over 700 structural haemoglobin variants have been identified, only three (Hb S, Hb C, and Hb E) reach high frequencies. The homozygous state for the sickle-cell gene results in sickle-cell anaemia, while the compound heterozygous state for the sickle-cell and Hb C genes results in Hb SC disease which, although milder than sickle-cell anaemia, also has important public health aspects. Haemoglobin E, which is the commonest structural haemoglobin variant globally, is innocuous in its heterozygous and homozygous states but, because it is synthesized at a reduced rate, it can interact with β thalassaemia to produce a condition called Hb E β thalassaemia, which is extremely common and is presenting an increasingly important health problem in many parts of Asia (*4*, *5*).

The clinical features of sickle-cell disorders reflect the propensity of the red cells to assume a sickled configuration when blood is oxygenated (*6*, *7*), leading to a shortened red-cell survival and a tendency to vaso-occlusion. Although patients with sickle-cell anaemia may adapt to their anaemia quite well, their illness is interspersed with acute episodes, or crises, which include episodes of sequestration of blood into the lung, liver or spleen, or the occlusion of cerebral vessels with resulting stroke. Furthermore, they are particularly prone to infection in early childhood and, indeed, at all ages. For reasons that are not yet fully understood, there is remarkable variability in the severity of sickle-cell disease (*8*). But even in populations such as those of eastern Saudi Arabia and/or parts of India, which because they have a high frequency of α thalassaemia and/or an unusual ability to produce Hb F in adult life (both of which when inherited with sickle-cell disease tend to result in milder illness), there is still a very high morbidity (*9*).

Although little is know about the mortality from "sickling" disorders in developing countries, it is clear that in sub-Saharan Africa many children die from them early in life. Both in the USA and in Jamaica the peak incidence of death among those affected with these disorders appears to be at 1–3 years of age, usually due to infection (*7*). Recent data from the USA suggest that among affected adults, the median age of death is 42 years for males and 48 years for females (*10*). Although Hb SC disease is milder than sickle-cell anaemia, it is associated with important complications, including a high frequency of aseptic necrosis of the femoral or humoral heads, haematuria, proliferative retinopathy, and a thrombotic tendency which, particularly in pregnancy and the puerperium, may lead to massive pulmonary thrombo-embolic disease and death (*7*).

Fig. 1. **The normal human haemoglobins.** The different haemoglobins found in the embryo, fetus and adult are shown, together with the gene clusters that regulate their production on chromosomes 11 and 16. The β-LCR and HS-40 are the main regulatory regions for these gene clusters.



Thalassaemias

The homozygous or compound heterozygous states for β thalassaemia also run a variable course, although

in a majority of cases, without transfusion, death occurs in the first few years of life (*2*). With adequate transfusion and the administration of the chelating agent, desferrioxamine, children may grow and develop well and survive into adult life (*11*, *12*). Unfortunately, desferrioxamine has to be given by continuous infusion via a pump and is expensive. If the drug is available at all in poorer countries, it appears that many children are receiving inadequate dosages and that many of them are dying in childhood or adolescence due to the effects of iron overload (*2*, *13*). The situation is further complicated by the fact that the common β thalassaemias of intermediate severity, notably Hb E β thalassaemia, exhibit a very wide clinical spectrum ranging from a transfusion-dependent disease to a condition that is compatible with normal survival and growth into adult life without treatment (*14*, *15*). Currently, the reasons for this extraordinary clinical heterogeneity are not fully understood.

The α thalassaemias are equally heterogeneous (*16*). The milder forms (termed α^+ thalassaemias because some α chains are produced by the chromosomes carrying the genetic determinant), though extremely common, only produce a mild hypochromic anaemia in their homozygous states. On the other hand, the α^o thalassaemias (so-called because they are associated with an absence of a chain synthesis) result in stillbirth in their homozygous states and extremely difficult pregnancies for mothers who carry these babies. The compound heterozygous states for α+ and α^o thalassaemia result in a condition called Hb H disease that varies in severity; at the more severe end, it may be a transfusion-dependent disorder.

The thalassaemias are extremely heterogeneous at the molecular level; over 200 different mutations of the β globin genes have been found in patients with β thalassaemia, and the α thalassaemias are almost as varied in their molecular pathology. Importantly, every high frequency population in the world seems to carry a few common mutations that are unique to a particular region, together with varying numbers of rare ones (*2*).

