

MANAGEMENT OF BIRTH DEFECTS AND HAEMOGLOBIN DISORDERS

REPORT OF A JOINT
WHO-MARCH OF DIMES MEETING

Geneva, Switzerland, 17-19 May 2006



WHO Library Cataloguing-in-Publication Data

Joint WHO-March of Dimes Meeting on Management of Birth Defects and Haemoglobin Disorders (2nd : 2006 : Geneva, Switzerland)

Management of birth defects and haemoglobin disorders : report of a joint WHO-March of Dimes meeting, Geneva, Switzerland, 17-19 May 2006.

1.Abnormalities – prevention and control. 2.Abnormalities – therapy. 3.Abnormalities - classification. 4.Genetics, Medical. 5.Prenatal diagnosis. 6.Developing countries. I.World Health Organization. II.March of Dimes. III.Title.

ISBN 92 4 159492 6

(NLM classification: QS 675)

ISBN 978 92 4 159492 9

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Printed by the WHO Document Production Services, Geneva, Switzerland

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EXECUTIVE SUMMARY

On 17-19 May 2006, the World Health Organization (WHO) and the March of Dimes Birth Defects Foundation held a joint meeting in Geneva entitled *The Management of Birth Defects and Haemoglobin Disorders*. The meeting was convened at the request of the WHO's Human Genetics Programme (HGN) following publication of the March of Dimes Global Report on Birth Defects in January 2006 (Christianson et al, 2006).

Meeting participants included 18 experts from developing and industrialized countries and nine staff from WHO Headquarters representing the following programmes: HGN, Newborn and Child Health, Classification and Terminology, Nutrition, Reproductive Health and Research, Disability and Rehabilitation and Making Pregnancy Safer.

The meeting had five goals. These were to (1) ratify the data on the global toll of birth defects presented in the 2006 March of Dimes Global Report on Birth Defects; (2) agree upon a definition of terms; (3) develop a five-year collaborative plan for strengthening care and prevention of birth defects in low- and middle-income countries, bearing in mind the different spectrum of genetic disorders that may occur; (4) develop a five-year plan for the WHO for strengthening care and prevention of haemoglobin disorders (sickle cell disease (SCD) and thalassaemias) in low- and middle-income countries; and (5) determine how potential stakeholders (WHO Regional Offices; international and national governmental agencies; foundations and other nongovernmental organizations; parent/patient and other lay support groups; the private sector; and donor organizations) could contribute to these efforts.

The following summarizes the meeting consensus for each of the five goals listed above.

- Participants endorsed the estimates in the March of Dimes Global Report, and they encouraged efforts to strengthen and expand the report's database. In addition, participants supported the report's recommendations for implementation and strengthening of programmes, including medical genetic services in low- and middle-income countries.
- Participants concluded that the term "birth defect" is synonymous with the term "congenital disorder" as defined and used by the HGN and agreed that both could be used interchangeably. The term "congenital anomalies" used currently in the 10th International Classification of Diseases Participants should be avoided. Participants encouraged the WHO's Classification and Terminology Unit in its development of the next version of the International Classification of Diseases (ICD 11) to actively engage those organizations and individuals necessary to develop an internationally acceptable classification of birth defects. The point of departure could be this committee's acceptance of the definition of the terms birth defect and congenital disorder as synonymous.
- Participants agreed that up to 70 percent of birth defects could be prevented, ameliorated or treated effectively, but that to do so on a global basis would require strengthening programmes, including medical genetic services, in low- and middle-income countries. Such services should build on a continuum involving pre-conception care, maternal health, management of labour, and newborn and child health care for infants and children with acute and chronic disorders. In addition, medical genetic services should have a strong base in primary health care and be integrated with secondary and tertiary health care services. Participants identified three priorities for action to assist in the initiation and development of services for the care and prevention of birth defects: (1) support continued research for the collection and refinement of birth defects data to assist the development of medical genetic services; (2) provide practical advice and support for countries

wishing to develop pre-conception and medical genetic services; and (3) promote human resource capacity development and technology transfer. Services for the care and prevention of birth defects must also link to and build on programmes in nutrition, immunization, infectious disease control and disability and rehabilitation, among others.

- Participants agreed that efforts must be made to improve the situation in developing countries where no services exist for the control of haemoglobin disorders. Activities could be conducted either through continued North/South partnerships or the development of South/South networks based on the Asian Thalassaemia Network model. Given the WHO's current focus on haemoglobin disorders, participants strongly encouraged the WHO to dedicate itself through its various organs to the accomplishment of this endeavour. By activating and organising these networks, the following priorities should be addressed: (1) support of continued research for the collection and refinement of data relevant for the control of haemoglobin disorders; (2) provision of practical advice and support for countries wishing to develop medical services for care and prevention of haemoglobin disorders; and (3) development of human resource capacity and technology transfer through training and education of clinicians, scientists, nurses, and counsellors, and the evolution of parent associations.
- The realization of Goals 3 and 4 in this report will require the combined efforts and political will of the WHO, its hierarchy, the HGN and, importantly, the WHO programmes associated with newborn and child health; reproductive health and research; nutrition; disability and rehabilitation; classification and terminology; and making pregnancy safer, among others. Progress will require that the WHO partner with other organizations dedicated to the care and prevention of birth defects. Also vital to the process is the experience and involvement of national patient/parent support organizations and existing and future North/South and South/South partnerships and networks. The roles and responsibilities of this consortium should include advocacy, technology transfer and capacity building, research, promotion of ethics, and finance.

1. BACKGROUND

The WHO and March of Dimes, in the late 1950s and early 1960s, recognized that health transition in industrialized nations would lead to the necessity of developing medical genetic services (Rose, 2003; Stevenson et al, 1966; WHO, 1964). Subsequently, based on the developing science and technology, individual- and family-directed medical genetic practice rapidly evolved, primarily in academic and tertiary medical centres (Penchaszadeh, 1992; Christianson and Modell 2004).

