

# Learning and Developmental Disabilities



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Learning and developmental disabilities (LDDs) include functional limitations that manifest in infancy or childhood as a result of disorders of or injuries to the developing nervous system (Institute of Medicine Committee on Nervous System Disorders in Developing Countries 2001). These limitations range from mild to severe and can affect cognition, mobility, hearing, vision, speech, and behavior. The known causes of LDD are numerous and include genetic factors, nutritional factors, infections, toxic exposures, trauma, perinatal factors, and multifactorial conditions (table 49.1). Selected causes of LDD that are not addressed in detail in this chapter are described in box 49.1.

Although information on the prevalence and impact of disabilities in low- and middle-income countries (LMICs) is scarce, five considerations support the conclusion that LDDs are a public health priority in LMICs today:

- *Prevalence.* Although each individual cause is relatively rare, taken together, LDD affects a large proportion of children. In high-income countries, 10 to 20 percent of children have an LDD (Benedict and Farel 2003). With improvements in child survival in LMICs, it is not known whether the prevalence of disabilities among children is increasing, as has been seen in wealthier countries (Winter and others 2002), but the few data available from LMICs suggest that the prevalence of specific causes and types of LDD may be even higher than in high-income countries. Examples include cognitive disabilities associated with prenatal iodine deficiency, brain infections, and blindness associated with vitamin A deficiency (Durkin 2002). The prevalence of childhood disabilities in LMICs is not well established, but it is likely higher than in high-income countries.
- *Lifelong duration.* By definition, LDDs have an early onset, with the causes frequently occurring in the prenatal period. These effects are typically lifelong, affecting learning and other neurological functions, educational achievement, quality of life, earning potential, and productivity across the life span.
- *Costs.* The extensive costs include the direct costs of acute care, outpatient health care services, long-term care, rehabilitation, and special education, as well as the indirect costs of morbidity and increased mortality (Waitzman, Romano, and Scheffler 1994). Additionally, the costs and effects extend beyond the individuals affected to include entire families. Health, careers and employment of parents, family disposable income, health and adaptation of siblings, and family interaction are adversely affected when a family member has an LDD (Stein and Jessop 2003). It is difficult to comprehend the extent of these effects, just as it is difficult to measure them and develop economic models that account for them.
- *Education and work.* As societies and economies become increasingly information-oriented and dependent on educated and literate workers, the impact of disabilities affecting cognition and learning becomes greater (Institute of Medicine Committee on Nervous System Disorders in Developing Countries 2001).
- *Proven interventions.* The prospects for preventing LDD and for improving outcomes are considerable and can be achieved, to some extent, by implementing interventions that have been shown to be effective and cost-effective elsewhere but that are not being implemented in LMICs.

This chapter provides an overview of the range of interventions likely to improve child development and educational

**Table 49.1** Categories of Causes of LDD

Category	Examples
<i>Genetic</i>	
Chromosomal	Down syndrome, chromosomal rearrangements
Segmental autosomal syndromes	Prader-Willi syndrome, Angelman syndrome
Sex-linked, single gene	Fragile X syndrome, Rett syndrome
Autosomal recessive	Phenylketonuria, Tay–Sachs disease
Autosomal dominant	Neurocutaneous syndromes, such as neurofibromatosis
<i>Multifactorial</i>	
Genetic and nutritional	Neural tube defects
<i>Nutritional</i>	
Prenatal: maternal iodine deficiency	Developmental iodine deficiency disorder
Childhood: vitamin A deficiency	Xerophthalmia, night blindness
<i>Infections</i>	
Prenatal or perinatal	Toxoplasmosis, rubella, cytomegalovirus, herpes, gonorrhea, syphilis, group B streptococcus, chlamydia, trichomonas vaginalis, bacterial vaginosis, herpes simplex virus, HIV
Postnatal or childhood	Encephalitis, meningitis, varicella, cerebral malaria, polio, trachoma, otitis media
<i>Toxic exposures</i>	
Prenatal	Alcohol, lead, mercury, antimicrobials (such as sulfonamides, isoniazid, ribavirin), anticonvulsants (such as phenytoin, carbamazepine), and other drugs (such as accutane, thalidomide)
Postnatal or childhood	Lead, mercury
<i>Other maternal disorders</i>	
Thyroid disease	Cerebral palsy
<i>Other perinatal complications</i>	
Brain injuries associated with premature birth, birth asphyxia	Cerebral palsy, cognitive disabilities, seizure disorders
<i>Injury</i>	
Traumatic brain injuries and other disabling injuries from vehicle crashes, child abuse and neglect, falls, burns, warfare, and so forth	Cognitive, motor, speech, vision, hearing, seizure, and behavioral disabilities
<i>Poverty, economic disadvantage</i>	
Social and cognitive deprivation	Mild mental retardation
<i>Unknown</i>	LDD of unknown cause

outcomes for children in LMICs. Evidence of cost-effectiveness is considered in some detail for three selected interventions. An overview of other key risk factors and conditions that result in LDD is provided. A research agenda is outlined for advancing knowledge of how to prioritize cost-effective interventions and how best to devote resources for the prevention of LDD in LMICs.

## LDD AND THE GLOBAL BURDEN OF DISEASE

Estimates for disability-adjusted life years (DALYs) (Mathers 2006) are not available to convey the full range of LDDs or their

risk factors. Attempts have been made to estimate the DALYs associated with specific causes of LDDs. For example, it is estimated that 9.8 million DALYs, or nearly 1 percent of the global burden of disease, are due to one relatively minor form of LDD, namely, mild mental retardation (MR) caused by lead ingestion from environmental sources (Fewtrell and others 2004). Since only a small fraction—probably much less than 10 percent—of LDD worldwide can be attributed to lead-induced mild MR, this estimate suggests that LDD as a whole must account for a large proportion, perhaps more than 10 percent of the global burden of disease. Where DALY estimates are available, we use them as a basis for economic analysis to estimate the costs of

## Interventions for the Prevention of Childhood Neurological Disabilities

### Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) is the most common neurological disorder in children in the United States, with an estimated prevalence of 3 to 11 percent. The prevalence is not known in LMICs, but as schooling increasingly becomes the norm, ADHD is likely to become more obvious. The burden of ADHD in settings of large class sizes will likely pose an increasing challenge. In addition to its major impact on school performance, ADHD affects family relationships and social competence, with lasting consequences. Children with ADHD are also at higher risk for injury, depression, and substance abuse. Worldwide, with the growing use in school settings of stimulants to control this chronic disorder, the impact on health care costs is potentially huge. Although there are a paucity of data on this topic, in one study, the cost of medicating children for ADHD was close to an average of US\$500 or more per child per year, and this figure is considered a substantial underestimate (Chan, Zhan, and Homer 2002).

### Autism Spectrum Disorders

All autism spectrum disorders (ASDs) are characterized by varying degrees of impairment in communication skills and social interactions and in restricted, repetitive patterns of behavior or interests. Although only 50 percent of children in the United States with ASDs are diagnosed before six years of age, this group of disorders can reliably be diagnosed by three years of age and in some cases by as early as 18 months. ASDs range from a severe form called *autistic disorder* to a milder form known as *Asperger syndrome*. Prevalence studies of ASDs in Asia, Europe, and North America estimate that 2 to 6 out of every 1,000 children have an ASD. Screening instruments using responses from children and parents are available. Evidence indicates that early intervention (ideally in optimal educational settings for at least two years during preschool) results in improved outcomes. Individuals with ASDs generally respond well to highly structured, specialized programs. A variety of medications is used to treat associated depression, anxiety, ADHD, seizures, and other behavioral symptoms. Adults with severe ASDs require intensive and constant supervision. Little information is available regarding the parental and service costs of ASDs. In a 2001 study in the United Kingdom, the lifetime cost

for a person with autistic disorder exceeded UK £12.4 million, with most of the expense related to living support and daily activities.

