



# Overview Document

**to the PHG Foundation Toolkit for  
Assessing Health Needs in relation  
to Congenital Disorders**

Version 1.0: November 2011

# A brief introduction to the Born Healthy programme

## Programme overview and rationale

Better health for mothers and children is at the heart of the Millennium Development Goals. The epidemiological transition in many low and middle income countries (LMIC) has been characterised by significant reductions in infant and child morbidity and mortality, especially from infectious diseases. As a consequence, congenital disorders (structural and functional abnormalities present from birth; also known as birth defects), account for an increasing proportion of ill-health, morbidity and mortality in the population.

**It has been recognised that the Millennium Development Goals for child mortality cannot be reached without progress in reducing the burden of congenital disorders. Significantly, in May 2010 the World Health Assembly (WHA) passed a resolution calling on member states to ‘prevent birth defects wherever possible, to implement screening programmes, and to provide on-going support and care to children with birth defects and their families’. In particular, the WHA resolution noted that ‘international technical guidance will be required to help ministries with ‘organized assessment of requirements and costs and with support in choosing priorities’.**

Growing evidence indicates that 70% of congenital disorders can be either avoided or appropriately managed, leading to substantial reductions in morbidity and disability, and improved survival and well-being. This can be achieved through simple and readily available medical and social interventions, as well as by accessing newer health technologies. Nevertheless, congenital disorders continue to be largely unrecognised as a significant public health problem, not least due to poor understanding of what is possible, together with resource constraints and competing priorities.

The Born Healthy Programme at the PHG Foundation has responded to the WHA resolution by creating a framework and a freely available toolkit, designed to help ministries and others at national and sub-national levels to assess health needs in relation to congenital disorders in their own countries, territories or regions, and make a rational, evidence-based case for the development of effective services for the care and prevention of these conditions. Users are also enabled to select priorities and implement appropriate actions to address identified needs. The ultimate goal of the programme is to improve health outcomes of people with congenital disorders, and to reduce the burden of these conditions globally and particularly in LMIC, where most of the burden of disease is found.

*We aim to provide governments and their health partners with the tools and data to build the evidence base and make the case for the development of services to tackle congenital disorders in their populations; and to use the toolkit as a focus for creating national and international momentum to secure better services for preventing congenital disorders and caring for those affected and their families, especially in low and middle income countries.*

*PHG Foundation Programme on Congenital Disorders (The Born Healthy Programme)*

# **Congenital Disorders: The global burden of disease, and opportunities for care and prevention**

## **What are ‘Congenital disorders’ or ‘Birth defects’?**

Congenital disorders may be classified into three groups: conditions with causes originating before conception, conditions with causes originating after conception but before birth, and conditions with unknown causes.

### **Congenital disorders with causes originating before conception**

These result wholly or partially from abnormalities in the genetic material (chromosomes and genes). They can be inherited or occur as isolated events and include chromosomal disorders, single gene disorders, and multifactorial disorders due to a combination of genetic and environmental factors (for further explanation of these terms, see Appendix 1). Genetic or partly genetic conditions account for approximately 80-90% of congenital disorders whose cause is known (40-45% of all congenital disorders).

### **Congenital disorders with causes originating after conception**

These are considered primarily non-genetic and are caused by external factors acting in the fetus. They include disorders caused by maternal conditions such as diabetes or iodine deficiency and those caused by teratogens such as maternal infections, prescribed and recreational drugs (including alcohol), environmental pollutants and physical agents, e.g. radiation. These environmental causes are thought to account for approximately 10-20% of congenital disorders whose cause is known (5-10% of all congenital disorders).

### **Unknown causes**

Approximately half of all congenital disorders have no recognised specific cause.

## **The global burden and distribution of congenital disorders**

Accurate figures for the burden of congenital disorders are lacking for many countries. For the purposes of this document, unless otherwise stated, estimates used are from the Modell Global Database of Constitutional Congenital Disorders (MGDB) compiled by Professor Bernadette Modell; these estimates are for 2005 (for more information on these figures see the document: Introduction to HNA and methodology). Data from the MGDB indicate that, every year, approximately 5 million babies are born with a severe genetic disorder or congenital malformation, and nearly 3 million children under the age of 5 years die as a result of these conditions. However, these broad figures conceal substantial variation, both among different world regions and, in some cases, among different ethnic or geographic groups within countries or regions.

