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## Controlling Birth Defects: Reducing the Hidden Toll of Dying and Disabled Children in Low-Income Countries

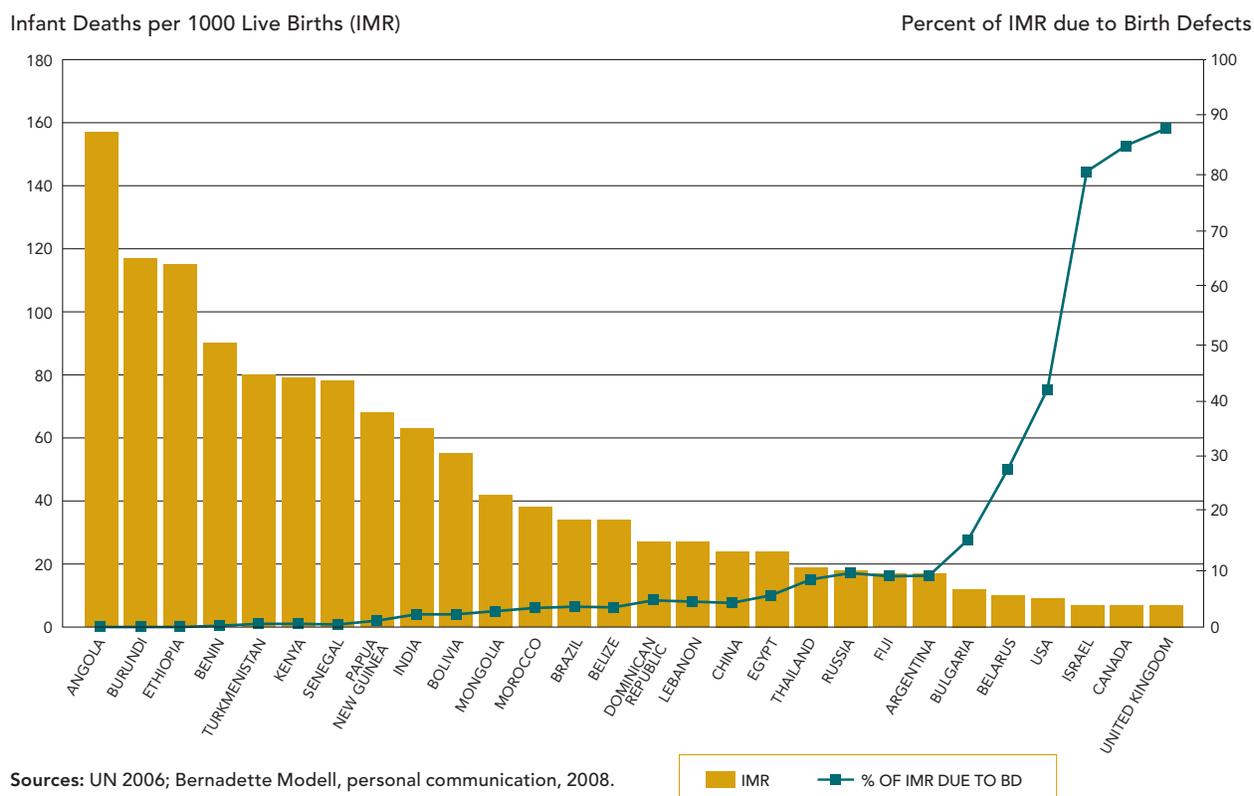
Every year, an estimated 7.9 million children are born with a serious birth defect of genetic or partly genetic origin.<sup>1</sup> Over 1 million more infants are born with serious birth defects of post-conception origin including those that result from maternal exposure to environmental agents (teratogens) such as alcohol, rubella, syphilis, and iodine deficiency that can harm the developing fetus (MOD 2006). Thus, an estimated 9 million infants – representing approximately 7 percent of all births – are born annually with a serious birth defect that may kill them or result in lifelong disability.

Serious birth defects can be lethal. At least 3.3 million children under 5 die from serious genetic or partly genetic

birth defects each year. An estimated 3.2 million of those who survive without appropriate care may be disabled for life. For those who survive, these disorders can cause lifelong mental, physical, auditory, and visual disabilities that exact a harsh human and economic toll on those affected, their families, and their communities (MOD 2006; WHO 2006).

Birth defects are a global problem, but their impact on infant and childhood death and disability is particularly severe in middle- and low-income countries where up to 94 percent of those born with birth defects and 95 percent of the children who die from birth defects occur.<sup>2</sup> The contribution of birth defects to infant and

FIGURE 1. RELATIONSHIP BETWEEN INFANT MORTALITY RATE (IMR) AND PERCENTAGE OF INFANT DEATHS DUE TO BIRTH DEFECTS IN THE ABSENCE OF KNOWN PREVENTIVE SERVICES BY COUNTRY, 2004



childhood mortality and morbidity has been consistently underestimated and neglected in assessments of childhood mortality and efforts to improve child health and survival. Only limited application of what is possible for the care and prevention of birth defects has occurred in middle- and low-income countries (MOD 2006).<sup>3</sup>

## The Hidden Toll of Birth Defects

Why has the global toll of birth defects been recognized only recently as a severe and emerging public health problem? Two reasons stand out: the health transition; and misperceptions about genetic conditions that are prevalent among health care providers, policymakers, and donor organizations.

