Disease Control Priorities related to Mental, Neurological, Developmental and Substance Abuse Disorders

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Introduction

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This volume brings together five chapters from *Disease Control Priorities in Developing Countries,* 2nd edition (DCP2 Jamison and others 2006). These chapters cover mental disorders, neurological disorders, learning and developmental disabilities, and alcohol and illicit opiate abuse. The purpose of this special package is similar to the overall objective of the parent volume - to provide information on cost-effectiveness of interventions for these specific groups of disorders. This information should contribute to reformulation of policies and programmes and reallocation of resources, eventually leading to reduction of morbidity and mortality.

Why these five chapters together? The primary reasons are both a conceptual basis and a practical consideration. Not only do these five chapters tend to cover brain and behaviour, but also most departments and ministries of health in developing countries deal with these areas together. Since the target readership of this volume includes policy makers and advisers in government departments in developing countries, it seemed sensible to publish these chapters together. In addition, these areas have many other commonalities - they are responsible for a large and increasing burden, they are still low priorities in the public health agenda, the resource gap for their control is especially high and the evidence for cost-effectiveness interventions against these disorders has become available only relatively recently. The Department of Mental Health and Substance Abuse, World Health Organization (WHO), which is co-publishing this volume, is responsible for all these five areas.

WHO also commissioned additional background reviews to support the work of Disease Control Priority Project; these are available on the DCPP website: (http://www.dcp2.org/page/main/Research.html) and cover the following topics.

- Suicide and Suicide Prevention in Developing Countries (Vijayakumar)
- An International Review of the Economic Costs of Mental Illness (Hu)
- An International Review of Cost-Effectiveness Studies for Mental Disorders (Knapp and others)
- Mental Health and Labor Markets Productivity Loss and Restoration (Frank and Koss)

The disorders and conditions covered in this volume are common and burdensome. Neuropsychiatry conditions together account for 10.96% of the global burden of disease as measured by DALYs (Mathers, Lopez, and Murray 2006). Alcohol as a risk factor is responsible for 3.6% DALYs and illicit drugs 0.6%. The burden associated with the full range of learning and developmental disabilities has not been estimated, but is likely to be substantial.

The proportion of the global burden of disease attributable to mental, neurological and substance use disorders together is expected to rise in future. The rise will be particularly sharp in developing countries, primarily because of the projected increase in the number of individuals entering the age of risk for the onset of disorders. These problems pose a greater burden on vulnerable groups such as people living in absolute and relative poverty, those coping with chronic diseases and those exposed to emergencies.

While these figures are large and impressive, there are many other varieties of burden that are not covered by the DALY methodology but are extremely important for these disorders. These include burden to family members (time, effort and resources spent or not availed in the care of a sick family member) and lost productivity at the level of individual, family or society in general. The DALY methodology also does not take into account externalities including harm to others (quite substantial for alcohol and illicit drug use). While the evidence for cost-effectiveness for interventions in this area using the DALY methodology is persuasive, it is likely that the case would be even stronger, if other kinds of burden are taken in account.

WHO has recognized the need for enhancing the priority given to mental and neurological disorders, learning and developmental disabilities, and alcohol and illicit opiate abuse in several of its recent publications (WHO 2000; WHO 2001; Room and others 2002; WHO 2004a; WHO 2004b). WHO has also recommended specific actions to be taken by countries to strengthen the services available to individuals suffering from these disorders (WHO 2001). However, the progress in achieving these objectives has been slow and insufficient.

The data showing the magnitude and the burden of mental, neurological and substance use disorders are repeatedly presented and discussed in international literature. Data showing the gap in resources and in treatment are also frequently discussed. Finally, the evidence about the availability of cost-effective interventions is becoming more available than in the past.

In spite of all these "arguments" (the burden, the gap and the availability of cost-effective interventions) still there is not enough clarity and understanding about the obstacles that actually prevent low and middle income countries to improve mental health care and increase their investment in mental health. The strong resistance to change and innovation in mental health care in most countries of the world have not been examined carefully. Some "reasons" to explain the fact that too little is happening in mental health in spite of the evidence that something effective can be done, have been provided: stigma about mental disorders prevent people to be treated, primary health care doctors are not properly equipped in recognizing and managing mild and moderate mental disorders, general practitioners and specialist do not recognize the important implications of comorbidity thus ignoring the mental health component of many physical diseases. These explanations are all true but probably many others are not considered and they may prove to have an equal or even bigger influence in preventing more and better investments in mental health.

However, better evidence on cost-effectiveness is likely to make the case for prioritization of these disorders stronger but there are other kinds of arguments that can help build the case (Patel, Saraceno, and Kleinman 2006). There is abundant evidence that mental health is closely linked with many global public health priorities. Mental health interventions or principles must be tied to many programmes dealing with physical health problems. The case is not that we need to prioritize depression because it is co-morbid with, for example, HIV/AIDS, but that planning a health initiative for HIV/AIDS without a depression intervention component would be denying individuals the best possible treatment for HIV/AIDS. It is unethical to deny effective, feasible and affordable treatment to millions of persons suffering from treatable disorders. Mental, neurological, developmental and substance use disorders are just as severe and disabling as various infectious diseases; those who suffer from these disorders need treatment, as without it they may be disabled for long periods. We should also be aware that those who suffer from these disorders are often unable to advocate for their rights of access to affordable, evidence-based treatments.

Besides the right to treatment, there is also the larger question of citizenship rights. Individuals with mental, neurological, developmental and substance use disorders remain one of the few groups of persons whose citizenship rights are systematically denied or abused by society. Ignorance, prejudice and discrimination result in large numbers of individuals suffering from these disorders being excluded from society- either by long-term incarceration in mental institutions or by denying them participation in work and family life. To put a stop to this, we will need to increase recognition of those rights in the community and among health workers, ensure those rights are monitored and enforced and provide technical and financial support for health care and legal systems to reform.

Centuries of neglect need to be compensated by positive action. Economic arguments need to be buttressed by social and humanistic arguments. Scientific evidence and economic costs and benefits need to be understood within the larger context of social responsibility.

What is needed is a radical change of paradigms for care of individuals with mental and neurological disorders, learning and developmental disabilities, and alcohol and illicit opiate abuse:

- From Exclusion to Inclusion: The "exclusion approach" is not focused on the patient's needs but rather on the environment's perception and needs. This approach results in an emphasis on security issues, including an over-estimate of dangerousness and a perception that mental disability makes people unable to take responsibility for themselves and others. Shifting the paradigm from exclusion to inclusion facilitates care in the community.
- From biomedical to biopsychosocial approach: In 1977, George Engel coined the expression "biopsychosocial" to describe the need in medicine for a new paradigm that would go beyond the traditional biomedical and reductionist model. Today, the adjective 'biopsychosocial' is frequently used to define that which is supposed to be an integral approach to medicine. However, it has become progressively more meaningless and ritualistic. This schism between the ritualistic use of holistic notions and the practice of medicine, which is still strongly oriented towards the biological paradigm, is particularly evident in the field of mental health. Shifting from a biomedical approach to a biopsychosocial one would cause important changes in the formulation of mental health policies, in the creation and financing of mental health programmes, in the daily practice of services and in the status of care providers. Such changes imply the recognition of the role of users and families, the recognition of the role of the community, not just as an environment, but as a generator of resources that must go hand in hand with the resources provided by the health services and finally, the recognition of the role of sectors beyond health, such as social security, social assistance, welfare and the economy in general.
- From Short Term Treatment to Long Term Care: A radical shifting of the care paradigm is required. Health systems are conceived and organized to respond to acute cases (hospital model). After the acute phase is resolved, the patient enters a limbo of infrastructures, human resources, skills and responsibilities. The question is, how can the entire health system serve the needs of the patient when he or she requires long term care? And this is not just for mental, neurological, learning and substance use disorders, but for many chronic conditions requiring long-term care (HIV/AIDS or tuberculosis, for example). In other words, we need a radical shifting from a model centred on the space location of the provider (hospitals, outpatient clinics) to one centred on a time dimension of the client.

- From Morbid to Co-Morbid: Real patients are more complex than pure diagnoses: real patients often have co-morbid diseases. Co-morbidity can occur within or across different medical disciplines: e.g., cardiology and oncology. Co-morbidity can also be inter-human; namely, within a microenvironment like a family (in the same family we may observe simultaneously - alcohol abuse in the husband, depression in the wife, learning disability in the child and domestic violence) or even in a macroenvironment (post-conflict communities, refugee camps, severely underprivileged urban settings). Current cost-effectiveness models fail to take full account of these real situations. Shifting the paradigm from vertical/mono-morbid interventions to co-morbidity settings enhances effectiveness and adherence; furthermore, a matrix approach can avoid the under-utilization or mis-utilization of human and financial resources. A mono-morbid paradigm will lead to vertical programmes where effectiveness is dispersed and expenditure is increased. A co-morbidity approach will instead facilitate the links between treatment of various disorders and enhancing compliance and adherence to treatments for co-morbid physical diseases. The gains from applying the cost-effective interventions analysed in this volume will therefore be even greater than the chapters suggest, if the health system can be made more responsive to co-morbid conditions.

It is hoped that the five chapters included in this volume will contribute towards effective control of mental, neurological, developmental and substance use disorders and facilitate adequate care of the affected individuals and support to their families. It is also hoped that the knowledge already gained will act as a stepping stone towards a more complete and integrated response to prevention and treatment of these disorders.

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Chapter **1**

Mental Disorders

Steven Hyman, Dan Chisholm, Ronald Kessler, Vikram Patel, and Harvey Whiteford

Mental disorders are diseases that affect cognition, emotion, and behavioral control and substantially interfere both with the ability of children to learn and with the ability of adults to function in their families, at work, and in the broader society. Mental disorders tend to begin early in life and often run a chronic recurrent course. They are common in all countries where their prevalence has been examined. Because of the combination of high prevalence, early onset, persistence, and impairment, mental disorders make a major contribution to total disease burden. Although most of the burden attributable to mental disorders is disability related, premature mortality, especially from suicide, is not insignificant. Table 1.1 summarizes discounted disability-adjusted life years (DALYs) for selected psychiatric conditions in 2001.

Mental disorders have complex etiologies that involve interactions among multiple genetic and nongenetic risk factors. Gender is related to risk in many cases: males have higher rates of attention deficit hyperactivity disorder, autism, and substance use disorders; females have higher rates of major depressive disorder, most anxiety disorders, and eating disorders. Biochemical and morphological abnormalities of the brain associated with schizophrenia, autism, mood, and anxiety disorders are being identified using approaches such as postmortem analysis and noninvasive neuroimaging. Major worldwide efforts under way to identify risk-conferring genes for mental disorders are proving challenging, but initial results are promising. Identifying the gene or genes causing or creating vulnerability for a disorder should help us understand what goes wrong in the brain to produce mental illness and should have a clinical effect by contributing to improved diagnostics and therapeutics (Hyman 2000).

Twin studies make it clear that environmental risk factors also play an important role in mental disorders; concordance for disease among identical twins, although substantially higher than among nonidentical twins, is still well below 100 percent (Kendler and others 2003). However, as is the case for genetic factors, investigation of environmental risk factors has proved difficult. For schizophrenia, where nongenetic components of risk may include obstetrical complications and season of birth (Mortensen and others 1999), perhaps as a proxy for infections early in life, research has been hampered by the modest proven effect of the nongenetic risk factors identified to date. For depression, anxiety, and substance use disorders, where environmental risk factors are more robust, adverse circumstances associated with risk, such as early childhood abuse, violence, poverty, and stress (Patel and Kleinman 2003) correlate with multiple disorders and could be affected by selection bias as well as by bias associated with self-reporting. Generalizable, prospective cross-cultural studies are needed to delineate nongenetic risk factors more clearly. Posttraumatic stress disorder (PTSD) is the mental disorder for which clear environmental triggers are best documented. Even here, though, enormous interindividual variability occurs in the threshold of stress severity associated with PTSD as well as in the evidence from twin studies of genetic influences on stress reactivity in triggering PTSD.

The last half of the 20th century saw enormous progress in the development of treatments for mental disorders. Beginning in the early 1950s, effective psychotropic drugs were discovered that treated the symptoms of schizophrenia, bipolar disorder, major depression, anxiety disorders, obsessive-compulsive disorder, attention deficit hyperactivity disorder, and others. The safety and efficacy of antipsychotic, mood-stabilizing, antidepressant, anxiolytic, and stimulant drugs have been established through a large number of randomized clinical trials. Psychosocial treatments have been

Table 1.1 Disease Burden of Selected Major Psychiatric Disorders, by World Bank Region

	World Bank region							
	Sub-Saharan Africa	**Latin America and the Caribbean**	**Middle East and North Africa**	**Europe and Central Asia**	**South Asia**	**East Asia and the Pacific**	**High-income countries**	**World**
Total population (millions)	668	526	310	477	1,388	1,851	929	6,159
Total disease burden (thousands of DALYs)	344,754	104,287	65,570	116,502	408,655	346,941	149,161	1,535,870
Total neuropsychiatric disease burden (thousands of DALYs)	15,151	18,781	8,310	14,106	37,734	42,992	31,230	168,304
Total burden (thousands of discounted DALYs per year)								
Schizophrenia	1,146	1,078	696	778	2,896	3,934	1,115	11,643
Bipolar disorder	1,204	883	567	668	2,237	3,118	1,056	9,733
Depression	3,275	5,219	2,027	4,268	14,582	14,054	8,408	51,833
Panic disorder	519	409	264	340	1,081	1,401	536	4,550
Total burden (DALYs per year per 1 million population)								
Schizophrenia	1,716	2,049	2,247	1,630	2,087	2,126	1,201	1,894
Bipolar disorder	1,803	1,678	1,830	1,400	1,612	1,685	1,137	1,583
Depression	4,905	9,919	6,544	8,944	10,507	7,594	9,054	8,431
Panic disorder	777	777	852	713	779	757	577	740
Percentage of total disease burden								
Schizophrenia	0.33	1.03	1.06	0.67	0.71	1.13	0.75	0.76
Bipolar disorder	0.35	0.85	0.86	0.57	0.55	0.90	0.71	0.63
Depression	0.95	5.00	3.09	3.66	3.57	4.05	5.64	3.37
Panic disorder	0.15	0.39	0.40	0.29	0.26	0.40	0.36	0.30
Percentage of neuropsychiatric disease burden								
Schizophrenia	7.56	5.74	8.38	5.52	7.67	9.15	3.57	6.92
Bipolar disorder	7.95	4.70	6.82	4.74	5.93	7.25	3.38	5.78
Depression	21.62	27.79	24.39	30.26	38.64	32.69	26.92	30.80
Panic disorder	3.43	2.18	3.18	2.41	2.86	3.26	1.72	2.70

Source: WHO Global Burden of Disease 2001 estimates recalculated by World Bank region (http://www.fic.nih.gov/dcpp/gbd.html).

developed and tested using modern methodologies. Brief, symptom-focused psychotherapies such as cognitive-behavioral therapies have been shown to be efficacious for panic disorder, phobias, obsessive-compulsive disorder, and major depression.

There is, however, an important caveat about the current knowledge base for treatment. As is the case for almost all of medicine, randomized clinical trials have been performed largely with highly selected populations in specialized research settings in industrial countries. A need exists to subject existing treatments to effectiveness trials in more representative populations and diverse settings, especially in developing countries. That limitation notwithstanding, a substantial body of knowledge exists to guide treatment. It is particularly unfortunate, therefore, that timely diagnoses and the application of research-based treatments significantly lag behind the state of knowledge in industrial and developing countries alike. As a result, substantial opportunities exist to decrease the enormous burden attributable to mental disorders worldwide by closing the gap between *what we know* and *what we do*.

Mental disorders are stigmatized in many countries and cultures (Weiss and others 2001). Stigma has been facilitated by-the slow emergence of convincing scientific explanations for the etiologies of mental disorders and by the mistaken belief that symptoms are caused by a lack of will power or reflect some moral taint. Recent scientific findings combined with educational efforts in some countries have begun to reduce the stigma (Rahman and others 1998), but shame and fear associated with mental illness remain substantial obstacles to help seeking, to diagnosis, and to treatment worldwide. The stigmatization of mental illness has resulted in disparities, compared with other illnesses, in the availability of care, in research, and in abuses of the human rights of people with these disorders.

This chapter focuses on the attributable and avoidable burden of four leading contributors to mental ill health globally: schizophrenia and related nonaffective psychoses,

bipolar affective disorder (manic-depressive illness), major depressive disorder, and panic disorder. The choice of these disorders is determined not only by their contribution to disease burden, but also by the availability of data for the cost-effectiveness analyses. Even where such data are available, they are often from industrial countries and extrapolation has been necessary. The exclusion of other mental disorders, such as childhood disorders, from analysis is not because the authors consider these disorders unimportant but because of the paucity of data. Also, this chapter does not specifically deal with the important issue of suicide. A background paper on suicide in developing countries has been developed as part of the Disease Control Priorities Project (DCPP) and is available (Vijayakumar, Nagaraj, and John 2004). The economic analysis presented in this chapter uses the cost-effectiveness analysis methodology specifically developed for the DCPP. The authors recognize that mental disorders impose costs and burdens on families as well as individuals that are not captured by the DALY. Treatment will alleviate some of this burden in addition to alleviating symptoms and disability.

