EXECUTIVE BOARD **EB118/5**
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Thalassaemia and other haemoglobinopathies

Report by the Secretariat

PREVALENCE OF HAEMOGLOBINOPATHIES

1. Haemoglobinopathies, mainly thalassaemias and sickle-cell anaemia, are inherited disorders. At present, about 5% of the world's population are carriers of a potentially pathological haemoglobin gene (i.e. healthy people who have inherited only one mutant gene from one parent). Each year about 300 000 infants worldwide are born with thalassaemia syndromes (30%) or sickle-cell anaemia (70%). Globally, the percentage of carriers of thalassaemia is greater than that of carriers of sickle-cell anaemia, but because of the higher frequency of the sickle-cell gene in certain regions, the number of affected births is higher than with thalassaemia.

2. Some haemoglobinopathy genes (*alpha-thal*, *beta-thal* and *HbS*) cause alpha-thalassaemia, beta-thalassaemia and sickle-cell anaemia, respectively, but others (*HbE* and *HbC*) cause severe clinical manifestations of the disease only when combined with one of the former genes. Because healthy carriers (up to 25% in some populations) were protected against the lethal effects of malaria, these hereditary anaemias were originally confined to the tropics and subtropics and present with high incidence rates. Although a single abnormal gene may protect against malaria, inheritance of two abnormal genes leads to the haemoglobin disease state and confers no such protection. Beta-thalassaemia is the most common haemoglobin disorder in the Mediterranean basin, the Middle East and Asia. Severe alpha-thalassaemia is common in south-east Asia, and sickle-cell anaemia predominates in Africa. Increasing global migration, however, has introduced haemoglobin disorders into many areas where they were not originally endemic (see Figure). In the United States of America, 10% of the population is at risk of sickle-cell anaemia, and in north-western Europe between 2% and 9% belong to the ethnic minorities at risk of haemoglobin disorders. In some south-east Asian countries up to 40% of the population may carry significant haemoglobin mutations, resulting in increased rates of infants born with thalassaemia.

Clinical features and treatment[1]

3. Children with thalassaemia are often healthy at birth, but become anaemic between the ages of six months and two years. Without diagnosis and treatment, most die from anaemia or infections in the first years of life. Patients with thalassaemia need regular transfusions of red blood cells (once or twice monthly) in order to maintain a mean haemoglobin concentration of about 9.0-10.5 g/dl. This treatment may improve their health, but unfortunately only in the short term. As a result of multiple transfusions over the years, various organs become severely overloaded with iron, and, in order to avoid death in adolescence, regular subcutaneous infusion of an iron-chelating agent is essential. When treatment combining transfusion and iron-chelating agent is started early and maintained, the patient's quality of life can be very good and the prognosis is optimistic. Many patients receiving this combined treatment are now well into their thirties or forties, and in high-income countries life expectancy is steadily rising towards normal values. However, even in developed countries, adolescents and young adults can find the treatment difficult to cope with.

4. Many problems still remain in the treatment of thalassaemia. Successful development of a more widely accessible and acceptable, oral iron-chelating agent could solve the problem of compliance in countries with limited resources, where morbidity and mortality are mainly caused by limited access to appropriate medical care. At the same time, careful clinical management greatly improves thalassaemics' quality of life and increases their life expectancy. However, older thalassaemics may have to contend with multiple conditions including early osteoporosis, cardiac disease, pulmonary hypertension and diabetes, some of which result from increased iron deposition in the endocrine glands and myocardial cells. Because of the complications associated with chronic haemoglobin disorders and the consequent years of disability, haemoglobinopathies are becoming a growing health-care problem in all affected regions but in particular the developing world.

5. In patients with beta-thalassaemia, bone-marrow transplantation is successful in more than 90% of cases; it is also less expensive than the conventional life-long treatment. In practice, however, a compatible donor can be found for less than 30% of patients, and the success rate of the intervention depends on their age and the quality of clinical management they have received throughout their lives. The decision to take the risk of transplantation can be very difficult. Pharmaceutical induction of haemoglobin F synthesis and gene therapy hold great promise for treating haemoglobin disorders, although more research is needed, particularly on gene therapy. Clinical trials, however, in both cases raise optimism and great hope for thalassaemics.