Population genetics and dynamics

There is now very strong evidence that the high frequency of the sickle-cell and α thalassaemia genes has been maintained by exposure of populations to malaria (*17*, *18*). For the sickle-cell gene, this reflects heterozygote advantage, while for the mild forms of α thalassaemia (the α^+ thalassaemias), it may be the result of homozygote and heterozygote protection. It seems very likely that the high frequency of β thalassaemia and Hb E is also due to heterozygote protection against malaria, although formal proof is still lacking. The resurgence of malaria in many parts of the world will serve to maintain these polymorphisms, but even if this selective force were removed it would take many generations for the gene frequencies of these conditions to fall significantly. There will be a slow decline among immigrant populations through lack of exposure to malaria and out-breeding, but these effects will only reduce very slowly the health problem posed by these conditions.

Any changes resulting from variation in selection or population dynamics will, however, be very small compared with the effect of the demographic transition that many countries have undergone over recent years. A remarkable example of this process was observed in Cyprus after the Second World War (*2*, *13*). Thalassaemia was not identified on the island until 1944, when, after a major malaria eradication programme and accompanying improvements in public health measures, it became clear that children on Cyprus exhibited a common form of anaemia that was not due to infection. This was identified as thalassaemia and, by the early 1970s, it was estimated that, if no steps were taken to control the disease, in about 40 years ca. 78 000 units of blood per annum would be required to treat all the severely affected children, 40% of the population would be donors, and the total cost to the health services would equal or exceed the island's health budget.

Global frequency and health burden posed by the inherited anaemias

The global distributions of sickle-cell disorders and Hb E are shown in Fig. 2 and those of the thalassaemias in Fig. 3. Representative carrier frequencies are shown in Table 2. The sickle-cell gene is distributed widely throughout sub-Saharan Africa, the Middle East and parts of the Indian sub-continent, where carrier frequencies range from 5% to 40% or more of the population. Hb E is found in the eastern half of the Indian sub-continent and throughout South-East Asia, where in some areas, carrier rates may exceed 60% of the population. Thalassaemia has a high incidence in a broad band extending from the Mediterranean basin and parts of Africa, throughout the Middle East, the Indian sub-continent, South-East Asia, Melanesia and into the Pacific Islands. The carrier frequency for β thalassaemia in these areas ranges from 1% to 20%, rarely greater, while that for the milder forms of α thalassaemia is much higher, ranging from 10–20% in parts of sub-Saharan Africa, through 40% or more in some Middle Eastern and Indian populations, to as high as 80% in northern Papua New Guinea and isolated groups in north-east India. The α^o thalassaemias are more restricted in their distribution, occurring at high frequencies only in parts of South-East Asia and the Mediterranean basin and therefore pose less of a global health problem that the β thalassaemias.

In a series of workshops, held under the auspices of WHO, attempts have been made to estimate the frequency and health burden of the thalassaemias and common haemoglobin variants.

These data are summarized (*3*) and have been reviewed recently (*13*). Detailed information about the frequency of different forms of thalassaemia and haemoglobin disorders in each population is not provided; rather, an overall estimate of the global problem of these diseases is given together with advice for their control and management. The frequency data are based on some published work augmented by personal data supplied by local clinicians (Dr B. Modell, personal communication, 2001). The most recent estimate (Table 1 and Fig. 4) suggests that annually there may be about 270 million carriers for important inherited disorders of haemoglobin and 300 000–400 000 births of infants with sickle-cell anaemia or serious forms of thalassaemia (*3*). Globally, WHO's South-East Asia Region, where the thalassaemias and Hb E predominate, is the most severely affected; sub-Saharan Africa has the second highest burden, reflecting the very high frequency of the sickle-cell gene. Further information of the different thalassaemia mutations has been reported more recently (*2*).

These data give only a very approximate estimate of the problems for health care services that will be posed by the haemoglobin disorders in the future. Unfortunately, few of them are based on micromapping of their frequency in different populations. Recent studies in Indonesia (*19*), for example, have shown just how patchy the frequency of haemoglobin disorders can be within relatively short geographical distances (Fig. 5). Estimates based on these data suggest that the annual number of births of babies with β thalassaemia major or Hb E β thalassaemia will be at least twice the number suggested by WHO (*3*). Similar studies in Sri Lanka have demonstrated how, even in a small island population, there may be considerable differences in the frequency of both β thalassaemia and Hb E in areas that are separated only by a few miles (*20*). Furthermore, where both thalassaemia and structural haemoglobin variants occur at a high frequency in the same population, e.g. β thalassaemia and Hb E, the relative frequency of β thalassaemia homozygotes or Hb E β thalassaemia compound heterozygotes will depend on the patterns of admixture between different population groups. For example, studies that we are currently carrying out in southern Viet Nam suggest that there are populations with high frequencies of either one mutation or the other, but there seems to be relatively little admixture between the two. Elsewhere in the country, particularly in large urban areas such as Ho Chi Min City, there is clear evidence of admixture.