A description of the major clinical features, natural course, epidemiology, burden, and treatment effectiveness for each group of disorders is given in the next section. For diagnostic criteria, readers are referred to *The ICD-10 Classification of Mental and Behavioral Disorders* (ICD-10) (WHO 1992) or *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IVTR) (American Psychiatric Association 2000). A discussion follows of population-level costs and cost-effectiveness of interventions capable of reducing the current burden associated with four disorders in different developing regions of the world (tables 1.2–1.6), before moving to a discussion of key issues and implications for mental health policy and improvement of services in developing regions of the world.

SCHIZOPHRENIA AND NONAFFECTIVE PSYCHOSES

Schizophrenia is a chronic disorder punctuated by episodes of florid psychotic symptoms, such as hallucinations and delusions. Hallucinations are sensory perceptions that occur in the absence of appropriate stimuli. Hallucinations may occur in any sensory modality but in schizophrenia are most commonly auditory—for example, hearing voices or noises. Delusions are fixed false beliefs that are not explained by the person's culture and that the patient holds despite all reasonable evidence to the contrary.

Patients also exhibit *negative symptoms*—that is, deficits in normal capacities, such as marked social deficits, impoverishment of thought and speech, blunting of emotional responses, and lack of motivation. Additionally, patients typically have cognitive symptoms, such as disorganized or illogical thinking and an inability to hold goal information in mind to make decisions or plan actions.

Natural History and Course

Schizophrenia, as defined in current diagnostic manuals, is almost certainly heterogeneous, but still does not comprise all nonaffective psychoses (NAPs). In addition to schizophrenia, NAPs include schizophreniform disorder, characterized by schizophrenia-like symptoms of inadequate duration to qualify as schizophrenia. Because they cannot be readily disentangled in community epidemiological surveys, schizophrenia and other NAPs are considered together. Because of the data available, however, the cost-effectiveness analyses reported below are restricted to schizophrenia. Despite likely etiological heterogeneity, schizophrenia exhibits consistency in its symptom pattern across those countries and cultures studied (Jablensky and others 1992).

Incidence studies show that onset of schizophrenia and other NAPs is typically in middle to late adolescence for males and late adolescence to early adulthood for females, although later onsets are observed. Childhood-onset cases are quite rare but particularly severe (Nicolson and Rapoport 1999). Often, schizophrenia is first diagnosed with the occurrence of an acute episode of florid psychotic symptoms. The first psychotic episode is often preceded by prodromal symptoms such as social withdrawal, irritability or dysphoria, increasing academic or work-related difficulties, and increasing eccentricity. However, such symptoms are not specific; studies of whether early diagnosis and intervention can improve outcomes are under way (McGorry and others 2002).

The course of schizophrenia is typically one of acute exacerbations of severe psychotic symptoms, followed by full or partial remission. Psychotic episodes may be followed by a full remission after the first and occasionally other early episodes, but over time, residual symptoms and disability typically continue between relapses (Robinson and others 1999). The time between relapses is markedly extended by maintenance treatment with antipsychotic drugs, generally at lower doses than are needed to treat acute episodes. Cognitive and occupational functioning tends to decline over the first years of the illness and then to plateau at a level that is generally well below what would have been expected for the individual. Residual impairment, though, has substantial cross-cultural variation for reasons that are not well understood. Schizophrenia has consistently been found in epidemiological surveys to be highly comorbid, usually with anxiety disorders, mood disorders, and substance use disorders (Kendler and others 1996).

Epidemiology and Burden

A great many studies of NAP incidence have been carried out in clinical samples. In a review of these studies, Jablensky (2000) found incidence estimates to be in the range of 0.002 to-0.011 percent per year for schizophrenia and 0.016 to 0.042-percent per year for overall NAP. Those annual estimates can be multiplied by the number of birth cohorts at risk to yield an estimate of lifetime risk in any one cohort.

Assuming conservatively that the main age range of risk is between ages 15 and 55, researchers estimate lifetime risk is in the range of 0.08 to 0.44 percent for schizophrenia and in the range of 0.64 to 1.68 percent for NAPs. Lifetime prevalence estimates from community epidemiological surveys of NAPs are quite consistent with those from clinical studies, in the range of 0.3 to 1.6 percent (see, for example, Hwu, Yeh, and Cheng 1989; Kendler and others 1996).

Although schizophrenia is a relatively uncommon disorder, aggregate estimates of disease burden are high—around 2,000 DALYs lost per 1 million total population (table 1.1)—because the condition is associated with early onset, long duration, and severe disability.

Interventions

A substantial body of evidence exists on the efficacy of various treatments for schizophrenia and NAP and on the effectiveness of various models of health care delivery for persons with these disorders. This evidence comes primarily from industrial countries. The efficacy data show conclusively that antipsychotic drugs reduce severity of the episodes, hasten resolution of florid symptoms, and reduce duration of hospitalization. Maintenance treatment with antipsychotic drugs prolongs the period between relapses (Joy, Adams, and Lawrie 2001).

A second generation of antipsychotic medications (also called *atypical*) is replacing older *neuroleptic* antipsychotic drugs throughout the industrial world. In some clinical trials, second-generation drugs show small advantages in efficacy over first-generation drugs, but their widespread adoption results from marked improvement in tolerability. Their relative lack of side effects compared with first-generation drugs has led to improved quality of life and improved treatment adherence. Second-generation drugs are not without side effects, however; for example, some are associated with substantial weight gain and increased risk of diabetes. One drug, clozapine, has greater efficacy than other antipsychotic drugs, but because of a 1 percent risk of agranulocytosis, its use requires weekly blood counts and is cumbersome and expensive.

Psychosocial interventions also play an important role in managing schizophrenia (Bustillo and others 2001). Cognitive-behavioral approaches to managing specific symptoms and improving medication adherence, group therapy, and family interventions all have demonstrated efficacy in improving clinical outcomes. Community-based models of mental health care delivery with case management and assertive outreach programs have been shown in health systems of industrial countries to be effective ways of managing schizophrenia in the community, for example, by reducing the need for hospital admissions. However, the applicability of these models to developing countries, as is discussed later, is hard to estimate because of differences in health system characteristics. Long-term remission rates for schizophrenia in developing countries appear to be significantly higher than those reported in industrial countries (Harrison and others 2001), likely resulting from such factors as strong family social support.

Despite their clear usefulness, current treatments do not prevent schizophrenia, and no clear evidence demonstrates that they induce full recovery or prevent premature mortality. Instead, treatment reduces time in episode of florid psychosis and increases time between episodes; thus treatment effects can be understood in terms of improvements in disability. Reported treatment effect sizes from meta-analyses in the literature, converted into improvements in the average level of disability (Andrews and others 2003; Sanderson and others 2004), show improvements (compared with no treatment) of 18 to 19 percent (antipsychotic drugs alone) and 30 to 31 percent (antipsychotic drugs with adjunctive psychosocial treatment). Placed on a disability scale of 0 to 1, where 0 equals no disability, an "average" case of schizophrenia moves from a disability level of 0.63 (untreated weight from the Global Burden of Disease study, Murray and Lopez 1996) to 0.43 to 0.54 (treated).

MOOD DISORDERS

The cardinal features of mood disorders are pervasive abnormalities in the predominant emotional state of the person, such as depressed, elated, or irritable. In mood disorders, these core emotional symptoms are accompanied by abnormalities in physiology, such as changes in patterns of sleep, appetite, and energy, and by changes in cognition and behavior. In developing countries, concurrent somatic symptoms are also commonly reported and may be the chief complaint. A generally accepted subclassification of mood disorders distinguishes unipolar depressive disorders from bipolar disorder (defined by the occurrence of mania). This distinction is based on symptoms, course of illness, patterns of familial transmission, and treatment response.

Bipolar Disorder

Bipolar disorder is characterized by episodes of mania and depression, often followed by relative periods of healthy mood (euthymia). Mixed states with symptoms of both mania and depression also occur. Mania is typically characterized by euphoria or irritability, a marked increase in energy, and a decreased need for sleep. Individuals with mania often exhibit intrusive, impulsive, and disinhibited behaviors. They may be excessively involved in goal-directed behaviors characterized by poor judgment; for example, a person might spend all funds to which he or she has access and more. Self-esteem is typically inflated, frequently reaching delusional proportions. Speech is often rapid and difficult to interrupt. Individuals with mania also may exhibit cognitive symptoms; patients cannot stick to a topic and may jump rapidly from idea to idea, making comprehension of their train of thought difficult. Psychotic symptoms are common during manic episodes. The depressive episodes of people with bipolar disorder are symptomatically

indistinguishable from those who have unipolar depressions alone. Unlike anxiety and unipolar mood disorders, which are more common in women, bipolar disorder has an equal gender ratio of lifetime prevalence, although the ratio of depressive-to-manic episodes is higher among bipolar women than men.

Natural History and Course. Retrospective reports from community epidemiological surveys consistently show that bipolar disorder has an early age of onset (in the late teens through mid-20s). Onset in childhood is increasingly recognized, although it-remains controversial. Late onset is less common. The vast majority of patients with bipolar disorder have recurrent episodes of illness, both mania and depression. Classic descriptions of bipolar disorder suggest recovery to baseline functioning between episodes, but many patients have residual symptoms that may cause significant impairment (Angst and Sellaro 2000). These states of mania, depression, and lesser (or absent) symptoms are used in the intervention analysis below.

The rate of cycling between mania and depression varies widely among individuals. One common pattern of illness is for episodes initially to be separated by a relatively long period, perhaps a year, and then to become more frequent with age. A minority of patients with four or more cycles per year, termed *rapid cyclers,* tend to be more disabled and less responsive to existing treatments. Once cycles are established, most acute episodes start without an identifiable precipitant; the best documented exception is that manic episodes may be initiated by sleep deprivation, making a regular daily sleep schedule and avoidance of shift work important in management (Frank, Swartz, and Kupfer 2000).

Bipolar disorder has consistently been found in epidemiological surveys to be highly comorbid with other psychiatric disorders, especially anxiety and substance use disorders (ten-Have and others 2002). The extent of comorbidity is much greater than for unipolar depressive disorders or anxiety disorders. Some individuals with classic symptoms of bipolar disorder also exhibit chronic psychotic symptoms superimposed on their mood syndrome. These individuals are said to have schizoaffective disorder. Their prognosis tends to be less favorable than for the usual bipolar patient, although somewhat better than for individuals with schizophrenia. Schizoaffective disorder may also be diagnosed when chronic psychotic symptoms are superimposed on unipolar depression. Individuals with this combination of symptoms have outcomes similar to patients with schizophrenia (Tsuang and Coryell 1993).

Epidemiology and Burden. Lifetime and 12-month prevalence estimates of bipolar disorder have been reported from a number of community psychiatric epidemiological surveys. Lifetime prevalence estimates are in the range 0.1 to 2.0 percent (Vega and others 1998; Vicente and others 2002), with a weighted mean across surveys of 0.7 percent. Prevalence estimates for past-year episodes have a similarly wide range (0.1 to 1.3 percent) (Vega and others 1998) and a weighted mean of 0.5 percent. It is important to note that good evidence exists suggesting that bipolar disorder has a wide subthreshold spectrum that includes people who are often seriously impaired even though they do not meet full DSM or ICD criteria for the disorder (Perugi and Akiskal 2002). This spectrum might include as much as 5 percent of the general population. The ratio of recent-to-lifetime prevalence of bipolar disorder in community surveys is quite high (0.71), indicating that bipolar disorder is persistent.

Epidemiological data show that bipolar disorder is associated with substantial impairments in both productive and social roles (Das Gupta and Guest 2002). Epidemiological evidence documents consistent delays in patients initially seeking professional treatment (Olfson and others 1998), especially among early-onset cases, as well as substantial undertreatment of current cases. Each of these characteristics—chronic, recurrent course; significant impairments to functioning; modest treatment rates—contributes to estimates of aggregate disease burden that approach those for schizophrenia (1,200 to 1,800 DALYs lost per 1 million population, making up more than 5-percent of the burden attributable to neuropsychiatric disorders as a whole—see table 1.1).

Interventions. Analyses of the primary treatment approaches for bipolar disorder are based on the three health states that characterize the disorder—mania, depression, and euthymia. Robust evidence from controlled trials shows that antipsychotic drugs and some benzodiazepines produce a relatively rapid reduction in symptoms of a manic phase. Mood-stabilizing drugs act more slowly, but they reduce the severity and duration of acute manic episodes. Maintenance treatment with two mood-stabilizing drugs—lithium and valproic acid (administered as sodium valproate)—has been shown to have significant, albeit partial, efficacy in reducing rates of both manic and depressive relapses. The drawback of lithium is that toxic levels are not much greater than therapeutic levels; thus, serum-level monitoring is required.

For the cost-effectiveness analyses, lithium and valproic acid, which have empirical data supporting their efficacy in treating and preventing manic and depressive episodes, were considered. Because evidence suggests that psychosocial approaches enhance compliance with medication (Huxley, Parikh, and Baldessarini 2000), adjuvant strategies also were assessed. The primary treatment effect was a change in the population-level disability associated with bipolar disorder (a weighted average of time spent in a manic, depressed, or euthymic phase of illness). Both an acute treatment effect—calculated as the product of initial response and reduced episode duration—and a prophylactic treatment effect were ascribed to lithium and valproic acid, resulting in an estimated improvement of close to 50 percent over the untreated composite disability weight of 0.445 (Chisholm and others forthcoming). This estimate then was adjusted for expected nonadherence to treatment in real-world clinical settings—

slightly lower for lithium than for valproic acid (Bowden and others 2000). A secondary effect of treatment—reduction of the case fatality rate by two-thirds—was also ascribed to lithium, though, because of an absence of current evidence, not to valproic acid (Goodwin and others 2003). This reduction was derived through a change in the standardized mortality ratio from 2.5 to 1.5, estimated on the basis of natural history studies reported for the prelithium era (for example, Astrup, Fossum, and Holmboe 1959; Helgason 1964) to the postlithium era (for example, Goodwin and others 2003).

Major Depressive Disorder

The core symptom of major depression is a disturbance of mood; sadness is most typical, but anger, irritability, and loss of interest in usual pursuits may predominate. Often the affected person is unable to experience pleasure (anhedonia) and may feel hopeless. In many countries of the developing world, patients will not complain of such emotional symptoms, but rather of physical symptoms, such as fatigue or multiple aches and pains.

Typical physiological symptoms that occur across cultures include sleep disturbance (most often insomnia with early morning awakening, but occasionally excessive sleeping); appetite disturbance (usually loss of appetite and weight loss, but occasionally excessive eating); and decreased energy. Behaviorally, some individuals with depression exhibit slowed motor movements (psychomotor retardation), whereas others may be agitated. Cognitive symptoms may include thoughts of worthlessness and guilt, suicidal thoughts, difficulty concentrating, slow thinking, and poor memory. Psychotic symptoms occur in a minority of cases.

Natural History and Course. Major depression is an episodic disorder that generally begins early in life (median age of onset in the mid to late 20s in community epidemiological surveys), although new onsets can be observed across the lifespan. Childhood onset is being increasingly recognized, although not all childhood precursors of adult depression take the form of a clear depressive disorder. Most individuals suffering from a-depressive episode will have a recurrence (Mueller and others 1999), with recurrence risk greater among those with early-onset disease. Many individuals do not recover completely from their acute episodes and have chronic milder depression punctuated by acute exacerbations (Judd and others 1998). The current term for chronic, milder depression lasting more than two years is *dysthymia.* Although the symptoms of minor depression are, by definition, less severe than those of a major depressive episode, chronicity ultimately makes even this lesser form of the illness very disabling in many cases (Judd, Schettler, and Akiskal 2002). Depression has consistently been found in epidemiological surveys to be highly comorbid with other mental disorders, with roughly half the people who have a history of depression also having a lifetime anxiety disorder. Comorbidities of depression and anxiety disorders are generally strongest with generalized anxiety disorder and panic disorder (Kessler and others 1996).

Epidemiology and Burden. Prevalence of nonbipolar depression has been estimated in a number of large-scale community epidemiological surveys. Lifetime prevalence estimates of having either major depressive disorder or dysthymia in these surveys are in the range 4.2 to 17.0 percent (Andrade and others 2003; Bijl and others 1998), with a weighted mean of 12.1 percent. Six- to 12-month prevalence estimates have a similarly wide range (1.9 to 10.9 percent) (Andrade and others 2003; Robins and Regier 1991), with a weighted mean of 5.8 percent. These wide differences in prevalence likely represent the difficulties inherent in self-reporting of conditions that are invariably stigmatized across cultures. Prevalence estimates are consistently highest in North America and lowest in Asia (with prevalence estimates of major depressive disorders generally a good deal higher than those of dysthymia).

Epidemiological data document consistent delays in patients initially seeking professional treatment for depression, especially among early-onset cases (Olfson and others 1998), as well as substantial undertreatment. For example, World Mental Health surveys in six Western European countries found that only 36.6 percent of people with active nonbipolar depression in the 12 months before the survey received any professional treatment for this disorder during the subsequent year (ESEMeD/MHEDEA 2000 Investigators 2004). The situation is even worse in developing countries, where the vast majority of people with depression who seek help do so in general health care settings and complain of nonspecific physical symptoms. Such individuals receive a correct diagnosis in less than one-quarter of cases and typically are treated with medicines of doubtful efficacy (Linden and others 1999).