### Infection

Numerous prenatal, perinatal, and postnatal infections can damage the developing nervous system or sensory pathways and cause long-term disabilities in children. The relative contribution of these infections to the burden of LDD is likely to vary by country. It will be influenced by overall infant mortality, postneonatal contribution to infant mortality, and regional difference in the distribution of the infections known to be associated with neurological sequelae during different periods in the early life cycle. A few of the most important infections that may result in LDD include the following:

- *Congenital rubella (chapter 20)*. This disease is a major global cause of preventable hearing impairment, blindness, and intellectual disability. The incidence of congenital rubella syndrome has been variably set at 0.5 to 2.2 out of every 1,000 live births in LMICs during epidemics, which occur every four to seven years (Cutts and others 1997). Though some LMICs have set elimination goals and vaccination has been noted to be cost-effective, only 28 percent of LMICs routinely vaccinate against rubella (Robertson and others 1997).
- *HIV/AIDS infection (chapter 18)*. Neurological problems in HIV-infected children vary in different parts of the world but may be as high as 40 to 50 percent (Bobat and others 1998). The developmental trajectory of infected children is confounded by maternal, social, and biological risk factors during pregnancy and early childhood. Maternal substance and drug abuse, more common in HIV-infected women, have an independent adverse effect on brain growth and neurodevelopmental outcome. Low birthweight and prematurity, poverty, protein calorie malnutrition, and micronutrient deficiencies—more frequently seen in HIV-infected children and particularly in LMICs—may similarly compromise early child development (Brouwers and others 1996).
- *Malaria (chapter 21)*. In Sub-Saharan Africa, malaria is the leading cause of childhood mortality and morbidity. Cerebral malaria is a well-known complication and

## Box 49.1

### (Continued)

may result in neurological sequelae in survivors, contributing significantly to the burden of LDD.

- *Bacterial meningitis (chapter 20)*. This disease results in long-term sequelae for many children, including approximately 40 percent of children who survive *Haemophilus influenzae* meningitis, 50 percent who survive pneumococcal meningitis, and 10 percent who survive meningococcal meningitis. Cost-effective immunization can prevent meningitis from all these causes.

### Alcohol

Prenatal alcohol exposure resulting in fetal alcohol syndrome may be the most common single preventable cause of MR worldwide (Viljoen 1999), but substantial challenges remain in diagnosing and preventing this disorder (see chapter 47). In addition to growth retardation and congenital heart disease, effects include ADHD, memory deficits, and mood disorders. Adults continue to have attention and social difficulties and higher rates of alcohol, nicotine, and drug dependence. Children exposed to even small amounts of alcohol (half a drink per day) in utero have poor outcomes, suggesting that abstinence should be recommended during conception and throughout pregnancy (Sokol, Delaney-Black, and Nordstrom 2003).

Although tools are available to help providers identify women who consume alcohol, detection of maternal alcohol exposure is a challenge. The overall rate of fetal alcohol syndrome for LMICs has been placed at 1 to 4.8 out of every 1,000 population (Sampson and others 1997) and is higher among low socioeconomic populations and subpopulations with particularly high alcohol intakes. If individuals with the full spectrum of fetal alcohol syndrome–related effects are included, this rate may be as high as 1 in every 100 births. A prevalence rate of 40.5 to 46.4 out of every 1,000 children in South Africa, the highest rate worldwide, is attributable to particular historical and social conditions (May and others 2000).

Public health measures to prevent prenatal alcohol exposure have had limited success, and rates have not changed over the past decade in the United States (Floyd and Sidhu 2004). These measures include putting warning labels on alcoholic beverages and broadcasting public messages about alcohol dangers during pregnancy. Improved outcomes might result from targeting the use of

screening tools for high-risk drinkers, who include women in prisons, drug rehabilitation centers, hospital emergency facilities, and sexually transmitted disease clinics (Sokol, Delaney-Black, and Nordstrom 2003). Little is known about the costs around the world. Annual costs for all individuals with fetal alcohol syndrome in the United States during 1998 was estimated at US\$4 billion, with lifetime care per person, for individuals requiring such care, at US\$1.4 million (Lupton, Burd, and Harwood 2004).

### Environmental Exposures

Children are more susceptible to environmental factors, including unsafe home environments, road traffic, and chemicals (see chapters 42 and 43). Even in high-income countries in Europe, mild MR resulting from lead exposure accounted for 4.4 percent of DALYs among children zero to four years of age. Legislative efforts are under way to eliminate lead from gasoline and other environmental sources of lead exposure in LMICs (Khan and Khan 1999; Alliance to End Childhood Lead Poisoning 2002). In the 0 to 19 years age group, injuries from all causes accounted for 19 percent of DALYs. The poor and vulnerable road users—pedestrians, cyclists, and motorcyclists—bear the greatest burden of road injuries. Nearly 25 percent of all nonfatally injured victims requiring hospitalization sustain a traumatic brain injury as a result of motor vehicle crashes (Peden and others 2004). Although the effectiveness of bicycle helmets for road safety is high, their use in LMICs is low (Thompson, Rivara, and Thompson 1999).

Interventions aimed at reducing children's exposure to environmental factors and injuries could result in substantial gains. Targeted action by region, even within a single country, is likely to prove most productive (Valent and others 2004).

### Nutritional Deficiency

Iodine deficiency from inadequate quantities of iodine in soil, water, and food affects 13 percent of the world's population, and an additional 30 percent are at risk (see chapter 28). Maternal iodine deficiency during pregnancy may result in an average loss of 15 IQ points in offspring, making it a leading preventable cause of MR. Iodine deficiency can be prevented with adequate consumption of iodized salt, which is now consumed by about 70 percent of households worldwide.

prevention of LDD. In this chapter, we estimated only costs of the interventions for Down syndrome (DS), neural tube defects (NTDs), and congenital hypothyroidism.

## IMPAIRMENT, DISABILITY, AND PARTICIPATION

Quantifying the impacts of LDD and their preventive interventions is complicated by the fact that these disorders can exist and be measured at multiple levels, including three levels distinguished by the World Health Organization (WHO) in *International Classification of Functioning, Disability, and Health* (WHO 2001):

- *impairment*, which refers to physiological or psychological defects or abnormalities, such as failure of the neural tube to close
- *function* or *disability*, which refers to the ability of an individual to perform a task, such as walking, seeing, hearing, learning language, and reading
- *participation*, which refers to the degree to which an individual participates in school, employment, social role, and recreational activities.

A given impairment may be associated with a range of functional outcomes. Some but not all of these may be recognized as disability. Disability is context specific and may vary from culture to culture. For example, conditions such as dyslexia, attention deficit and hyperactivity disorder (ADHD), and mild MR may be especially disabling in school but not as noticeable in nonacademic settings and environments where schooling is optional. Environmental factors and social stigma may determine the participation of people with disabilities more than do the functional deficits themselves. Some interventions may be designed to enhance participation (for example, ramps, accessible public toilets, inclusive education), whereas others may target impairment and disability (for example, nutritional fortification, surgery, rehabilitation, special education, newborn screening, and early treatment).

## THREE LEVELS OF PREVENTION

Prevention of LDD involves primary, secondary, and tertiary prevention activities:

- *Primary prevention* includes efforts to control the underlying cause or condition that results in disability. Examples include (a) maternal antiretroviral therapy to reduce the risk of mother-to-child transmission of HIV and (b) fortification of the food supply to prevent birth defects such as spina bifida and iodine deficiency disorders.
- *Secondary prevention* aims at preventing an existing illness or injury from progressing to long-term disability. Examples include newborn screening for metabolic disorders followed

by dietary restrictions to prevent damage to the nervous system and effective emergency medical care for head injury.

- *Tertiary prevention* refers to rehabilitation and special educational services to mitigate disability and improve functional and participatory or social outcomes once disability has occurred.