A range of determinants, from the individual level to wider societal factors, affect the occurrence and severity of congenital disorders. Examples of specific risk factors include advanced parental age, consanguinity, residence in or origin from places where malaria is common, micronutrient deficiencies (folate and iodine), and infection during pregnancy. Table 1 shows estimated birth prevalence and total numbers of births each year for different types of congenital disorders. Birth prevalence is affected by access to, or implementation of, prevention interventions such as prenatal diagnosis and termination of pregnancy, and folic acid fortification of food.

**Table 1:** Estimated annual worldwide births affected by genetic disorders or congenital malformations (source: MGDB)

Type of congenital disorder	Birth prevalence (/1000 live births)	Estimated annual affected births worldwide (based on annual births of 133 million and rounded to nearest 5,000)
Haemoglobin disorders <sup>1</sup>	2.8	375,000
Consanguinity-associated single gene disorders	4.3	570,000
G6PD-related neonatal jaundice <sup>2</sup>	1.3	170,000
Other single gene disorders <sup>3</sup>	4.4	585,000
Rhesus haemolytic disease of the newborn	0.7	95,000
Chromosomal disorders	2.8	370,000
Congenital malformations <sup>4</sup>	21.2	2,820,000

<sup>1</sup> Includes sickle cell disease (2.4/1000) and thalassaemias (0.4/1000).

<sup>2</sup> Does not include life-threatening haemolytic crises due to G6PD deficiency.

<sup>3</sup> Includes dominant conditions presenting by age 1yr (1.4/1000), baseline X-linked (1.33/1000) and baseline recessives (1.7/1000).

<sup>4</sup> Includes intractable malformations (5.2/1000) and correctable malformations (16.0/1000). Congenital malformations include partly genetic conditions (such as neural tube defects), and some conditions caused by environmental factors (for example, limb reduction defects caused by thalidomide), as well as malformations with no known cause).

### Single-gene disorders and genetic risk factors

The most common single-gene disorders worldwide are the haemoglobin disorders (sickle cell disease and thalassaemias), glucose-6-phosphate dehydrogenase (G6PD) deficiency, and cystic fibrosis. The haemoglobin disorders, with about 375,000 affected births per year, are particularly prevalent in malarial regions. Sub-Saharan Africa accounts for about 85-90% of the 325,000 babies born annually with sickle cell disease, and affected populations in Europe, the United States and the Caribbean largely originate from this region. Thalassaemias (50,000 affected births per year) are prevalent in the Eastern Mediterranean, Middle East, North Africa, South and East Asia. Glucose-6-phosphate dehydrogenase deficiency, a genetic risk factor for pathological neonatal jaundice and haemolytic anaemia, also occurs with increased prevalence in malarial regions, and in populations originating from these regions; affected births occur predominantly in Africa, the Middle East, Asia and the Caribbean. Cystic fibrosis occurs mainly in populations originating from northern and Western Europe.

A major risk factor for autosomal recessive genetic disorders is consanguineous marriages. Approximately 570,000 babies with autosomal recessive genetic disorders are born to consanguineous parents each year. Consanguineous unions are customary in many countries of North Africa, South and Central Asia, and the Middle East.

Rhesus incompatibility is a genetic risk factor for haemolytic disease of the newborn. This condition occurs mainly in LMIC which lack preventive programmes of maternal screening and anti-D prophylaxis.

In addition to these conditions, all populations have a baseline birth prevalence for single-gene diseases of about 4.4/1000 live births. These conditions include dominant conditions presenting by the age of 1 year, and recessive conditions other than haemoglobin disorders and G6PD deficiency. Although the conditions included in this 'baseline' category are individually rare, collectively they account for about 585,000 affected births per year.

### **Chromosomal disorders**

About half of the 370,000 annual births affected by chromosomal disorders are accounted for by Down's syndrome. The major risk factor for this condition is advanced maternal age (>35 years). Lack of access both to family planning and to services for prenatal diagnosis and prevention, are key determinants of its occurrence.

### **Multifactorial disorders**

Multifactorial congenital disorders usually present as malformations of organs, limbs or body systems (cardiovascular, digestive, nervous, respiratory etc.). Congenital malformations affect about 2.8 million births per year. The most common multifactorial disorders are congenital heart disease (approximately 675,000 affected births per year); conditions such as neural tube defects (226,000 annual affected births) and orofacial clefts (157,000 births per year affected by isolated cleft lip or palate) are also significant.