Depression is consistently found in community surveys to be associated with substantial impairments in both productive and social roles (Wang, Simon, and Kessler 2003). As with bipolar depression, but exacerbated by its high incidence, the recurrent nature and disabling consequences of (unipolar) depression mean that overall disease burden estimates are high in all regions of the world (5,000 to 10,000 DALYs per 1 million population, as much as 5 percent of the total burden of disease from all causes; table 1.1). Depression is, in fact, ranked as the fourth leading cause of disease burden globally and represents the single largest contributor to nonfatal burden (Ustun and others 2004).

Interventions. Efficacy has been demonstrated for several classes of antidepressant drugs and for two psychosocial treatments for depression (Paykel and Priest 1992). The older tricyclic antidepressants (TCAs) and newer drugs, including the selective serotonin reuptake inhibitors (SSRIs), have similar efficacy. The newer drugs have milder side-effect profiles and are consequently more likely to be tolerated at therapeutic doses (Pereira and Patel 1999). SSRIs have not been widely used in developing countries because of their higher

cost, although as the patent protection expires, this situation is likely to change (Patel 1996). Of the psychosocial treatments with demonstrated efficacy, the most widely accepted are cognitive-behavioral approaches. Alone or in combination, drug and psychosocial treatments speed recovery from acute episodes. Maintenance treatment with drugs decreases relapse risk (Geddes and others 2003). Some evidence suggests that a course of psychotherapy may also delay relapses. Although most of the clinical trials have been carried out in industrial countries, at least three high-quality trials have demonstrated the efficacy of antidepressants, group therapy, or both in developing countries (Araya and others 2003; Bolton and others 2003; Patel and others 2003).

For the cost-effectiveness analyses, depression was modeled as an episodic disorder with a high rate of remission and subsequent recurrence, and with excess mortality from suicide (Chisholm and others 2004). None of the selected depression interventions was accorded a reduction in case fatality, however, owing to the lack of robust clinical evidence that antidepressants or psychotherapy in themselves alter the relative risk of death by suicide (Storosum and others 2001). The main modeled impact of intervention targeted toward episodic treatment of a new depressive episode was a reduction in the duration of time depressed, equivalent to an increase in the remission rate (25 to 40 percent improvement over no treatment; Malt and others 1999; Solomon and others 1997). In addition, all interventions were attributed a modest improvement in the level of disability for an unremitted depressive episode (10 to 15 percent), resulting from increased proportions of cases moving from more to less severe health states. For the estimated 56-percent of prevalent cases eligible for maintenance treatment (at least two lifetime episodes), an additional effect of efficacious maintenance treatment was incorporated into the analysis by reducing the incidence of recurrent episodes by 50-percent (Geddes and others 2003). Estimates of intervention effectiveness include the positive change that would occur naturally and also incorporate any placebo effect, which, in the treatment of depression, is not inconsiderable (Andrews 2001).

ANXIETY DISORDERS

Anxiety disorders are a group of disorders that have as their central feature the inability to regulate fear or worry. Although anxiety in itself is likely to feature in the clinical presentation of most patients, somatic complaints such as chest pain, palpitations, respiratory difficulty, headaches, and the like are also common, and these symptoms may be more common in developing countries. A number of different types of anxiety disorder exist, some of which are now briefly described.

The central feature of *panic disorder* is an unexpected panic attack, which is a discrete period of intense fear accompanied by physiologic symptoms such as a racing heart, shortness of breath, sweating, or dizziness. The person may have an intense fear of losing control or of dying. Panic disorder is diagnosed when panic attacks are recurrent and give rise to anticipatory anxiety about additional attacks. People with panic disorder may progressively restrict their lives to avoid situations in which panic attacks occur or situations from which it might be difficult to escape should a panic attack occur. They commonly avoid crowds, traveling, bridges, and elevators, and ultimately some individuals may stop leaving home altogether. Pervasive phobic avoidance is described as agoraphobia.

Generalized anxiety disorder is characterized by chronic unrealistic and excessive worry. These symptoms are accompanied by specific anxiety-related symptoms such as sympathetic nervous system arousal, excessive vigilance, and motor tension. *Posttraumatic stress disorder* follows serious trauma. It is characterized by emotional numbness, punctuated by intrusive reliving of the traumatic episode, generally initiated by environmental cues that act as reminders of the trauma; by disturbed sleep; and by hyperarousal, such as exaggerated startle responses.

Social anxiety disorder (*social phobia*) is characterized by a persistent fear of social situations or performance situations that expose a person to potential scrutiny by others. The affected person has intense fear that he or she will act in a way that will be humiliating. Separating social anxiety disorder from extremes of normal temperament, such as shyness, is difficult. Nonetheless, social anxiety disorder can be quite disabling. *Simple phobias* are extreme fear in the presence of discrete stimuli or cues, such as fear of heights.

The core features of *obsessive-compulsive disorder* are obsessions (intrusive, unwanted thoughts) and compulsions (performance of highly ritualized behaviors intended to neutralize the negative thoughts and emotions resulting from the obsessions). One symptom pattern might be repetitive hand washing beyond the point of skin damage to neutralize fears of contamination.

Natural History and Course

The anxiety disorders differ in their age of onset, course of illness, and symptom triggers. One of these disorders, PTSD, is dependent for its etiology on one or more powerfully negative life events. Although the anxiety disorders are discussed as a group, panic disorder is chosen because of the available data for the purposes of the cost-effectiveness analysis.

Prevalence estimates of anxiety disorders based on community epidemiological surveys vary widely, from a low of 2.2 percent (Andrade and others 2003) to a high of 28.5 percent (Kessler and others 1994), with a weighted mean across surveys of 15.6 percent. Prevalence estimates for anxiety disorders in the past 6 to 12 months have a similarly wide range (1.2 to 19.3-percent) (Andrade and others 2003; Kessler and others 1994), with a weighted mean of 9.4 percent. Despite wide variation in overall prevalence, several clear relative prevalence patterns can be seen across surveys. Specific phobia is generally the most prevalent lifetime anxiety disorder,

with social phobia generally the second most prevalent lifetime anxiety disorder. Panic disorder and obsessive-compulsive disorder are generally the least prevalent.

These surveys also provide evidence about the persistence of anxiety disorders, indirectly defined as the ratio of 6-month or 12-month to lifetime prevalence. This ratio averages approximately 60 percent for overall anxiety disorders, indicating a high rate of persistence across the life course. The highest persistence is generally found for social phobia, and the lowest for agoraphobia. These estimates of high persistence are consistent with results obtained from longitudinal studies of patients (Yonkers and others 2003).

Anxiety disorders have consistently been found in epidemiological surveys to be highly comorbid both among themselves and with mood disorders (for example, de Graaf and others 2003). The vast majority of people with a history of one anxiety disorder typically also have a second anxiety disorder, while more than half the people with a history of either anxiety or mood disorder typically have both types of disorder. Retrospective reports from community surveys consistently show that anxiety disorders have early average ages of onset. An-impressive cross-national consistency can be seen in these patterns, with an estimated median age of onset of anxiety at approximately 15.

Epidemiological surveys have also looked at the treatment of anxiety disorders. As with depression, consistent evidence in these surveys suggests that delays in initially seeking professional treatment for an anxiety disorder are widespread after first onset (Olfson and others 1998). This finding is especially true among early-onset cases. Epidemiological data also show that only a minority of current cases receive any formal treatment in Western countries, whereas treatment of anxiety disorders is virtually nonexistent in many developing countries. The most recently published surveys, the World Mental Health surveys in six Western European countries, found that only 26.3 percent of people with an active anxiety disorder in the 12-months before the survey received any professional treatment (ESEMeD/MHEDEA 2000 Investigators 2004).

Anxiety disorders have consistently been found to be associated with substantial impairments in both productive roles (for example, work absenteeism, work performance, unemployment, and underemployment) and social roles (social isolation, interpersonal tensions, and marital disruption, among others) (see, for example, Kessler and Frank 1997). As noted earlier, for the purposes of this chapter, one of the anxiety disorders—panic disorder—has been chosen to describe interventions and undertake cost-effectiveness analysis. Panic disorder is as disabling as obsessive-compulsive disorder and PTSD, accounts for about one-third of all seriously impairing anxiety disorders, is one of the most common anxiety disorders presenting for treatment, and imposes an estimated burden of 600 to 800 DALYs per 1 million population.

Good evidence exists that both drug and psychosocial treatments are effective for managing anxiety disorders. Antidepressant drugs (both older TCAs and SSRIs) have been shown to be effective for the treatment of several anxiety disorders, including panic disorder, reducing the duration and intensity of the disorder. Although high-potency benzodiazepines are efficacious for panic disorder, these drugs carry a risk of dependence and are not considered the first line of treatment. Psychosocial treatments, especially cognitive-behavioral therapy, are also effective in diminishing both panic attacks and phobic avoidance.

Interventions for Panic Disorder

Although evidence-based interventions for panic disorder have yet to be evaluated or made widely available in developing countries, the potential population-level impact of a number of interventions—including older and newer antidepressants, anxiolytic drugs (benzodiazepines), and psychosocial treatments—was examined. Interventions reduce the severity of panic attacks and improve the probability of making a full recovery. Effect sizes for symptom improvement were drawn from a meta-analysis of the long-term effects of intervention of panic disorder (Bakker and others 1998) and converted into an equivalent change in disability weight (Sanderson and others 2004). Concerning remission, a number of controlled and naturalistic studies (for example, Faravelli, Paterniti, and Scarpato 1995; Yonkers and others 2003) reveal a consistent remission rate of 12 to 13 percent for pharmacological and combination strategies—except for benzodiazepine use, for which the evidence is that longer-term recovery is actually worse than placebo (Katschnig and others 1995)—which represents a 62 percent improvement in efficacy over the untreated remission rate (7.4 percent).

COST-EFFECTIVENESS METHODS AND RESULTS

This section estimates the burden attributed to schizophrenia, bipolar disorder, depression, and panic disorder that could be averted (through scaling up) by proven, efficacious treatments. It is followed by calculations of the expected cost and cost-effectiveness of such treatments. Analysis is conducted at the level of six low- and middle-income geographical World Bank regions.

Estimation of Population-Level Effectiveness of Treatments

In modeling the impact of mental health interventions, we used a state-transition model (Lauer and others 2003) that traces the development of a population, taking into account births, deaths, and the disease in question. In addition to population size and structure, the model makes use of a number of epidemiological parameters (incidence and prevalence, remission, and cause-specific and residual rates of mortality) and assigns age- and gender-specific disability weights to both the disease in question and the general population. The output of the model is an estimate of the total healthy life years experienced by the population

over a lifetime period (100 years). The model was run for a number of possible scenarios, including no treatment at all (natural history), current treatment coverage, and scaled-up coverage of current as well as potential new interventions. For the treatment scenarios, an implementation period of 10 years was used (thereafter, epidemiological rates and health state valuations return to natural history levels). The model derived the number of additional healthy years gained (equivalent to DALYs averted) each year in the population compared with the outcome for no treatment at all. DALYs averted in future years were discounted at a rate of 3 percent (reflecting a societal preference for health benefits to be realized sooner), but no age-weighting was used.

Estimation of the baseline epidemiological situation that would prevail without treatment used incidence and prevalence estimates from the Global Burden of Disease 2000 study of the World Health Organization (WHO) (see online Global Burden of Disease documentation for the four disorders at http://www.who.int/evidence/bod). Current pharmacological-or psychosocial treatments do not exert a primary preventive effect on the onset of the four conditions (although some-evidence exists that treating depression in parents may reduce risk for offspring), indicating that currently observed incidence rates coincide with those that would pertain under no treatment. Prevention of recurrences of acute episodes (secondary prevention) has been demonstrated for maintenance treatments for major depression and bipolar disorder. Maintenance treatment with antipsychotic drugs decreases the risk of recurrent acute episodes of schizophrenia. For each condition, a range of treatment strategies was considered and assessed, including older (and widely available) psychotherapeutic drugs, newer pharmacotherapies, psychosocial treatments, and combination treatments (see table 1.2 for a list of interventions included).

Estimation of Population-Level Treatment Costs

Cost estimation followed the principles and procedures described in chapter 7 of DCP2 for carrying out economic analyses of disease control priorities in developing countries. For depression and panic disorder, treatment was assumed to occur in a primary care setting, whereas for schizophrenia and bipolar disorder, which often produce highly disruptive behaviors, both hospital- and community-based outpatient service models were derived and compared. Both program- and patient-level costs were identified and estimated. Program-level costs included the infrastructure and administrative support for implementing mental health treatments, as well as training inputs (for example, two to three days per trainee were estimated for training primary care doctors and case managers in psychotropic medication management). Patient-level resource inputs included medication regimens (for example, fluoxetine, 20 milligrams daily), laboratory tests (for example, lithium blood levels), primary care visits (including any contacts with a-case manager), and hospital outpatient and inpatient care. Estimated patient-level resource inputs for each of the four disorders were informed by empirical economic evaluative studies (for example, Patel and others 2003; Srinivasa Murthy and others 2005) as well as a multinational Delphi consensus study of resource use for psychiatric disorders in seven developing countries (Ferri and others 2004). Region-specific unit costs or prices were applied to all resource inputs (see Mulligan and others 2003) to give an annual cost for each case as well as for all cases at the specified level of treatment coverage. Costs incurred over the 10-year implementation period were discounted at 3 percent and expressed in U.S. dollars (rather than international dollars, which attempt to adjust for differences in purchasing power between countries).

Coverage

In each World Bank region, treatment costs and effects were ascribed to the population in need, both at current levels of-intervention coverage and at a scaled-up, target level of coverage (80 percent for schizophrenia, 50 percent for the other conditions). Target coverage levels were predicated on the basis of what could feasibly be achieved given existing rates of treatment (Ferri and others 2004; Kohn and others 2004), as well as on prerequisites for increased coverage, such as recognition of common mental disorders in primary care. Estimation of current regional levels of effective coverage is hampered by lack of data; nevertheless, an attempt was made to approximate the expected proportion of the diseased population receiving evidence-based pharmacological and psychosocial treatments (Ferri and others 2004; Kohn and others 2004), plus those in contact with traditional healers (the effectiveness of which was conservatively approximated by ascribing a placebo effect size for each disorder).

Results

Tables 1.3 through 1.6 provide estimates of the population-level effects (measured in DALYs averted), costs, and cost-effectiveness of each intervention by world region for the four types of psychiatric disorder considered in this chapter. A number of key findings emerge from this analysis.

Treatment Effectiveness. Results for schizophrenia and bipolar disorder are similar (albeit at differing coverage levels), ranging from less than 100 DALYs averted per 1 million population under the current situation in Sub-Saharan Africa and South Asia to 350 to 400 DALYs averted per 1 million population for combination drug and psychosocial interventions in Europe and Central Asia and East Asia and the Pacific. Second-generation (atypical) antipsychotic drugs were considered slightly more effective than first-generation drugs (on the basis of a modest intrinsic efficacy difference and differences in tolerability and adherence); lithium was considered modestly more effective as a mood-stabilizing drug than valproate (on the basis of its additional positive effect on suicide rates). Adjuvant psychosocial treatment in combination with pharmacotherapy significantly added to expected

Table 1.2 Interventions for Reducing the Burden of Major Psychiatric Disorders in Developing Countries

Disorder	Intervention	Example
Schizophrenia	Older (neuroleptic) antipsychotic drug	Haloperidol
Treatment setting: hospital outpatient	Newer (atypical) antipsychotic drug	Risperidone
Treatment coverage (target): 80 percent	**Older antipsychotic drug and psychosocial treatment**	Haloperidol plus family psychoeducation
	Newer antipsychotic drug and psychosocial treatment	Risperidone plus family psychoeducation
Bipolar affective disorder	Older mood-stabilizing drug	Lithium carbonate
Treatment setting: hospital outpatient	Newer mood-stabilizing drug	Sodium valproate
Treatment coverage (target): 50 percent	**Older mood-stabilizing drug and psychosocial treatment**	Lithium plus family psychoeducation
	Newer mood-stabilizing drug and psychosocial treatment	Valproate plus family psychoeducation
Depression	Episodic treatment	
Treatment setting: primary health care	**Older TCA**	Imipramine or amitriptyline
Treatment coverage (target): 50 percent	**Newer antidepressant drug (SSRI; generic)**	Fluoxetine
	Psychosocial treatment	Group psychotherapy
	Older antidepressant drug and psychosocial treatment	Amitriptyline plus group psychotherapy
	Newer antidepressant drug and psychosocial treatment	Fluoxetine plus group psychotherapy
	Maintenance treatment	
	Older antidepressant drug and psychosocial treatment	Imipramine plus group psychotherapy
	Newer antidepressant drug and psychosocial treatment	Fluoxetine plus group psychotherapy
Panic disorder	Benzodiazepines	Alprazolam
Treatment setting: primary health care	**Older TCA**	Amitriptyline
Treatment coverage (target): 50 percent	**Newer antidepressant drug (SSRI; generic)**	Fluoxetine
	Psychosocial treatment	Cognitive therapy
	Older antidepressant drug and psychosocial treatment	Amitriptyline plus cognitive therapy
	Newer antidepressant drug and psychosocial treatment	Fluoxetine plus cognitive therapy

Source: Authors' own estimates and recommendations.
Note: Interventions in **bold** are the most cost-effective treatments of choice.

population-level health gain. With the exception of Europe and Central Asia, less than 10 percent of the disease burden currently is being averted, whereas the implementation of combined interventions at a scaled-up level of coverage is expected to avert 14 to 22 percent of the burden of schizophrenia (coverage level, 80 percent) and 17 to 29 percent of the burden of bipolar disorder (coverage level, 50 percent).