## UNINTENDED CONSEQUENCES OF SUCCESSFUL OR PARTIALLY SUCCESSFUL INTERVENTIONS

Interventions to reduce mortality and morbidity may be followed by increases in the prevalence of LDD. Examples include the following:

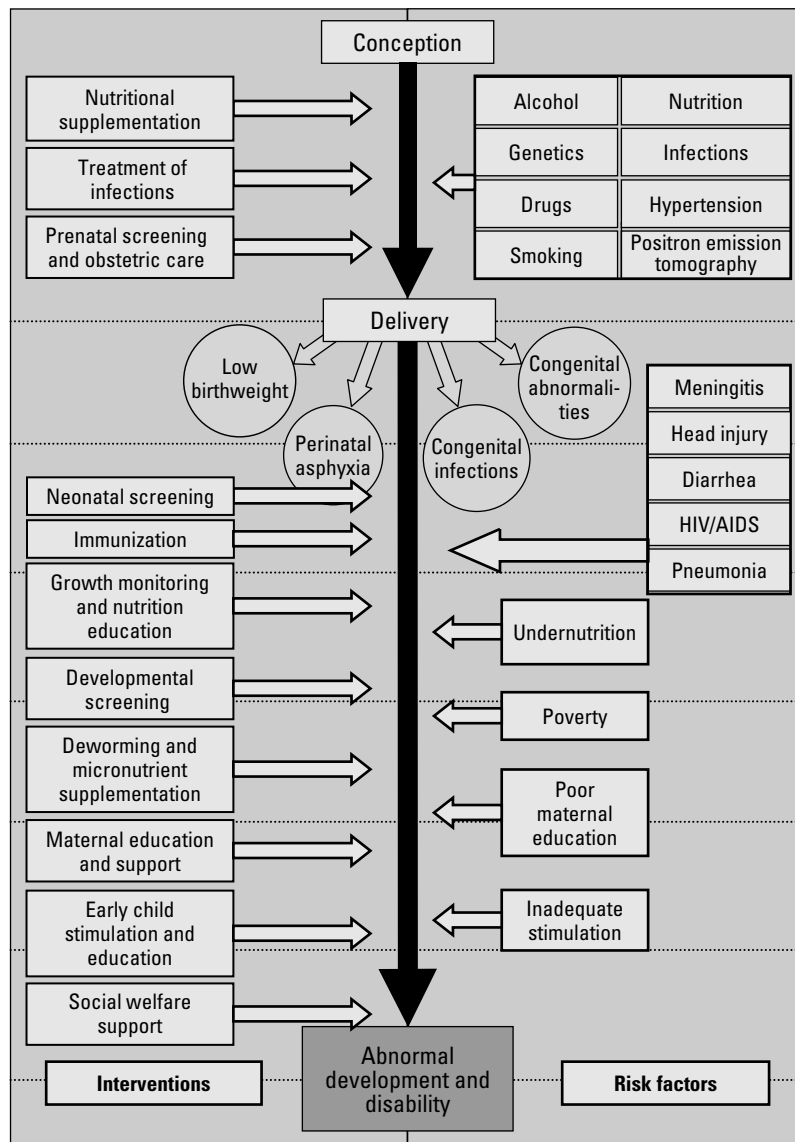
- Improved survival of very low birthweight infants at high risk for LDD may cause the prevalence of disability in the population to increase at the same time that it increases the absolute number of survivors without disabilities.
- Rubella vaccination programs with less than optimal coverage will prevent infections in those vaccinated but leave unvaccinated girls at risk for acquiring rubella infection during their childbearing years (rather than during childhood, as might be expected in the absence of a vaccination program), thereby increasing the risk of congenital rubella infection and disability in the population.
- Newborn screening and treatment for phenylketonuria in infancy and childhood prevent MR, but phenylalanine dietary restriction for women with phenylketonuria during their childbearing years is essential to prevent prenatal neurological damage and MR in their offspring.

## OTHER FACTORS LEADING TO INCREASES IN MEASURED PREVALENCE

Progress in the field of LDD may result in increases in the recognized prevalence of disability and in social and economic costs, as in the following examples:

- Increased availability of services may increase the number of children with recognized disabilities. Just as it is ethically problematic to screen for disorders for which no services can be offered, expansion of case finding becomes justified and ethically demanded as services become available, with the potential result of increasing the measured prevalence of disability.
- As educational expectations and awareness of LDD increase, the prevalence of recognized disability may increase.

In consideration of these trends and relationships between public health advances and increases in disability, it may not be realistic to expect short-term control of disability or cost savings following interventions that reduce mortality, even if those



Source: Authors.

**Figure 49.1** Causal Pathways for LDD

interventions have a net positive effect on public health. The costs of disability and its prevention may increase initially in the wake of interventions that successfully reduce mortality. Figure 49.1 summarizes the causal pathways and potential interventions for the prevention of LDD.

## INTERVENTIONS IN LOW- AND MIDDLE-INCOME COUNTRIES

Numerous interventions are effective in preventing LDD. Table 49.2 provides a summary of these interventions classified on two axes. The horizontal axis distinguishes whether the intervention would accomplish primary, secondary, or tertiary

prevention of disability. The vertical axis distinguishes four levels of evidence for cost-effectiveness:

- evidence available for LMICs
- evidence available for high-income countries only
- evidence for cost-effectiveness not available, but cost-effectiveness can be estimated from existing data
- evidence not available, but potential for benefits exists.

The literature indicates that the economic outcomes of a given intervention may vary widely for two reasons:

- Variations exist across populations, even within the same country, in the prevalence of the disorder, the cost of health care, and the existing infrastructure available to implement the intervention.



**Table 49.2** Classification of Interventions to Prevent LDD

	<b>Primary (prevention of condition that can lead to disability)</b>	<b>Secondary (prevention of disability once condition has occurred)</b>	<b>Tertiary (rehabilitation or prevention of further disability once disability has occurred)</b>
Evidence for cost-effectiveness available for LMICs	Food fortification ( <i>folic acid</i> and iodine <sup>a</sup> ) Rubella vaccine <sup>a</sup> Hemophilus vaccine Removal of lead from paint and fuel Vitamin A supplementation (vision) Measles vaccine		
Evidence for cost-effectiveness available for high-income countries only		<i>Prenatal screening for DS and prevention of DS births</i> <i>Newborn screening for metabolic disorders followed by interventions to prevent disability</i>	
Evidence for cost-effectiveness not available, but cost-effectiveness can be estimated from existing data	Malaria prevention <sup>b</sup>	Early detection and care of neonatal jaundice Management of malaria Treatment for otitis media Prevention and treatment of neonatal complications through emergency obstetric and pediatric services Eyeglasses Hearing aids Detection and treatment of maternal thyroid disorders	Special education Prosthetics Braille Sign language Occupational, physical, and speech therapies Surgery Residential care Assistive devices
Evidence for cost-effectiveness not available, but potential for benefits exists	Fetal alcoholism prevention Trauma prevention (bicycle helmets, burns) Prevention of shaken baby syndrome and child abuse	Dehydration/diarrhea treatment Postnatal combined cognitive stimulation and nutritional intervention Therapeutic stimulants for treatment of ADHD	<i>Community-based rehabilitation</i>

*Note:* Italicized text represents somewhat detailed consideration of cost-effectiveness included in this chapter.  
a. Covered in chapter 56, but chapter emphasis is not on implications for preventing developmental disabilities.  
b. Covered in detail in chapter 21.

- Differences between studies exist in analytical methods used, such as the willingness to pay versus the human capital approach to valuation, and in cost categories, such as whether to include parental time costs. Though these differences make cross-population comparisons difficult, the overall evidence of cost-effectiveness is demonstrated by repeated findings that the benefits of a particular intervention outweigh the costs in a number of different settings.

Current evidence suggests that three interventions are cost saving: folic acid fortification to prevent NTDs, prenatal screening and selective pregnancy termination to prevent DS, and neonatal screening and treatment for congenital hypothyroidism (CH).

Too little is known about the fourth type of intervention, community-based rehabilitation, to evaluate it. There is a paucity of knowledge and a history of failed interventions for the prevention of premature birth and the disabilities associated with premature birth.

**Neural Tube Defects: Burden and Cost-Effectiveness of Folic Acid Fortification**

NTDs, which are the most common malformation of the central nervous system, result from failure of the neural tube to close during the first month of pregnancy. Anencephaly typically results in pregnancy loss, stillbirth, or neonatal death. Spina bifida (open spine defect) is associated with a range of

functional deficits (requiring multiple surgical and rehabilitative interventions), including paralysis of the lower extremities and often primary enuresis and cognitive disabilities. Large geographic variations in the prevalence of NTDs exist both within and between countries. The burden of disease is highest in South Asia and lowest in LMICs of Europe and Central Asia. Similarly, deaths from NTDs are high in South Asia but lowest in high-income countries. Estimates suggest that almost all NTD disease burden is concentrated in the age group zero to four years (Mathers 2006).