### **Disorders with environmental causes**

The most important non-genetic causes of congenital disorders are congenital infections, maternal illness and malnutrition, and recreational and therapeutic drugs. Accurate information is not available for the birth prevalence of many congenital disorders with environmental causes but the number of affected births is likely to be many hundreds of thousands per year. Congenital disorders with environmental causes may have a wide range of manifestations including learning disability, growth retardation and congenital malformations.

Congenital syphilis is a major cause of infant mortality in LMIC, as a result of lack of education, poor sexual health, low social status of women, and health services unable to diagnose and treat sexually transmitted infections early. Congenital rubella is more prevalent in countries where immunisation programmes are under-developed. Maternal diabetes is a significant problem in high-income countries, affecting around 0.5% of pregnancies, and is likely to be increasingly important in LMIC as access to western lifestyle and diet increase levels of obesity. Congenital hypothyroidism caused by maternal iodine deficiency occurs mainly in iodine-deficient populations without access to iodised salt.

The most important recreational drug linked to congenital disorders is alcohol, which in some regions (for example, the Western Cape Province of South Africa) is a major cause of congenital disability in children and may become a growing problem in societies where social constraints on alcohol consumption by women are lessening. Little reliable information is available on the prevalence of congenital disorders caused by medications used to treat conditions such as heart disease, epilepsy, or infectious diseases, especially in countries where pharmaceutical use is largely unregulated.

Figures 1 and 2 show the global distribution of births potentially affected by single-gene diseases, chromosomal disorders and congenital malformations (that is, in the absence of any preventive interventions). Figure 1, showing the estimates presented as potential affected births per 1000 births, gives an indication of the global distribution of risk factors for congenital disorders. The contributions of haemoglobin disorders, and of recessive diseases related to consanguinity, are particularly striking. In Figure 2, incidence is expressed in terms of potential new cases per 100,000 population per year. Because this way of representing the data takes birth rates into account, it gives some idea of the relative magnitude of the

burden of disease in different world regions and, in particular, the substantial burden of disease in Africa, the Middle East and South Asia.

## Care and prevention of congenital disorders

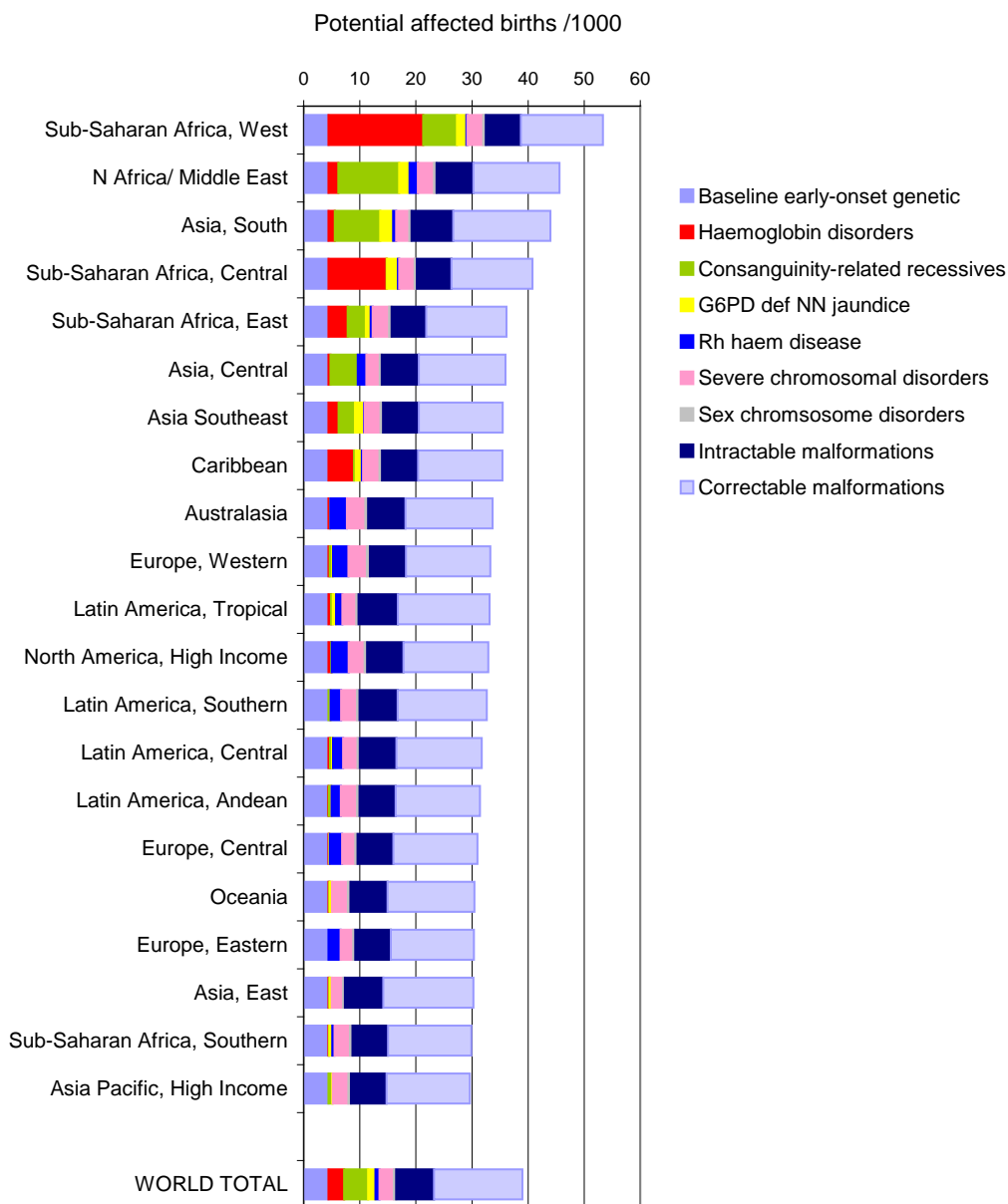
Many congenital disorders (particularly those with environmental causes) are readily preventable by simple, relatively low-cost interventions such as nutritional supplements (folic acid and iodine), management of maternal health problems such as diabetes, and immunisation and other means of infection control.