For primary care treatment of common mental disorders, including depression and panic disorder, current levels of effective coverage avert only 3 to 8 percent of the existing disease burden, whereas scaling up of the most effective interventions to a coverage level of 50 percent could be expected to avert more than 20 percent of the burden of depression and up to one-third of the burden of panic disorder. Considered at a population level, episodic treatments for depressive episodes did not differ substantially within regions (averting 10 to15 percent of current burden); more substantial health gain is expected by-providing maintenance treatment to individuals with recurrent depression (approximately 1,200 to 1,900 DALYs averted per 1 million population; 18 to 23 percent of burden). Such an approach has been found to reduce the risk of relapse by half. Although the evidence to date from developing regions is meager, our results suggest that SSRIs such as fluoxetine, alone or in combination with psychosocial treatment, are the most effective treatments for panic disorder, with health gains considerably better than those estimated for benzodiazepine anxiolytic drugs such as alprazolam.

Treatment Costs. Community-based service models for schizophrenia and bipolar disorder were found to be appreciably less costly than hospital-based service models (for example, interventions for bipolar disorder were 25 to 40 percent less costly). The total cost per capita of community-based outpatient treatment with first-generation antipsychotic or mood-stabilizing drugs, including all patient-level resource needs as well as infrastructural support, ranged from US$0.40 to US$0.50 in Sub-Saharan Africa and South Asia to US$1.20 to US$1.90 in Latin America and the Caribbean and in Europe and Central Asia (equivalent patient costs per year, US$170 to US$300 and US$300 to US$800, respectively). The cost per capita for interventions using second-generation (atypical) antipsychotic drugs still under patent is much higher (US$2.50 to US$5.00). By contrast, some of the newer antidepressant drugs (SSRIs) are now off patent, and their use in treating depression and panic disorder was accordingly costed at their generic, nonbranded price. The patient-level cost of treating a 6-month episode of depression ranged

Table 1.3 Cost-Effectiveness Results: Schizophrenia

Model definition: **Treatment setting: (a) hospital-based; (b) community-based** **Treatment coverage: 80 percent**	**World Bank region**					
	Sub-Saharan Africa	**Latin America and the Caribbean**	**Middle East and North Africa**	**Europe and Central Asia**	**South Asia**	**East Asia and the Pacific**
Total effect (DALYs averted per year per 1 million population)						
Current situation	74	136	115	258	87	148
Older (neuroleptic) antipsychotic drug	149	219	214	254	177	231
Newer (atypical) antipsychotic drug	160	235	230	273	190	248
Older antipsychotic drug plus psychosocial treatment	254	373	364	353	300	392
Newer antipsychotic drug plus psychosocial treatment	261	383	373	364	308	403
Total cost (US$ million per year per 1 million population)						
Current situation	0.42	2.07	1.31	3.13	0.51	1.11
Hospital-based service model						
Older (neuroleptic) antipsychotic drug	0.60	3.09	2.40	2.24	0.74	1.18
Newer (atypical) antipsychotic drug	2.80	6.33	5.41	6.16	3.36	4.63
Older antipsychotic drug plus psychosocial treatment	0.67	3.27	2.56	2.36	0.81	1.26
Newer antipsychotic drug plus psychosocial treatment	2.87	6.56	5.61	6.31	3.44	4.73
Community-based service model						
Older (neuroleptic) antipsychotic drug	0.40	1.58	1.42	1.17	0.44	0.66
Newer (atypical) antipsychotic drug	2.59	4.85	4.45	5.11	3.07	4.12
Older antipsychotic drug plus psychosocial treatment	0.47	1.81	1.61	1.32	0.52	0.75
Newer antipsychotic drug plus psychosocial treatment	2.67	5.09	4.66	5.28	3.16	4.22
Cost-effectiveness (US$ per DALY averted)						
Current situation	5,695	15,192	11,400	12,134	5,900	7,533
Hospital-based service model						
Older (neuroleptic) antipsychotic drug	4,047	14,123	11,205	8,793	4,164	5,120
Newer (atypical) antipsychotic drug	17,433	26,893	23,543	22,530	17,702	18,700
Older antipsychotic drug plus psychosocial treatment	2,623	8,781	7,040	6,685	2,693	3,212
Newer antipsychotic drug plus psychosocial treatment	10,996	17,146	15,027	17,329	11,164	11,746
Community-based service model						
Older (neuroleptic) antipsychotic drug	2,668	7,230	6,618	4,595	2,499	2,855
Newer (atypical) antipsychotic drug	16,174	20,583	19,352	18,685	16,178	16,622
Older antipsychotic drug plus psychosocial treatment	**1,839**	**4,847**	**4,431**	**3,745**	**1,743**	**1,917**
Newer antipsychotic drug plus psychosocial treatment	10,232	13,313	12,485	14,481	10,239	10,484

Source: Authors' own estimates.
Note: Intervention data in **bold** are the most cost-effective treatments of choice.

Table 1.4 Cost-Effectiveness Results: Bipolar Disorder

Model definition: **Treatment setting: (a) hospital-based; (b) community-based** **Treatment coverage: 50 percent**	**World Bank region**					
	Sub-Saharan Africa	**Latin America and the Caribbean**	**Middle East and North Africa**	**Europe and Central Asia**	**South Asia**	**East Asia and the Pacific**
Total effect (DALYs averted per year per 1 million population)						
Current situation	79	128	97	199	93	153
Older mood-stabilizing drug (lithium)	292	336	296	381	319	389
Newer mood-stabilizing drug (valproate)	211	300	273	331	278	351
Older mood-stabilizing drug plus psychosocial treatment	312	365	322	413	346	422
Newer mood-stabilizing drug plus psychosocial treatment	232	330	300	365	306	386
Total cost (US$ million per year per 1 million population)						
Current situation	0.31	1.22	0.74	1.27	0.42	0.67
Hospital-based service model						
Older mood-stabilizing drug (lithium)	0.61	2.77	1.92	2.03	0.82	1.30
Newer mood-stabilizing drug (valproate)	0.79	2.87	2.04	2.20	1.03	1.53
Older mood-stabilizing drug plus psychosocial treatment	0.63	2.79	1.95	2.05	0.84	1.32
Newer mood-stabilizing drug plus psychosocial treatment	0.81	2.90	2.08	2.22	1.06	1.55
Community-based service model						
Older mood-stabilizing drug (lithium)	0.46	1.78	1.20	1.37	0.59	0.93
Newer mood-stabilizing drug (valproate)	0.64	1.91	1.36	1.57	0.82	1.17
Older mood-stabilizing drug plus psychosocial treatment	0.48	1.80	1.23	1.39	0.62	0.95
Newer mood-stabilizing drug plus psychosocial treatment	0.67	1.95	1.39	1.59	0.85	1.19
Cost-effectiveness (US$ per DALY averted)						
Current situation	3,967	9,518	7,668	6,398	4,463	4,373
Hospital-based service model						
Older mood-stabilizing drug (lithium)	2,091	8,246	6,478	5,341	2,553	3,348
Newer mood-stabilizing drug (valproate)	3,727	9,579	7,501	6,648	3,709	4,358
Older mood-stabilizing drug plus psychosocial treatment	2,016	7,644	6,036	4,957	2,424	3,119
Newer mood-stabilizing drug plus psychosocial treatment	3,480	8,800	6,937	6,100	3,459	4,016
Community-based service model						
Older mood-stabilizing drug (lithium)	1,587	5,295	4,068	3,608	1,862	2,394
Newer mood-stabilizing drug (valproate)	3,057	6,386	4,971	4,727	2,943	3,338
Older mood-stabilizing drug plus psychosocial treatment	**1,545**	**4,928**	**3,823**	**3,359**	**1,787**	**2,241**
Newer mood-stabilizing drug plus psychosocial treatment	2,874	5,908	4,645	4,359	2,765	3,092

Source: Authors' own estimates.
Note: Intervention data in **bold** are the most cost-effective treatments of choice.

Table 1.5 Cost-Effectiveness Results: Depression

Model definition: Treatment setting: primary health care Treatment coverage: 50 percent	World Bank region					
	Sub-Saharan Africa	Latin America and the Caribbean	Middle East and North Africa	Europe and Central Asia	South Asia	East Asia and the Pacific
Total effect (DALYs averted per year per 1 million population)						
Current situation	133	264	218	308	218	243
Episodic treatment: older antidepressant drug (TCA)	599	995	920	874	987	891
Episodic treatment: newer antidepressant drug (SSRI)	632	1,049	971	925	1,042	941
Episodic psychosocial treatment	624	1,036	958	936	1,028	927
Episodic psychosocial treatment plus older antidepressant	745	1,237	1,144	1,100	1,228	1,107
Episodic psychosocial treatment plus newer antidepressant	745	1,237	1,144	1,100	1,228	1,107
Maintenance psychosocial treatment plus older antidepressant	1,174	1,953	1,806	1,789	1,937	1,747
Maintenance psychosocial treatment plus newer antidepressant	1,174	1,953	1,806	1,789	1,937	1,747
Total cost (US$ million per year per 1 million population)						
Current situation	0.36	0.90	0.63	0.74	0.56	0.67
Episodic treatment: older antidepressant drug (TCA)	0.30	1.28	0.96	0.81	0.47	0.47
Episodic treatment: newer antidepressant drug (SSRI)	0.66	1.86	1.47	1.39	1.04	0.99
Episodic psychosocial treatment	0.37	1.67	1.27	0.97	0.55	0.53
Episodic psychosocial treatment plus older antidepressant	0.50	1.96	1.53	1.21	0.77	0.72
Episodic psychosocial treatment plus newer antidepressant	0.90	2.60	2.10	1.85	1.40	1.29
Maintenance psychosocial treatment plus older antidepressant	0.96	3.44	2.77	2.19	1.45	1.38
Maintenance psychosocial treatment plus newer antidepressant	1.80	4.80	3.99	3.56	2.81	2.59
Cost-effectiveness (US$ per DALY averted)						
Current situation	2,692	3,414	2,905	2,391	2,546	2,777
Episodic treatment: older antidepressant drug (TCA)	**505**	**1,288**	**1,039**	**929**	**478**	**533**
Episodic treatment: newer antidepressant drug (SSRI)	1,042	1,771	1,516	1,501	1,003	1,048
Episodic psychosocial treatment	592	1,611	1,330	1,035	537	570
Episodic psychosocial treatment plus older antidepressant	674	1,586	1,335	1,104	627	653
Episodic psychosocial treatment plus newer antidepressant	1,203	2,101	1,834	1,682	1,140	1,161
Maintenance psychosocial treatment plus older antidepressant	**817**	**1,760**	**1,533**	**1,226**	**749**	**788**
Maintenance psychosocial treatment plus newer antidepressant	1,535	2,459	2,211	1,990	1,449	1,481

Source: Authors' own estimates.
Note: Intervention data in **bold** are the most cost-effective treatments of choice.

Table 1.6 Cost-Effectiveness Results: Panic Disorder

Model definition: Treatment setting: primary health care Treatment coverage: 50 percent	World Bank region					
	Sub-Saharan Africa	Latin America and the Caribbean	Middle East and North Africa	Europe and Central Asia	South Asia	East Asia and the Pacific
Total effect (DALYs averted per year per 1 million population)						
Current situation	49	94	64	88	57	90
Anxiolytic drug (benzodiazepine)	144	182	170	183	168	195
Older antidepressant drug (TCA)	232	290	272	290	269	312
Newer antidepressant drug (SSRI; generic)	245	307	287	307	284	330
Psychosocial treatment (cognitive-behavioral therapy)	233	292	273	292	270	313
Older antidepressant plus psychosocial treatment	262	329	308	329	304	353
Newer antidepressant plus psychosocial treatment	276	346	324	346	320	372
Total cost (US$ million per year per 1 million population)						
Current situation	0.06	0.13	0.08	0.07	0.05	0.10
Anxiolytic drug (benzodiazepine)	0.10	0.20	0.15	0.15	0.10	0.12
Older antidepressant drug (TCA)	0.09	0.18	0.14	0.14	0.08	0.11
Newer antidepressant drug (SSRI; generic)	0.15	0.27	0.21	0.23	0.16	0.20
Psychosocial treatment (cognitive-behavioral therapy)	0.11	0.27	0.21	0.17	0.09	0.11
Older antidepressant plus psychosocial treatment	0.15	0.32	0.26	0.23	0.13	0.17
Newer antidepressant plus psychosocial treatment	0.22	0.41	0.34	0.32	0.22	0.26
Cost-effectiveness (US$ per DALY averted)						
Current situation	1,192	1,378	1,208	824	948	1,109
Anxiolytic drug (benzodiazepine)	681	1,075	892	842	572	629
Older antidepressant drug (TCA)	**369**	**619**	**508**	**474**	**305**	**339**
Newer antidepressant drug (SSRI; generic)	**630**	**865**	**747**	**741**	**567**	**606**
Psychosocial treatment (cognitive-behavioral therapy)	468	927	786	594	338	365
Older antidepressant plus psychosocial treatment	556	977	844	685	443	474
Newer antidepressant plus psychosocial treatment	788	1,188	1,050	918	671	709

Source: Authors' own estimates.
CBT = cognitive behavioral therapy
Note: Intervention data in **bold** are the most cost-effective treatments of choice.

from as little as US$30 (older antidepressants in Sub-Saharan Africa or South Asia) to US$150 (newer antidepressants in combination with brief psychotherapy in Latin America and the Caribbean). Total annual costs for all incidents of depressive episodes receiving treatment, including training and other program-level costs, were as much as US$2 to US$5 per capita for a maintenance treatment program using newer antidepressants, three times more costly than episodic treatment with newer antidepressant drugs only. Patient-level resource inputs for panic disorder interventions cost US$50 to US$200 per case per year, and overall costs including program costs of training and administration amounted to US$0.10 to US$0.30 per capita.

Cost-Effectiveness. Compared with both the current situation and the epidemiological situation of no treatment (natural history), the most cost-effective strategy for averting the burden of psychosis and severe affective disorders

in developing countries is expected to be a combined intervention of first-generation antipsychotic or mood-stabilizing drugs with adjuvant psychosocial treatment delivered through a community-based outpatient service model, with a cost-effectiveness ratio of below US$2,000 in Sub-Saharan Africa and South Asia, rising to US$5,000 in Latin America and the Caribbean (equivalent to more than 500 DALYs averted per US$1 million expenditure in Sub-Saharan Africa and South Asia and 200 DALYs averted in Latin America and the Caribbean). Currently, the high acquisition price of second-generation antipsychotic drugs makes their use in developing regions questionable on efficiency grounds, although this situation can be expected to change as these drugs come off patent. By contrast, evidence indicates that the relatively modest additional cost of adjuvant psychosocial treatment reaps significant health gains, thereby making such a combined strategy for schizophrenia and bipolar disorder treatment more cost-effective than pharmacotherapy alone.

For more common mental disorders treated in primary care settings (depressive and anxiety disorders), the single most cost-effective strategy is the scaled-up use of older antidepressants (because of their lower cost but similar efficacy compared with newer antidepressants). However, as the price margin between older and generic newer antidepressants continues to diminish, generic SSRIs—which have milder side effects and are more likely to be taken at a therapeutic dose (Pereira and Patel 1999)—can be expected to be at least as cost-effective and, therefore, the pharmacological treatment of choice in the future. Because depression is often a recurring condition, proactive care management, including long-term maintenance treatment with antidepressant drugs, represents a cost-effective way of significantly reducing the enormous burden of depression that exists in developing regions now (400 to 1,300 DALYs averted per US$1 million expenditure).

POLICY AND SERVICE IMPLICATIONS

Many attempts have been made during the past 50 years to have-mental health care placed higher on national and international agendas. In 1974, a WHO Expert Committee on the Organization of Mental Health Services in Developing Countries (WHO 1975) made the following recommendations:

- Develop a national mental health policy and create a unit within the Health Ministry to implement it.
- Budget for workforce development, essential drug procurement, infrastructure development, data collection, and research.
- Decentralize service provision and integrate mental health into primary health care.
- Train and supervise primary health care providers in mental health using specialist mental health staff.

Thirty years later, international agencies, nongovernmental organizations, and professional bodies continue to make those exact recommendations. One reason for the lack of action in mental health has been the paucity of information on the cost-effectiveness of mental health interventions. Advocacy without the necessary science can readily be ignored in countries with massive health problems and meager resources. This chapter aims to address this deficiency.

Symptoms of mental disorders are often attributed to other illnesses, and mental disorders are often not considered health problems (Jacob 2001). Many nonscientific explanations for mental illness exist, and stigma exists to varying degrees everywhere (Weiss and others 2001) with widespread delays or failure to seek appropriate care (James and others 2002).