## THE HEALTH TRANSITION

The decline in infant and childhood mortality rates in most countries in the 20th century is a public health triumph.<sup>4</sup> Improvements in socioeconomic, educational, and health care conditions, and the strengthening of infrastructure in high-income countries, began in the first half of the last century and led to significant improvements in health (Garret 2000; Howson 2000). The “health transition” is initially marked by a decline in infant and under-5 mortality from infectious diseases and malnutrition, which predominate in the early years of life (World Bank 1993). At the same time, however, mortality from birth defects has remained constant. As a result, birth defects assume a greater proportional cause of infant mortality as countries develop. This point is demonstrated in Figure 1 on page 1.

### EXAMPLES OF STEPS TAKEN BY HIGH-INCOME COUNTRIES IN THE 1950S AND 1960S TO CONTROL BIRTH DEFECTS

1. Improved collection and use of data on the prevalence and types of birth defects, genetic diseases, and genetic predispositions to common conditions at the national level; and on the mortality, disability, and human and economic costs associated with these conditions.
2. Promoted the use of these data by governmental and nongovernmental agencies to build political will and to advocate for increased funding in support of care and prevention.
3. Defined goals of genetic and other services for care and prevention in terms of individual/family well-being and of public health, with an emphasis on better understanding the concerns, needs, and expectations of the community.
4. Improved prenatal and perinatal services. Examples include promotion of family planning, expanding rubella immunization before pregnancy, and implementing folic acid fortification of commonly consumed foods.
5. Organized genetic and other services for care and prevention in a comprehensive and integrated manner.
6. Selected public health programs and targets according to prevalence, severity, and predicted outcome.
7. Respected ethical principles and cultural diversity by properly assessing the health beliefs, traditions, religious observances, and social expectations of individuals and communities before setting program goals.
8. Trained health care professionals in best practices in care and prevention of birth defects and in the practical application of medical genetics toward this end. This was accomplished at both the undergraduate and postgraduate levels. Programs in genetic counseling were also established.
9. Educated the public on the steps they can take to promote a healthy outcome of pregnancy, including the avoidance of teratogens during gestation, particularly alcohol, and on the importance of knowing how and when to access prenatal care.
10. Encouraged the formation of parent/patient organizations to draw attention to the need for improved clinical services and preventive programs and to assert their right to be treated with dignity and without discrimination.

Source: MOD, 1937-1995.

Middle-income and some low-income countries are currently following the high-income countries through the health transition about 40 years later. In 2001, most middle-income and a few low-income countries had achieved demographic profiles similar to the United States in 1960 (UNICEF 2003). If middle- and low-income countries introduce the same services that high-income countries did in the 1950s and 1960s within the next 20 years, they could achieve the same rate of control that high-income countries now enjoy (see Box on page 2). In other words, up to 70 percent of birth defects would either be prevented or, with proper care, cured or ameliorated (MOD 2006; WHO 2006).

### WHY HAVE BIRTH DEFECTS BEEN A HIDDEN CONDITION?

Several misunderstandings underlie the reasons why care and prevention of birth defects have been accorded relatively low priority by international donors, health agencies, and national governments.

The first is that health policymakers are generally unaware of the global toll of birth defects and associated disabilities because data documenting the extent of the problem have been lacking. Prior to the 2006 March of Dimes report, there was a paucity of data on the birth prevalence of birth defects in middle- and low-income countries. Constrained diagnostic capability, poor health-related statistics, lack of birth defect surveillance and registries, and reliance on hospital-based rather than population-based studies led to a systematic underestimation of the toll of birth defects in these regions (Penchaszadeh 2000; WHO 1999, 1985).

A second misunderstanding is the widespread belief that effective care and prevention of birth defects require costly, high-tech interventions that are beyond the national health budgets of low- and middle-income countries. In fact, the bulk of care for and prevention of birth defects is most appropriately carried out routinely in primary and secondary care settings (Christianson and Modell 2004; MOD 2006; WHO 1985, 1999).

A third misunderstanding, which follows from the last, is that programmatic attention to care and prevention of birth defects will necessarily draw funding away from other high-priority interventions in maternal and child health. Because risk factors for birth defects – including advanced maternal age, poverty, maternal medical complications, infection, poor nutrition, smoking, and alcohol and drug use, to name

a few – are common to other adverse maternal and child health outcomes, interventions to reduce birth defects will contribute to overall women’s, maternal, neonatal, and child health. Care and prevention of birth defects should be considered an integral and cost-effective arm of public health programs directed at saving the lives of and reducing disability among women, newborns, and children. In fact, some interventions, such as fortification of food with micronutrients, benefit the entire population.

## The Origins of Birth Defects

It was only in the 20th century that the causes of birth defects were delineated, allowing for their categorization into three broad groups: birth defects originating in the pre-conception period (due primarily to genetic and partly genetic causes); birth defects arising after conception but before birth; and birth defects of unknown cause.

### BIRTH DEFECTS OF PRE-CONCEPTION ORIGIN

Most birth defects originate before conception and are due to abnormalities of the genetic material – chromosomes and genes. Partly genetic birth defects are due to a combination of genes that puts the fetus at risk in the presence of specific fetal environmental factors. Genetic abnormalities can be inherited (found in families) or they can occur as an isolated event in a particular pregnancy. These abnormalities include chromosomal abnormalities, single gene defects, and

TABLE 1. PERCENTAGE OF BIRTH DEFECTS BY CAUSE IN HIGH-INCOME COUNTRIES

CAUSE	~%
<b>Pre-conception</b>	
Chromosome disorders	~6
Single gene disorders	~7.5
Multifactorial malformations	20 – 30
<b>SUBTOTAL</b>	<b>~40</b>
<b>Post-conception</b>	
Teratogens	7 – 8
Intrauterine abnormalities*	~2
<b>SUBTOTAL</b>	<b>~10</b>
<b>Unknown cause</b>	<b>~50</b>
<b>TOTAL</b>	<b>100</b>

Source: Turnpenny and Ellard 2005

multifactorial disorders caused by the interaction of genes and the environment.