6. The availability of diagnosis and treatment inevitably leads to a cumulative increase in the number of patients needing care. Increased life expectancy also adds to the overall cost per patient, which can have serious financial implications for countries, especially those with limited resources. A 10-year projection shows that it will be impossible for most countries to provide optimal treatment for all affected patients. Effective prevention is essential in order to liberate the resources needed for the adequate treatment of those already living with thalassaemia. For example, in the early 1980s in Cyprus, once a prevention policy was implemented, up to 95% of affected births were avoided. That intervention stabilized the annual cost of patient care at a small fraction of the projected cost without prevention, and improved significantly the quality of treatment provided to patients. All components

[1] Prevention, treatment and management of sickle-cell anaemia were discussed by the Board at its 117th session, which adopted resolution EB117.R3 on sickle-cell anaemia (see documents EB117/2006/REC/1 and EB117/2006/REC/2, summary record of the fifth meeting). The Fifty-ninth World Health Assembly also considered sickle-cell anaemia (see document A59/9).

of prevention and treatment should be considered together, existing initiatives should be supported and services introduced gradually, starting in areas where this is most feasible.

Prevention

7. Preventing thalassaemia is based on identifying individuals at risk through carrier screening programmes or family history and providing adequate information on risk and possibilities to reduce that risk. Beta-thalassaemia has a unique feature: healthy carriers can be identified by simple, inexpensive and accurate blood tests. Carrier couples can, therefore, be detected and informed of genetic risk before starting a family. Screening is affordable and an accessible way to detect carriers, and can be offered in a range of settings in different societies: in high school, before marriage, or in antenatal clinics. Carrier couples detected in this way are informed of the genetic risk and the options available for reducing it, which usually include prenatal diagnosis.

8. Most couples at risk for thalassaemia request prenatal diagnosis of haemoglobinopathies. The standard diagnostic method is chorionic villus sampling and DNA analysis around 10-12 weeks of pregnancy. Screening and counselling programmes can lead to a significant reduction in affected births. These programmes can be audited through interviews with parents who have affected children even though screening and counselling had been available. In most cases, affected births stem from the failure of the health system adequately to inform parents of the possibility of risk and prevention rather than their rejection of fetal testing.

9. The appropriate strategy for initiating thalassaemia prevention depends on the setting. In some societies the starting point is the provision of prenatal diagnosis for couples who are aware of their risk, either through screening or because they already have an affected child. This approach greatly reduces the numbers of affected births. Alternatively, in societies where prenatal diagnosis is not yet available, screening may be offered to people of reproductive age. This strategy leads to a smaller reduction in the number of affected births, but also usually to demand for prenatal diagnosis services.

10. Effective prevention approaches to thalassaemia have now been demonstrated in many countries with diverse carrier-screening programmes. For example, in Cyprus, Greece, the Islamic Republic of Iran and Italy, premarital screening for thalassaemia is standard practice and national audit data are available; most at-risk couples are identified in time to be offered early diagnosis for the first pregnancy. The majority of such couples use this service and produce healthy offspring. In the United Kingdom of Great Britain and Northern Ireland and other north-western European countries where prenatal diagnosis is generally available, screening is offered during pregnancy. Screening programmes need to be supported by public education and regulatory structures so that individuals may make informed decisions and that people are protected against discrimination as a consequence of their test results.

11. Some national programmes that promote carrier screening have in turn stimulated social changes, including the acceptance, in many countries, of the termination of pregnancies where the fetus has been shown to have a serious genetic disorder. This has led to the development of appropriate technologies and services in Bahrain, the Islamic Republic of Iran and Saudi Arabia. Increasingly, prevention programmes are being accepted and introduced in many parts of Asia such as China, India, Indonesia, Malaysia, Maldives, Singapore and Thailand.

12. Genetic counselling is essential to protect the autonomy of the individual or couple and to fulfil their right to maximum information about the disorder and the options available. To be effective, thalassaemia services must be sensitive to cultural practices, and appropriate for the given social

context. Counselling also must be sensitive to the cultural, religious and ethical views of the individual or couple. The success of genetic counselling depends crucially on its educational, voluntary and non-prescriptive nature.

Management

13. The delivery of thalassaemia services should be integrated at all levels of health care so as to take full advantage of existing resources and maximize efficiency. The primary health-care level should be the basis of actions, with emphasis on programmes that use simple, affordable technology and reach a large proportion of the community. Such actions include public education in genetics, detection of genetic risks in the community through attention to and recording of family history during patients' contacts with the health system, premarital genetic counselling, and encouragement of reproduction at optimal maternal ages.

14. Nationwide programmes are unlikely to be organized by developing countries from the outset, because they have other priorities and insufficient infrastructures to deliver the service. The initial aim should, therefore, be to establish one or more reference centres with the capacity to develop appropriate approaches for prevention and treatment. As demand increases, these services can be transferred to other centres within the country or in neighbouring countries. A close working relationship between the primary-care provider and the centre is essential for appropriate care. Staff in the centre should facilitate the formulation of effective national programmes that are integrated into the national health services, draw up guidelines and educational materials, and coordinate and cooperate with national parent-patient associations. Regional expert working groups on thalassaemia management are urgently required to coordinate the activities of such centres.