1.1 Role of the WHO

In 1985, a group of WHO experts anticipated that the health transition in middle- and low-income nations would require the need for medical genetic services in the foreseeable future (WHO, 1985). Based on experiences gained in low- and middle-income countries from the implementation of medical services for the haemoglobin disorders, the expert advisory committee recognized such services would be fundamentally different from those in industrialized nations, because of differences both in culture and in the relative incidences of specific genetic diseases. The model of academic and tertiary care services in industrialized countries would need to be translated into a more holistic community-based strategy, incorporating public health approaches applied through primary health care and closely linked to secondary and tertiary services (WHO, 1989, 1996a; Alwan and Modell, 1997).

The HGN subsequently produced a series of reports supporting this approach providing guidelines for birth defect surveillance (WHO, 1993); the care and prevention of common genetic disorders, including the haemoglobin disorders (WHO, 1994, 1996b,c); and for ethics (WHO, 1998a). Additional reports expanded on the need to initiate and develop services for care and prevention of birth defects in low- and middle-income countries (WHO, 1998b, 1999, 2000; WHO/ICBD/EUROCAT, 2003).

In 2002, the WHO's Advisory Committee on Health Research published a report, entitled *Genomics and World Health*, which stated that it "should be considered in the primacy of fundamental overarching strategies to improve health" including "development of health systems, improved education and classical public health approaches to disease control and prevention and health promotion" (WHO, 2002a). In May 2004, the WHO's World Health Assembly (WHA) endorsed *Genomics and World Health*, adopting it as a relevant WHO resolution (WHO, 2004b).

This year, the Executive Board/117 adopted a resolution on sickle cell anaemia (WHO, 2006a) and made recommendations to the forthcoming WHA to support national and international activities on the control of SCA worldwide. Subsequently, similar discussions on SCD was held at the WHA/59 of this year and on thalassaemia and other haemoglobinopathies at the EB/118 and similar resolutions have been adopted (WHO, 2006b,c).

1.2 Role of the March of Dimes

The March of Dimes Foundation, a non-governmental organization was created in 1938 at the behest of President Franklin D. Roosevelt to combat polio. In 1958, recognizing the implications of health transition, the March of Dimes Foundation redirected its mission, which is currently to improve the health of babies by preventing birth defects, premature birth, and infant mortality. In 1998, the March of Dimes Birth Defects Foundation extended its mission internationally through the creation of its Global Programmes (Rose, 2003). Since 2003, the March of Dimes in its NGO capacity has been in official relations with the WHO.

In 2000, Global Programmes began to document the global toll of birth defects. This effort culminated in the publication in January 2006 of the *March of Dimes Global Report on Birth Defects: the Hidden Toll of Dying and Disabled Children* (Christianson et al, 2006). The March of Dimes report, endorsed by its National Board of Trustees and the American Academy of Pediatrics, features a database of modelled estimates of birth prevalence of common birth defects of genetic or partly genetic origin for 191 countries. The report recognized the principles and practices proposed in previous WHO documents, and it offered phased recommendations for

developing medical genetic services for the care and prevention of birth defects in middle- and low-income nations. The report's recommendations were designed to be implemented within existing systems of primary health care and to link to and strengthen current programmes in women, maternal, newborn and child health; nutrition; disability and rehabilitation; and disease surveillance, among others.

Publication of the March of Dimes Global Report (Christianson et al, 2006) and recent consideration of the WHO Executive Board on the need to control genetic diseases (WHO, 2005a) and on the importance of care and prevention of sickle cell disease (WHO, 2006a) prompted a joint WHO-March of Dimes *Meeting on the Management of Birth Defects and Haemoglobin Disorders*.

2. MEETING GOALS

The meeting had five goals. These were to (1) review the data on the global toll of birth defects and recommendations for care and prevention presented in the 2006 March of Dimes Global Report on Birth Defects (Christianson et al, 2006); (2) agree upon a definition of terms; (3) develop a collaborative plan for strengthening care and prevention of birth defects in low- and middle-income countries; and (4) develop a five-year plan for the WHO for strengthening care and prevention of haemoglobin disorders (sickle cell disease and thalassaemia) in low- and middle-income countries; and (5) determine how potential stakeholders (WHO Regional Offices; international and national governmental agencies; foundations and other nongovernmental organizations; parent/patient and other lay support groups; the private sector; and donor organizations) could contribute to these efforts.

2.1 Goal 1: Review the Data on the Global Toll of Birth Defects and Recommendations for Care and Prevention Presented in the 2006 March of Dimes Global Report on Birth Defects

The March of Dimes Global Report on Birth Defects estimates that 7.9 million infants are born annually with a serious birth defect of genetic or partly genetic origin. Of these births, 94 percent (7.4 million) occur in middle- and low-income countries. The estimated birth prevalence of these disorders ranges from 40 per 1,000 live births in high-income countries to a maximum of 82 per 1,000 live births in low-income countries. Over 3.3 million children under age five die each year from birth defects, with the majority of these deaths occurring in low- and middle-income countries. These deaths, whether due directly to the birth defect or a consequence of the birth defect being a co-morbid factor, have long been unrecognized.

The haemoglobin disorders, sickle cell anaemia and thalassaemias, contribute significantly to the global toll of birth defects. Although these disorders occur most frequently in tropical countries in which malaria was or still is a major killer, they contribute to mortality and disability in many other countries because of population migration. Approximately 7 percent of the world's population is a carrier for haemoglobin disorders, and between 300,000 and 500,000 infants with the severe, heterozygous forms of these diseases are born each year (World Bank, 2006).