**Folic Acid.** Folate is a vitamin that occurs naturally in green leafy vegetables, legumes, citrus, and other foods. Folic acid (FA) is an easily absorbed synthetic form of folate that can be delivered as a dietary supplement or through FA fortification of flour or other common staple foods. NTDs can be reduced by 70 percent if women consume 400  $\mu\text{g}$  of FA daily around the time of conception and until closure of the neural tube. At a population level, either supplementation or fortification of the food supply is necessary to ensure that 400  $\mu\text{g}$  of FA is consumed at the critical period of fetal development, as this dose is higher than can reasonably be consumed by relying on naturally occurring folate in foods. Fortification is much more likely than supplementation to reach the population at risk because the benefit of enhanced FA intake occurs early, typically before the pregnancy is recognized. Fortification is of particular value to women who may not receive prenatal care until the third trimester.

This section considers only evidence of cost-effectiveness of FA fortification in LMICs with respect to the benefit of preventing NTDs. Additional health benefits can be expected with respect to stroke, heart disease, and cancer.

**Cost-Effectiveness of Folic Acid Fortification** A cost-benefit analysis of grain fortification in the United States (Romano and others 1995) included costs related to the addition of FA to food, to annual testing and surveillance, to a one-time packaging change, and to potential (though not substantiated) adverse health effects associated with undiagnosed vitamin B<sub>12</sub> deficiency. Benefits included avoided costs of NTDs, such as mortality costs (particularly for anencephaly) and costs of caring for those with spina bifida. The benefits of fortification outweighed costs with cost-benefit ratios of 1 to 4.3 for low-level fortification and 1 to 6.1 for high-level fortification.

Cost-effectiveness relative to status quo of FA fortification depends on several factors:

- Costs of food fortification depend on the types and quantity of food that are fortified and the level of fortification.
- The proportion of the target population reached by the fortified food is important since, in most LMICs, many people consume food produced on their own farms or within their villages.

- Grains from large mills are relatively cheap to fortify; more resources are required to fortify grains milled in smaller neighborhood mills.
- The amount of folate consumed by different populations in the absence of fortification varies.
- Prevalence of NTDs varies across populations, and the cost-effectiveness increases with prevalence.

Costs of food fortification may be lower in high-income countries, where most people consume cereals processed in a few large mills, equipment for fortification is likely to be in place, and quality assurance is facilitated. In contrast, mills in LMICs lack fortification equipment and capital, and running costs are higher in the short run.

**Costs of Food Fortification** For optimal daily consumption, the actual level of food fortification (defined as  $\mu\text{g}$  of FA per 100 grams of the food item) should be adjusted for storage and other losses so that a daily dose of 400  $\mu\text{g}$  is achieved. Food items that should be fortified depend on specific dietary habits. Staples such as rice and flour are obvious choices; salt, sugar, bread, milk, and edible oils are promising candidates. There are economies of scale in FA fortification. It can be and usually is carried out in conjunction with other forms of fortification, such as iron, iodine, and vitamin A fortification. Many food items are already fortified in high-income countries. Other factors to be considered in the choice of food for fortification are items that are centrally processed and allow for quality control. Soy sauce in China is an example: it is consumed on a daily basis by 70 percent of the population and is prepared in a few large factories.

The recommended fortification level is thus 240  $\mu\text{g}$  per 100 grams of the staple food. This fortification rate is assumed for all regional strata where the per capita staple consumption per day is less than 300 grams. Wheat, rice, maize, or a combination of these foods is the staple in most countries. The recommended level of FA fortification varies from 150  $\mu\text{g}$  to 240  $\mu\text{g}$  per 100 grams of cereal. So that women receive a daily dose of 400  $\mu\text{g}$ , the target cereals for fortification should be those for which daily per capita consumption is at least 200 grams. In Sub-Saharan Africa, daily per capita cereal consumption exceeds 200 grams only if wheat, rice, and maize are considered together.

Quality assurance is done through analytic testing of fortified products to confirm FA levels. Quality assurance costs in the United States are estimated at US\$0.64 cents per ton of fortified grain in quality assurance costs.

The costs of FA fortification include the cost of FA, setup, and analytic testing. The analysis is done using two different cost estimates: US\$0.15 and US\$0.50 per ton of grain fortified. The cost of FA determines the cost of premix added to the flour. FA is almost never added alone; usually FA, iron, zinc, and niacin are added in combination. The material cost of FA alone is about US\$0.10 to US\$0.20 per metric ton of milled



wheat. However, a more realistic cost for the premix (including other supplements) is about US\$0.50 per metric ton of milled wheat. This higher estimate is conservative and does not account for the health benefits from the other supplements. Either way, the per capita costs are only a few cents in each region. The low per capita cost in high-income countries of US\$0.009 assumes that 80 percent of the cereal supply is fortified. In South Asia, where NTDs have the highest burden, the per capita cost is estimated at US\$0.067 (Bagriansky n.d.).

**Benefits of Folic Acid Fortification** The cost-effectiveness of FA fortification in terms of its cost per DALY and per death averted assumes that the fortification strategy will reduce the incidence of NTDs by 50 percent. The costs are relatively high because of the high cost of FA. Even a few cents per capita becomes expensive if the per capita prevalence of NTD is very low.

**Other Costs and Benefits** The benefits of FA fortification outweigh the costs. The benefits estimated here are conservative for three reasons:

- Strokes and coronary deaths are also prevented by FA fortification and occur more frequently than NTDs.
- The percentage of NTDs that can be prevented by FA fortification may be greater than 50 percent, because up to 70 percent of NTDs can be prevented by 400 µg of periconceptional FA daily.
- These estimates do not take account of the costs of clinical care and management for complications when NTDs are not prevented.

### **Interventions to Prevent Disability Caused by Down Syndrome**

Screening programs are critical public health interventions that use universal or targeted screening tests to identify potential causes or cases of LDD, including DS.

**Prenatal and Neonatal Screening.** Prenatal screening for genetic abnormalities allows parents to determine whether to continue with an affected pregnancy, whereas neonatal screening's fundamental purpose is to improve the infant's prognosis through early diagnosis and treatment.

A number of LDDs have been screened for in high-income countries since the 1960s, and researchers have conducted economic evaluations of these screening programs, including those for Tay-Sachs disease carriers, DS (Cusick and others 2003), sickle cell disease (Panepinto and others 2000), phenylketonuria (Lord and others 1999), and several other inborn errors of metabolism (Insinga, Laessig, and Hoffman 2002).

**Estimates for Prenatal Screening, Diagnosis, and Selective Pregnancy Termination for Down Syndrome.** DS is the most

common genetic cause of mental retardation. Identifying a fetus with DS before birth and giving parents the option to terminate the pregnancy early can help decrease the burden of the disease on families and society. During counseling, parents may receive information about the consequences of DS, which will allow them to make an informed decision about the best care for the newborn or about termination of the pregnancy. Prenatal screening services provide an opportunity to profoundly reduce the impact of MR. The cost-effectiveness of prenatal screening for DS is based on two parameters: efficacy (by assessing the false positive rate of screening procedures and the number of fetal losses caused by screening) and financial costs (costs of screening per DS pregnancy averted). On the basis of the evidence, the best screening method is proposed, and sensitivity of the parameters of interest to the LMIC is tested. No formal comparisons are made between the costs of screening and care for a person with DS. The purpose of this analysis is to suggest the most cost-effective way of screening that provides families with information about the health of the child; it is not a cost-benefit analysis of whether a couple should terminate a pregnancy.

**Burden.** DS is caused by trisomy of chromosome 21—an extra chromosome rather than the usual diploid form—and is a major cause of severe MR (IQ less than 50 with substantial deficits in adaptive behavior). The incidence of DS is higher than the birth prevalence because many fetuses are spontaneously miscarried and, in some cases, selectively terminated. In the absence of prenatal screening and intervention, most DS conceptions (71 percent) result in spontaneous abortion; another 3 percent result in stillbirth, and 26 percent result in live birth with subsequent LDD (Kline, Stein, and Susser 1989). Because the incidence of DS cannot be determined without doing surveillance of all conceptions, the frequency of DS is typically measured in terms of prevalence per 1,000 live births rather than in terms of incidence. Thus, the population prevalence of DS varies depending on the maternal age structure (steep increase after age 35 years) as well as the availability and use of prenatal diagnosis followed by selective termination. Estimates from 10 LMICs range widely, from 0.1 out of every 1,000 live births in Indonesia to 4.4 out of every 1,000 live births in Pakistan (Institute of Medicine 2003). Most studies, in both high-income countries and LMICs, show DS birth prevalence in the range of 1.0 to 1.6 out of every 1,000 births. The birth prevalence of DS is likely higher in LMICs because of a higher proportion of births among women over age 35 (11 to 15 percent) relative to that in high-income countries (5 to 9 percent) (Kline, Stein, and Susser 1989) and possibly because of differential access to prenatal screening for chromosomal abnormalities.