Primary prevention of genetic conditions may in some cases be achieved by interventions such as preconception carrier screening to inform choice of marriage partner, targeted advice and risk estimation in large consanguineous families affected by congenital disorders, and family planning services to reduce births in women over 35. In countries where prenatal diagnosis and termination of pregnancy are legal and socially acceptable in cases of severe fetal abnormality, this means of prevention may also be offered during pregnancy to couples who wish to avoid the birth of an affected child.

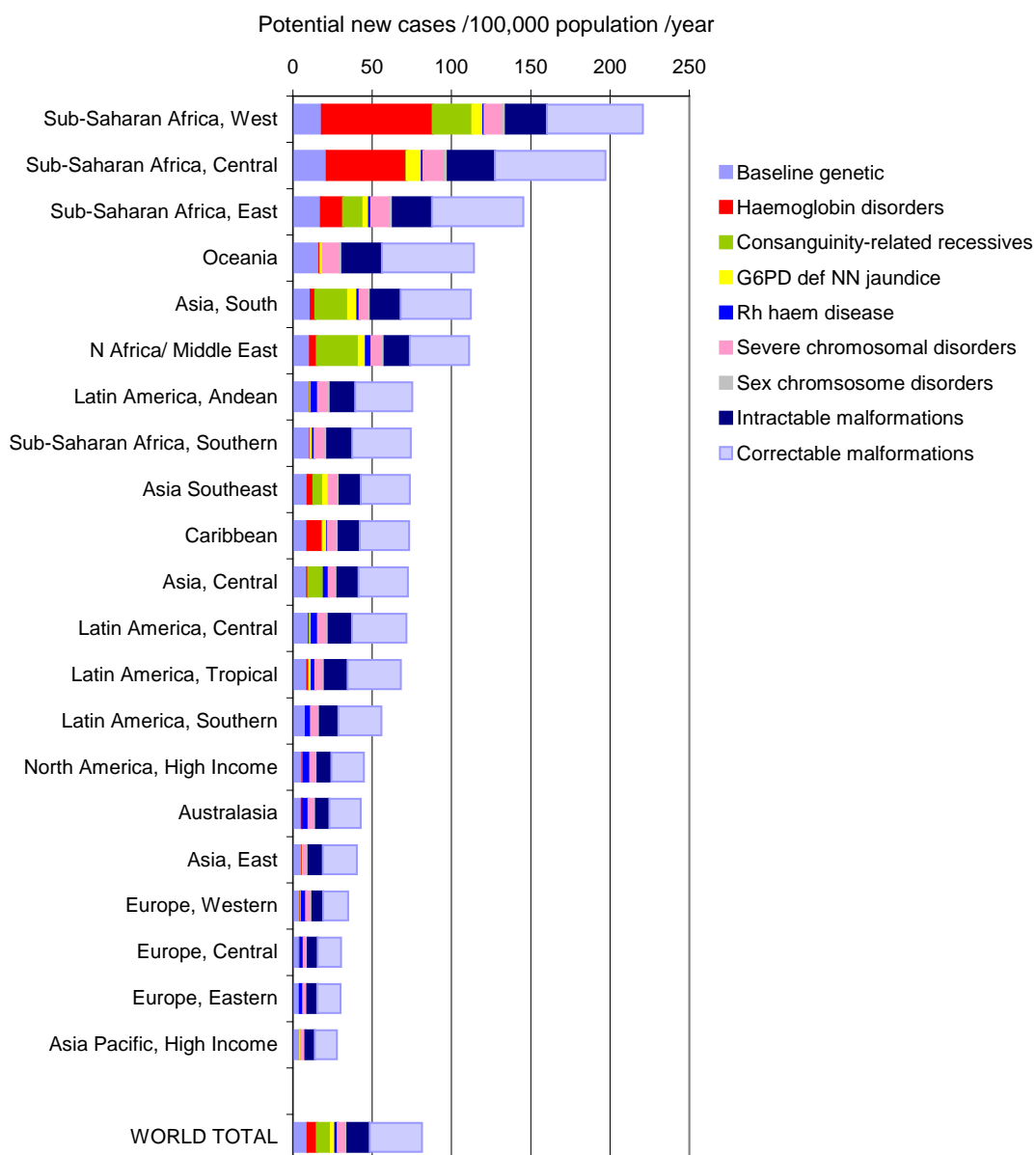
Treatments for individuals born with congenital disorders include both surgical and non-surgical interventions. Although some complex types of open-heart surgery, for example, are likely to be beyond the reach of many countries, more routine surgical interventions for some heart defects and for malformations such as orofacial clefts and club foot, may be feasible in these countries, and are likely to be cost-effective in enabling affected individuals to live independent lives. Non-surgical interventions include, for example, dietary modification or hormone therapy (e.g. for phenylketonuria or congenital hypothyroidism respectively), blood transfusion (with iron chelation therapy if necessary) for haemoglobin disorders, and physiotherapy and enzyme replacement therapy for cystic fibrosis. Social and educational support, both for the individual and the wider family group, are also important aspects of care.