Table 1 on page 3 presents the percentage of birth defects by cause in industrialized countries. A brief description of this table follows.

### CHROMOSOMAL ABNORMALITIES

Chromosomal abnormalities are changes in the number or the structure of chromosomes that result in a gain or loss of genetic material. They account for approximately 6 percent of birth defects in industrialized countries (Turnpenny and Ellard 2005). Down syndrome, generally caused by an extra chromosome 21 (trisomy 21) is the most common chromosomal abnormality.

### SINGLE GENE DEFECTS

Single gene defects are caused by alterations in gene structure (mutations) that result in abnormal cell functioning. More than 6,000 single gene defects have been described (OMIM 2000). Single gene defects account for an estimated 7.5 percent of all birth defects in industrialized countries (Turnpenny and Ellard 2005).

### MULTIFACTORIAL DISORDERS

The concept of multifactorial inheritance was proposed by Boris Ephrussi in 1953 and is now broadly accepted (Passarge 1995). This category accounts for an estimated 20 percent to 30 percent of all birth defects, many of which are lethal (Turnpenny and Ellard 2005). Multifactorial birth defects, alternately called congenital malformations, involve a single

organ, system, or limb, and include congenital heart disease, neural tube defects, cleft lip and/or cleft palate, and clubfoot.

Multifactorial inheritance is also the cause of the many common diseases with a genetic predisposition that present later in life. These diseases are usually systemic and do not involve malformations. Examples include hypertension, diabetes, stroke, mental disorders, and cancer.

### BIRTH DEFECTS OF POST-CONCEPTION ORIGIN

Birth defects originating after conception are nongenetic in origin. The genetic material inherited by the fetus is normal and the birth defect is caused by an intrauterine environmental factor, such as teratogens that interfere with normal growth and development of the embryo or fetus, mechanical forces that deform the fetus, or vascular accidents that disrupt the normal growth of organs.

The three most significant causal groups of teratogens are: congenital infections, maternal illness and altered maternal metabolism, and recreational and therapeutic drugs. Examples of these three categories include rubella and toxoplasmosis, maternal insulin-dependent diabetes mellitus and iodine deficiency, and alcohol and antiepileptic drugs, respectively (Latin American Centre for Perinatology/Women Maternal and Reproductive Health 2008; MOD 2006).

Birth defects due to teratogens are among the more readily preventable (Christianson and Modell 2004), and pregnancies in middle- and low-income countries, compared with high-income countries, are more likely to be at risk from potential teratogens for several reasons. These include increased frequency of intrauterine infection, poor maternal

TABLE 2: ESTIMATED NUMBERS AND PERCENTAGE OF ANNUAL TOTAL BIRTH DEFECTS, EARLY DEATHS DUE TO BIRTH DEFECTS, AND UNDER-5 DEATHS FOR LOW-, MIDDLE-, AND HIGH-INCOME COUNTRIES

	LOW-INCOME COUNTRIES	MIDDLE-INCOME COUNTRIES	HIGH-INCOME COUNTRIES	TOTAL
Annual total birth defects (millions)	4.75	2.64	0.49	7.9
	60%	34%	6%	
Annual early deaths of birth defects (millions)	2.38	0.79	0.14	3.3
	72%	24%	4%	
Annual under-5 deaths (millions)	8.8	1.8	0.6	11.2
	80%	16%	4%	

Sources: MOD 2006; UNICEF 2003; UNICEF 2001.

nutrition, low socioeconomic and educational levels, lack of environmental protection policies, and poorly regulated access to medication (Penchaszadeh 2002).

An estimated 5 percent to 10 percent of all birth defects in industrialized nations are of post-conception origin (Turnpenny and Ellard 2005). The estimate for lower-income countries is 10 percent to 15 percent (Christianson and Modell 2004).

### **BIRTH DEFECTS OF UNKNOWN CAUSE**

As noted in Table 2, a specific cause cannot be designated in approximately 50 percent of all children born with birth defects. Some of these birth defects may be due to new autosomal dominant mutations, submicroscopic chromosome deletions, or uniparental disomy (Turnpenny and Ellard 2005). Causes for birth defects continue to be identified, so the percentage of birth defects of unknown cause can be expected to decrease in the future.

## **Global Epidemiology of Birth Defects**

The birth prevalence of serious genetic and partly genetic birth defects is generally considered to be similar throughout the world. However, several factors contribute to variations in populations between and within countries and across regions (Christianson and Modell 2004; MOD 2006; WHO/ICBDMS/EUROCAT 1998).

### **FACTORS CONTRIBUTING TO THE GLOBAL VARIATION IN BIRTH PREVALENCE OF COMMON BIRTH DEFECTS**

**Malaria.** Compared with noncarriers, healthy carriers of recessive genes for hemoglobin disorders (sickle cell anemia and Thalassemia) and glucose-6-phosphate dehydrogenase (G6PD) deficiency have a well-documented survival advantage against the lethal effects of malaria. As a result, carriers are more likely to reach reproductive age. Over time, this has led to an increase in the population prevalence of these genes in tropical regions. Consequently, the birth prevalence of thalassemia, sickle cell disease, and G6PD deficiency is high in malaria-endemic regions of the world such as Sub-Saharan Africa, the Eastern Mediterranean and North Africa, Southeast Asia, and the Western Pacific (Clegg and Weatherall 1999; Modell and Kuliev 1989; Mokenhaupt and others 2004; WHO 1996).