**Life Expectancy and Quality of Life.** Life expectancy for children with DS is substantially lower than that of the general

**Table 49.3** Distribution of DALYs Lost to and Deaths Caused by Down Syndrome, by World Bank Region, 2002

Region	DALYs	Deaths
East Asia and the Pacific	4,101,694	1,328
Europe and Central Asia	507,723	652
High income countries	199,215	2,113
Latin America and the Caribbean	214,346	1,979
Middle East and North Africa	347,898	1,311
South Asia	2,005,766	11,336
Sub-Saharan Africa	478,851	4,967

Source: Mathers and others 2006.

population. Congenital heart disease occurs in 40 to 60 percent of children with DS and accounts for 30 to 35 percent of deaths. Survival and life expectancy of children with DS have increased dramatically: In a 1940–60 birth cohort in England, only 50 percent of infants with DS survived beyond age two. By comparison, in 1981–85, 90 percent survived beyond age five (McGrother and Marshall 1990). Table 49.3 describes the estimated total deaths caused by DS by region, as well as the estimated total DALYs lost.

DS is always associated with cognitive impairment. Disability can range from mild to profound, and most children are affected moderately (IQ 40–55). Early intervention and therapy can improve functional outcomes. Of children with DS, 60 to 80 percent have hearing loss, and approximately 70 percent have ophthalmologic problems. As life expectancy of DS individuals has increased, many grow to adulthood and face an increased risk of early onset Alzheimer's disease, cataracts, hearing loss, hypothyroidism, and degenerative vascular disease.

**Costs of Care.** Based on 1988 data, the estimated incremental lifetime economic costs of DS are US\$410,000 per case or US\$647,709 in 2004 dollars (Waitzman, Romano, and Scheffler 1994). In another study, the estimate of per capita incremental costs of DS, converted to 2004 dollars, include net medical costs of US\$168,567, developmental services costs of US\$80,530, special education costs of US\$171,593, and total costs of US\$420,690 (Waitzman, Romano, and Scheffler 1994).

An estimate of lifetime costs per live born baby with DS—including education, health, and lost productivity costs—ranged from US\$137,000 in 1990 to US\$515,000 in 1993 (Gilbert and others 2001). Net savings using the annual program of screening, diagnosis, and selective termination was estimated to be US\$885, with costs of US\$446,000 per 10,000 pregnancies for a program that detects and prevents 9.7 DS births per year and a lower bound estimate of US\$137,000 of potential lifetime costs per 9.7 births prevented.

The increased life span of individuals with DS and accompanying age-associated morbidity impose heavy demands on

medical care and community services, as well as on sustained support from family members. It is also important to note that dollar costs of care for a DS child in LMICs would be much lower than such costs in high-income countries because of lower prices as well as lower treatment intensity. For example, in some countries, congenital heart disease, which affects 40 to 60 percent of DS children, cannot be treated effectively. This lack of treatment will lower costs of care as well as life expectancy, and cost estimates will vary for each individual area or region.

**Cost-Effectiveness of Prenatal Screening, Diagnosis, and Selective Pregnancy Termination.** Prenatal screening can be implemented to allow selective termination of DS pregnancies and prevention of disability related to DS in the population. This intervention raises ethical, social, and cultural concerns for some individuals and populations that may preclude its applicability.

A screening program incorporating maternal serum triple screening in all pregnant women, regardless of maternal age, yields an excellent DS detection rate and is associated with a low false-positive rate (Wald and others 2003). DS pregnancies yield lower levels of alpha-fetoprotein and unconjugated estriol but have elevated levels of human chorionic gonadotropin compared with other pregnancies. Ultrasound evaluation of the fetus neck thickness improves screening sensitivity. It is also useful when used in conjunction with serum screening (Wald and others 2003). A positive screening result is followed by diagnosis using amniocentesis or chorionic villus sampling (CVS).

Although both diagnostic procedures are guided by ultrasound to reduce risk, they are invasive, are more expensive than the screening procedure, and carry a small risk of miscarriage of an unaffected pregnancy. Thus, only a select group screening positive for possible trisomy 21 are offered the invasive diagnostic procedures. Amniocentesis, which involves the aspiration of amniotic fluid, is performed between the 14th and 16th weeks of pregnancy. CVS involves aspiration of villi and can be performed between the 10th and 12th weeks of pregnancy. Although CVS can be performed earlier in the pregnancy, amniocentesis is easier to perform and is more widely used in the second trimester. Following diagnostic confirmation of DS, parents are provided with genetic counseling and the option of terminating the pregnancy.

Although DS risk increases with maternal age, most births occur in younger women and, therefore, two-thirds of all DS births occur in younger mothers (Ross and Elias 1997). If prenatal diagnosis is available only for mothers 35 years or older, only 33 percent of DS births will be detected. Studies demonstrate that heavy reliance on maternal age to screen for DS may not be desirable in LMICs. Maternal age factor is not so useful in settings where early marriage and motherhood are the norm and most DS pregnancies involve mothers younger than 35 (Gupta and others 2001). Therefore, maternal serum screening

of all pregnant women is important in preventing DS births and achieving cost-effectiveness (Wald and others 2003).

**Procedure Costs** Genetic screening and counseling services are expensive. Even after initial high fixed costs to establish prenatal screening services, provision of high-quality services requires staff training, equipment, and laboratory maintenance. A recent report suggests establishing genetic screening services when other public health interventions have reduced the infant mortality rate to the range of 20 to 40 out of every 1,000 live births (Institute of Medicine 2003). Above this level, other public health interventions may have greater benefits.

The breakdown of tasks is as follows:

- *screening costs*, which consist of laboratory expenses (consumables and staff); informing women of results (by mail if negative, by phone if positive); service costs (processing results and monitoring the service); training in ultrasound measurement of neck skin translucency; and overhead expenses
- *diagnostic costs*, which comprise counseling before CVS or amniocentesis, equipment and staff for these procedures, laboratory expenses (consumables and staff), and overhead expenses
- *costs of termination of selected pregnancies*, which include surgical dilation, evacuation (11 to 13 weeks), or medical termination with mifepristone (after 13 weeks).

We assume infrastructure exists for prenatal screening, diagnosis, and intervention. We use the following costs: triple serum test, US\$70; amniocentesis, US\$1,200; genetic counseling, US\$100; and termination of pregnancy, US\$2,000. These cost estimates have been widely used in the literature (Cusick and others 2003). However, the medical costs can be significantly lower in LMICs and will also vary across and within countries.

**Cost-Effectiveness and Efficacy** We assume that 100 percent of women attend a prenatal clinic between 10 and 14 weeks of gestation and are offered tests in the first trimester, or between 15 and 19 weeks for the tests in the second trimester. We discuss the effect of low uptake of prenatal care and its effect on cost-effectiveness of prenatal screening programs in our sensitivity analysis.

In terms of economic considerations, it is desirable to balance the probability of the birth of a DS child with the risk of procedure-related miscarriage. Sensitivity of prenatal screening and the false-positive rates vary widely, depending on the method used. The risk of procedure-related miscarriage can vary from 0.04 to 0.8 percent (Nyberg and others 1998). We use the conservative fetal loss rate of 0.9 percent (Gilbert and others 2001) for both procedures.