Despite the availability of effective treatment, 50-80 percent of children with sickle cell anaemia and 50,000-100,000 children with β -thalassaemia die each year in low- and middle-income countries. Survival is frequently associated with disability from anaemia, haemolytic crises, stroke, infection and other complications. Weatherall et al recently documented the significant contribution of the haemoglobin disorders to the global tally of disability-adjusted life years (DALYs) (Weatherall et al, 2006).

After reviewing these data, participants endorsed the estimates in the March of Dimes Global Report, and they encouraged efforts to strengthen and expand the report's database. Such efforts could include active identification of existing data on birth defects mortality, disability and economic costs and emphasizing data collection as part of future programmes for care and prevention. The report's estimates of childhood death differ appreciably from the WHO's figures of childhood deaths from congenital anomalies, and this difference cannot be explained solely by the difference in definition between birth defects and congenital anomalies (Bryce et al, 2005; WHO, 2005b; Christianson et al, 2006). March of Dimes estimates, thus, should not be taken to represent official estimates of WHO.

In addition, meeting participants supported the report's recommendations for implementation and strengthening of programmes, including medical genetic services, in low- and middle-income countries. They also affirmed the recommendations of two previous WHO reports that preceded the March of Dimes report (WHO, 2000, 1999; Christianson et al, 2006).

2.2 Goal 2: Agree Upon a Definition of Terms

The development of coherent health policy and appropriate services requires detailed, reliable epidemiologic and burden of disease data (Murray and Lopez, 1998). The first step in obtaining these data is to clearly define and classify the disorders under review. Broad agreement on a definition of disorders that are congenital, that is 'existing from birth' or of prenatal aetiology has been lacking to date (New Shorter Oxford English Dictionary, 1993; WHO, 1998b).

The preferred term of the March of Dimes for this group of disorders is "birth defects" and it defines these as abnormalities of structure or function, including metabolism, which are present from birth. This definition reflects that some birth defects are clinically obvious at birth, while others manifest later in life. The March of Dimes recognizes that the term birth defects is not universally accepted. It uses the term, however, because it is broadly used and recognized.

The term, "serious birth defects," is considered by the March of Dimes to encompass disorders that are life threatening or have the potential to result in disability. Their aetiology includes genetic disorders (single gene defects and chromosomal abnormalities) and partly genetic disorders (multifactorial congenital malformations); non-genetic disorders which are the consequence of abnormal fetal environmental factors, including teratogens that disturb normal growth and development of the embryo or fetus; mechanical forces that deform the fetus; vascular accidents that disrupt the normal growth of organs and limbs; and, as yet, unknown causes (Christianson et al, 2006).

The term, birth defects, has also been used by a number of others including the HGN, the International Clearinghouse of Birth Defects Surveillance and Research (ICBDMS) (WHO, 1998b, 1999, 2003) and more recently the United States Surgeon General in his report on the 2005 2nd International Conference on Birth Defects and Disabilities in the Developing World in Beijing (Carmona, 2005).

However, the HGN prefers the term "congenital disorder," which is defined as any potential pathological condition arising before birth, including all disorders caused by environmental, genetic and unknown factors, whether they are evident at birth or become manifest later in life (WHO, 2000, 1985). WHO has also used the terms "congenital malformations, deformations and chromosomal abnormalities" which are classified in its 10th revision of the International Classification of Diseases (ICD 10) primarily on an anatomical basis, rather than by aetiology or pathogenesis (WHO, 1992).

Collectively, these disorders comprise what the WHO Burden of Disease Unit calls "congenital anomalies" (Shibuya and, Murray, 1998). Congenital anomalies are macroscopic morphological anomalies present from birth. A major problem with this term is that it excludes functional birth defects including non-syndromic, congenital disability (intellectual, physical, visual and auditory disability and epilepsy), common single gene disorders such as the haemoglobin disorders, glucose-6-phosphate dehydrogenase deficiency, cystic fibrosis, oculocutaneous albinism, spinal muscular atrophy and inborn errors of metabolism. It also excludes many common teratogen-induced birth defects, including congenital syphilis, congenital rubella syndrome and iodine deficiency (WHO, 1992). Unfortunately, the ICD 10 continues to be widely used for the purposes of gathering and exchanging data related to birth defects.

After review of these issues, meeting participants concluded that the term "birth defect" is synonymous with the term "congenital disorder" as defined and used by the HGN and they agreed that both could be used interchangeably. This agreement ended over two decades of uncertainty.

Participants further encouraged the WHO's Classification and Terminology Unit, in its development of the next version the International Classification of Diseases (ICD 11) to actively engage those organizations and individuals necessary to develop an internationally acceptable classification of birth defects. The point of departure could be this committee's acceptance of the definition of the terms birth defect and congenital disorder as synonymous.

2.3 Goal 3. Develop a Collaborative Action Plan for Strengthening Care and Prevention of Birth Defects in Low- and Middle-income Countries

Meeting participants agreed that up to 70 percent of birth defects can be prevented, ameliorated or treated effectively, but that to do so on a global basis would require the strengthening of programmes, including medical genetic services, in low- and middle-income countries. Such services should build on a continuum involving peri-conception care, maternal health, management of labour, and newborn and child health care for infants and children with acute and chronic disorders. Services for the care and prevention of birth defects must also link to and build on programmes in nutrition, immunization, infectious disease control and disability and rehabilitation, among others. In addition, medical genetic services should have a strong base in primary health care and be integrated with secondary and tertiary health care services (WHO, 1985, 1996a, 1999, 2000; Alwan and Modell, 1997; Christianson et al, 2006; Czeizel et al, 1993).