When care is sought, a hierarchy of interventions comes into play, ranging from self-help, informal community support, traditional healers, primary health care, specialist community mental health care, and psychiatric units in general hospitals to specialist long-stay mental hospitals. The mix of interventions depends on the availability of resources within a country or region (Saxena and Maulik 2003). The more resource-constrained the country or region is, the greater is the reliance on self-help, informal community support (especially family-based), and primary health care.

Traditional healers are often the first source individuals with mental illness and their families turn to for professional assistance (see, for example, Abiodun 1995). A recent review of common mental disorders among primary health clinics and traditional healers in urban Tanzania showed that the prevalence of common mental disorders among those attending traditional healers was double that of patients at primary health care centers (Ngoma, Prince, and Mann 2003). Traditional healers are a heterogeneous group and include faith healers, spiritual healers, religious healers, and practitioners of indigenous or alternative systems of medicine. In some countries, they are part of the informal health sector, but in other countries, traditional healers charge for their services and should be considered part of the private health care sector. Often, traditional healers have high acceptability and are accessible; at times, traditional healers work closely (and apparently effectively) with conventional mental health services (Thara, Padmavati, and Srinivasan 2004). Alternatively, animosity and competition can exist, and recent examples of human rights violations by traditional healers demonstrate the heterogeneity of this group of providers.

The formal diagnosis and treatment of mental disorders occur in both primary and specialist health services. Examples in nearly a dozen countries now show it is feasible and practicable to treat common mental disorders in primary health care settings (for example, Chisholm and others 2000; De Jong 1996; Mohit and others 1999). The challenge is to enhance systems of care by taking effective local models and disseminating them throughout a country.

Concern has been expressed that the more sophisticated psychotherapies used in mental health care are beyond the human resources of developing countries. However, basic

psychological therapies can be effective, though there is some evidence, at least for depression, that the newer drug therapies are more cost-effective than psychological therapies (Patel and others 2003). Psychoeducational family intervention has been shown to be suitable for rehabilitation in schizophrenia in rural China (Ran and others 2003) and to be cost-effective compared with other standard treatment (Xiong and others 1994). Evidence also shows that nurses can replace physicians as primary health care providers in certain circumstances without loss of effectiveness (Climent and others 1978). Primary care practitioners need support to develop skills and experience in diagnosing and treating mental disorders: they need a sustainable supply of medicines, access to supervision, and incentives to see patients with mental illness (Abas and others 2003). Community approaches using low-cost, locally available resources may improve treatment adherence and clinical outcomes even in rural and underresourced settings (Chatterjee and others 2003; Srinivasa Murthy and others 2005).

In most countries, acute inpatient beds are being moved from mental hospitals into general or district hospitals. Although this policy potentially improves accessibility and increases the links with, and support provided to, primary mental health care, concerns can be raised as to whether general hospitals can adapt to provide adequate services to people with severe mental disorders. However, such services have been-effectively established in a number of countries (see, for example, Alem and others 1999; Kilonzo and Simmons 1998), showing this form of service delivery to be feasible when it is clinically indicated.

Nongovernmental organizations are important providers of mental health care. An estimated 93 percent of African and 80-percent of Southeast Asian countries have nongovernmental organizations in the mental health sector. They provide diverse services—including advocacy, informal support, housing, suicide prevention, substance misuse counseling, dementia support, rehabilitation, research, and other programs—that complement, or-in some cases substitute for, public and private clinical services (Levkoff, Macarthur, and Bucknall 1995; Patel and Thara 2003).

Services for children and adolescents, the majority of the population in many developing countries, are even more deficient than those for adults. Priority needs to be given to these services (Rahman and others 2000). At the other end of the life spectrum, many developing countries are facing aging populations with grossly underdeveloped aged care services (Levkoff, Macarthur, and Bucknall 1995). The high level of civil conflict and natural disasters requires attention to postconflict and posttrauma mental health conditions. The prevalence of these disorders is demonstrated by a recent study (Livanou, Basoglu, and Kalendar 2002) showing that, of 1,000 survivors of the August 1999 earthquake in Turkey, the incidence of PTSD was 63 percent and of depression was 42 percent.

Specialist mental health providers, especially mental hospitals, tend to focus the services they provide on the lower-prevalence, higher-disability disorders, such as schizophrenia and bipolar disorder. Modern treatments, if available and used, allow most patients to be treated effectively out of hospital. Specifically, the use of antipsychotic and mood-stabilizing drugs and the development of strategies for community-based treatment have led to the closing of large numbers of psychiatric inpatient beds in many countries and their replacement with community services and general hospital psychiatric units (for example, Larrobla and Botega 2001).

However, in some countries, the majority of psychotic patients remain in long-term inpatient facilities that engage in custodial care, which is often of poor quality; moreover, basic rights are often violated at such facilities (van Voren and Whiteford 2000). Even if the quality of care is reasonable, accessibility is a problem: these hospitals are often situated in urban areas, but populations are largely rural and have limited transportation (Saraceno and others 1995). Furthermore, the concentration of resources in these facilities can leave little for other service components (Gallegos and Montero 1999). For example, in Indonesia, 97 percent of the mental health budget is spent on public mental hospitals (Trisnantoro 2002). For many developing countries, the debate about the role of, or problems with, mental hospitals is subsumed within a gross deficiency of psychiatric beds of any kind.

The priority for virtually all countries is generating sufficient resources for primary mental health care and deciding how to expand and best use scarce specialist resources. The quality of care is often very poor, and huge variations exist in resource availability between countries (Saxena and Maulik 2003; WHO 2001). Very few countries have what could be considered an optimal mix of these services, and there are no universally accepted planning parameters. However, conceptual models for developing national mental health policy and guidelines for service planning exist that can be useful in developing countries (Tansella and Thornicroft 1998; Townsend and others 2004; WHO 2003).

CONCLUSION: PUBLIC SUPPORT FOR A COST-EFFECTIVE INTERVENTION PACKAGE

In developing countries, much of the mental health care spending is reported to be out of pocket. Individuals purchase modern and traditional treatments if they can afford to do so. Although a large private health sector exists in low-income countries (Mills and others 2002), the quality and cost vary. Although unregulated markets fail in health, they fail even more in mental health. It is unlikely that a country will be able to rely on an unregulated private sector to deliver services that will reduce the burden of mental disorders.

In addition to being a large and growing component of disease burden, mental disorders meet virtually all the criteria by which we determine the need for government involvement in health care (Beeharry and others 2002). They affect the poor, cause externalities, and inflict catastrophic costs; moreover, private demand is inadequate. Indeed, the authors

Table 1.7 Costs and Effects of a Specified Mental Health Care Package

	World Bank region					
	Sub-Saharan Africa	**Latin America and the Caribbean**	**Middle East and North Africa**	**Europe and Central Asia**	**South Asia**	**East Asia and the Pacific**
Total effect (DALYs averted per year per 1 million population)						
Schizophrenia: older antipsychotic drug plus psychosocial treatment	254	373	364	353	300	392
Bipolar disorder: older mood-stabilizing drug plus psychosocial treatment	312	365	322	413	346	422
Depression: proactive care with newer antidepressant drug (SSRI; generic)	1,174	1,953	1,806	1,789	1,937	1,747
Panic disorder: newer antidepressant drug (SSRI; generic)	245	307	287	307	284	330
Total effect of interventions	1,985	2,998	2,779	2,862	2,867	2,891
Total cost (US$ million per year per 1 million population)						
Schizophrenia: older antipsychotic drug plus psychosocial treatment	0.47	1.81	1.61	1.32	0.52	0.75
Bipolar disorder: older mood-stabilizing drug plus psychosocial treatment	0.48	1.80	1.23	1.39	0.62	0.95
Depression: proactive care with newer antidepressant drug (SSRI; generic)	1.80	4.80	3.99	3.56	2.81	2.59
Panic disorder: newer antidepressant drug (SSRI; generic)	0.15	0.27	0.21	0.23	0.16	0.20
Total cost of interventions	2.9	8.7	7.0	6.5	4.1	4.5
Cost-effectiveness (DALYs averted per US$1 million expenditure)						
Schizophrenia: older antipsychotic drug plus psychosocial treatment	544	206	226	267	574	522
Bipolar disorder: older mood-stabilizing drug plus psychosocial treatment	647	203	262	298	560	446
Depression: proactive care with newer antidepressant drug (SSRI; generic)	652	407	452	502	690	675
Panic disorder: newer antidepressant drug (SSRI; generic)	1,588	1,155	1,339	1,350	1,765	1,649

Source: Authors' own estimates.

recognize that the main measure of outcome used in this and other chapters—the disability-adjusted life year—is limited to capturing change in service user–level symptoms, disability, recovery, and case-fatality. The DALY does *not* capture the positive change that treatment may have on a number of other significant consequences of mental disorders, including family burden (in particular, productive time and household resources given up in the care of the sick family member) and lost productivity, at the level of both the individual and the household (treatment accelerates return to paid work or usual household activities) and, by implication, at the level of society in general. The evidence base for these productivity increases, although modest in volume, constitutes an important additional argument alongside "cost per DALY" considerations for investing in mental health.

The total budgetary requirements and health consequences of a cost-effective package of mental health care can begin to be mapped out by selecting one intervention for each of the four disorders considered in this chapter. Although the data available for this exercise have limitations and will need to be refined with further research, table 1.7 summarizes the estimated costs and effects of a package consisting of (a) outpatient-based treatment of schizophrenia and bipolar disorder with first-generation antipsychotic or mood-stabilizing drugs and adjuvant psychosocial treatment, (b) proactive care of depression in primary care with generic SSRIs (including maintenance treatment of recurrent episodes), and (c) treatment of panic disorder in primary care with generic SSRIs. The estimated benefit of such a package would be an annual reduction of 2,000 to 3,000 DALYs per 1 million population, at a cost of US$3 million to US$9 million (that is, US$3 to US$4 per capita in Sub-Saharan Africa and South Asia, and US$7 to US$9 per capita in Latin America and the Caribbean). Accordingly, for every US$1 million invested in-such a mental health care package, 350 to 700 healthy years of-life would be gained over what would occur without intervention.

At a country level, data such as those presented in this chapter can be used to estimate the proportion of burden

currently averted, the proportion that can be averted with current knowledge and optimal coverage, and the burden not able to be averted with current knowledge. Such modeling has been done for some countries (for example, Andrews and others 2004).

Although much remains to be learned about the etiology and treatment of mental disorders, the potential clearly exists for a considerable reduction in the burden caused by them. For-these gains to be made, the challenge is to overcome the cultural, financial, and structural barriers that prevent people from seeking and receiving treatment. We need to close the gap between what we know and what we do in treating mental disorders. We can alleviate the substantial burden of these disorders and reverse or limit many of the devastating social and economic impacts.

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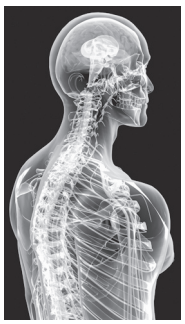
Chapter **2**

Neurological Disorders



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Historically, policy makers and researchers have used mortality statistics as the principal measure of the seriousness of diseases, based on which countries and organizations have launched disease control programs. Mortality statistics alone, however, underestimate the suffering caused by diseases that may be nonfatal but cause substantial disability. Many neurological and psychiatric conditions belong in this category. The absence of some neurological disorders from lists of leading causes of death has contributed to their long-term neglect. When the relative seriousness of diseases is assessed by time lived with disability rather than by mortality, several neurological disorders appear as leading causes of suffering worldwide.

World Health Organization data suggest that neurological and psychiatric disorders are an important and growing cause of morbidity. The magnitude and burden of mental, neurological, and behavioral disorders is huge, affecting more than 450-million people globally. According to the Global Burden of-Disease Report, 33 percent of years lived with disability and 13 percent of disability-adjusted life years (DALYs) are due to neurological and psychiatric disorders, which account for four out of the six leading causes of years lived with disability (Mathers and others 2003).

Unfortunately, the burden of these disorders in developing countries remains largely unrecognized. Moreover, the burden imposed by such chronic neurological conditions in general can be expected to be particularly devastating in poor populations. Primary manifestations of the impact on the poor—including the loss of gainful employment, with the attendant loss of family income; the requirement for caregiving, with further potential loss of wages; the cost of medications; and the need for other medical services—can be expected to be particularly devastating among those with limited resources. In addition to health costs, those suffering from these conditions are also frequently victims of human rights violations, stigmatization, and discrimination. Stigmatization and discrimination further limit patients' access to treatment. These disorders, therefore, require special attention in developing countries.

This chapter addresses Alzheimer's disease (AD) and other dementias, epilepsy, Parkinson's disease (PD), and acute ischemic stroke. These conditions are current or emerging public health problems in developing countries, as assessed by high prevalence, large numbers of people who are untreated, and availability of inexpensive but effective interventions that could be applied on a large scale through primary care. Unfortunately, reliable population-based data from developing countries on the epidemiology of these and other neurological disorders are extremely limited. Some other important neurological conditions that cause high morbidity, such as headache, are not covered because of difficulties in recommending evidence-based interventions in developing countries.

ALZHEIMER'S DISEASE AND OTHER DEMENTIAS

Dementia is a deterioration of intellectual function and other cognitive skills that is of sufficient severity to interfere with social or occupational functioning. Of the many diseases that lead to dementia, AD is the most common cause worldwide among people age 65 and older, followed by vascular dementia, mixed dementia consisting of AD plus vascular dementia, and dementia caused by general medical conditions. Although distinguishing AD from other causes of dementia is important, particularly for treatment with acetylcholines-

terase inhibitors, the burden from all causes of dementia is similar. Although the discussion in this chapter deals mostly with AD, the role of treatable dementias in developing countries is important as it can reduce the burden of caring in families.

Prevalence and Incidence Rate

More than 100 prevalence studies of AD and other dementias have been reported throughout the world. The prevalence of dementia has generally been found to double with every five-year increase in age, from 3 percent at age 70 to 20 to 30 percent at age 85 (Henderson and Jorm 2000). Studies in developing countries have shown a prevalence of dementia ranging from 0.84 to 3.50 percent (Chandra and others 1998; Hendrie and others 1995; Rajkumar, Kumar, and Thara 1997). Several studies have reported the incidence rate of AD and other dementias in Europe and the United States (Jorm and Jolley 1998). Compared with incidence rates in developed countries, very low age-specific incidence rates of AD and other dementias have been reported from developing countries (Chandra and others 2001; Hendrie and others 2001).

A comparison of data from developed and developing countries raises several important questions. The reported differences in the prevalence of AD and other dementias across countries could be due partly to methodological differences or could be due to genuine differences caused by variations in diet, education, life expectancy, sociocultural factors, and other risk factors. The low incidence reported from Ballabgarh, India, and Ibadan, Nigeria, raises the possibility of environmental factors or gene-environment interactions in the causation of AD. At the same time, multi-infarct dementia is more common-than primary degenerative dementia in China (Li and others 1991), which also suggests variation in risk factors across countries.

Risk and Protective Factors and Survivorship

Three separate genes (APP, PS1, and PS2) are linked to early-onset, familial AD. Another gene (APO E4) is a risk factor for late-onset, nonfamilial cases (Henderson and Jorm 2000). Other genes have been implicated but not confirmed in large studies. Other risk factors reported in the literature include increasing age, positive family history of dementia, female gender (but this factor is controversial), lower level of education, several medical conditions, and exposure to such environmental factors as organic solvents and aluminum (Henderson and Jorm 2000).

Protective factors reported in the literature include a higher level of education, a specific gene (APO E2), the intake of antioxidants, and the use of some anti-inflammatory medications (Henderson and Jorm 2000). The use of estrogen supplements for women was believed to be a protective factor for AD (Henderson 1997), but a recent study of women taking a combination of estrogen and progesterone showed that these women had twice the risk of developing dementia than women taking a placebo (Shumaker and others 2003).

Studies from developed countries have reported median survival after the onset of dementia symptoms ranging from 5.0 years to 9.3 years (Walsh, Welch, and Larson 1990). In developing countries, the reported median survival was 3.3 years for all demented subjects and 2.7 years for those with AD (Chandra and others 1998).

Burden of Disease

Burden of disease estimates of AD and other dementias include vascular dementia, unspecified dementias, and other unclassified degenerative diseases of the nervous system. Mathers and others (2003) estimate DALYs for all dementias as 17,108,000, with the burden being almost twice as much for females (11,016,000) as for males (6,092,000). Because dementia is a disease of older ages, the burden from dementia is generally greater in high-income countries, where life expectancy is higher, diagnosis is better, and better treatment leads to increased longevity. Note, however, the relatively high burden in East Asia and the Pacific and South Asia relative to their level of economic development (table 2.1).

The bulk of care for those with dementia in developing countries is provided by the family at home, where the main caregivers are spouses (36 percent) and children (42 percent) (Prince 2000). Women in both developed and developing countries are usually the main caregivers (Prince 2000). Studies in developed countries indicate that caregivers' psychological well-being is a key factor in patients' admission to nursing or residential care (Levin, Moriarty, and Gorbach 1994).

In estimating the overall costs of care for dementia, one must emphasize the value of reducing the burden on caregivers. Caregiving can result in social isolation, psychological stress, and high rates of depression (Buck and others 1997). However, the methodology for estimating the costs of informal care needs to be standardized.