Efficacy of prenatal screening is defined as the number of unaffected fetuses lost due to prenatal testing per each DS birth

averted (Institute of Medicine 2003). The goal is to minimize this ratio. The efficacy of prenatal screening varies with prevalence, and the primary determinant of variations in prevalence of DS is the age structure of women giving birth. The prevalence of DS and the efficacy of prenatal screening increase with the percentage of births to mothers over the age of 35. In this analysis, a 90 percent rate of selective termination is used (Waitzman, Romano, and Scheffler 1994). On this basis, the number of fetal losses per DS birth avoided varies from 7.13 (for 1 in 10,000 prevalence) to 0.16 (for 44 in 10,000 prevalence). Therefore, in countries with low prevalence of DS, such as Indonesia, more unaffected fetuses are lost than DS births averted because of screening. In areas where the ratio of unaffected fetal losses to DS births avoided is above 1, the efficacy of screening for DS is questionable.

Because of higher loss rates for CVS, we use a 1.5 percent fetal loss rate in our sensitivity analysis (Lippman and others 1992). Other costs not considered in this study are the psychological effects of a positive test on the parents, anxiety that may persist from a false-positive test, and potential complications resulting from pregnancy termination. Complications from termination may vary (Stray-Pedersen and others 1991) and may not be the same in LMICs, which should be taken into account. The sensitivity rate for the triple serum test followed by the amniocentesis is 62.3 percent in the clinical trials (Vintzileos and others 2000), and the uptake of amniocentesis is 90 percent for affected mothers and 80 percent for unaffected mothers (Waitzman, Romano, and Scheffler 1994). We assume the false-positive rate of 5 percent. The false-positive rate affects the probability of losing an unaffected fetus as a result of invasive testing that follows serum screening.

*Financial cost-effectiveness* is defined as the screening costs per DS birth averted. It is presented in table 49.4. Cost-effectiveness is the highest in countries with high birth prevalence of DS, given that women have access and receive prenatal care. Costs of prenatal screening and termination per DS birth averted vary from US\$1,497,390 in Indonesia (for 1 in 10,000 prevalence) to US\$37,185 in Pakistan (44 in 10,000 prevalence). A similar relationship is seen between prevalence and cost per DALY. In our analysis, we use costs data that are based on estimates from developed countries. Because costs of care will vary widely across and within countries, cost estimates should be done for individual regions. Lower costs of care will reduce cost-effectiveness of prenatal screening for DS. However, even after the cost adjustment, it is unlikely that the benefits will completely go away, because of the large difference between a relatively cheap screening program and high burden of disease of DS.

**Sensitivity Analysis** The results of the analysis above depend on assumptions that may not hold in some LMICs. For example, if many women accept screening but few decide to have an amniocentesis, cost-effectiveness will be adversely affected. The

**Table 49.4** Financial Cost-Effectiveness and Efficacy of Prenatal Screening and Pregnancy Termination for the Prevention of Down Syndrome Births

Representative country	DS births per 100,000 population (birth prevalence)	DS births detected	Cost per 100,000 population (US\$)	Cost per DS birth detected (US\$)	DS births prevented	Cost of detection and termination (US\$)	Cost per DS birth avoided (US\$)	US\$ per DALY	Unaffected fetal losses	Fetal losses per DS birth prevented
<i>East Asia and the Pacific</i>										
Indonesia	10	5.61	7,546,188	1,345,851	5.05	7,556,281	1,497,390	14.88	36.0	7.13
<i>Europe and Central Asia</i>										
Hungary	56	31.40	7,574,655	241,237	28.26	7,631,174	270,041	38.31	35.98	1.27
<i>High-income countries</i>										
Canada	120.79	67.73	7,614,750	112,433	60.95	7,736,658	126,926	36.09	35.96	0.59
<i>Latin America and the Caribbean</i>										
Argentina	160	89.71	7,639,014	85,150	80.74	7,800,496	96,612	22.50	35.94	0.45
<i>Middle East and North Africa</i>										
Israel	100	56.07	7,601,884	135,579	50.46	7,702,810	152,643	22.14	35.96	0.71
<i>South Asia</i>										
Pakistan	440	246.71	7,812,290	3,1666	222.04	8,256,364	37,185	4.12	35.84	0.16
<i>Sub-Saharan Africa</i>										
South Africa	210	117.75	7,669,956	65,139	105.9	7,881,901	74,377	16.46	35.92	0.34

public health benefits of screening for DS in socioeconomically deprived areas are small because of low uptake of amniocentesis (Ford and others 1998). With lower uptake rates of amniocentesis, both efficacy and financial cost-effectiveness are adversely affected as a result of low detection rates, and the number of unaffected fetal losses decreases. It is also important to note that, in some countries, many women may not have access to prenatal care or may not seek prenatal care and prenatal testing. In such areas, programs that try to reduce DS prevalence will have limited success, especially if a population at greater risk of DS is not tested.

Cost-effectiveness is often measured per DS birth averted since reduction in DS prevalence is the ultimate goal of prenatal testing. In many cultures, an abortion is not an acceptable option. Acceptance of elective termination of pregnancy may also vary across ethnicities and other subgroups within a given country. A study in California found the uptake of termination following the DS diagnosis varied from 47.5 percent for Hispanics to 65.8 percent for whites and 70.8 percent for Asians (Cunningham and Tompkinson 1999). If few families decide to terminate pregnancy to avoid having a child with severe disability, cost-effectiveness per DS birth averted will be adversely affected, and the screening program may fail to reduce the birth prevalence of DS. If a large percentage of families are opposed to induced abortion of fetal DS, the uptake of amniocentesis also will be low.

Because fetal losses following CVS are often higher than those for amniocentesis, efficacy analysis should be conducted assuming a 1.5 percent fetal loss risk attributable to invasive testing in the first trimester. With higher fetal losses, the efficacy of the prenatal screening is adversely affected, although the cost-effectiveness will not change.

In addition, assuming a higher false-positive rate of 8.3 percent increases the number of invasive tests on unaffected mothers and the number of unaffected fetal losses, thus adversely affecting the efficacy of the prenatal testing (Vintzileos and others 2000).

The analysis presented above is limited to an evaluation of the cost-effectiveness of prenatal screening for DS only. Some serum markers (for example, alpha-fetoprotein) will identify other abnormalities, the benefits of which are not included in this analysis.

**Equity and Access** The desirable policy is that women of similar risk for DS have equal access to diagnostic tests. With limited access to prenatal care, the introduction of the screening programs can have small public health effects. Although the approach used in cost-effectiveness analysis is optimization of societal net benefit, the policies to be recommended for the prevention of disability must also consider individuals' freedom in decision making at each step of the prenatal diagnosis. Successful policies need to be based on cost-effectiveness



estimates that take into account the needs, sensitivities, and values of individuals and cultures (Institute of Medicine 2003).

### **Interventions to Prevent Disability Caused by Congenital Hypothyroidism**

For CH, like DS, screening programs are critical public health interventions.

#### **Neonatal Screening in Low- and Middle-Income Countries.**

When considering the costs and benefits associated with a CH screening program, one must first have an estimate of how prevalent CH is in the population so that the avoided costs associated with disability can be calculated. It is important to note that in high-income countries and in several middle-income countries screening is usually done for a series of conditions rather than for a single disorder. This fact is likely to affect the cost. In several of these conditions, the treatment includes dietary modification as well as costly prepared foods and formulas. Policies in countries where this type of screening occurs include labeling of food to alert potentially vulnerable consumers.

Several studies have examined the prevalence of CH in specific populations, with substantially varying results. A review of 13 studies reporting findings on CH prevalence identified through individual screening programs found the lowest rate to be 1 case of CH per over 6,000 screened in Thailand (Wasant, Liammongkolkul, and Srisawat 1999). Contrasting this is the highest rate reported: 1 case in 1,000 screened in Pakistan (Lakhani and others 1989). Prevalence can vary not only from one country to the next, but also within countries, depending on different analyses or subpopulations within one country. These variations demonstrate the need for identifying the appropriate population in order to conduct economic evaluations of screening interventions.

According to three cost-benefit analyses of CH screening (Layde, Von Allmen, and Oakley 1979; Barden and Kessel 1984), the benefits included savings from institutionalization, special education, medical care, lost parent and child productivity, and slightly decreased life expectancy. The costs included those of the screening program as well as the cost of treating detected cases. Overall, CH screening programs are substantially cost saving, with a cost-benefit ratio as high as 1 to 8.9 in high-income countries (Dhondt and others 1991). Such savings have not yet been evaluated in LMICs. Because the treatment is inexpensive and highly effective, it is anticipated that CH screening would also be substantially cost saving in LMICs.