Medical genetic services should emphasize both care *and* prevention. Care includes the recognition and diagnosis of birth defects; treatment involving therapeutic, surgical and neurodevelopmental therapy; and counselling with psychosocial support. Care can be cost-effective as is seen, for example, with the diagnosis and surgical treatment of common malformations such as certain cardiac defects and cleft lip and palate (WHO, 1999, 2002c; Christianson and Modell, 2004; Christianson et al, 2006).

Care, however, can also be expensive, particularly for disorders that require long-term treatment. This has been documented in the treatment of thalassaemias in Cyprus, Thailand and Iran. In these instances, reducing the toll of mortality, disability and costs from birth defects can often best be accomplished through a combination of care and establishment of services for the prevention of birth defects (WHO, 2000; Weatherall and Clegg, 2001; Angastiniotis et al, 1986; Christianson et al, 2006; Weatherall et al, 2006).

Preventive services depend initially on the implementation of basic reproductive health approaches, best provided as part of pre-conception care. Such services include family planning and optimizing women's health through, for example, improving the diet, treating significant illnesses such as insulin-dependent diabetes mellitus and epilepsy optimally, and controlling teratogenic infections, and the use of family histories to identify families and individuals at risk of a genetic condition (Scheuner et al, 1997). Meeting participants agreed that all countries are potentially capable of providing these services (WHO, 1999, 2004a, 2005a ; Christianson and Modell, 2004; Christianson et al, 2006).

Table 1 lists basic reproductive approaches to prevent birth defects that meeting participants agreed are appropriate for low- and middle-income countries.

For countries where needs and resources allow, the next step is the implementation of medical genetic services, with genetic counselling, prenatal diagnosis and associated services for risk identification and management. Table 2 lists medical genetic services for birth defects that meeting participants agreed are appropriate for low- and middle-income countries.

Priorities for Care and Prevention of Birth Defects in Low- and Middle-income Countries

Meeting participants identified three priorities for action to assist in the initiation and development of services for the care and prevention of birth defects: (1) support continued research for the collection and refinement of birth defects data to assist the development of medical genetic services; (2) provide practical advice and support for countries wishing to develop medical genetic services; and (3) promote human resource capacity development and technology transfer.

Priority 1: Support continued research and the collection and refinement of data relevant for the development of medical genetic services

The March of Dimes Global Report database provides modeled estimates of the birth prevalence of genetic birth defects for 191 countries. While providing an important first step, the authors recognised that the March of Dimes database needs to be expanded and refined.

Meeting participants agreed that there is, thus, a need for the ongoing identification and collection of high-quality data on the birth prevalence of birth defects in low- and middle-income countries. Efforts should be made to identify existing datasets and collect new data as a routine part of future interventions. Particular attention needs to be paid to the collection of data on birth defects-related mortality, disability and disability-adjusted life years (DALYs).

In addition, participants recognised that the collection of data does not necessarily require expensive investigations (e.g. molecular data). For example, the medical genetic services of low- and middle-income countries could be very much enhanced if doctors and nurses were able to prepare and make initial interpretations of accurate family trees.

The effectiveness of care and prevention programmes for birth defects in low- and middle-income countries is limited. Cuba was the first country to develop comprehensive medical genetic services (Hereadero, 1992). South Africa, in the face of an HIV/AIDS pandemic, is making progress towards such a service based, in part, on experiences gained from undertaking community-based primary health care services in a rural area (Christianson et al, 2000; National Department of Health (S. Africa), 2001). The successes in the prevention of neural tube defects in China in a study of folic acid supplementation and in Chile as a result of national fortification of flour with folic acid also are documented (Hertrampf and Cortés, 2004; Berry et al, 1999). There is a need for additional information of this type.

The toll of birth defects includes, besides the burden on birth prevalence, mortality and morbidity, an economic cost to individuals, communities, and countries. Limited information and an approach to costing of care in middle- and low-income nations are available for the haemoglobin disorders, particularly thalassaemias (Weatherall, 2006; WHO, 2000, 1994; Alwan and Modell, 1997). Almost no information is available in middle- and low-income nations on the financial implications of birth defects in general or of other individual birth defects. Without this information it will be difficult to persuade international agencies and governments of middle- and low-income nations of the importance of developing national programmes for the care and prevention of birth defects. Close interaction with health economists towards developing better knowledge of the economic aspects of birth defects is, therefore, imperative. In addition, effective models from the haemoglobinopathy management programmes described under Goal 4 could be partly applied to other congenital disorders, especially through community outreach and the use of the primary care teams. In doing so, however, it should be recognised that the haemoglobin disorders are easier to diagnose and monitor than other autosomal recessive disorders because the carrier test is simple and cheap and allows cascade testing in large families.

The study of the ethical, legal and social issues (ELSI) of human genetics has, to date, been largely pursued and reflective of issues in industrialized nations. It is, thus, recognized by many working in middle- and low-income countries that much of the discussion of ELSI should be directly applicable to their varied social, cultural, religious and legal milieu (WHO, 1996a, 1998a). Meeting participants agreed that ELSI needs to be integrated with knowledge and experience gained from development of medical genetic services in middle- and low-income nations into a broader framework and discussion.

Priority 2: Provide practical advice and support for countries wishing to develop medical services for the care and prevention of birth defects

Countries initiating and developing medical genetic services for birth defects require assistance. The approach to developing and implementing a structured national medical genetic service plan using a multidisciplinary task team was previously documented by the HGN (WHO, 2000, 2002b). Advice and practical assistance should be available from internationally-recognized and designated expert advisors. Individual experts have successfully assisted several countries including Egypt, Iran, South Africa, and Thailand; however, the use of a team of experts covering a broad range of expertise and with a structured approach would be preferable. The importance of the role of WHO collaborating centres, experts and regional groups cannot be over-estimated.