Interventions

As of now, there is no cure for AD, but some measures can provide symptomatic relief to patients and caregivers.

Population-Based Interventions. No firm evidence indicates that any form of population-based intervention can prevent AD or that the progression of cognitive decline in old age can be halted or reduced. However, growing inferential evidence suggests that reducing the risk of brain trauma in earlier life, for example, by mandating seat belt and crash helmet use, may help prevent dementia in later life (Gentleman, Graham and Roberts 1993).

Personal Interventions. There is a reduction in brain levels of the neurotransmitter acetylcholine in patients suffering from AD. Drugs that inhibit acetylcholinesterase, the enzyme responsible for metabolizing acetylcholine, cause an increase in brain acetylcholine. Evidence from randomized trials has

Table 2.1 Disability-Adjusted Life Years by Cause and Region, 2001
(thousands)

Condition	Global total			East Asia and the Pacific	Europe and Central Asia	Latin America and the Caribbean	Middle East and North Africa	South Asia	Sub-Saharan Africa	High-income countries
	Both sexes	Males	Females							
AD and other dementias	17,108	6,092	11,016	4,110	1,612	1,215	292	1,955	450	7,468
Epilepsy	6,223	3,301	2,922	1,303	354	737	248	1,741	1,373	464
PD	2,325	1,124	1,202	435	228	90	81	303	100	1,086
Cerebrovascular disease	72,024	35,482	36,542	25,832	12,616	3,936	1,948	13,184	5,125	9,354

Source: Mathers and others 2006.

confirmed that, for patients with mild to moderate AD, cognitive performance benefits, at least in the short term, from the use of acetylcholinesterase inhibitors (Foster and others 1996). Despite this benefit to patients, the practical benefits of treatment with acetylcholinesterase inhibitors are mainly attributable to the lowered caregiver burden. The benefits of using acetylcholinesterase inhibitors for other dementias have yet to be proven.

The behavioral and psychological symptoms of dementia are a major source of stress to family members providing care to patients. Training family caregivers in behavioral management techniques, including problem solving, memory training, and reality orientation, has been shown to reduce the level of agitation and anxiety in people with dementia (Brodaty and Gresham 1989; Haupt, Karger, and Janner 2000). Use of low doses of antipsychotic medications, which calm the patient and reduce symptoms such as aggression and wandering, have been shown to reduce caregiver stress, but these improvements have not been quantified (Melzer and others 2004).

Interventions that have specifically targeted stress and depression among caregivers and have shown positive results include caregiver training, counseling and support for caregivers, and cognitive and behavioral family interventions (Marriott and others 2000). Limitations to the implementation of such strategies include the need for training by specialists, which makes these strategies less suitable for developing countries. The challenge for developing countries is to develop culturally appropriate interventions that can be delivered within existing resources, such as supporting families in their role as caregivers.

Treating underlying disease and risk factors for cardiovascular disease can help prevent future cerebrovascular disease that could lead to multi-infarct dementia. Other conditions, such as hypothyroidism or vitamin B_{12} deficiency, which could lead to or aggravate dementia, are easily treatable, and the costs of treatment are much lower than the costs of dementia care.

In Western countries, the model of care for patients with moderate to severe dementia is based on skilled, long-term care in institutions. However, such long-term care institutions do not exist in developing countries, and if they were set up, they would be extremely expensive and beyond the reach of most patients and their families. Thus, the model of care in developing countries should be based on home care, along with providing training and support for family caregivers.

Interventions that should not be pursued include the use of multiple medications, which can be detrimental in older age groups, particularly unproven medications such as cerebral activators and neurotropic agents. In addition, in many developing countries, dementia is still equated with "madness," and patients are sometimes taken to traditional healers. Community education has a role to play in eliminating such practices.

EPILEPSY

Epilepsy is a common brain disorder characterized by two or more unprovoked seizures. Seizures are discrete events caused by transient, hypersynchronous, abnormal neuronal activity. Seizures may occur in close temporal association with a variety of acute medical and neurological diseases, such as acute stroke, sepsis, or alcohol withdrawal. However, the vast majority of seizures have no immediate identifiable cause.

Epilepsy can be broadly divided into three categories: idiopathic epilepsy (for example primary generalized childhood-onset absence epilepsy), which is thought to have a genetic basis; secondary or symptomatic epilepsy, which is caused by a-known central nervous system injury or disorder, such as infection, stroke, traumatic brain injury, or cerebral dysgenesis; and cryptogenic epilepsy, for which there is no clear evidence of an etiological factor. Idiopathic and cryptogenic cases represent approximately 70 percent of epilepsy cases; the remaining 30-percent are symptomatic (secondary).

Prevalence, Incidence Rate, Remission, and Mortality

The generally accepted estimate of the prevalence of active epilepsy globally is in the range of 5 to 8 per 1,000 population, but investigators from African and Latin American countries report at least double the prevalence reported elsewhere (Leonardi and Ustun 2002).

The incidence rate of epilepsy in developed countries is-approximately 43 per 100,000 (Kotsopoulos and others 2002).-In developing countries, the incidence rate of epilepsy is-higher, with a median of 69 per 100,000 (Kotsopoulos and others 2002).

Based on follow-up of patients under treatment by general practitioners in the United Kingdom, Cockerell and others (1997) report that after nine years 86 percent of epilepsy patients had achieved a remission of three years, and 68 percent had achieved a remission of five years. Thus, data from developed countries suggest a good outcome of seizure control in most patients with treatment. In developing countries, although many people with new onset seizures do not receive treatment, some proportion of patients go into spontaneous remission even without treatment (Mani and others 1993). However, the actual remission rate in developing countries is yet to be documented in population-based studies.

The risk of premature death in people with epilepsy is two to three times higher than for the general population. In addition to sudden unexplained death, which occurs in up to 1 in 100 patients with severe refractory epilepsy, additional mortality results from accidents and suicide. However, the exact cause of the increased risk is not known in most cases.

Risk Factors

A reported risk factor for idiopathic (presumed genetic) epilepsy is family history of epilepsy. Reported risk factors for symptomatic epilepsy include prenatal or perinatal causes (obstetric complications, prematurity, low birthweight, neonatal asphyxia). Recent data suggest that the effect of obstetric complications or neonatal asphyxia may have been overemphasized. Prematurity, low birthweight, and neonatal seizures may be independent risk factors as well as markers of underlying disease. Other causes include traumatic brain injuries, central nervous system infections, cerebrovascular disease, brain tumors, and neurodegenerative diseases. Developmental disabilities are not a risk factor for epilepsy in themselves, but they may be associated with seizure disorder (Casetta and others 2002; Leone and others 2002).

Treatment Gap

Epilepsy affects about 50 million people worldwide, of whom approximately 80 percent live in developing countries (WHO 2000). The difference between the number of people with active epilepsy and the number who are being appropriately treated in a given population at a given point in time is known as the *treatment gap*. Meinardi and others (2001) estimate that 90 percent of people with epilepsy in developing countries are inadequately treated. Possible reasons for the high treatment gap include fear of stigmatization, cultural beliefs, lack of knowledge about the medical nature of epilepsy, illiteracy, economic issues, distance to health facilities, inadequate supply of antiepileptic drugs (AEDs), and lack of prioritization by health authorities (Wang and others 2003). Even in the developed world, patients who live in isolated rural regions or inner-city slums and those who are isolated from the majority because of cultural factors may suffer a treatment gap.

Faith Healers

Many people with epilepsy seek treatment from faith healers, to whom they pay large sums in cash or in kind for treatment with no beneficial medical effects. Karaagac and others (1999) find that in Silivri, Turkey, 65 percent of 49 people with epilepsy had visited religious figures at the onset or during the course of the disease. A study from rural India revealed that 44 percent of children with epilepsy had sought help from traditional practitioners, whereas approximately 33 percent had received help from both qualified and traditional practitioners (Pal and others 2002). Native Americans still seek traditional healing ceremonies for epilepsy instead of—or in addition to—Western medicine.

Patient Compliance

In a study in rural Thailand, only 57 percent of people with epilepsy were 100 percent compliant with treatment, possibly because of misunderstanding of the instructions (48 percent), forgetfulness (16 percent), and economic limitations (13 percent) (Asawavichienjinda, Sitthi-Amorn, and Tanyanont 2003). To improve compliance in a rural African community, medical personnel visited the community every 6 months and provided a long-term supply of medications; this effort led to a substantial increase in compliance at 20 months (Kaiser and others-1998). In India, Desai and others (1998) demonstrate the dependency of compliance on access to free treatment. Inadequate communication between doctors and patients influences compliance negatively (Gopinath and others 2000).

Burden of Disease

The burden of disease (BOD) estimates for epilepsy include epilepsy and status epilepticus. Mathers and others (2003) estimate the DALYs for epilepsy as 6,223,000, with slightly higher rates for males (3,301,000) than for females (2,922,000). Many risk factors for epilepsy are linked with a lower level of economic development; thus, the burden is highest in South Asia followed by Sub-Saharan Africa (table 2.1). A notable observation is the reportedly low burden in the Middle East and North Africa, despite parts of that region being relatively underdeveloped. Epilepsy imposes a large economic burden on patients and their families. It also imposes a hidden burden associated with stigmatization and discrimination against patients and even their families in the community, workplace, school, and home. Social isolation, emotional distress, dependence on family, poor employment opportunities, and personal injury add to the suffering of people with epilepsy.

Interventions

Currently, there are no preventive measures for idiopathic or cryptogenic epilepsy; however, much can be done to prevent secondary seizures.

Population-Based Interventions. Public health policies, such as better perinatal care by well-trained birth attendants (particularly in rural areas) and strategies to control severe head injuries (for example, by means of laws requiring motorcyclists to wear helmets and prohibiting drunk driving), can modify risk factors for epilepsy and thereby reduce the incidence and prevalence of epilepsy. Policies to control neurocysticercosis (for instance, building latrines in rural areas) can serve to prevent such infections. Mass deworming for neurocysticercosis has not been shown to be effective in the long term (Pal, Carpio, and Sander 2000) but was effective in a campaign in Ecuador (M. Cruz, personal communication, 2004).

Estimates indicate that 70 to 80 percent of people in developing countries live in rural and remote areas and have no easy access to skilled medical care. Strategies that involve training community-based health care providers who practice in these communities to identify and manage patients with epilepsy should be considered.

Policies are needed to ensure the continuous availability of cheap and efficacious medications, such as phenobarbital, to all-epilepsy patients. Campaigns to educate communities about-the medical nature of epilepsy and to dispel myths and misconceptions about epilepsy could reduce stigma against epilepsy and thereby encourage patients to seek medical treatment.

Personal Interventions. Researchers, primarily in high-income countries, have tested (a) the efficacy of both older AEDs (such as phenobarbital, phenytoin, carbamazepine, and valproic acid) and newer AEDs (such as lamotrigine, oxcarbazepine, and topiramate) in controlling seizure frequency and (b) the safety of these AEDs when prescribed alone or in combination. Some, but not all, of the new AEDs may be better tolerated in monotherapy and have fewer long-term adverse effects than older AEDs. However, no study has shown any difference in efficacy between the older and newer medications (Aldenkamp, De Krom, and Reijs 2003). Newer medications are more expensive and, for people in most developing countries, are practically impossible to access. In some low-income countries, however, even older AEDs are not available, and when they are, their supply is irregular.

Newer AEDs are generally recommended as add-on or adjunctive drugs for better seizure control in patients with refractory epilepsy already on AEDs. The first AED will render approximately 50 percent of patients seizure free. Approximately 20 to 40 percent of patients who do not respond to the first AED will respond to the introduction of a second AED, with a greater than 50 percent decrease in seizure frequency (Schapel and others 1993).

The Global Campaign against Epilepsy, which is jointly sponsored by the World Health Organization, International League against Epilepsy, and International Bureau for Epilepsy, advocates using phenobarbital to close the high treatment gap-in low-income countries. As a first step, all patients with epilepsy should be given phenobarbital, so that the majority of-patients responsive to phenobarbital will be appropriately-treated. In resource-poor countries, phenobarbital can-be provided for as little as US$5 to US$10 per year. Phenobarbital has extremely low abuse potential. Its side effects—predominantly sedation, possible mild cognitive impairment, and depression—have limited its use in industrial countries. In developing countries, however, side effects are less important than uncontrolled seizures, and they can be diminished by using the lowest possible effective doses. Thus, phenobarbital is-the drug of choice for large-scale, community-based programs, particularly in rural and remote areas of developing countries.

In recent years, some centers in both developed and developing countries have been performing surgery on cases of *refractory epilepsy,* that is, on patients who do not respond to any AEDs. Before centers can undertake such surgery, however, they must have the requisite expertise, facilities, and equipment, including a skilled neurosurgeon. Proper selection of patients—for example, those with mesial temporal pathology on MRI—is extremely important. A meta-analysis of studies of people who underwent epilepsy surgery in developed countries shows that 58 percent are seizure free and 10 to 15 percent have reduced seizure frequency (Engel and others 2003). After surgery, even if patients are seizure free, medication should be continued for one to two years (Engel and others 2003).

PARKINSON'S DISEASE

PD is characterized by bradykinesia, resting tremor, cogwheel rigidity, postural reflex impairment, progressive course, and good response to dopaminergic therapy. Other distinct forms of parkinsonism include relatively rare genetic forms and the less common neurodegenerations with multiple system involvement or significant striatal lesions (for example, progressive supranuclear palsy or multiple system atrophy). Parkinsonism secondary to external causes, such as manganese poisoning or carbon monoxide poisoning, although now rare, is referred to as secondary parkinsonism. Because the burden of these diseases to the patient is similar to or greater than that for PD and there is no evidence for addressing these disorders separately, they will not be distinguished here.

Prevalence, Incidence Rate, and Mortality

Prevalence estimates vary widely across populations (Tanner and Goldman 1996; Zhang and Roman 1993). Recent reports, contrary to previous reports, suggest that the preva-

lence in developing and developed countries may be similar (Marras and Tanner 2002). Few incidence studies have been performed, and none in developing countries. Van Den Eeden and others (2003) report the incidence rate of PD in the United States as approximately 13 per 100,000 person-years. Men are affected more commonly than women (Tanner and Goldman 1996). Lower PD incidence in African Americans—and by extension Africans—has been suggested but is controversial (Van Den Eeden and others 2003). Most mortality estimates available for developed countries show about a twofold overall increased mortality, independent of age, in those with PD (Berger and others 2000).

Causes and Risk Factors

The cause of PD is unknown. A specific environmental risk factor has not been identified. Pure genetic forms account for 10 to 15 percent of cases or fewer. Increasing age and male gender are risk factors worldwide (Marras and Tanner 2002). Exposure to toxins, head trauma, frequent infections, diets high in animal fat, and midlife adiposity have been reported to increase PD risk, but none do so consistently (Tanner and Goldman 1996). The most consistent association is an inverse association with cigarette smoking and caffeine consumption, suggesting a protective effect (Ascherio and others 2001).

Burden of Disease

The BOD estimates for PD include Parkinson's disease and secondary parkinsonism. Mathers and others (2003) estimate the DALYs for PD as 2,325,000, with the burden being slightly higher in females (1,202,000) than males (1,124,000). Though male gender is a risk factor for PD, the higher burden in females may reflect their longer life span. As PD is a disease of older ages, the burden from PD is generally higher in high-income countries, where life expectancy is higher, diagnosis is better, and better treatment leads to increased longevity. However, the burden is high in East Asia and the Pacific and South Asia relative to that in other regions (table 2.1).

The economic burden of PD includes direct costs, such as for medication, physicians, hospitals, and chronic care facilities. Estimated indirect costs resulting from the loss of labor of-both patients and caregivers typically exceed direct costs. The quality of life of both patients and caregivers is adversely affected.

Interventions

Treatment of PD is based on symptomatic relief, except for preventing secondary parkinsonism caused by neurotoxins.

Population-Based Interventions. No determinants of PD amenable to population-based interventions have been identified.

Personal Interventions. Specific curative or neuroprotective treatments for PD have not been established. Interventions are-primarily directed at palliation of symptoms and include pharmaceuticals, surgery, physical therapy, and—in some countries—traditional medicines.

Levo-dopa (l-dopa), l-dopa/decarboxylase inhibitor is the most widely used therapy for PD. It provides partial relief of all PD symptoms. Despite its benefits, chronic side effects after long-term use can cause significant morbidity.

Researchers in developing countries have studied the use of traditional medicines for PD. Clinical trials have shown that the seeds of *Mucuna pruriens,* which contain l-dopa, are a safe and effective treatment for PD (Parkinson's Disease Group 1995), and in animal studies, they are two to three times more effective than synthetic l-dopa dose per dose (Hussain and Manyam 1997). This substance is available in ayurvedic formulations in India at a much lower cost than that of synthetic antiparkinsonian drugs. Another traditional medicine is derived from *Banisteriopsis caapi,* which tribal societies of the Amazonian jungle use to make a potent hallucinogenic brew. It reportedly showed dramatic positive effects on rigidity and akinesia in 15-patients with postencephalitic parkinsonism (Lewin and Schuster 1929). A third traditional option is tai chi, a basic exercise in traditional Chinese medicine that may help with some of the motor deficits of PD.