**Migration.** People moving to different countries and regions embed their single gene defects into the populations they enter. For example, sickle cell anemia was spread from Africa to the Americas and the Caribbean by the slave trade, and porphyria was introduced to South Africa by the emigration of the Dutch for trading purposes in the 17th century. In the instance of urbanization, the movement of people from rural regions and traditional lifestyles to towns and cities may put them at increased risk of birth defects due to combined genetic predisposition and exposure to teratogens such as fetal alcohol syndrome (Auburger and others 1990; Avila-Giron 1973; Jenkins 1990; WHO 1996; WHO/World Alliance 1999; WHO/ICBDMS/EUROCAT 1998).

**Parental consanguineous marriage.** This social custom, involving the marriage of cousins or uncles and nieces, is accepted by at least 20 percent of the world's population. Consanguineous marriages increase the birth prevalence of autosomal recessive birth defects, almost doubling the risk of neonatal and childhood death from birth defects (Bittles 1990; Bittles and others 1991; Castilla and others 1991; Christianson and others 2000; Liascovich and others 2001; Modell and Kuliev 1989; Murdock 1967; Rittler and others 2001; WHO 1996).

**Advanced maternal age.** Advanced maternal age (35 or older) is associated with an increased birth prevalence of chromosomal trisomies, particularly Down syndrome. In middle- and low-income countries, a high percentage of women give birth over the age of 35 years without the availability of community education and universally available and accessible family planning services, medical genetic screening, prenatal diagnosis, or associated services. The birth prevalence of chromosomal aneuploidies is therefore high in these countries (WHO 1996; WHO/World Alliance 1999).

**Poverty.** Reduced socioeconomic circumstances are associated with an increased birth prevalence of birth defects. Mothers in poverty are more likely to be malnourished before and during pregnancy, and are at greater risk of exposure to environmental teratogens such as alcohol and maternal infection (WHO/ICBDMS/EUROCAT 1998).

**Level of health care.** The birth prevalence of birth defects is influenced by the national level of available and accessible health care, especially reproductive and maternal health services. These health care services are capable of preventing Down syndrome, common single gene defects, neural tube defects and congenital malformations, fetal alcohol

syndrome, congenital syphilis, iodine deficiency disorder, and congenital rubella syndrome. The availability and accessibility of neonatal (newborn) and child health care services influences the infant and childhood mortality rates, including those for infants and children born with birth defects, thus affecting overall population prevalence (Christianson and Modell 2004; Penchaszadeh 2000; WHO/World Alliance 1999).

### **GLOBAL DISTRIBUTION IN BIRTH PREVALENCE OF COMMON BIRTH DEFECTS**

The estimated annual birth prevalence of genetic and partly genetic birth defects ranges from just over 40 per 1,000 live births in high-income countries to 82 per 1,000 live births in some low-income countries. Five common disorders account for approximately 25 percent of these birth defects: congenital heart defects (1,040,800); neural tube defects (323,900); hemoglobin disorders, sickle cell disorders and thalassaemias (307,900); Down syndrome (217,300); and G6PD deficiency leading to neonatal jaundice with kernicterus or significant hemolysis in later life (177,000) (MOD 2006).

Table 2 presents the estimated numbers and percentage of annual total birth defects, annual early deaths due to birth defects, and annual under-5 deaths for low-, middle- and high-income countries.

Equivalent data for children with birth defects caused by teratogens are not available. In industrialized countries, teratogens cause between 5 percent and 10 percent of birth defects (Turnpenny and Ellard 2005). Middle- and low-income nations have a higher birth prevalence, an estimated 10 to 15 per 1,000 live births, of teratogen-induced birth defects (Christianson and Modell 2004).

### **SINGLE GENE DEFECTS**

The birth prevalence of single gene defects in high-income nations is approximately 3.6 per 1,000 live births (Baird and others 1988). In many middle- and low-income countries, the rate is higher because of the high birth prevalence of common recessive disorders associated with a selective advantage for carriers to the lethal effects of malaria and because of consanguineous unions that increase the birth prevalence of autosomal recessive disorders.

Single gene defects fall into two broad groups: common recessive disorders (>1 in 10,000 to 1,000 live births) and rare single gene defects.

### **COMMON RECESSIVE DISORDERS**

These include four major disorders: the hemoglobin disorders, G6PD deficiency, oculocutaneous albinism in Sub-Saharan Africa, and cystic fibrosis.

Hemoglobin disorders (sickle cell anemia and thalassemias) are the most common lethal inherited disorders in humans and originated in tropical Africa, Asia, and the Mediterranean. These disorders have spread via migration throughout the world (Angastiniotis and Modell 1998; Modell and Darlison 2008; Stuart and Nagel 2004). Currently, an estimated 307,900 children are born annually with a severe hemoglobin disorder. Of this number, 60 percent to 70 percent are in Sub-Saharan Africa, where an estimated 224,200 infants are born annually with sickle cell disorder. The majority die before age 5 (Akinyanju 1989; Fleming and others 1979). Thalassemias are prevalent in the Mediterranean region, the Middle East, South and East Asia, and the Pacific, with carrier rates ranging from 2 percent to 19 percent (WHO 1994).