Determinants of outcomes include, but are not restricted to, the country's level of development; access to and quality of health and other services; coverage of services and interventions; cultural, religious, ethical and legal issues. Table 2 illustrates the contributions of different types of preventive intervention (including tertiary prevention to avoid disability and prevent complications and deterioration) to reducing the burden of congenital disease.

**Figure 1:** Estimates of potential affected births in different world regions in the absence of preventative strategies (source: MGDB)



**Figure 2:** Estimates of potential new cases in different world regions in the absence of preventative strategies (source: MGDB)





**Table 2:** Relative contributions of preventive interventions for congenital disorders with genetic causes<sup>1</sup>

Group of Disorders	Birth Prevalence (per 1,000 live births)	Intervention (Primary, Secondary, Tertiary)	Maximum Postnatal Lives Saved (per 1,000 live births)	Maximum Reductions %	Estimated Average Increase in Longevity Per Head of Population (Years)
Congenital Malformations	36.5	Pediatric Surgery (3°)**	17.70	48.5	1.24
		Folic Acid Supplement (1°)**	11.50	31.5	0.81
		Prenatal Diagnosis (2°)**	3.50	9.6	0.25
		<b>Total Congenital Malformations:</b>	<b>32.70</b>	<b>89.6</b>	<b>2.30</b>
Chromosomal Disorders	3.8	Family Planning (1°)**	0.75	19.7	0.05
		Prenatal Diagnosis (2°)**	0.50	13.2	0.04
		<b>Total Chromosomal: Disorders:</b>	<b>1.25</b>	<b>32.9</b>	<b>0.09</b>
Genetic Risk Factors*	2.4	Routine Antenatal and Neonatal Care (3°)**	2.40	100.0	0.17
Inherited Disorders (severe, early onset)	11.5	Genetic Counselling (1°)**	1.73	15.0	0.12
		Neonatal Screening (3°)**	0.70	6.1	0.05
		Prenatal Diagnosis (2°)**	1.15	10.0	0.08
		<b>Total Inherited:</b>	<b>3.60</b>	<b>31.1</b>	<b>0.25</b>
<b>Total:</b>	<b>54.2</b>		<b>39.9</b>	<b>73.7</b>	<b>2.80</b>