Although many of the international expert advisors will be employed in the academic sector of their countries, it should be cautioned that developing countries need input from practitioners who know how to establish and maintain services. Thus, it may be counter-productive to offer molecular genetic expertise in a country which does not gather precise family trees.

Priority 3: Support the development of capacity in human resources and technology transfer

The meeting participants agreed that building capacity in human resources is essential. Doctors, nurses and other health care workers—particularly in primary health care—must be educated and trained in the services required for the care and prevention of birth defects and there is country experience on which to draw. For example, Chile, Cuba, and South Africa have developed curricula and methods to train primary health care workers in care and prevention of birth defects, and Chile is currently assessing the use of telemedicine for this purpose. South Africa, in collaboration with the March of Dimes is doing the same.

There is an equal need for technology transfer and training in support of appropriate laboratory services. Again, there is experience on which to draw. North/South partnerships have been instrumental in developing laboratory expertise for thalassaemia diagnosis and carrier screening in Eastern Mediterranean and Asian countries (WHO, 1989, Alwan and Modell, 1997).

The potential of the WHO to provide invaluable assistance and impetus to technology transfer and capacity building is significant and this should be undertaken through coordination via the structures and influence of its Regional Offices (WHO, 2002b, 2004a).

2.4 Goal 4: Develop a Five-year Plan for the WHO for Strengthening Care and Prevention of Haemoglobin Disorders (Sickle Cell Disease and Thalassaemia) in Low- and Middle-income Countries

As a result of carrier protection against malaria, the inherited disorders of haemoglobin are the commonest diseases due to the effect of a single defective gene. Inherited haemoglobin disorders fall into two main groups: structural haemoglobin variants and the thalassaemias, which are caused by defective globin production. The commonest structural haemoglobin variants are haemoglobins S, C and E. The homozygous state for Hb S results in sickle cell anaemia, which occurs most frequently in Africa, the Middle East and India. The compound heterozygous state for haemoglobins S and C, Hb SC disease, which occurs frequently in Africa, also presents a considerable health burden. Haemoglobin E, which reaches extremely high frequencies in many parts of Asia, results in only a very mild form of anaemia in homozygotes but, because it is produced at a reduced rate and behaves like a mild form of β -thalassaemia, it is of considerable public health importance (Weatherall et al, 2006)

There are two important forms of thalassaemia, α - and β -thalassaemia. The milder forms of α -thalassaemia (the α^+ -thalassaemias) occur at very high frequencies throughout the tropical world whereas the more severe forms (the α^0 -thalassaemias) are restricted to Southeast Asia and some of the Mediterranean populations. The homozygous states for β thalassaemia usually result in profound anaemia from early life that requires regular blood transfusion for survival. Compound heterozygotes for β -thalassaemia and Hb E have a condition called Hb E β -thalassaemia which is extremely common in many parts of Asia and which has a clinical course which ranges between that of severe β -thalassaemia to a milder, intermediate form of the disease. Homozygosity for the severe forms of α -thalassaemia results in stillbirth, while compound heterozygosity for the mild and severe forms produce a disease of intermediate severity.

Carrier frequencies for the haemoglobin disorders are available (WHO, 1994; Weatherall and Clegg, 2002). Although these data are approximate mainly because of the marked variation in gene frequency of these conditions in different parts of individual countries, it is clear that the haemoglobin disorders pose an increasingly serious health problem, particularly in developing countries that are passing through the health transition; babies who would have died of these conditions early in life in the past are now surviving to present for diagnosis and management. For example, it is estimated that 200,000 to 300,000 babies are born with sickle cell anaemia in Africa each year and approximately 100,000 are born

with this condition in the Middle East and India. Similarly, it is estimated that over the next 20 years, 100,000 cases of Hb E- β thalassaemia will be added to the Thai population and 20,000 β thalassaemia homozygotes will be born each year in Southern China. Currently in Thailand, there are about 600,000 children with severe forms of thalassaemia. A preliminary attempt at describing the haemoglobin disorders in terms of disability-adjusted life year (DALY) losses is reported by Weatherall et al (2006).

Services for the Care and Prevention of Haemoglobin Disorders

Progress towards the care and prevention of haemoglobin disorders has resulted largely from the evolution of North/South partnerships which started in the 1970s and which have evolved, in a few cases, to South/South networks more recently (Angastiniotis, 1986; WHO, 1994, 2000; Modell and Kuliev, 1998; Weatherall et al, 2006).

Because the haemoglobin disorders were the first to be explored at the protein and molecular levels, and led the way towards studies at the molecular basis of genetic disease, a number of centres in the developed countries gained expertise in the diagnosis and management of these conditions, and their prenatal diagnosis, in the 1970s. By developing sustained partnerships with the developing countries it was possible to transfer this expertise and hence to develop national programmes for the control of the haemoglobin disorders in a number of developing countries. Programmes of this type resulted in major improvements in the care and prevention of the thalassaemias in Mediterranean countries and later in the Middle East and parts of India, and of sickle cell anaemia in the Caribbean. Recently, a few programmes of this type have been developed for the control of sickle cell anaemia in parts of Africa (Weatherall et al, 2006).

More recently, based on these advances, a South/South thalassaemia network is developing in Asia, the objective of which is to allow those countries which have expertise in the control of the thalassaemias to help develop this expertise in countries in which it is completely lacking (Weatherall et al, 2006).

This pattern for the evolution of programmes for the better management of genetic disease was endorsed by a report, Genomics and World Health, published by the WHO (WHO, 2002a). However, these improvements in the control of the haemoglobin disorders have been almost totally reliant on partnerships and networks built up by individual doctors and parent associations. There has been no support except advice from the international health agencies or charities and at the present time only six Asian countries have thalassaemia control programmes which are recognised by their governments (Thailand, Malaysia, Sri Lanka, Singapore, Maldives, China). Malaysia, for example, has embarked on a programme of training thalassaemia counsellors in preparation for a nation-wide population screening for the thalassaemia trait among secondary school students. A similar situation exists in the case of sickle cell disease in Africa and India. And many developing countries have no expertise at all in the care and prevention of these conditions.