More than 5 million infants are born annually with G6PD deficiency, an X-linked recessive disorder of varying severity, mainly in tropical Sub-Saharan Africa, the Eastern Mediterranean and North Africa, South and East Asia, and the Pacific. An estimated 177,000 of these infants are at risk for the severe adverse effects of G6PD deficiency including neonatal jaundice and possible kernicterus. Ninety-nine percent of these babies are born in middle- and low-income countries (Christianson and Modell 2004; MOD 2006).

Oculocutaneous albinism is highly prevalent in Sub-Saharan Africa, ranging from 1 in 3,900 to 1 in 5,000 people. It is also prevalent in clusters, characterized by geographic isolation and parental consanguinity in South America (Baillet and others 2001; Castilla and Adams 1990; Castilla and Sod 1990; Keeler 1970). Affected individuals are prone to skin cancer, the susceptibility for which increases with age and proximity to the equator. It is a cause of early death in Tanzania and Nigeria. Only 10 percent of those affected survive beyond 30 years of age (Kromberg 1992; Kromberg and others 1989; Luande and others 1985).

Cystic fibrosis is the most common single gene defect in Caucasian populations, with a birth prevalence of approximately 1 in 2,000 live births. It is considered rare in other populations, but reports of birth prevalence of 1 in 2,560 and 1 in 2,608 live births in Jordan and Egypt, respectively, challenge that assumption (Alwan and Modell 1997).

## RARE SINGLE GENE DEFECTS

The birth prevalence of rare single gene defects is generally more than 1 in 10,000. Collectively, these rare disorders also add significantly to the burden of infant and child health. This includes, particularly for middle- and low-income nations, disorders such as hemophilia, for which treatment is available but expensive.

## CHROMOSOMAL DISORDERS

The risk of chromosomal aneuploidies, particularly Down syndrome, increases with advancing maternal age. Middle- and low-income countries have a high birth prevalence of chromosomal trisomies. The birth prevalence of Down syndrome can be as high as 2 to 3 per 1,000 live births in middle- and low-income countries because of limited access to family planning, a high percentage of pregnant women of advanced maternal age (35 years or older) and deficient or absent prenatal screening, diagnosis, and associated services. By comparison, the birth prevalence of Down syndrome is as low as 1.2 per 1,000 live births in high-income countries (Modell and others 1992; WHO 1996). An estimated 217,300 infants with Down syndrome are born each year, the majority succumbing in middle- and low-income countries to early infant or childhood death from congenital heart disease and infection. In South America, 55 percent of infants with Down syndrome die prior to their first birthday and in South Africa 65 percent die before age 2 (Castilla and others 1998; Christianson and others 1995; MOD 2006).

## MULTIFACTORIAL DISORDERS

Multifactorial birth defects, which present as congenital malformations of single systems, organs, or limbs, are the most common type of birth defect. Approximately 4.94 million affected infants are born each year. Many affected children can be successfully and cost-effectively treated, mainly by pediatric surgery. Thus, the toll from multifactorial disorders depends largely on the level of health care services in a country.

Congenital heart defects occur in 4 to 8 per 1,000 live births, and about 90 percent of affected cases have a multifactorial etiology (Rimion and others 2002; Seashore and Wappner 1996). Over a million infants are born each year with multifactorial congenital heart defects (MOD 2006).

Neural tube defects, spina bifida, anencephaly, and encephalocele occur in over 300,000 newborns annually

(CDC 2005; MOD 2006). The birth prevalence of neural tube defects varies with geographic location, socioeconomic class, and ethnicity. They are preventable to a significant degree by food fortification and periconception folic acid supplementation.

Multifactorial inheritance accounts for the majority of cleft lip, with or without cleft palate, with birth prevalence ranging from 0.3 per 1,000 live births in African American populations, 1 per 1,000 in Caucasians, 2 per 1,000 in Japanese, and 3.6 per 1,000 live births in Native North Americans (WHO 2002).

## TERATOGEN-ASSOCIATED BIRTH DEFECTS

Teratogen-induced birth defects are more common in middle- and low-income countries because of poverty, increased frequencies of intrauterine infection, maternal malnutrition including maternal alcohol abuse, lack of environmental protection policies, poorly regulated access to medication, and lack of availability of health care (Penchaszadeh 2002). The four most common causes of teratogen-induced birth defects are congenital syphilis, congenital rubella syndrome, congenital iodine deficiency disorder, and fetal alcohol syndrome. Other significant teratogens include maternal insulin-dependent diabetes and maternal use of antiepileptic drugs.

## CONGENITAL SYPHILIS

Syphilis is probably the most common congenital infection, but there are no global estimates delineating its burden. Congenital syphilis is a major cause of perinatal mortality particularly in many middle- and low-income countries; and those who survive are at risk for brain damage, blindness, and hearing loss. In Sub-Saharan Africa, anywhere from 6 percent to 16 percent of pregnant women have active syphilis (Murray and Lopez, 1998). In Haiti, 52 percent of infants with congenital syphilis die before their first birthday (Fitzgerald and others 1998; MOD 2002; Murray and Lopez 1998; WHO 2005a).

## CONGENITAL RUBELLA SYNDROME

Approximately 25 percent of infants born to mothers who contract rubella in the first trimester of pregnancy have congenital rubella syndrome (CRS). In countries with successful rubella immunization programs, CRS has been largely eliminated. In the remaining 50 percent of countries, more than 100,000 infants are born with CRS annually (WHO 2000b).