\*G6PD deficiency and Rhesus hemolytic disease of the newborn \*\*1° = Primary prevention 2° = Secondary prevention 3° = Tertiary prevention

<sup>1</sup>Reprinted, with permission, from the Annual Review of Genomics and Human Genetics, Volume 5 ©2004 by Annual Reviews [www.annualreviews.org](http://www.annualreviews.org)

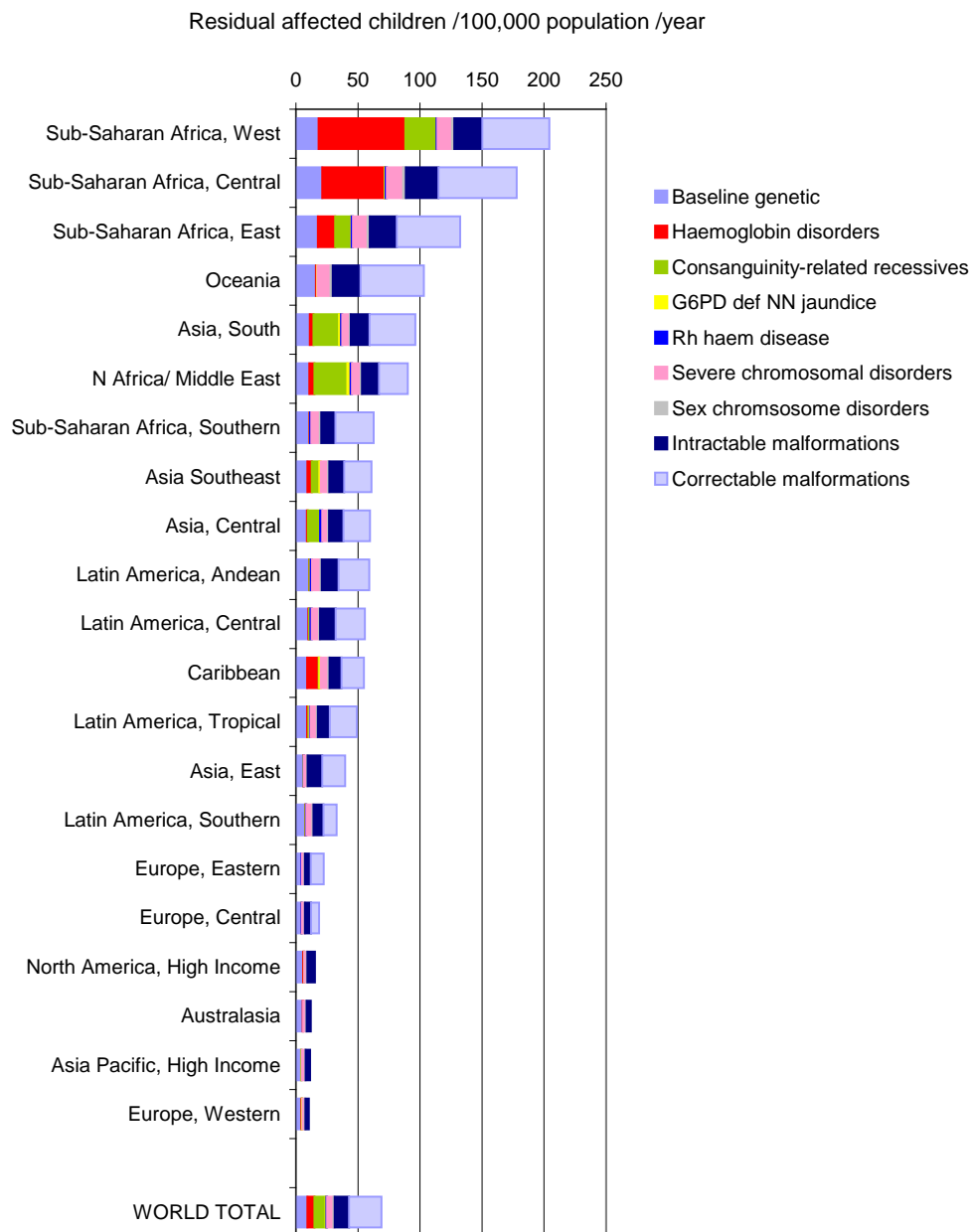
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Figure 3 shows estimates of residual numbers of affected children per 100,000 population per year in different world regions; that is, allowing for the effects of prevention, early diagnosis and treatment. Comparing Figure 2 and Figure 3 highlights the effectiveness of preventive interventions and treatment in high-income countries, and the huge potential for improved prevention and treatment in Africa, the Middle East and South Asia in particular, but also in Latin America, South-East Asia and Central Asia.