Given these limitations, the data shown in Table 1, Table 2, and Fig. 5 represent only the minimal estimates of the likely health burden that will be posed by the haemoglobin disorders in the future. Furthermore, in many cases, they are not based on projected increases in birth rates for particular countries.

Because of these uncertainties about the frequencies of the haemoglobin disorders and about the time that it will take for many countries to pass through the demographic transition such that babies with these conditions will present for treatment, it is even more difficult to assess the burden that such disorders will impose on health provision. It should also be remembered that, as more of these babies survive and present for treatment, the population of patients on long-term therapy will steadily expand; the more effective the treatment, the greater the burden on health care services. For example, it has been estimated that over the next 20 years approximately 100 000 cases of Hb E β thalassaemia will be added to the Thai population (*21*) and that 20 000 β thalassaemia homozygotes will be born each year in the southern provinces of China (*2*).

Fig. 2. **Global distribution of haemoglobins S and E**

Fig. 3. **Global distribution of α and β thalassaemia**

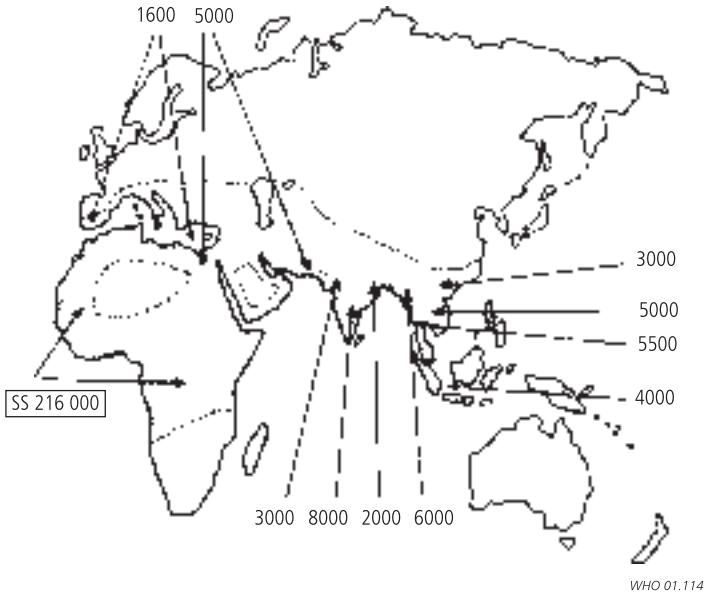
Table 1. **Global summary of approximate numbers of annual births of babies with severe haemoglobin disorders** (modified from ref. *3*)

Area	Population ($\times 10^6$)	Births ($\times 10^6$)	Births of homozygotes of compound heterozygotes ($\times 10^3$)[a]
Sub-Saharan Africa	650	30	230
Americas	730	17.5	5
South-East Asia	3150	84	120
Eastern Mediterranean and Europe	780	11	1.6
Western Pacific	30	0.5	0.2
Total	5340	143.0	356.8[b]

[a] The disorders vary according to the region. In Africa, sickle-cell anaemia accounts for most of the cases, while in Asia β thalassaemia, Hb E β thalassaemia and α^0 thalassaemia are the most important disorders.

[b] May be an underestimate; accurate gene frequencies for many populations are not available, and birth rates are based on current figures rather than future projections.

Fig. 4. **Estimated frequencies of annual number births of babies with severe haemoglobin disorders.** The data for Africa reflect sickle-cell anaemia, while the rest of the data refer to their different forms of thalassaemia.