## IODINE-DEFICIENCY DISORDER

UNICEF considers iodine deficiency the most important cause of preventable brain damage and intellectual disability, with most cases caused before birth. Iodine deficiency, common in inland, arid, and mountain regions, causes spontaneous abortion, perinatal death, and childhood intellectual, motor, and auditory disabilities (Iodine Deficiency Disorder). The severity depends on the level of maternal deficiency. In 1998, an estimated 60,000 babies were born worldwide with severe iodine-deficiency disorder (cretinism), and an estimated 28 million pregnancies were still at risk of less severe iodine-deficiency disorder from maternal iodine deficiency (UNICEF 1998).

## FETAL ALCOHOL SPECTRUM DISORDER

Fetal alcohol spectrum disorder (FASD) comprises a range of effects, from mild to severe, including intellectual disability, behavior problems, growth retardation, and congenital heart defects that can occur in an individual whose mother drank alcohol during pregnancy (SAMHSA 2005). In Seattle, Washington, the prevalence of FASD between 1975 and 1981 was estimated to be 9.1 per 1,000 live births (Sampson and others 1997). The prevalence of fetal alcohol syndrome (FAS), the most severe end of the FASD spectrum, is much higher in other regions of the world. In the Western Cape Province of South Africa, more than 4 percent of 6- to 7- year-old school children had FAS. Comparable studies in urban Johannesburg found 2.7 percent of children with fetal alcohol syndrome (Croxford and Viljoen 1999; May and others 2000; Viljoen and others 2003). This raises concern about the prevalence of FAS in middle- and low-income countries where alcohol is available and used by women of reproductive age (Rosenthal and others 2005).

## MATERNAL INSULIN-DEPENDENT DIABETES MELLITUS

Infants born to mothers with maternal insulin-dependent diabetes mellitus (IDDM) have up to a threefold increased risk of having a serious birth defect. The risk is reduced if diabetic control is optimized. IDDM affects 0.5 percent of pregnancies in industrialized countries and is an increasing problem in middle- and low-income countries where diabetic control is also poor (Khoury and others 1989).

## ANTIEPILEPTIC DRUGS

Children born to mothers on antiepileptic drugs, particularly phenytoin and sodium valproate, are at risk of developing anticonvulsant embryopathy, major malformations, growth retardation, intellectual disability, and hypoplasia of the mid-face and fingers (Hernández-Díaz and others 2000). This risk is greater for infants in middle- and low-income countries where the mothers' anticonvulsant therapy is less likely to be well controlled, multiple drug therapies are used, and cheaper, more teratogenic drugs (such as phenytoin) are more likely to be used (MOD 2006).

## Care and Prevention of Birth Defects

### CARE

Care for people with birth defects includes diagnosis and treatment. The latter should include medical genetic counseling with psychosocial support (WHO 1999). As a general principle, as much care as possible should take place close to the patient's home and so should be undertaken in a primary health care setting. Referral for treatment should be contemplated only when a diagnosis is not possible or when further management such as pediatric surgery will improve the prognosis.

Effective care depends on accurate diagnosis, which should be possible for most common birth defects. Accurate diagnosis allows practitioners to plan further care, taking into account the circumstances of the family, community, and medical services. Where a definitive diagnosis is not available, identifying the component disabilities and other clinical problems that constitute the disorder enables similar planning of treatment, therapeutic, surgical and neurodevelopmental therapies, and genetic counseling.

Treatment for newborns and children with birth defects can be provided feasibly and effectively in low-income settings. There are a number of good examples of this in the literature. For example, in a study of long-term, community-based treatment of children with sickle cell anemia in the Apapa District of Lagos, Nigeria, that was conducted in the years 1988 to 1995, mortality rates among patients decreased from 21 percent to 0.6 percent per year and the number of annual hospital admissions declined from 350 to 25 (Akinyanju and others 2005). Another example involved the treatment of children with thalassemia using blood transfusions and iron-chelating agents begun in Iran in the 1970s. Approximately 1,200 infants

with thalassemia were being born annually at that time. By 1992, 15,000 people with thalassemia were living in Iran, in contrast to the approximate 2,000 projected to be alive if no care system were available. While the success of the program led to higher treatment costs, it helped spur the government to establish a national thalassemia prevention program, thus demonstrating the synergy between care and prevention (Samavat and Modell 2004; WHO 2000a). Further description of both the Nigerian and Iran examples are provided in the 2006 March of Dimes report (MOD 2006).

## PREVENTION

There are three levels of prevention.

**Primary prevention** seeks to ensure that individuals are born free of birth defects by being conceived normally and not being damaged in the early embryonic period (the first eight weeks after conception when the mother may not be aware she is pregnant). Services for the primary prevention of birth defects include basic reproductive health approaches, which should be part of established women's, maternal, newborn, and child health services in all middle- and low-income countries. These include: family planning; optimizing women's diets; detecting, treating, and preventing maternal infections; optimizing women's health through the control of such diseases as insulin-dependent diabetes mellitus and epilepsy; and pre-conception screening for common recessive disorders. With its emphasis on ensuring normal conception and early pregnancy, primary prevention is the most important of all three levels.