Currently, the evolution of programmes for the control of haemoglobin disorders has reached three levels. First, in many developed countries these services are well established although there are still some deficiencies, particularly in governmental application of control programmes. Second, in many developing countries there is considerable expertise in the diagnosis and management of the haemoglobin disorders yet they have not been supported by adequate recognition or support by their governments. Thus although there may be satisfactory diagnostic services only a minority of richer families are able to afford adequate prevention or treatment and the mean survival of patients with these conditions is still unacceptably low. Finally, in many developing countries no services for the control or management of the haemoglobin disorders exist.

Priorities for a Five-Year Programme in the Care and Treatment of Haemoglobin Disorders

Either through continued North/South partnerships or the development of South/South networks based on the Asian Thalassaemia Network model, over the next five years an effort must be made to improve the situation in

developing countries where no services exist for the control of these conditions. Given the WHO's current focus on haemoglobin disorders it is anticipated that it will dedicate itself through its various organs to the accomplishment of this endeavour. By activating and organising these networks, the following priorities should be addressed.

Priority 1: Support continued research for the collection and refinement of data relevant for the control of haemoglobin disorders

The development of simple research programmes into important aspects of the haemoglobin field, hitherto neglected, is required. Low- and middle-income countries in which the haemoglobin disorders are common need more information about their carrier frequency. These data are necessary to determine a country's birth prevalence, distribution and the economic consequence of haemoglobin disorders and advise them about the structure and the economic requirements for their care and prevention services. Carrier frequency determination requires micro-surveys, that is the analysis of a few hundred people from every region of a particular country. The screening methods for all the haemoglobin disorders are simple and cheap, and a programme of this type simply requires adequate organisation and training in the technology required. The importance of obtaining this information cannot be overemphasised (WHO, 1994; Weatherall et al, 2006). In many developing countries with multi-ethnic populations, use of a Thalassaemia Registry to collect clinical and laboratory data on severe forms of thalassaemia can provide useful information on the needs for long-term care of the disease and result in the development of cost-effective preventive strategies (Setianingsih et al, 1998; Thong et al, 2005).

A recent preliminary cost-benefit analysis of service issues related to the haemoglobin disorders concluded that specialised treatment centres and neonatal screening programmes are cost-effective approaches towards the control of sickle cell anaemia and, at least in some countries, the thalassaemias (Weatherall et al, 2006). Further economic data of this kind are urgently required.

Information is also required on local environmental influences on mortality and morbidity of these disorders, and how best to combat these. Numerous questions on best practices in the care and prevention of the haemoglobin disorders need answering. For example, it has been shown unequivocally that neonatal screening and the initiation of prophylactic penicillin can save the lives of many children with sickle cell disease in some countries, but what is the pattern of death due to infection in children with this condition in Africa? Would prophylactic penicillin save a similar number of lives in Africa or India? What is the effect of malaria on sickle cell disease in Africa or on thalassaemia in Asia?

Recent examples of such research that can inform policy development are available from two haemoglobin disorder programmes: the significant reduction of mortality and morbidity from sickle cell disease in Lagos, Nigeria, by the implementation of basic primary health care interventions and the development and effectiveness of thalassaemia services in Iran. (WHO, 2000; Samavat and Modell, 2004; Akinyanju et al, 2005).

As with birth defects generally there are issues related to the application of ethical principles developed in a western environment being applicable to the different social, cultural and religious circumstances of low- and middle-income countries. Among these is the question of whether the approach to genetic counselling developed for Western medicine is appropriate elsewhere. More information about the best methods for genetic counselling and social support for families with the haemoglobin disorders in different cultures is vital (WHO, 2000; Weatherall and Clegg, 2001; Weatherall et al, 2006).

Priority 2: Provide practical advice and support for countries wishing to develop medical services for care and prevention of haemoglobin disorders

The continued North/South partnerships and the development of South/South networks based on the Asian Thalassaemia Network, is the model for the next five years on which the initiation and development of control programmes for haemoglobin disorders in middle- and low-income nations should be based. One example of a successful North/South

partnership is the collaboration between research institutions in Malaysia and Australia that has resulted in the first-ever clinical and molecular description of beta thalassaemia major among the Kadazandusun people, a major indigenous tribe of north Borneo (Thong et al, 1999). Attention should be paid to those Asian countries where there is no expertise in thalassaemia and this could be achieved through the further evolution of the current Asian Thalassaemia Network. In the case of sickle cell disease, it is particularly vital to develop similar networks in Africa and separate networks for India and the Middle East; there are major differences in the pattern of evolution of sickle cell anaemia in these regions. This programme should be evolved under the control of groups of experts from each of these regions, or where there is no expertise by the development of North/South interactions.

The WHO could help greatly in defining appropriate regions and in helping to recruit the local experts required to form South/South regional networks or even North/South networks. It could also help in enabling the local regional networks to develop education programmes and technical workshops and, in particular, it could play an active role in trying to persuade the government of the high-frequency countries of the importance of these conditions in their national health programmes (WHO, 2002b).

Haemoglobinopathy control programmes based on WHO approaches and recommendations have been established in different countries and in each WHO Region. Appropriate thalassaemia programmes are now being developed in a number of European countries, such as Cyprus, Greece, Italy, UK, as well as, in Brazil, China, India, Islamic Republic of Iran, Myanmar, Pakistan, Thailand, Tunisia, Turkey. Feasibility studies on thalassaemia control now exist in Bahrain, Egypt, the Maldives and Saudi Arabia. SCD programmes have been established in Cuba and are being initiated in Nigeria and Ghana.