Children with thalassaemia major, and a varying proportion of those with Hb E β thalassaemia, will require transfusion. Recent estimates from the studies of gene frequencies in Indonesia, based on the premise that only half of the patients with Hb E thalassaemia will require transfusion, suggest that it will be necessary to find 1.25 million units of blood each year to manage the thalassaemia population (*19*). Since these patients require red cells, the blood has to be processed and also screened for hepatitis B and C viruses, human immunodeficiency virus (HIV), and, in many countries, malarial parasites. Because the children involved die of iron overload if iron derived from transfusion is not removed, and because current iron chelation regimens are extremely expensive, basic treatment of these diseases is very costly. The cost of diagnostic technology, medical staff, hospital admissions for complications, and other items that are difficult to define, add to this burden. Although the management of sickle-cell anaemia is less expensive, over the lifetime of a patient it is also very costly because of the propensity to infection and high frequency of vascular occlusive complications.

There have been very few attempts to quantify the economics of managing the haemoglobin disorders. WHO has made a very approximate estimate(*3*), although because of variation in costs of health care between countries the data offer only the broadest guidelines. In a recent study in Sri Lanka, where the frequency of β thalassaemia and Hb E is relatively low compared with many other populations of the Indian sub-continent and South-East Asia, it was estimated that the future management of thalassaemia would consume 5–10% of the island's current expenditure on health (*20*).

Control and management of haemoglobin disorders

Currently, countries can be divided into three general categories in terms of the patterns of control and management of the haemoglobin disorders (*2*, *13*). First, in some Mediterranean countries, control programmes consisting of screening and antenatal diagnosis have succeeded in reducing the frequency of new births of β thalassaemia by between 80% and close to 100% (*22*, *23*). Specialized clinics also provide optimum management of established cases. Second, in some of the richer industrialized countries where the prevalence is increasing because of immigration of patients from high-frequency regions, facilities for control and management have been developed but there are still major problems in reaching immigrant groups with different cultural backgrounds. Finally, in many of the countries of the developing world that have undergone a demographic transition, provision of service is still hampered by major economic and organizational difficulties and many affected infants and children are dying with undiagnosed, untreated or under-treated disease.

Studies in the richer countries have shown that the prognosis for patients with sickle-cell anaemia may be improved considerably by establishing neonatal screening programmes augmented by the early use of prophylactic oral penicillin and the effective management of intercurrent infections (*24*). There have also been advances in the control of stroke by the use of long-term transfusion regimens (*25*), and with an increased understanding of the mechanisms of pulmonary and splenic sequestration crises, and the judicious use of exchange or top-up transfusion, the management of these life-threatening complication is improving (*26*). There is also evidence that the frequency of painful vaso-occlusive episodes can be reduced by the administration of hydroxyurea (*27*), although it is still uncertain