**Burden.** Congenital hypothyroidism is a common cause of MR that can be prevented by newborn screening and treatment. By the end of the 1970s, neonatal screening programs had been established in many regions of Canada, Europe, Japan, and the United States. Thyroid hormone is required for

normal brain development, and little or no thyroid hormone in the neonatal period results in damage to the nervous system. Various causes of anatomical maldevelopment of the thyroid gland are responsible for CH, and several genes have been implicated. With biochemical newborn screening (best conducted in centralized regional laboratories) using dried blood spots and diagnosis in the first few weeks of life, MR is avoidable. Without appropriate treatment, two-thirds of patients with CH have low IQ, and 30 percent experience severe or profound cognitive disability (Beaulieu 1994). Even with appropriate treatment, some subtle intellectual impairment and behavior deficits may still occur—the mean IQ may be approximately 10 points lower than that of the general population (Tillotson and others 1994). In the United States, infants are screened as newborns and again at two to six weeks of age to detect missed cases. For optimal outcomes, lifelong treatment with thyroid hormone is required, with subsequent monitoring and adjustments recommended every 3 to 12 months until growth and puberty are complete. Many females born with CH are now reaching childbearing age and require increased dosages of thyroid hormone during pregnancy for optimal neuropsychological outcome in their offspring.

**Costs of Care.** Estimated lifetime costs of care for the child with CH include the following (Barden and Kessel 1984):

- *Institutional care.* At the time of the study, 15 percent of congenital hypothyroid individuals were institutionalized from age 5 to 70.
- *Foster care.* About 25 percent of congenital hypothyroid cases received foster care from age 5 to 20.
- *Residential care.* Such care was provided for 40 percent of affected cases.
- *Special education expenditures.* Such expenses varied with the level of MR (15 percent severe, 25 percent moderate, and 40 percent mild).

In 2004, estimated lifetime costs of CH care is US\$191,000, with a 6 percent discount rate. This estimate of the financial costs of care for an affected person is fairly conservative; it does not take into account lost productivity of the person with CH, a potential loss of income attributable to the time inputs of the family members who are taking care of the affected person, or effects on quality of life.

**Cost-Effectiveness of Neonatal Screening.** Table 49.5 presents cost-effectiveness analysis of neonatal screening for representative countries in the World Bank regions. Screening costs include blood sample collection, laboratory costs, discounted lifetime treatment cost, and costs of care for those missed by the screening. Specimen collection and laboratory costs (Barden and Kessel 1984; OTA 1988) constitute (in 2004 dollars) US\$989,000 and US\$969,000, respectively, per

**Table 49.5** Cost-Effectiveness of Neonatal Screening for Congenital Hypothyroidism by World Bank Region

Representative country	CH births per 100,000 (birth prevalence)	CH births detected	Program costs for screening and treatment (US\$)	Cost per disability averted (US\$)	Cost without testing (US\$)	Cost savings (US\$)
<i>East Asia and the Pacific</i>						
Thailand	23.94	22.74	2,236,661	98,366	4,342,987	2,106,326
<i>Europe and Central Asia</i>						
Estonia	34.97	33.22	2,407,937	72,492	6,344,406	3,936,468
<i>High-income countries</i>						
United States	25.00	23.75	2,253,200	94,872	4,536,250	2,283,050
<i>Latin America and the Caribbean</i>						
Mexico	40.7	38.67	2,496,991	64,580	7,385,022	4,888,032
<i>Middle East and North Africa</i>						
Saudi Arabia	36.25	34.43	2,427,813	70,509	6,576,658	4,148,845
<i>South Asia</i>						
Pakistan	100.00	95.00	3,417,801	35,977	18,145,000	14,727,199
<i>Sub-Saharan Africa</i>						
South Africa	24.13	22.93	2,239,768	97,686	4,379,292	2,139,524

100,000 children tested. Lifetime discounted (at 6 percent) treatment costs are US\$6,292.64 in 2004 dollars (Barden and Kessel 1984). Analysis of costs and benefits in table 49.5 shows that, although screening for the population as a whole requires considerable investment and infrastructure, the burden from the disorder is high and treatment is cheap. Screening all newborns is beneficial compared with the high costs of lifelong care for the affected individuals. Cost savings are positive for all representative countries despite high variance in the prevalence of CH. Even for a low birth prevalence estimate of 4 out of every 100,000 in Thailand (Wasant, Liammongkolkul, and Srisawat 1999), the cost savings would be US\$106,326.

Effectiveness of the newborn screening in identifying the affected infants depends on the ability of the screening program to collect blood samples from all infants in the first week and to perform tests in time to initiate treatment. This effort may be difficult in some settings, where infants are born at home or released on the first day after birth and do not have contact with the health care system in the first month of their lives (Sack, Feldman, and Kaiserman 1998). The wider the coverage of the screening program, the higher will be the cost savings of screening. Also, follow-up screening for those infants who test as false negative will increase sensitivity to 100 percent and improve cost-effectiveness of the program.

In our cost-effectiveness analysis, we assumed the lifetime care and treatment costs to be similar to those estimated for the United States. However, medical costs may vary significantly among and within countries. Such variation is unlikely to alter

the cost-effectiveness analysis, because the difference between program and treatment expenditures and lifetime costs will remain even after we scale the medical costs.

The analysis presented above is limited to an evaluation of the cost-effectiveness of neonatal screening for CH. For minimal extra cost, collected blood samples for CH can also be used to identify other inherited disorders, including phenylketonuria, maple syrup urine disease, and other inborn errors of metabolism. Without the benefits of early detection and treatment for these conditions, the result is severe MR.

### Community-Based Rehabilitation

Community-based rehabilitation is a set of low-cost approaches to providing rehabilitation services such as physical therapy, occupational therapy, prosthetics, and assistive devices for people with disabilities in developing countries. Such rehabilitation also aims to minimize stigmatization of people with disabilities and to support inclusive education and integration of people with disabilities into society. WHO and other organizations have actively promoted community-based models for providing rehabilitation services—including services for children with developmental disabilities—in resource-poor settings (Institute of Medicine Committee on Nervous System Disorders in Developing Countries 2001).

Although 80 percent or more of the world's people with disabilities live in developing countries, only 2 percent have access to rehabilitation services (WHO Community-Based



Rehabilitation 1982). If families of people with disabilities are taken into account, the number of people experiencing the effects of disability is estimated to be up to 25 percent of the world population. Community-based rehabilitation is designed to expand access to rehabilitation services in poor and rural areas by providing training in rehabilitation techniques to individuals with disabilities, their family members, and others in their communities. It also attempts to change negative attitudes toward disability and to remove barriers in the physical environment that prevent people with disabilities from fully participating in society.

**Costs.** In the community-based rehabilitation model, community interventions are shifted from institutions and centers to the homes and communities of people with disabilities and are carried out largely by family members and volunteers. By using volunteer workers and the existing infrastructure in the communities, this form of rehabilitation minimizes costs of delivering services and is assumed to be cost-effective relative to the alternative institution-based rehabilitation (Institute of Medicine Committee on Nervous System Disorders in Developing Countries 2001; WHO Community-Based Rehabilitation 1982; Lagerkvist 1992). Institutional care has higher costs because it relies on paid staff, medical equipment, building maintenance, and medical costs. Some advocate for provision of institutional, center-based, medical, and community-based approaches in a complementary fashion. In a Zimbabwean community-based rehabilitation project two-thirds of the patients were referred to hospitals or clinics (Rottier and others 1993). Annual costs for training workshops and salaries of rehabilitation workers amounted to US\$60,000 to treat 1,614 individuals with disabilities.

Little information is available about the full costs of community-based rehabilitation and how they vary across disabilities, age groups, and societies. The cost-effectiveness of such rehabilitation or whether its costs are lower than alternative rehabilitation models is unknown. It is usually implemented in settings where no other rehabilitation models exist. The costs to consumers in terms of their efforts, time, and money may be substantial (Thomas and Thomas 1998). No formal estimates are available of time costs and opportunity costs to family members involved in community-based rehabilitation. Meeting the needs of a family member with a disability may prohibit or disrupt labor force participation of the caregiver and reduce family income. This need for caregiving may especially affect women (Giacaman 2001). The effectiveness of community-based rehabilitation in improving functional outcomes for children with cerebral palsy in Bangladesh showed no improvement, but researchers unexpectedly found a significant increase in reported stress and symptoms of depression in the mothers of children in the community-based rehabilitation intervention group (McConachie and others 2000).