Surgical treatment for PD by deep brain stimulation is generally recommended to address the loss of efficacy of dopaminergic drugs. For most patients, it is not effective independent of drugs. Although a few will have dramatic improvement and may be able to reduce or stop drugs, this effect is generally temporary. Criteria for selection of patients for deep brain stimulation include those with advanced disease who are responsive to l-dopa, not demented, and in good general health. Additional considerations are the high cost of the equipment, the need for-trained personnel to program the device, and—in most cases—the need for several visits to a medical center to program the-stimulator correctly, with periodic returns to adjust the settings.

STROKE

Stroke, also known as *cerebrovascular accident* or *brain attack,* is a syndrome caused by an interruption in the flow of blood to part of the brain caused either by occlusion of a blood vessel (*ischemic stroke*) or rupture of a blood vessel (*hemorrhagic stroke*). The interruption in blood flow deprives the brain of nutrients and oxygen, resulting in injury to cells in the affected vascular territory of the brain. The occlusion of a blood vessel can sometimes be temporary and present as a reversible neurological deficit, which is termed a *transient ischemic attack*. Even though stroke is a clinical diagnosis, brain imaging is required to distinguish ischemic stroke from hemorrhagic stroke. When imaging is unavailable, clinical scores can be useful to identify patients with intracerebral

hemorrhage (Allen 1983; Poung-varin, Viriyavejakul, and Komontri 1991).

Frequency of Types of Strokes, Prevalence, Incidence Rate, Mortality, and Disability after Stroke

In most parts of the world, about 70 percent of strokes are due-to ischemia, 27 percent are due to hemorrhage, and 3 percent are of unknown cause (Gunatilake, Jayasekera, and Premawardene 2001). Approximately 25 percent of all ischemic strokes are due to cardioembolic causes, with the proportion being higher among younger individuals. In some parts of the-world—for instance, China and Japan—hemorrhagic strokes account for a greater proportion of all strokes, ranging from 17.1 to 39.4 percent in China (Zhang and others 2003) to 38.7 percent in Japan (Fukiyama and others 2000).

Comparable data do not exist for all parts of the world. Most morbidity data from Southeast Asian countries, for example, are hospital based and are, thus, likely to be underestimates, because many stroke patients die before they are brought to the hospital. Mortality data are also likely to be underestimates, because verifying the cause of death is usually difficult.

In India, the prevalence of stroke has been estimated at 203-per 100,000 population older than 20 (Anand and others 2001). The male-to-female ratio was one to seven. In Taiwan, China, the crude point prevalence was 592 per 100,000 (Huang, Chiang, and Lee 1997).

He and others (1995) report the age-adjusted stroke incidence of 117 per 100,000 population in China. The annual incidence of stroke in China is reported to have increased in both men and women, with an average annual percentage change of 4.5 and 4.2 percent, respectively (Wang, Zhao, and Wu 2001). In Japan, the age-adjusted annual incidence of stroke was 105 per 100,000 (Fukiyama and others 2000). Wide variation within these countries and a high risk of death after the first stroke in the first year in Japan have been reported. Investigators believe that those observations are due to variations in the prevalence of hypertension and the consequent larger proportion of hemorrhagic stroke (Kiyohara and others 2003).

Walker and others (2000) report the yearly age-adjusted mortality rate per 100,000 for age group 15 to 64 ranged from 35 to 65 in men and 27 to 88 in women in Tanzania. When compared with the rates in England and Wales—11 for men and 9 for women—these rates are extremely high. The authors postulate that the high rates in Tanzania are due to untreated hypertension. Many developed countries have experienced a steep decline in stroke mortality in recent decades, but the rate of decline has fallen substantially in recent years (Liu, Ikeda, and Yamori 2001; Sarti and others 2000). Mortality from stroke has increased in some Eastern European countries (Sarti and others 2000).

Approximately 15 percent of patients die shortly after a stroke. Of the remaining 85 percent, approximately 10 percent recover almost completely, and 25 percent recover with minor impairments (National Stroke Association 2002). Thus, approximately 40 percent experience moderate to severe impairments that require special rehabilitative care. About 10-percent will require care in a nursing home or other long-term facility.

Risk Factors

Risk factors for stroke in general are similar to those for cardiovascular disease. Moreover, risk factors for first stroke and recurrence of stroke are also similar if they remain uncontrolled after the first attack (see chapter 33 of DCP2).

Increasing age, particularly after 55, is one of the most important risk factors for stroke (Thorvaldsen and others 1995). Although stroke is more prevalent among men, stroke-related fatality rates are higher among women (Goldstein and others 2001). Hypertension is the most important modifiable determinant of both first and recurrent stroke (Eastern Stroke and Coronary Heart Disease Collaborative Research Group 1998). The association between blood pressure and stroke in-East Asian populations seems stronger than in Western populations (Eastern Stroke and Coronary Heart Disease Collaborative Research Group 1998). Other risk factors include smoking, environmental exposure to tobacco smoke, dyslipidemia, atrial fibrillation, diabetes and impaired glucose tolerance, generalized and abdominal obesity, physical inactivity, excess alcohol consumption, increased homocysteine levels, drug abuse, hemostatic factors, and existing cerebrovascular disease (Goldstein and others 2001).

In developing countries, rheumatic heart disease leading to embolic stroke is also a major cause. This risk factor is declining in importance with the control of rheumatic fever. Dehydration in postpartum women can lead to a stroke, particularly in remote areas where deliveries are conducted at home.

Burden of Disease

The BOD estimates for stroke include subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction, and sequelae of cerebrovascular disease. Mathers and others (2003) estimate the DALYs for cerebrovascular disease as 72,024,000, with the burden being almost similar for females (36,542,000) and males (35,482,000). The burden is highest in East Asia and the Pacific, followed by South Asia and by Europe and Central Asia (table 2.1). The burden in Sub-Saharan Africa is higher than in the Middle East and North Africa, which may suggest an etiology for stroke other than atherosclerotic disease.

Health experts anticipate that the number of stroke cases will increase, particularly in developing countries, because of aging populations and increased exposure to major risk factors. Corresponding to this increase in the number of stroke cases will be an increase in the number of people with disabilities surviving after stroke.

Interventions

Several intervention strategies are available for stroke, but only a few can be applied in developing countries.

Population-Based Interventions. Public health policies to address risk factors for stroke include tobacco and alcohol control, laws to provide labels showing the fat content of foods, and public education about the harm caused by high-fat foods. Public health programs to control rheumatic fever will reduce rheumatic heart disease and the subsequent risk of embolic strokes. Better training of birth attendants will reduce the risk of peripartum hemorrhage, which leads to puerperal strokes.

Personal Interventions. Modification of adverse lifestyle and major risk factors such as hypertension, diabetes, high lipid levels, smoking, and alcohol abuse is beneficial both for primary prevention and recurrence of stroke. Some evidence indicates that the decline in the incidence of stroke observed in many countries is due to better management of hypertension (MacWalter and Shirley 2002). Special consideration should be given to the profile of risk factors in developing countries, which include not only recognized risk factors in developed countries but also locally relevant risk factors, such as rheumatic heart disease and puerperal stroke.

Treatment strategies for acute ischemic stroke include the following:

- *General management.* Overall medical care of patients with an acute stroke is important. Attention to complications such as bronchoaspiration, fluid and electrolyte imbalance, and control of blood sugar, as well as prevention of deep vein thrombosis, is crucial. Experience in developed countries suggests that specialized stroke units provide the best care for acute stroke patients (Smaha 2004), but in developing countries, particularly in rural areas, where hospital beds are scarce and most patients are attended by general physicians, such units are impractical.
- *Platelet antiaggregants.* Aspirin can prevent early stroke recurrence if given during the acute phase of stroke (within 48 hours) (Chinese Acute Stroke Trial Collaborative Group 1997; International Stroke Trial Collaborative Group 1997). The adverse effects of aspirin (cerebral hemorrhage and gastrointestinal complications) appear to be dose related, and most agree that using a low dose of aspirin is prudent (Antithrombotic Trialists' Collaboration 2002). Since aspirin can aggravate a hemorrhagic stroke, simple guidelines for the use of platelet antiaggregants should be developed and could be based on scales such as the Siriraj score to rule out hemorrhage (Poungvarin, Viriyavejakul, and Komontri 1991).
- *Thrombolytic therapy.* Tissue plasminogen activator and recombinant tissue plasminogen activator (rt-PA) can be used to halt a stroke by dissolving the blood clot that is blocking blood flow to the brain (National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group 1995). Thrombolytic therapy can increase bleeding and must be used only after careful patient screening, with a CT scan of the brain within three hours of stroke symptom onset, to exclude an intracranial bleed. It also requires appropriately trained physicians to administer the medication. These prerequisites for the administration of thrombolytic agents restrict its use to selected centers in developing countries.

Strategies for prevention of recurrence of stroke apply equally to individuals who have experienced a transient ischemic attack and to those who have experienced a complete stroke. These strategies include the following:

- *Platelet antiaggregants.* Aspirin therapy is effective in preventing recurrence of stroke, with low daily doses being at least as effective as higher daily doses (Antithrombotic Trialists' Collaboration 2002). When compared with aspirin, clopidogrel has a slight benefit among those who have had a-previous stroke, myocardial infarction, or symptomatic peripheral arterial disease. Clopidogrel is an effective and safe alternative for patients who do not tolerate aspirin. Although clopidogrel may be slightly more effective than aspirin, it is also more expensive. Antiplatelet combination therapy using agents with different mechanisms of action, such as the combination of extended release dipyridamole and aspirin, has been shown to reduce the risk of stroke over aspirin alone (Sacco, Sivenius, and Diener 2005). In contrast, combination therapy with aspirin and clopidogrel offers no advantage over aspirin alone and also increases the risk of hemorrhage (Diener and others 2004).
- *Anticoagulant therapy.* Anticoagulation with warfarin should be considered in stroke patients with atrial fibrillation, because of its clear efficacy in preventing embolic strokes, provided that patients are appropriately monitored (European Atrial Fibrillation Trial Study Group 1993; Mohr-and others 2001). Anticoagulant therapy also reduces the risk of embolic stroke in patients with rheumatic heart disease. However, anticoagulation can be hazardous in developing countries because of the lack of monitoring facilities.
- *Surgical treatment.* In patients with symptomatic carotid disease with stenosis of 70 percent and in asymptomatic patients with high-grade stenosis, carotid endarterectomy has been shown to be more beneficial than medical care-alone (Asymptomatic Carotid Atherosclerosis Study 1995;-Asymptomatic Carotid Surgery Trial Collaborative Group-2004; North American Symptomatic Carotid Endarterectomy Trial Collaborators 1991). However, inappropriate selection of patients or high intraoperative complications could obviate such benefits. Carotid angioplasty has been suggested as an alternative to-carotid endarterectomy in management of severe internal carotid

artery disease, but its advantages and disadvantages have yet to be clearly established (Naylor, London, and Bell 1997). Carotid endarterectomy for stroke prevention is available at only a few centers in developing countries, which makes its widespread use impractical.

The goal of rehabilitation after a stroke is to enable individuals who have experienced a stroke to reach the highest feasible level of independence as soon as possible. Successful rehabilitation depends on the extent of brain damage, skill of the rehabilitation team, length of time before rehabilitation is started, and support provided by caregivers. Because each stroke patient has specific rehabilitation needs, customizing the rehabilitation program is important. Rehabilitation therapies include several complementary approaches:

- physical therapy, which helps stroke patients relearn simple motor activities, such as walking
- occupational therapy, which helps patients relearn everyday activities, such as eating and drinking
- speech therapy, which helps patients relearn language and speaking skills
- counseling, which can help alleviate some of the mental and emotional problems that result from stroke.

Comprehensive rehabilitation in a multidisciplinary stroke unit reduces deaths, disability, and the need for long-term institutional care (Smaha 2004), but such facilities are extremely limited in developing countries. Home-based rehabilitation services can prevent long-term deterioration in activities of daily living, although the absolute impact is relatively modest (Outpatient Service Trialists 2002). However, in developing countries, the vast majority of patients will be treated either at home by a general physician or in a small community hospital where no skilled rehabilitation therapist is available.

COST-EFFECTIVENESS OF INTERVENTIONS IN-DEVELOPING COUNTRIES

We determined incremental cost-effectiveness ratios (ICERs) for selected interventions for each condition by calculating total DALYs lost by a population because of the condition with and without treatment and then dividing the difference by the-treatment cost. The disability weights used are presented in-table 2.2. All analyses in this section followed the volume editors' standardized guidelines for economic analysis, region-specific age structures, and underlying mortality rates. We converted nontradable inputs into U.S. dollars at the market exchange rate. We assumed that the costs of tradable inputs were internationally consistent, as were costs associated with surgical treatments. Table 2.3 presents the costs of drugs and medical services. No fixed costs were assumed; therefore, our results are not linked with the extent of treatment coverage.

Table 2.2 Disability Weights Used in ICER Analysis

Weight	AD and other dementias	Epilepsy	PD	Acute stroke	Recurrent stroke
Untreated	0.627	0.15	0.392[a]	0.278[b]	0.556
Treated	0.627[c]	0	0.316	0.235[b]	n.a.[d]

Source: Mathers and others 2006.
n.a. = not applicable.
a. Treatment for PD is assumed to be effective for a maximum of 10 years. We also assume that a patient reverts to the untreated disability weight after 10 years.
b. Disability is assumed to last a maximum of 10 years; then we assume the patient recovers fully.
c. The patient is assumed to experience no benefit from treatment. Benefits are in the form of reduced caregiver hours.
d. Treatment does not change the disability weight following a recurrent stroke; only the likelihood of experiencing a second stroke is reduced.

AD and Other Dementias

We analyzed the use of acetylcholinesterase inhibitors in the treatment of AD on the basis of the following assumptions: first, only patients who were older than 60 at the time of onset were considered; second, the treatment has no long-term benefits—that is, it does not reduce patient disability and has no effect on mortality.

We computed the benefits of reduced caregiver hours on the basis of reports that the improvement in cognitive function in AD patients associated with treatment using acetylcholinesterase inhibitors was a 1.2 point change in the global assessment scale for cognitive function, as measured by the Mini Mental State Examination. A 1 point improvement in the-score was associated with a 0.56 hour per day reduction in-caregiver hours, or roughly 205 hours per year (Marin and others 2003).

The cost of using acetylcholinesterase inhibitors per hour of caregiver time saved averaged US$13 across low- and middle-income countries (LMICs) and was at least US$11 in specific regions (the regions are the same as those in table 2.1). This amount is substantially more than the wage rate in these regions, which would generally not exceed US$1 to US$1.50 per hour, even for hired caregivers specifically trained to care for AD patients. We, therefore, conclude that the use of acetylcholinesterase inhibitors in developing countries is not efficient from an economic perspective. Calculating the cost per DALY averted for acetylcholinesterase inhibitors would not be meaningful, because we assume no benefit to the patient. Finally, the use of acetylcholinesterase inhibitors is uncommon in developing countries; therefore, reducing its use is not an important concern.

Epilepsy

We analyzed the cost-effectiveness of phenobarbital in the treatment of epilepsy, and the results are shown in table 2.4. We assumed that phenobarbital was provided to all patients. The cost of using phenobarbital per DALY gained in LMICs was US$89. Table 2.4 shows that the benefits of phenobarbital are large relative to its cost.

Table 2.3 Input Requirements for Interventions by Condition

Condition	Visits to primary health care doctor in outpatient department		Primary health care worker visits to patient in home or patient visits to see the worker in outpatient department		Specialist care in outpatient department		Inpatient care		Annual drug costs (US$)
	Patients using the service[a] (percent)	Visits per year	Patients using the service (percent)	Visits per year	Patients using the service (percent)	Visits per year	Patients using the service (percent)	Length of stay	
AD and other dementias									
Acetylcholinesterase inhibitors	100	4	100	12	100	2	5	7	638
Antipsychotics	100	12	100	12	25	6	5	7	10
Epilepsy									
Phenobarbital	100	2	100	6	10	2	1	3	1
Lamotrigine[b]	100	2	100	6	10	2	1	3	144
Surgery	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	2,600[c]
PD									
Levodopa/carbidopa	100	3	100	6	100	2	1	5	71
Ayurvedic preparations	100	3	100	6	100	2	1	5	19
Deep brain stimulation	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	37,000
Stroke (acute attack)									
Aspirin	n.a.	n.a.	100	1	100	1	100	14	3
Heparin	n.a.	n.a.	100	1	100	1	100	14	691
rt-PA	n.a.	n.a.	100	1	100	1	1	7	1,777[d]
Stroke (prevention of recurrence)									
Aspirin	100	4	100	6	100	1	n.a.	n.a.	3
Dipyridamole and aspirin	100	4	100	6	100	1	n.a.	n.a.	64
Carotid endarterectomy	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	6,216

Source: Authors.

n.a. = not applicable.

a. Percentage of patients receiving the specified treatment.

b. Nondrug treatment costs for lamotrigine are not included in the cost-effectiveness analyses because they are accounted for in the phenobarbital treatment costs. Lamotrigine is taken in addition to phenobarbital.

c. Epilepsy surgery also requires screening at a cost of US$600 per screened patient. Because only half of screened patients are eligible for surgery, the cost amounts to US$1,200 per treated patient.

d. This treatment requires testing for eligible patients. The costs of screening ineligible patients include all the same hospital and doctor costs as treatment, as well as 80 percent of the drug cost to account for the diagnostic CT.