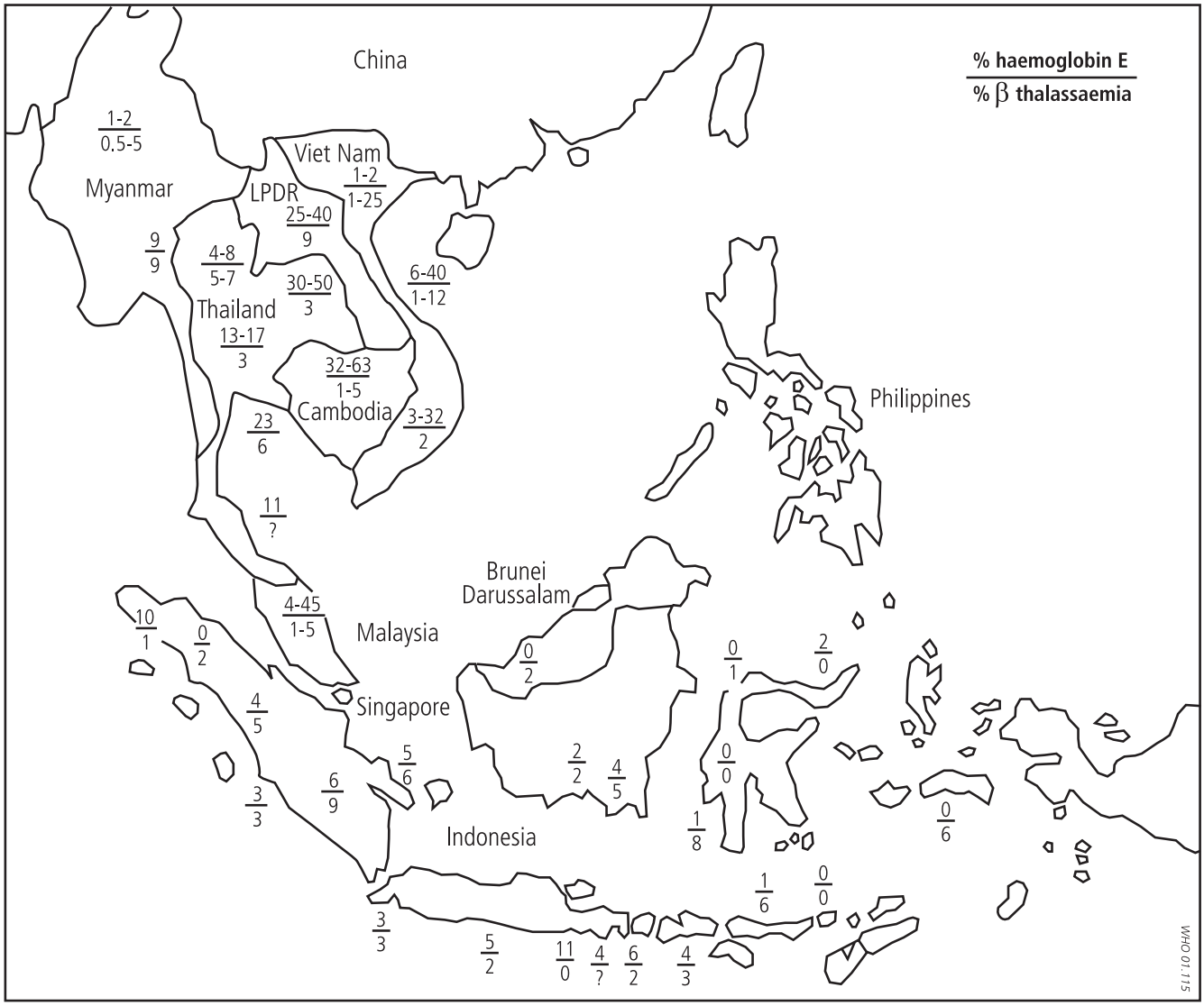
Table 2. **Some representative carrier frequencies for the imported haemoglobin disorders**[a]

Haemoglobin S	Carrier frequency (%)	Haemoglobin E	Carrier frequency (%)	β Thalassaemia	Carrier frequency (%)	α^o Thalassaemia	Carrier frequency (%)	α^+ Thalassaemia	Carrier frequency (%)
Africa	19–27	**India**		**Italy**	0.5–19	Thailand	3–4	**Italy**	4.1
Nigeria	6–24	West Bengal	2–4	Sardinia	11–19			Sardinia	12.6
The Gambia	5–15	Assam	6–51			Lao People's Demographic Republic	2		
Senegal	1–23			Cyprus	15–17			Cyprus	14
Guinea	2–28	Bangladesh	6						
Liberia	2–15			Greece	6–19			Greece	8
Côte d'Ivoire	3–22	Sri Lanka	1–3			Southern China	1–2		
Mali	7–29			Turkey	1–11	China, Province of Taiwan	1–4	Portugal	10
Ghana	3–22	Myanmar	5–30					Israel	1–17
Benin	7–29			Jordan	3.5			Eastern Saudi Arabia	50–60
Niger	5–23	Thailand	4–53			Sardinia	[b]	Turkey	3
Cameroon	8–34			Saudi Arabia	1–2				
Central African Republic	1–21	Cambodia	12–80			Greece	ca. 1–2	**Former Soviet Union**	
Gabon	8	Lao People's Democratic Republic	7–48	Israel	1–20	Cyprus	[b]	Azerbaijan	9
Democratic Republic of the Congo	2–0	Viet Nam	0–70	Islamic Republic of Iran	4–5			**India**	
Angola	4–24							Orissa	50
Zambia	6–27	**China**		Iraq	2–3			Koya Dora (tribal group)	80
Uganda	4–30	Hupei	2					Bombay	15
United Republic of Tanzania	10–38	Malaysia	3–40	**Former Soviet Union**				Sri Lanka	15
Kenya	2–32	Indonesia	1–11	Azerbaijan	6			Nepal (Tharuethnic subgroup))	80
Sierra Leone	16–30			Tajikistan	5			Pakistan	11–15
Eastern Mediterranean				**India**				Thailand	15–75
Saudi Arabia	1–29			Bengalis (tribal group)	3			Lao People's Democratic Republic	40
Iraq	0–22			Assam	0.3–5			Viet Nam	6
India				Chitrapur Saraswats (tribal group)	4			**China**	
Madras	20			Lohnas	13			Guangxi	15
Andhra Republic Pradesh	17			Bombay (Banushali)	15			Guangdong	4
Madhya Pradesh	20			Pakistan	1–8			Jiangxi	3
Gujarat	30			**Africa**				Province of Taiwan	1–8
Orissa	25			Algeria	3			Malaysia	2–7
				Libyan Arab Jamahiriya	7			Indonesia	1–13
				Egypt	2–4			Papua New Guinea	20–80
				Sudan	5			Melanesia	9–60
				Burkina Faso	2.6			Micronesia/ Polynesia	2–16
				Koulango tribe (Burkina Faso)	1			**Africa**	
				Mali	3			Nigeria	11–50
				Liberia	1–12			Kenya	40–50
				Nigeria	1			Zambia	40
				Myanmar	0.5–1			Senegal	20
				Thailand	1–11			Benin	40
				Lao People's Democratic Republic	6			Algeria	10
				Cambodia	3				
				Viet Nam	0–4				
				China					
				Southern Provinces	2				
				Indonesia	0–11				
				Vanuatu					
				Maewo	13				