In many countries, there are national support associations which are linked internationally through the Thalassaemia International Federation (TIF). TIF organizes international meetings, bringing together patients and doctors, and provides information, encouragement and support in developing appropriate services in countries (TIF, 2003). The WHO, its collaborating centres, TIF and other non-governmental organizations could explore ways to increase public knowledge of haemoglobin disorders and contribute to a global public dialogue about improving of medical genetic services.

Regional WHO offices could play a major role in monitoring the progress of the networks and reporting back to individual governments. This support could also include the drafting of regional guidelines on care and prevention of birth defects and the advocating of research. The regional offices for Africa, South-East Asia and the Eastern Mediterranean have included haemoglobin disorders among their planned activities.

Priority 3: Human resource capacity development and technology transfer

The basic requirements for the development of programmes for the control of the haemoglobin disorders have been described in detail in several publications (TIF, 2003; WHO, 1994, 2000; Alwan and Modell, 1997; Weatherall and Clegg, 2001; Weatherall et al, 2006). They involve the combination of intensive education programmes combined with the development of clinical and diagnostic services, which must be established simultaneously.

The education programmes include clinicians, scientists, nurses, counsellors, and the evolution of parent associations. The basic clinical services involve education about the diagnosis and treatment of the disorders backed up by laboratory services for screening and heterozygote identification, the diagnosis of the major haemoglobin disorders and, in countries in which it is acceptable, facilities for prenatal diagnosis and bone-marrow transplantation.

The curricula and experience necessary to undertake such education and training programmes and to integrate this into the programmes for the

establishment of haemoglobin disorder services in low- and middle-income nations is available. All that is required is reasonable financial sponsorship and collaboration between the WHO/HGN, the WHO's Regional Offices, national governments and individuals and organizations committed to achieving control of haemoglobin disorders.

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.

In some countries, programmes for the care of haemoglobin disorders can also be the prototype of the genetic management of other, non-haematological disorders. Therefore, the paediatric neurologist or immunologist in developing countries will benefit from awareness of the blood disorder care networks.

2.5 Goal 5: Determine How Potential Stakeholders Can Contribute to the Activities Outlined in Goals 3 and 4

The realization of Goals 3 and 4 in this report will require the combined efforts and political will of the WHO, its directorship, the HGN and, most important, the WHO programmes associated with newborn and child health; reproductive health and research; nutrition; disability and rehabilitation; classification and terminology; and making pregnancy safer, among others. Meeting participants were encouraged by the WHO's focus on the haemoglobin disorders as this will provide a framework for future coordination and action on care and prevention of birth defects generally. Progress will require that the WHO partner with other organizations dedicated to the care and prevention of birth defects, including the March of Dimes Birth Defects Foundation, U.S. Centers for Disease Control and Prevention (CDC), International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), World Alliance of Organizations for the Management and Prevention of Birth Defects (WAO) and International Genetic Alliance (IGA), the European Surveillance of Congenital Anomalies (EUROCAT) and the TIF. Also vital to the process is the experience and involvement of national Patient/Parent support organizations and existing and future North/South and South/South partnerships and networks. The roles and responsibilities of this consortium should include advocacy, technology transfer and capacity building, research, promotion of ethics and finance.

Advocacy

Several misperceptions help to explain why care and prevention of birth defects, including haemoglobin disorders, have received little attention from international donors and health agencies. These include a lack of awareness of the harsh global toll of birth defects; the erroneous belief that effective care and prevention require costly, high-technology interventions that are beyond the health budgets of low- and middle-income countries; and concern that attention to birth defects will draw funding away from other high-priority maternal, newborn and child health priorities.

Meeting participants agreed, therefore, that it is vitally important that the nature and benefits of medical genetics services be promoted to WHO Regional Offices, national Ministries of Health policy makers and senior public health, primary health care, obstetric and paediatric practitioners. Ideally, this could be accomplished through in-depth courses in Community Genetics held under the auspices of WHO Regional Offices and targeted to specific audiences and population needs. For example, special attention would be given to haemoglobin disorders in those regions or countries in which they are common.

Technology Transfer and Capacity Building

As noted earlier in this report, implementation and strengthening of programmes, including medical genetics services in low- and middle-income countries, requires both professional education and training and funding for the laboratory and other services necessary in support. This is a recognised function of the WHO and its organs. Capability in this area is also available in the organisations attending the meeting and in existing North-South and South-South partnerships. Meeting participants agreed that there is considerable potential in the WHO to provide impetus to

technology transfer and capacity building through coordination of these resources via the structures and influence of its Regional Offices. The process of technology transfer could begin with the accurate preparation of the pedigree, interpretation of the mode of inheritance, decision-making about the best molecular investigations to perform and on whom in the family, and then progress to evidence-based therapeutic measures.

Surveillance

There is a need for improved data on the global toll of birth defects, including birth prevalence, mortality and disability. Birth defects surveillance is most often conducted at the local level—e.g., the California Birth Defects Registry. Regional networks—e.g., EUROCAT and international networks such as the ICBDSR exist, but are few in number. WHO and its partners like the March of Dimes can play an important role in identifying, qualifying and incorporating data on birth defects prevalence, mortality, disability, and the economic costs of action or inaction.

Almost no information is available from these countries on the financial implications of action or inaction on birth defects in general or on the costs or benefits of other interventions such as newborn screening. It is, thus, critical that the WHO work with partner organizations, including those represented at the meeting and others such as the National Institutes of Health or European Union to encourage such evaluation.