**Secondary prevention** aims to reduce the number of children born with birth defects. This is achieved through medical genetic screening and prenatal diagnosis that detects birth defects and offers the couple genetic counseling and therapeutic options. To make informed decisions affecting the outcome of pregnancy, parents need the best information available about their specific set of circumstances. This includes the diagnosis, if possible, affecting their fetus; the cause; the consequences for the fetus; available options for treatment and prognosis as far as this is available; and the risks for recurrence and whether this might be reduced. Secondary prevention requires prenatal diagnosis, which must be accompanied by genetic counseling that includes descriptions of the tests available, with their scope and attendant risks.<sup>5</sup>

**Tertiary prevention** is directed toward the early detection and cure and amelioration of problems once a child

with a birth defect is born. Interventions include early recognition and diagnosis, including by newborn screening if available; medical treatment of complications; surgical repair of congenital malformations such as cleft lip and palate and congenital heart defects; and neurodevelopmental therapy programs to infants and children with disabilities. It also includes palliative care for children dying from the consequences of their birth defect. In middle- and low-income countries, the medical treatment, neurodevelopmental therapy, and palliative care need to be managed in primary health care settings as much as possible (Christianson and Modell 2004; Christianson and others 2000; WHO, 1985, 1999).

## IMPORTANCE OF INTEGRATING SERVICES FOR CARE AND PREVENTION

In 1985, WHO defined the aim of medical genetic services as helping people with a genetic disadvantage to live and reproduce as normally as possible. Thus, to live normally, people with a genetic disadvantage require services for care; to reproduce normally, they require services for prevention (WHO 1985). Because multiple approaches are needed for care and prevention, services for care are often considered separately from preventive services. However, successful control of birth defects requires that strategies for care and prevention of birth defects be integrated and combine the best possible patient care with prevention through such public health measures as rubella immunization, fortification of flour with folic acid, family planning, community education, population screening, genetic counseling, and services for premarital and prenatal diagnosis. This process of integrating care and preventive services and its application to country-level care are described in the 2000 WHO report on primary health care approaches for care and prevention of birth defects (WHO 2000a).

Health policymakers should note the importance of supporting capacity in human resources as an underlying strategy in ensuring effective care and prevention. Given that the primary health care provider is often the first point of contact for a person at risk of or with a birth defect, physicians, nurses, and allied health professionals—particularly in primary health care—should be educated and trained in the services required for effective control of birth defects. This approach has been successful in a number of low-income countries, and these examples should be considered in the setting of future policy (MOD 2006; WHO 2006).

## Priorities for Action

Experience shows that the care and prevention of birth defects is feasible and can be cost-effective. None of the following priorities for action require development of new vertical programs. In fact, the priorities are designed to be integral components of existing women's, maternal, newborn, and child health programs. In addition, the priorities target all women of childbearing age and not just mothers, newborns, and children. This approach underscores the importance of pre-conception health and that good health practices, including regular access to health care, must be established before conception if the pregnancy and its resulting newborn are to be as healthy as possible.

The following actions should be taken to prevent birth defects and improve the care of affected children in middle- and low-income countries. These steps can be implemented in two phases, according to the economic level, health service capacity, and health priorities of the country.

### PRIORITIES FOR ACTION: PHASE 1

#### Diagnosis

- Train primary health care practitioners (including physicians, nurses, allied health professionals, and workers) in the fundamentals of the recognition and causes of birth defects. This includes learning to take and assess a relevant history, including a family history in the form of a family tree, and to detect and collate physical signs of birth defects (dysmorphic features and malformations) that are externally obvious. With this rudimentary training, primary care practitioners will be able to:
  - Suspect or recognize that a particular clinical problem is a birth defect.
  - Suspect or identify any disabilities that their patient may have as a result of a birth defect (this is important as treatment, genetic counseling and psychosocial support can be offered in many cases even without a definitive diagnosis).
  - Make a definitive diagnosis when possible, particularly for common birth defects.
- Conduct physical examinations of all newborns before hospital or clinic discharge.

#### Treatment

- Train primary care physicians to implement basic medical treatment for such problems as cardiac failure and pneumonia and to assist in the monitoring of treatment on patients cared for in secondary and tertiary health care.
- Establish surgical services for children with birth defects in designated units in secondary and tertiary health care. A recent exception to this has been the use of the Ponsetti method to treat clubfoot in primary care settings in Brazil and Uganda.
- Train primary health care practitioners in basic rehabilitation for people with birth defects. Examples include neurodevelopmental therapies such as speech, occupational, and physiotherapy.
- In countries where the availability of potential trainees is limited, community-based rehabilitation may be substituted. With this strategy, parents and community members are trained and then use local resources to assist the disabled to integrate into society.
- Provide training in genetic counseling with psychosocial support. Such services offer people with or at risk of developing a birth defect and their family members information on the nature, cause, available treatment, and prognosis of the birth defect, and also on the risk of recurrence and ways to reduce this risk.
- Because early death from birth defects is common in middle- and low-income countries, train health care practitioners in terminal/palliative care, including counseling and psychosocial support.
- Promote lay support organizations, including patient/parent support groups, to improve patient care and birth defect prevention by facilitating community and professional education and advocating for increased funding for research on the causes of birth defects.

#### Prevention

- 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:

- Decrease the birth prevalence of Down syndrome by reducing the number of pregnancies among women of advanced maternal age.
- Allow women with affected children the option of not having more 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 and supplementation. This will:
  - Prevent iodine deficiency in women during pregnancy and thereby prevent the cognitive impairment resulting from iodine deficiency in their children.
  - Decrease neural tube defects and other malformations.
- 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 antiepileptic drugs.
  - Women on Warfarin for deep vein thrombosis or cardiac conditions.

#### **PRIORITIES FOR ACTION: PHASE 2**

For countries where needs and resources allow, the next step is the implementation of medical genetic services, with genetic counseling, prenatal diagnosis, and associated services for risk identification and management. The following recommendations for medical genetic services for birth defects should be priorities for low- and middle-income countries with needs and appropriate resources.