[a] Sources include ref. *2, 3, 19, 32* and the authors unpublished data. The figures are for limited surveys and cannot be extrapolated to entire populations.

[b] α^o thalassaemia is well documented but population frequencies not known.

Fig. 5. **The distribution of haemoglobin E and β thalassaemia in south-east Asia** (LPDR = Lao People's Democratic Republic).



whether this type of therapy has any long-term potential for the generation of leukaemia or related bone marrow malignancies. It is clear, however, that many patients with sickle-cell anaemia require the expertise of specialized centres and lifelong medical care and surveillance.

The management of the serious forms of β thalassaemia has also improved. Ideal transfusion regimens to allow normal growth development have been established and, with the use of effective chelation therapy, many patients are now surviving to adulthood (*28*, *29*). However, many problems remain. Even with adequate chelation therapy, many children experience impairment of growth or sexual maturation, probably reflecting the extreme sensitivity of the hypothalamic/pituitary axis to iron. More importantly, because of the complexities of the delivery of desferrioxamine, compliance still remains a serious problem. As in the case of the sickling disorders, optimal management of the serious forms of thalassaemia requires the development of specialized centres and, over the lifetime of a patient, is extremely expensive.

Future priorities

So far, the importance of the haemoglobin disorders has not been recognized by health demographers in their predictions for the change in the pattern of disease in the first part of the new millennium (*30*). However, although accurate frequency data are still scarce, enough is known to provide some indication of the burden on health services that these diseases will pose, particularly for the poorer countries. It is vital therefore that international health agencies and the governments of countries where these diseases are common are made aware of the problem and start to plan the most economic and effective approach to their control. A general approach has been outlined in several WHO publications and has been discussed in detail recently (*2*, *3*, *13*). Here we can only summarize briefly some of the major issues that will have to be faced in the immediate future.

With the exception of bone marrow transplantation, which is expensive and is only available for the limited number of patients with compatible sibling

donors, there is no definitive cure for any of the genetic disorders of haemoglobin. Although a great deal of work is being directed at corrective gene therapy or other approaches to genetic manipulation (*2*), it seems likely that it will be a considerable time before they come to clinical practice and that, when they do, they are likely to be extremely expensive and only available in richer countries. Thus the immediate aim should be to try to develop control programmes and more focused and economic approaches to management of established cases.

There are several critical pieces of information that are urgently required as a background to developing control and management programmes. First, so that governments can be given more accurate and realistic data about the likely burden of the disease, micromapping studies need to be carried out to obtain better data about its frequency. Screening for the important forms of thalassaemia and sickle-cell disease is accurate and cheap, and the various approaches that can be used have recently been reviewed (*2*). Second, more needs to be known about the natural history, mechanisms for clinical variability, and most appropriate ways to manage Hb E ß thalassaemia, which is so common throughout the Indian subcontinent and South-East Asia. Many patients with this condition are being given blood transfusions unnecessarily and valuable resources are being wasted. We need to learn much more about how to identify those patients that genuinely need treatment.