**Figure 3:** Estimates of residual affected numbers of children per 100,000 population, allowing for effects of prevention, early diagnosis and treatment (source:MGDB)



Many affected children die prematurely, and those who do not die often require on-going care. A tension is often perceived between the goals of care and prevention for congenital disorders: for some treatable (but not curable) conditions, improvements in care lead to an increase in life expectancy, with huge associated costs for on-going medical and social support. Examples include blood transfusion and iron chelation treatment for thalassaemia,

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treatment of cardiac conditions in Down's syndrome, and enzyme replacement therapy for inborn errors of metabolism.

It is a fundamental principle of medical ethics that all people are entitled to the best possible care, and it should be the goal of all countries, regardless of income, to do their best to provide it. The definition of "best possible care" will, however, inevitably depend on prevailing social, economic and political conditions. Care and prevention should be seen as linked aims: provision of care, and realisation of the on-going commitment it represents, may lead to pressure for the availability of preventive services and interventions.

## Health services for congenital disorders

Effective health services for congenital disorders take a holistic approach to care and prevention that includes:

- Population, public health and environmental health services
- Family planning, women's and reproductive health care services
- Prenatal services
- Maternity services
- Newborn services, including screening for, and diagnosis of, congenital disorders
- Paediatric services, including diagnosis, treatment, care and management
- Life-long medical, social and family support services for those with congenital conditions.

Services should be well integrated with each other and with other relevant clinical and social services to provide a coherent pathway of care. The establishment and maintenance of effective services require political commitment, public health and clinical leadership, adequate resources, professional education and training, coordination and teamwork. Registers, surveillance systems and research, to provide epidemiological data and monitor the effectiveness of services and interventions, are important to build a sound evidence base for policy development, planning and action.

## KEY REFERENCES

Christianson A, Howson CP, Modell B March of Dimes global report on birth defects. The hidden toll of dying and disabled children. March of Dimes Birth Defects Foundation. 2006. White Plains, New York.

Christianson A, Modell B Annu Rev Genomics Hum Genet 2004 5:219-65.

Modell Global Database of Constitutional Congenital Disorders

## **APPENDIX 1: GENETIC AND PARTLY GENETIC CONGENITAL DISORDERS**

Chromosomal disorders result from changes in the number and structure of chromosomes. Down's syndrome (trisomy 21) is the most commonly recognised chromosomal disorder. Those affected present with varying degrees of learning disabilities and many can function well in society. However, they are vulnerable and may have a number of other health and social problems and needs. Examples of other trisomies include Patau syndrome (trisomy 13) and Edward's syndrome (trisomy 18). Both lead to stillbirth or early death. Examples of disorders of the sex chromosomes include Turner's and Klinefelter's syndromes, which are usually not recognised until adolescence.

Single gene disorders result from mutations in the sequence of a single gene. Examples of autosomal recessive single gene disorders include haemoglobinopathies (such as sickle cell disease), cystic fibrosis, albinism, and various inborn errors of metabolism. Examples of autosomal dominant single gene disorders include neurofibromatosis-1 and Huntington's disease. Examples of X-linked disorders include fragile X syndrome, haemophilia, glucose-6-phosphate dehydrogenase deficiency, and Duchenne and other muscular dystrophies. Genetic risk factors such as maternal Rhesus negativity are also determined by single genes.

Disorders with multifactorial causes include malformations of single or multiple organs and limbs, and common diseases that usually present later in life, such as coronary heart disease, dementias and diabetes; the latter are not included here.