**Efficacy.** Other attempts to evaluate community-based rehabilitation in different settings and for a range of outcomes include one for preschool children with disabilities in rural Guyana. The children showed significant improvement after six months in the program, and noticeable improvements in the attitudes of parents and others toward children with disabilities were seen (O'Toole 1988). Community-based rehabilitation programs in the Philippines and Zimbabwe found gains in activities of daily living and communication as well as higher rates of starting school and employment after six months in the program (Lagerkvist 1992). Similarly, people with disabilities participating in a community-based rehabilitation program in Botswana showed high levels of independence in activities of daily living; 20 percent of adults were working, and most school-age children were attending class (Lundgren-Lindquist and Nordholm 1996).

Some have questioned the efficacy of community-based rehabilitation and its ability to expand access for people with disabilities. Many people with disabilities do not patronize such programs, and many who do try leave dissatisfied (Kassah 1998). After initial diagnosis, only half of the identified individuals with disabilities continued (Rottier and others 1993). Community-based rehabilitation programs also face the difficulty of working in diverse communities with unique cultural, religious, economic, and social conditions, making it difficult for a single model to meet the needs for rehabilitation services in developing countries (Crishna 1999).

### **Prevention of Premature Birth**

Premature birth—after 20 weeks but before 37 weeks—is a powerful predictor of death and disability. Infants born before 28 weeks of gestation have a 50-fold increased risk of cerebral palsy (Drummond and Colver 2002) and heightened risk of sensory, cognitive, and educational impairment (Taylor and others 2004). The rate of preterm births in the United State has increased steadily since 1990 (MacDorman and others 2002). Survival of infants born before 34 weeks requires intensive and expensive medical care (Gilbert, Nesbitt, and Danielsen 2003), and the global survival rate differs depending on neonatal care availability (Lorenz and others 2001). Infection or inflammation of the placenta is common in preterm pregnancies (Goldenberg and Culhane 2003), and many deaths attributed to asphyxia may be caused by maternal, placental, or neonatal infection. The cerebral palsy rate is significantly higher in premature infants whose births are monitored electronically (Shy and others 1990). With the exception of magnesium sulfate administered to women in preterm labor (Crowther and others 2003), no specific interventions result in decreased cerebral palsy among premature infants (Crowther and Henderson-Smart 2004).

Dietary supplements might decrease the frequency of low-birthweight births and perhaps the frequency of marked prematurity. In Bangladesh, where the rate of preterm labor

was high, women who went into labor before term were older, shorter, thinner, less educated, and more disadvantaged economically, with closer spacing of births (Begum, Buckshe, and Pande 2003). Deaths attributable to prematurity in LMICs are seldom due to poor management and are largely related to poor health facilities (Pattinson 2004).

### Electronic Fetal Monitoring in Labor

For decades most cerebral palsy and a major share of MR, epilepsy, and learning and behavioral disorders of childhood were considered to be due to deprivation of oxygen supply to the fetus during birth. Recent research confirms that only a minority of cerebral palsy cases, as well as associated MR and seizures, are related to markers of birth asphyxia (Nelson and Ellenberg 1986; Torfs and others 1990). Low Apgar scores, the need for respiratory support, and neonatal seizures are more commonly due to etiologies other than asphyxia, most notably intrauterine exposure to infection (Wu and others 2003). So that medical workers could recognize the onset of asphyxia and “rescue” the fetus, continuous electronic fetal monitoring (EFM) of the fetal heart rate during labor was introduced in the 1970s. This intervention was disseminated before being tested in randomized trials to compare continuous electronic monitoring with intermittent observation by stethoscope (auscultation). Since the introduction of EFM, fetal death in labor has decreased, the cesarean section rate has quadrupled (Natale and Dodman 2003), and the rate of cerebral palsy has remained steady. Accordingly, EFM cannot be recommended for use in LMICs. Intermittent auscultation with a stethoscope appears to be the appropriate way to monitor fetal status during labor.

### RESEARCH AGENDA FOR PREVENTION OF DISABILITIES IN LOW- AND MIDDLE-INCOME COUNTRIES

Research needed as a basis for developing policies and interventions to prevent LDD in low- and middle-income countries includes basic research, epidemiology, and evaluations of early interventions, clinical treatments, prevention strategies, and health services that are culturally appropriate and feasible. Suggested research priorities include the following:

- etiology and prevention of adverse pregnancy outcomes associated with LDD, such as low birthweight, preterm birth, intrauterine growth retardation, and related factors
- community-based rehabilitation, including effectiveness, cost-effectiveness, and social effects of different models for providing rehabilitation services and special education to children with LDD in LMICs

- methodological and prevalence studies to ensure that the impacts of LDD are effectively measured by DALYs or other international indicators
- cost-effectiveness of interventions to prevent specific nutritional, infectious, genetic, and other causes of LDD
- impact on child development of multiple insults and risk factors especially common in LMICs, such as neurotoxic exposures, trauma, infectious disease or malnutrition, poverty, maternal illiteracy, and other social factors
- health services research related to access to prenatal care and prenatal and newborn screening and evaluation of components of the public health system that might impair or enhance integration of services for patients with LDD
- prevalence of ADHD and a cost-benefit analysis of the use of psychotropic medications
- prevalence and costs of autism spectrum disorders
- strategies to improve interventions for the prevention of fetal alcohol syndrome and to develop effective intervention programs for children affected by prenatal alcohol exposure
- evaluation of criteria for newborn screening and effects of new technology on measured incidence, costs, and system effectiveness
- evaluation of financing of successful newborn screening and treatment programs
- model systems of care for individuals diagnosed through newborn screening from infancy to adulthood.

### SUMMARY

Many potential interventions exist for the prevention of LDDs, and relatively few are being implemented for the benefit of children in LMICs. The following three interventions are effective and cost-effective in preventing LDD:

- Folic acid fortification of the food supply can reduce the occurrence of NTDs by 50 percent or more. This intervention was found to be highly cost-effective in the United States; however, in low-income countries, high capital and running costs may compromise cost-effectiveness, at least in the short run.
- Prenatal screening and selective pregnancy termination to prevent DS are highly cost-effective under some conditions but raise ethical, social, and cultural concerns that may preclude their applicability in some LMICs. Screening is not only expensive; it also has negative health outcomes: the false-positive rates and the subsequent anxiety, a risk of miscarriage of an unaffected pregnancy, and the resulting potential complications from pregnancy termination. Another concern is that, where access to prenatal care is limited, the potential for public health benefits of prenatal screening will be small.

- Neonatal screening and treatment for CH is highly cost-effective in developed countries, where it provides a low-cost strategy for preventing MR. For minimal extra cost, collected blood samples from newborns can also be used to identify and prevent the disabling effects of other inborn errors of metabolism, such as phenylketonuria and maple syrup urine disease. However, when only a part of the newborn population is reached by screening, high costs will be incurred to care for those missed by the screening, thereby reducing the cost-benefit ratio.

For another type of intervention considered, community-based rehabilitation, costs and benefits have not been quantified sufficiently to allow evaluation. Such rehabilitation is designed to expand access to services in poor and rural areas, to change negative attitudes toward disability, to lower the costs of delivering services, and to enhance the participation of persons with disabilities in society. The benefits of community-based rehabilitation may come at a high cost in terms of time and financial resources of family members.

Another intervention, electronic fetal monitoring in labor, has been shown to be unsuccessful in preventing childhood neurological disability associated with premature birth: the risk of cerebral palsy was significantly higher in infants delivered using EFM. Consequently, this intervention is not recommended for use during labor.

DALY estimates are not available to convey the full range of LDDs or their risk factors. However, available data are consistent with the possibility that these disabilities account for a large proportion of the global burden of disease. Quantifying the impacts of LDDs and their preventive interventions is complicated by the fact that these disorders can exist at multiple levels and that disability is context-specific, with impacts that may vary across cultures. Several research priorities for improving knowledge and developing policies and interventions to prevent LDD in LMICs are suggested.

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