15. A barrier to implementing effective haemoglobinopathy services in countries is lack of awareness about genetic diseases. Countries need to improve understanding and awareness at community level. Furthermore, all relevant medical education and training courses should include modules on genetic counselling, the application of genetics to public health and the associated ethical, legal and social issues. Some policy-makers believe that medical genetic services need expensive high-technology laboratory equipment, and hence are not a priority for developing countries. In fact, DNA diagnostic methods have been radically simplified over the past 10 years. Public education and genetic counselling, as well as many genetic diagnostic tools, may be integrated into primary care, even in low-resource settings.

16. Research and surveillance are important for the planning and evaluation of appropriate interventions. There are currently insufficient data on the epidemiology of haemoglobinopathies, the demand for genetic services, and the quality, use and outcomes of genetic services in developing countries. Efficient surveillance systems (registries and databases) and continued investment in haemoglobin disorder research are fundamental to successful public health interventions, particularly in low-resource settings.

17. In many developing countries haemoglobinopathies are becoming more evident and this prominence is the driving force for the acceptance and introduction of genetic services. Successful outcomes of the use of these services may provide a model for introducing genetic approaches to the control of other chronic childhood diseases. Before an effective programme can be drawn up, health authorities, health professionals and expert centres have to perceive haemoglobin disorders as a public health problem. Each country needs to formulate a strategy appropriate to the local epidemiology, current service structure and available resources.

18. In order to prevent and successfully manage haemoglobinopathies in both developed and developing countries, WHO continues to cooperate with the Thalassaemia International Federation, a nongovernmental organization in official relations with WHO. The Federation, which represents 91 countries, supports a significant number of WHO activities relating to thalassaemia management. In particular, through its educational programme, it has published books for health professionals and organized numerous international, national and local workshops and courses on the clinical management of thalassaemia. Collaboration has focused on the improvement of diagnosis, prevention and clinical management of the disease, as well as on education of the public and health-care professionals.

19. The importance of hereditary diseases (including haemoglobin disorders) has been recognized at the regional level. Meetings of experts in the African Region, The Region of the Americas, the South-East Asia and the Eastern Mediterranean regions strongly advocated further regional work on haemoglobinopathies in order to define local priorities, problems and approaches, especially as different WHO regions have different needs, depending on the epidemiology and the economic and social characteristics of individual countries. The regional offices for Africa, South-East Asia and the Eastern Mediterranean have included haemoglobin disorders among their planned activities.

20. In resolution WHA57.13 on genomics and world health, the Health Assembly urged Member States to mobilize resources for action. At its 116th session, the Executive Board noted the report on control of genetic diseases,[1] and at its subsequent session, adopted resolution EB117.R3 on sickle-cell anaemia. A report submitted to the Fifty-ninth World Health Assembly highlights the role of nongovernmental organizations and WHO collaborating centres (in Brazil, China, Cuba, Cyprus, Greece, India, Italy, Saudi Arabia, Thailand, United Kingdom of Great Britain and Northern Ireland and United States of America) that support prevention and management of haemoglobin disorders.[2] Regional expert working groups, further partnerships at national, regional and global levels, and high-level advocacy are needed to ensure that governments of the most affected countries and international aid agencies are fully aware of the extent of the problem and pay close attention to thalassaemia and other haemoglobinopathies.