##### **Pre-conception**

- Use of family history as a screening tool for birth defects and genetic conditions.
- Carrier risk identification using family pedigrees and DNA analysis of identified individuals (cascade screening).

- Population carrier screening for common recessive disorders, the hemoglobin disorders (FBC and indices, electrophoresis, DNA), and cystic fibrosis (DNA).

##### **Antenatal**

- Rhesus negativity.
- Down syndrome (advanced maternal age, maternal serum, ultrasound).
- Neural tube defects (maternal serum and ultrasound).
- Major malformations (fetal anomaly scanning).
- Carrier screening for common recessive disorders, the hemoglobin disorders (FBC and indices, electrophoresis, DNA), and cystic fibrosis (DNA).

##### **Postnatal**

- Neonatal screening (using Guthrie cards). The following conditions should be considered when feasible. Additional screening tools and conditions may be added as needed and feasible.
  - Congenital hypothyroidism.
  - Sickle cell disorders.
  - Neonatal jaundice /G6PD deficiency.
  - Common inborn errors of metabolism.

#### **PRIORITIES FOR WHO AND OTHER INTERNATIONAL ORGANIZATIONS**

Normative functions are essential and neglected underpinnings of care and prevention at the country level, and are best undertaken by international health organizations including the WHO. The following are priorities for WHO and other international organizations.

- Educate the community, health professionals and workers, policymakers, the media, and other stakeholders about birth defects and the opportunities for effective care and prevention. To achieve this end, each ministry of health should designate someone with responsibility for coordinating strategies for care and prevention. These strategies need to be woven into existing public health strategies. Ministries do not need to create a new position, but a knowledgeable, trained, and effective person should be responsible.
- Develop an international consensus around the need for a clear definition and classification of the

major birth defects under review. Broad agreement on a definition of congenital disorders or of prenatal etiology has been lacking (WHO 2006; WHO 1998).

- Expand surveillance for the collection of data on birth prevalence, mortality, disability, natural history, outcomes, and economic costs associated with birth defects. Use the data collected for:
  - Epidemic surveillance, allowing for better observation of geographic and temporal fluctuations in the frequencies of different birth defects that may shed insight on possible causation.
  - Audit of the effectiveness of public health interventions to provide information on how these interventions might be improved.

## Conclusion

Over 3.3 million children die from birth defects each year. The impact of birth defects is particularly severe in developing countries where more than 90 percent of births and 95 percent of deaths of children with serious birth defects occur.

When disability is considered, the global toll of birth defects reflects an even harsher reality. Many infants burdened with serious birth defects die early in life, particularly in low-income countries, and those who survive almost always have the potential to be disabled, either as a direct or indirect result of their affliction. Improvements in patient care have

contributed significantly to decreased levels of disability in individuals born in rich countries. However, only limited application of this knowledge and technology has occurred in lower-resource countries, which currently do not have comprehensive services for care and prevention, and where 85 percent of the world's 6 billion people live.

Despite perceptions to the contrary, cost-effective approaches are available in low-income countries for the care of children with serious birth defects and for reducing the risk of having a child with a serious birth defect. The priorities for action proposed build on public health efforts by broadening the current scope of woman, maternal, newborn, and child health services in primary health care and developing secondary and tertiary medical genetic services.

In 2000, the United Nations announced its Millennium Development Goals for 2015, which included the health goal of reducing child mortality by two-thirds from its 1990 base (MDG-4) (WHO 2005b). By the start of 2004, the UN had already fallen behind its projections of where it should have been in order to meet this goal. Recent publications have concluded that the MDG-4 goal cannot be met unless the international community does more to reduce neonatal deaths (Lancet 2005; WHO 2005c). We argue that such efforts must also recognize the global contribution of birth defects to infant and childhood mortality and disability if they are to succeed.

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## End Notes

1. Birth defects are abnormalities of structure or function, including metabolism, which are present from birth. Serious birth defects are life threatening or have the potential to result in disability (physical, intellectual, visual or hearing impairment, or epilepsy). Several thousand different birth defects have been identified. Some birth defects are clinically obvious at birth; others may only be diagnosed later in life. The authors accept that the term "birth defect" is not considered appropriate by some, so the term congenital disorder has been accepted as an equivalent option.
2. This paper refers to three categories of countries based on 2004 gross national income (GNI) per capita. These are high-income (industrialized) countries, which have a GNI of \$10,065 or greater; and middle- and low-income countries (sometimes referred to as developing countries), which have GNIs of \$826 to \$10,065 and less than \$826, respectively (World Bank, 2005).
3. The authors refer to the "care and prevention" of birth defects and not the inverse for an important reason. While the emphasis of prevention before care may be acceptable in high-income countries where there are good care services, such an approach in middle- and low-income nations where care is often limited can be construed as eugenic. Thus, care of children with birth defects should be the first priority in lower-income countries, or as Christianson and colleagues noted in this regard in 2000, "Care is an absolute, prevention is the ideal" (Christianson et al., 2000).
4. There are notable exceptions where the drop in infant and child mortality rates has slowed or even reversed in recent years. These include many of the countries in Sub-Saharan Africa and Afghanistan (UNICEF, 2003). These countries are frequently affected by war, civil strife or poor governance. In the case of some, including South Africa and Botswana, the primary cause is the HIV/AIDS pandemic.
5. The authors maintain a policy of neutrality on the issue of abortion. If termination of pregnancy is discussed with parents in the course of prenatal care, this discussion must be within the limits of the legal terms of reference of the country. Health care providers must not give directive or coercive advice, are obliged to respect the religious and moral beliefs of the parents, and should abide by and support their decisions.

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