Finance

To date, the funding of programmes for the control of birth defects in low- and middle-income countries, including the haemoglobin disorders, has been limited and obtained on an *ad hoc* basis, available largely through funding from the North half of North/South partnerships (WHO, 1994, 2000). This has been supplemented in individual countries by the raising of funds by local charities, industry, and parent associations. Programmes for care and prevention of birth defects, including the haemoglobin disorders, have received virtually no major support from larger international organizations or funding agencies. In addition, because of a lack of government support in many countries, these programmes have been extremely difficult to sustain and expand.

Two options are available to resolve the current paucity of financing of medical genetic services for the care and prevention of haemoglobin disorders and other birth defects. Both involve the initial recognition by the WHO at the highest level—the World Health Assembly—of the global burden of birth defects and the need for medical genetic services in middle- and low-income nations. Were this to happen, political will in support would be forthcoming given the harsh global toll of birth defects and financing for medical genetic services would be more readily available from national governments. In addition, international health organizations would be more predisposed to consider funding programmes for research, care, and prevention of birth defects.

TABLE 1: Basic reproductive approaches to prevent birth defects that are appropriate for low- and middle-income countries

- Promote family planning, allowing couples to space pregnancies, plan family size, define the ages at which they wish to begin and complete their families and reduce the proportion of unintended pregnancies and support health education of the public, particularly of women and girls. This will:
 - ✓ reduce the overall rate of birth defects
 - ✓ decrease the birth prevalence of Down syndrome by reducing the number of mothers of advanced maternal age
 - ✓ allow women with affected children the option of not having further children
 - ✓ introduce women to the concepts of reproductive choice
- Before and during a woman's reproductive years, ensure a healthy, balanced diet and access to adequate quantities of macronutrients (protein, carbohydrates and fats) and micronutrients, including iodine, provided through universal salt iodization and folic acid through fortification of staple foods or supplementation, where these approaches are required. This will:
 - ✓ prevent iodine deficiency disorders in women during pregnancy and thereby prevent the cognitive impairment resulting from iodine deficiency in their offspring.
 - ✓ decrease neural tube defects and other malformations
 - ✓ prevent birth defects due to common teratogens such as alcohol and recreational drugs
- Control infections in all women before and during pregnancy. In particular,
 - ✓ prevent and treat syphilis
 - ✓ prevent congenital rubella syndrome through immunization with rubella vaccine
- Optimize maternal health through control of chronic illnesses associated with increased risk of birth defects. Target, in particular:
 - ✓ insulin-dependent diabetes mellitus
 - ✓ epilepsy and its control with anti-epileptic drugs
 - ✓ women on Warfarin for deep vein thrombosis or cardiac conditions

TABLE 2: Medical genetic screening for birth defects that are appropriate for low- and middle-income countriesPreconception

- Use of family history as a screening tool for birth defects and genetic conditions
- Carrier identification using family pedigrees
- Carrier screening for common recessive disorders, the haemoglobin disorders (FBC & indices, electrophoresis, DNA) and cystic fibrosis (DNA)

Antenatal

- Rhesus negativity
- Down syndrome (advanced maternal age, maternal serum, ultrasound)
- Neural tube defects (maternal serum & ultrasound)
- Major malformations (fetal anomaly scanning)
- Carrier screening for common recessive disorders, the haemoglobin disorders (DNA) & cystic fibrosis (DNA)

Postnatal

- Neonatal screening (using Guthrie cards)
 - ✓ Congenital hypothyroidism
 - ✓ Sickle cell disorders
 - ✓ Neonatal jaundice /G6PD deficiency
 - ✓ Inborn errors of metabolism

3. CONCLUSION

In 1964, as a result of the health transition, the then Director General of the WHO recognized the need for the development of medical genetic services in industrialized nations (WHO, 1964). Twenty years later, the expert advisory group recognized that the health transition in low- and middle-income countries would require the same need for services for the care and prevention of birth defects within the foreseeable future, and they established the basic and enduring principles on which these services would be based (WHO, 1985).

The WHO-March of Dimes meeting participants agreed unanimously that services for the care and prevention of birth defects in general, and for haemoglobin disorders in specific, should now be a priority for WHO in low- and middle-income nations. The steps required for implementing both, as indicated in this report, are similar. Establishing services for the care and prevention of birth defects in low- and middle-income countries will reduce mortality and disability from haemoglobin disorders worldwide. Similarly, establishing services for the care and prevention of haemoglobin disorders in high-risk populations will provide a framework and experience that can be applied to reducing the toll of other birth defects. In considering these steps, participants agreed that two principles should guide development of the proposed future action: *Health for All* and *Common Good*.

The late Dr LEE Jong-wook, the former Director-General of the WHO, was a member of the WHO generation that gave the world the concept of *Health for All*. Dr Lee believed that "Turning that vision into reality calls for clarity both on the possibilities and on the obstacles that have slowed and in some cases reversed progress towards meeting the health needs of all people" (Lee, 2003).

Infants and children with birth defects are a particularly vulnerable and under-recognised group in low-and-middle income nations. The initiation and development of services for the care of these at-risk populations and implementation of services for the prevention of birth defects would honour Dr LEE's belief in the importance of *Health for All*. Given that infants and children are also members of their families and communities, the establishment of services that reduce the harsh toll of birth defects in these vulnerable populations should also be viewed as a *Common Good*.

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5. ACKNOWLEDGEMENTS

The co-sponsors thank Ms Soleil Labelle of HGN and Ms Rachel Diamond of the March of Dimes for their organization and administrative support of the meeting. They also gratefully acknowledge the participation of WHO staff, not associated with HGN, but who work on programmes related to aspects of care and prevention of birth defects: Dr Robert Jakob, Dr Martin Weber, Dr Erin Mclean, Dr Mario Meriardi, Dr Federico Montero, and Dr Jelka Zupan. Their contributions were essential to the success of the meeting.

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