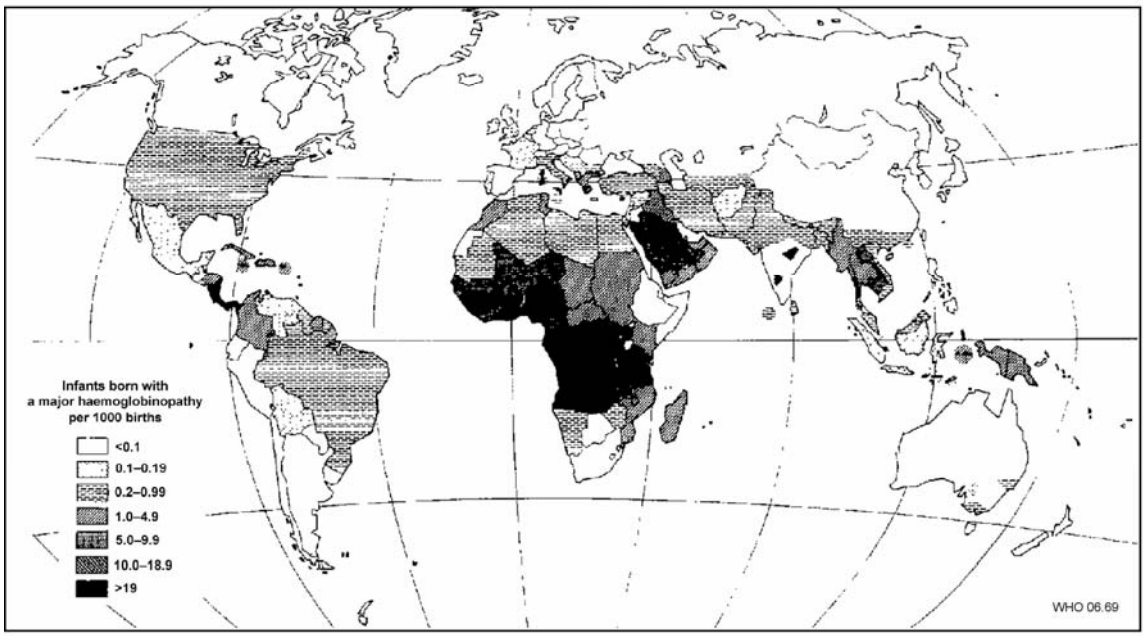
ACTION BY THE EXECUTIVE BOARD

21. The Board is invited to consider the following draft resolution.

[1] Document EB116/2005/REC/1, summary records of the first meeting (section 4) and the second meeting.

[2] Document A59/9.

Global distribution of haemoglobinopathies (thalassaemia and sickle-cell disease): number of affected infants per 1000 births



Thalassaemia and other haemoglobinopathies

The Executive Board,

Having considered the report on thalassaemia and other haemoglobinopathies;[1]

Recalling resolution WHA57.13 on genomics and world health, resolution EB117.R3 on sickle-cell anaemia and the recognition by the Executive Board at its 116th session of the role of genetic services in improving health globally and in reducing the global health divide;[2]

Concerned at the impact of genetic diseases, and of haemoglobinopathies (thalassaemia and sickle-cell anaemia) in particular, on global mortality and morbidity, especially in developing countries, and by the suffering of patients and families affected by the disease;

Recognizing that the prevalence of thalassaemia varies between communities, and that insufficiency of relevant epidemiological data may hamper effective and equitable management;

Deeply concerned that thalassaemia and other haemoglobinopathies are not officially recognized as priorities in public health;

[1] Document EB118/5

[2] See document EB116/2005/REC/1, summary record of the first meeting, section 4.

Deploring the current inequality worldwide of access to safe and appropriate genetic services;

Aware that effective programmes for thalassaemia must be sensitive to cultural practices and appropriate for the given social context;

Recognizing that the management of haemoglobinopathies raises specific ethical, legal and social issues that require appropriate consideration,

1. URGES Member States:

(1) to design, implement and reinforce in a systematic, equitable and effective manner, comprehensive national, integrated programmes for prevention and management of thalassaemia and other haemoglobinopathies, including surveillance, dissemination of information, awareness-raising and screening, such programmes being tailored to specific socioeconomic and cultural contexts and aimed at reducing the incidence, morbidity and mortality associated with these diseases;

(2) to develop their capacity to monitor thalassaemia and other haemoglobinopathies and to evaluate the impact of national programmes;

(3) to intensify the training of all health professionals in high-prevalence areas;

(4) to develop and strengthen medical services, within existing primary health-care systems, in partnership with parent or patient organizations;

(5) to promote community education, including health counselling and ethical, legal and social issues associated with haemoglobinopathies;

(6) to promote international cooperation in combating haemoglobinopathies;

(7) in collaboration with international organizations, to provide support for basic and applied research on thalassaemia;

2. REQUESTS the Director-General:

(1) to raise awareness of the international community of the global burden of thalassaemia and other haemoglobinopathies, and to promote equitable access to health services for prevention and management of these diseases;

(2) to provide technical support and advice to Member States in framing of national policies and strategies for prevention and management of thalassaemia and other haemoglobinopathies;

(3) to promote and support intercountry collaboration in order to expand the training and expertise of personnel, and to provide support for the further transfer of affordable technologies and expertise to developing countries;

(4) to continue WHO's normative functions by drafting guidelines on prevention and management of thalassaemia and other haemoglobinopathies with a view to elaborating regional plans and fostering the establishment of regional groups of experts;

(5) to promote, support and coordinate research on thalassaemia and other haemoglobinopathies in order to improve the duration and quality of life of those affected by such disorders.

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