Screening and antenatal diagnosis programmes have been applied widely in Mediterranean populations (*22*, *23*). Their success has been based on the excellence of public education programmes about the disease, followed by the development of effective screening regimens and facilities for antenatal detection. For religious, cultural, organizational, and economic reasons, programmes of this type may be much more difficult to establish in the large mainland populations of the Indian subcontinent and South-East Asia. Clearly, it will be for individual governments and communities to decide how far they want to go down this road but, as a start, education programmes should be established, backed up with facilities for carrier screening on a voluntary basis. This type of approach is the bedrock on which further population control programmes can be built, if and when individual countries wish to pursue them.

Although the carrier states for the important haemoglobin disorders can be identified by relatively simple and cheap laboratory techniques, it will be essential for every country where the frequency of these disorders is high to establish at least one central reference laboratory that can carry out mutation analysis. Fortunately, DNA diagnostics are becoming cheaper and more efficient and it should be possible to provide services of this type on a centralized basis to form the background for both screening and diagnostic services for large communities. Similarly, high frequency populations will need several centres where there is expertise in the clinical management of these conditions. Blood transfusion services will have to be involved in developing these services at an early stage, particularly regarding the potential requirement for blood products and the type of screening that is required. Similarly, efforts to provide more accurate methods of costing control and treatment of these diseases are required.

Hitherto, genetic diseases have not been considered to be an important global health problem (*30*). Indeed, while many countries are still suffering from the effects of infectious disease and malnutrition this may remain the case. However, there is clear evidence that, as the demographic pattern of disease changes, genetic conditions assume an increasingly important part of the provision of care, particularly for children. In developed countries it has been estimated that genetic disease constitutes up to 40% of the requirements for chronic care in paediatric practice (*31*). Because of the unusually high frequency of the haemoglobin disorders in many tropical countries, the same kind of pattern will be seen as disease due to malnutrition and infection is controlled. So far, there is little evidence that many international health care agencies or governments have appreciated this fact. Although much good work has been done by WHO working groups in this area, and by a variety of voluntary agencies, there is, to date, little sign that much notice has been taken of their efforts. Because the planning of adequate programmes for the control and management of the haemoglobin disorders takes a long time, it is important that a start is made without further delay. ■

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Conflicts of interest: none declared.

Résumé

Hémoglobinopathies congénitales : un problème de santé publique d'importance croissante

Malgré les avancées majeures dans le domaine de la pathologie moléculaire et de la physiopathologie des hémoglobinopathies congénitales ainsi que dans la lutte contre ces maladies et leur prise en charge, des milliers de nourrissons et d'enfants qui en sont atteints meurent faute de soins médicaux appropriés. Ce problème ira très probablement en s'aggravant au cours des 20 prochaines années car, la mortalité de l'enfant due aux infections et à la malnutrition diminuant, un plus grand nombre de nourrissons atteints d'hémoglobino-

pathies survivront et auront besoin d'un traitement. Bien que l'OMS et diverses organisations bénévoles aient déjà tenté d'attirer l'attention des autorités sanitaires sur ces maladies, celles-ci sont rarement jugées assez importantes pour figurer parmi les futures priorités de santé publique. Comme il faut un temps considérable pour acquérir les compétences nécessaires à l'élaboration de programmes de lutte contre les hémoglobinopathies et de prise en charge des cas, les acquisitions des pays développés devront être transmises rapidement aux pays où ces maladies sont très fréquentes.

Resumen

Hemoglobinopatías hereditarias: un problema creciente de salud mundial

Pese a los grandes avances de nuestros conocimientos sobre la patología molecular, la fisiopatología y el control y manejo de las hemoglobinopatías hereditarias, miles de lactantes y niños afectados por esas enfermedades están muriendo por falta de atención médica apropiada. Este problema se agravará sin duda a lo largo de los próximos 20 años, dado que, como consecuencia de la disminución de la mortalidad infantil por infecciones y malnutrición, aumentará el número de niños con trastornos de la hemoglobina que sobrevivirán y necesitarán tratamiento. Aunque la OMS y diversas instituciones benéficas han procurado difundir información sobre estas enfermedades, rara vez se las considera lo suficientemente importantes para incluirlas entre las futuras prioridades de la atención sanitaria. Se necesita bastante tiempo para adquirir la competencia técnica que requiere el desarrollo de programas de control y tratamiento de estas hemoglobinopatías, por lo cual es necesario que los países desarrollados transmitan las lecciones aprendidas a los países con alta incidencia de esos trastornos.

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