We did not look at other AEDs, such as phenytoin or carbamazepine, because the costs of those medications are much greater than that of phenobarbital, but their effectiveness is essentially the same (Aldenkamp, De Krom, and Reijs 2003). Although their use may be justified for specific medical reasons, phenobarbital is much more cost-effective.

We analyzed treatment options for patients who are refractory to treatment with phenobarbital. We assumed that such cases were treated either with a combination of phenobarbital and lamotrigine or with a combination of phenobarbital and-surgery. We used the cost for epilepsy surgery of US$2,600, in accordance with a study from Colombia, and applied it to all-regions (Malmgren and others 1996; Tureczek, Fandino-Franky, and Wieser 2000). We assumed that roughly half of surgery recipients experience no more seizures and that the remaining half continue to take phenobarbital despite undergoing surgery. Our evaluation of the surgical option included the costs of diagnostic services and the costs associated with screening patients who ultimately may not be eligible for surgery. For patients in LMICs who are refractory to phenobarbital, the ICER of the add-on drug lamotrigine was US$3,000, and the ICER of the surgical option plus phenobarbital was US$3,100. The difference between phenobarbital and the other two options was significant in all regions.

Among refractory epilepsy patients eligible for surgery and-according to postoperative outcome studies conducted in-developed countries, surgery may be of comparable cost-effectiveness to treatment with a combination of phenobarbital and lamotrigine. Because effectiveness data for developing countries are not available, this calculation is based on cost estimates from a study in Colombia and estimates of the effectiveness of surgery from developed countries. If the surgical outcome in developing countries were worse than in developed countries, the cost-effectiveness of surgery would be lower. Furthermore, we note a number of limitations to the use of surgery in refractory epilepsy, particularly in developing countries, along with the lack of long-term follow-up data on the outcome of surgery. We stress that the primary treatment of epilepsy is with phenobarbital, and effective treatment of epilepsy lies in more efficient use of this highly cost-effective medication to close the treatment gap.

Parkinson's Disease

We evaluated three interventions for PD: a combination of l-dopa and carbidopa, traditional medicines such as the ayurvedic treatment used in India, and deep brain stimulation. We assumed that treatment for all three modalities was effective for 10 years from the onset of treatment. The ICERs in LMICs for these three modalities were US$1500, US$750 and US$31,000, respectively (table 2.4). On the basis of the cost of medication and evidence from clinical trials of effectiveness (Parkinson's Disease Group 1995) and from animal studies (Hussain and Manyam 1997), we found that ayurvedic treatment was the most cost-effective option. The relatively favorable ICER for ayurvedic treatment is due to the extremely low medication cost of this intervention. The relatively high ICER for deep brain stimulation was largely attributable to the extremely high cost of surgery. Table 2.4 shows DALYs gained for US$1 million of health expenditure.

Stroke

We evaluated two sets of interventions for stroke: treatment of acute stroke and prevention of secondary stroke. We assumed that stroke sufferers have fully recovered 10 years after their last stroke.

We evaluated aspirin, heparin, and rt-PA for the treatment of acute stroke. The International Stroke Trial Collaborative Group (1997) reports that, within 14 days of the onset of stroke, mortality with heparin treatment is less than with a placebo; however, after six months, mortality is actually greater for patients treated with heparin than with a placebo—that is, there is a negative cost per DALY gained if this effect is incorporated. The estimates presented here are based on the change in the short-term mortality risk. For LMICs, the cost per DALY averted using aspirin was US$150 (table 2.4). The equivalent costs of interventions using rt-PA and heparin were US$1,300 and US$2,700, respectively. The costs of heparin are higher than the costs of rt-PA, despite the expensive equipment required for rt-PA, because of the lower effectiveness of heparin.

Table 2.4 presents DALYs averted for US$1 million of health expenditure for the three treatments. The cost per DALY gained using aspirin is a conservative estimate, because the use of aspirin has additional benefits in terms of preventing a recurrence of stroke.

Table 2.4 shows the costs of preventing a second stroke within two years of the first stroke. For LMICs, aspirin was the least expensive option at US$3.80 per single percentage point decrease in the risk of a second stroke within two years of the first. This rate translates to roughly US$70 per DALY gained (table 2.4). Combining dipyridamole with aspirin, because of higher cost, was slightly more expensive at roughly US$5.20 per single percentage point decrease in recurrent stroke risk for a single individual, or about US$93 per DALY. In contrast, carotid endarterectomy was US$87 for an equivalent decrease in individual recurrence risk or almost US$1,500 per DALY. The aspirin monotherapy option for preventing a recurrence of stroke was the most cost-effective approach only in South Asia and Sub-Saharan Africa, largely because of the relatively low costs of nontradable inputs, such as hospital and doctors' fees, in those regions. Low input costs of nontradables increase the relative importance of drug costs in determining the most cost-effective intervention; therefore, the cheaper drug, aspirin, was most cost-effective. Table 2.4 shows that, though US$1 million would be most effectively spent on aspirin alone in South Asia and Sub-Saharan Africa, investment in aspirin and dipyridamole treatment would result in a greater DALY gain in the other regions.

Table 2.4 Results from Cost-Effectiveness Analysis of Interventions for Alzheimer's Disease, Epilepsy, Parkinson's Disease, and Stroke, by World Bank Region

Condition	Low- and middle-income countries	East Asia and the Pacific	Europe and Central Asia	Latin America and the Caribbean	Middle East and North Africa	South Asia	Sub-Saharan Africa
AD							
Cost per care hour reduced using acetylcholinesterase inhibitors (US$)	11	11	12	13	12	11	11
Epilepsy							
Incremental costs of DALYs gained per year of treatment compared with no treatment (US$)							
Phenobarbital	89	78	122	261	165	54	25
Phenobarbital and lamotrigine	2,994	3,306	2,945	4,301	3,344	2,872	1,490
Phenobarbital and surgery	3,060	3,411	3,049	3,477	2,904	3,097	1,788
Number of DALYs gained per US$1 million per year							
Phenobarbital	11,262	12,799	8,185	3,828	6,072	18,581	39,632
Phenobarbital and lamotragine	334	302	340	232	299	348	671
Phenobarbital and surgery	327	293	328	288	344	323	559
PD							
Incremental costs of DALYs gained per year of treatment compared with no treatment (US$)							
Levodopa/carbidopa	1,512	1,398	1,760	2,254	1,944	1,311	1,281
Ayurvedic preparation	751	638	1,000	1,494	1,184	551	520
Levodopa/carbidopa and deep brain stimulation	31,114	26,941	29,310	29,444	30,770	31,347	34,069
Number of DALYs gained per US$1 million per year							
Levodopa/carbidopa	662	715	568	444	514	763	781
Ayurvedic preparation	1,331	1,568	1,000	669	845	1,815	1,922
Levodopa/carbidopa and deep brain stimulation	32	37	34	34	32	32	29

Stroke (treatment of acute attack)							
Incremental costs of DALYs gained per year of treatment compared with no treatment (US$)							
Aspirin	149	109	104	574	534	118	112
Heparin	2,675	2,185	1,318	4,952	5,443	2,967	2,940
rt-PA	1,278	1,169	648	2,158	2,516	1,630	1,623
Number of DALYs gained per US$1 million per year							
Aspirin	6,691	9,209	9,633	1,742	1,873	8,463	8,942
Heparin	374	458	759	202	184	337	340
rt-PA	783	856	1,543	463	398	613	616
Stroke (prevention of recurrence)							
Incremental costs of percent recurrence risk averted after 2 years of treatment (US$)							
Aspirin	4	3	6	9	7	2	2
Dipyridamole and aspirin	5	5	6	8	7	4	4
Carotid endarterectomy	87	87	87	87	87	87	87
Incremental costs of DALYs gained per 2 years of treatment compared with no treatment (US$)							
Aspirin	70	60	59	233	196	52	34
Dipyridamole and aspirin	93	95	63	194	186	96	69
Carotid endarterectomy	1,458	1,614	836	2,001	2,234	1,759	1,284
Number of DALYs gained per US$1 million per 2 years of treatment							
Aspirin	14,313	16,569	16,866	4,285	5,093	19,348	29,373
Dipyridamole and aspirin	10,752	10,555	15,969	5,150	5,384	10,369	14,572
Carotid endarterectomy	686	620	1,197	500	448	568	779

Source: Authors.

RECOMMENDATIONS

The use of acetylcholinesterase inhibitors for treating patients with AD, as assessed by the number of caregiver hours saved, suggests that this intervention is not cost-effective. This finding, combined with the limited efficacy of acetylcholinesterase inhibitors, suggests that they should not be widely used in developing countries. Instead, giving low doses of antipsychotic medication to patients with any form of dementia who also have behavioral problems may be a better option for reducing caregiver stress, although this possibility has not been systematically evaluated.

Phenobarbital is by far the most cost-effective intervention for managing epilepsy and should be recommended for widespread use in public health campaigns against epilepsy in LMICs. For those patients who do not respond to phenobarbital, the addition of lamotrigine is advisable rather than surgery, because of the resource-intensive evaluation and infrastructure required for epilepsy surgery.

Indigenous systems of medicine, such as the ayurvedic medicines used in India, are much more cost-effective than Western medications or surgical procedures for managing patients with PD. Other countries may wish to test and standardize such medications for their own use.

Aspirin is by far the most cost-effective intervention both for treating acute stroke and for preventing a recurrence of stroke. It is easily available in developing countries, even in rural areas.

RESEARCH AND DEVELOPMENT AGENDA

The populations of most developing countries are aging rapidly. Many neurological disorders frequently occur in the elderly, posing an emerging public health problem. As a result, developing countries should begin or expand their research and development agendas to address issues related to the prevention, identification, and management of neurological disorders. In the short term, they should focus on early identification, optimum treatment, and amelioration of distress and handicaps and on reduction of the social and economic burden on patients and their families. In the long term, they should develop and implement strategies for primary prevention of neurological disorders. Specific areas for research and development include the following:

- *Conducting population-based epidemiological studies in developing countries.* Population-based data from developing countries are insufficient, which limits evidence-based planning. In addition, such data may also suggest important hypotheses for research if they identify genuine differences across regions (for example, the reported difference in the incidence of AD in developed and developing countries). In addition, the identification of risk or protective factors would be useful in the primary prevention of such diseases.
- *Enhancing existing health care delivery systems.* In most developing countries, approximately 70 to 80 percent of patients live in rural areas, where medical care is frequently provided by nonphysician health care providers or, at best, by a general physician. Limitations in the availability of health care have resulted in a huge treatment gap for many neurological disorders. For such situations, a simple model for the management of neurological disorders by existing community-based health care providers, trained to provide such services, would be helpful. Research is needed on optimum referral systems for more difficult cases that local communities will accept and can afford. Strategies for home-based care of patients need to be systematically evaluated.
- *Developing cheaper and more efficacious medicines.* Many currently available medications have significant side effects and are too expensive for many patients in developing countries. Newer medications need to be developed with lower costs, fewer side effects, better efficacy, and less frequent dose schedules.
- *Promoting the use of indigenous systems of medicine.* Many people in developing countries use local indigenous medicines. More research needs to be done on the pharmacological properties of those medications (see chapter 69 of DCP2).
- *Launching stigma removal campaigns.* The stigmatization of patients with neurological disorders and of their families is still prevalent, particularly in rural and remote areas, and it often prevents patients from seeking and obtaining appropriate medical care. Effective strategies to address this issue need to be developed and implemented on a large scale.

MISSED OPPORTUNITIES

Many research studies have reported that the incidence of AD is-lower in developing countries than in Western countries. Migration studies, such as those looking at the migration of Africans to the United States, have shown a change in the risk for AD within one or two generations. This finding suggests that developing countries may have some protective factors that rapidly change on migration to developed countries. Despite this information being available for more than 25 years, no systematic efforts have been made to identify these protective factors. Given the rapid adaptation of Western lifestyles in developing countries, identifying these factors is important before the opportunity is permanently lost.

The successful use of phenobarbital for treating epilepsy was first described in 1912. Not only is it effective for many types of-epilepsy, but it is also inexpensive. Nevertheless, despite its availability for more than 90 years and its modest cost, the treatment gap for epilepsy still exceeds 90 percent in many developing countries.

Indigenous systems of medicine, such as for the treatment of PD, have been used for centuries in developing countries. However, their utility has not been fully exploited.

Despite evidence of the benefit of control of hypertension in-the primary prevention of stroke, most efforts in developing countries are directed at treatment of stroke. This approach not-only is more expensive but also is less beneficial to the patient.

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Chapter **3**

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 3.1). Selected causes of LDD that are not addressed in detail in this chapter are described in box 3.1.

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 outcomes for children in LMICs. Evidence of cost-

Table 3.1 Categories of Causes of LDD

Category	Examples
Genetic	
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
Multifactorial	
Genetic and nutritional	Neural tube defects
Nutritional	
Prenatal: maternal iodine deficiency	Developmental iodine deficiency disorder
Childhood: vitamin A deficiency	Xerophthalmia, night blindness
Infections	
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
Toxic exposures	
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
Other maternal disorders	
Thyroid disease	Cerebral palsy
Other perinatal complications	
Brain injuries associated with premature birth, birth asphyxia	Cerebral palsy, cognitive disabilities, seizure disorders
Injury	
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
Poverty, economic disadvantage	
Social and cognitive deprivation	Mild mental retardation
Unknown	LDD of unknown cause

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 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)

Box 3.1

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 of DCP2).* 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 of DCP2).* 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 of DCP2).* In Sub-Saharan Africa, malaria is the leading cause of childhood mortality and morbidity. Cerebral malaria is a well-known complication and may result in neurological sequelae in survivors, contributing significantly to the burden of LDD.

Box 3.1

(*Continued*)

- *Bacterial meningitis (chapter 20 of DCP2).* This disease results in-long-term sequelae for many children, including approximately 40 percent of children who survive *Haemophilus* influenza 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 of DCP2). 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 of DCP2). 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 of DCP2). 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.

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

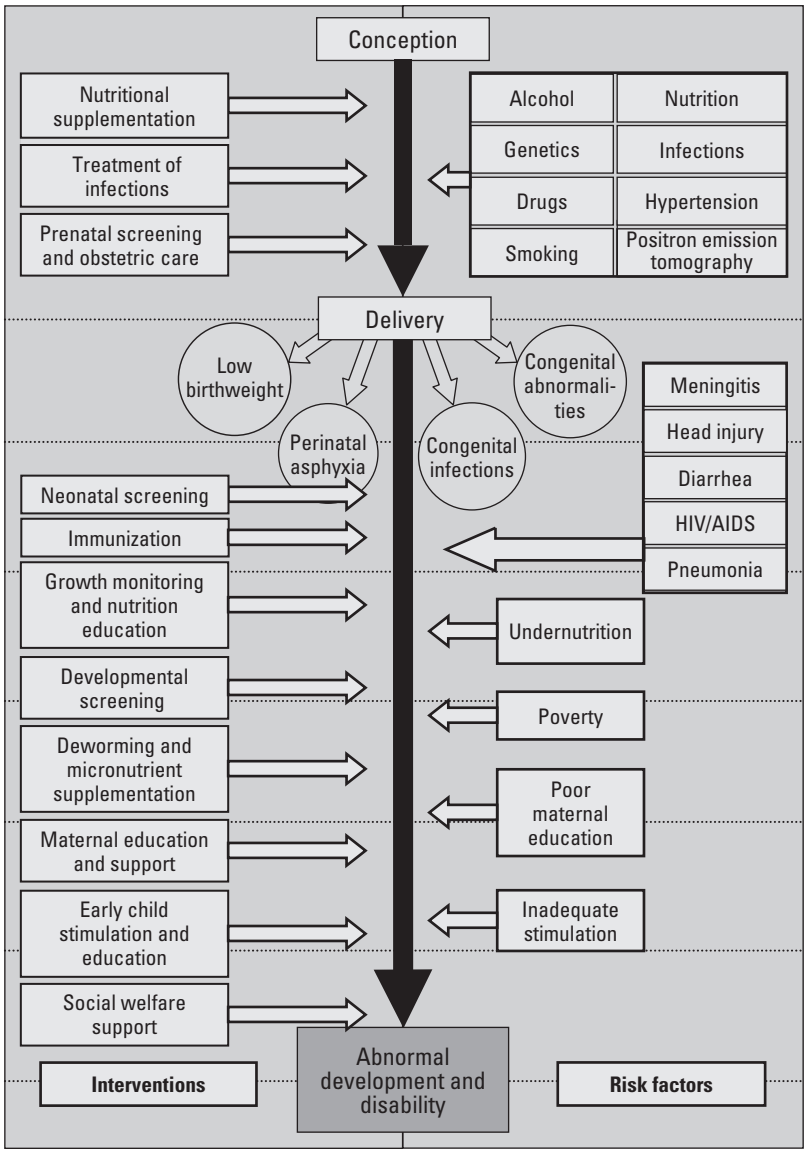
Progress in the field of LDD may result in increases in the recognized prevalence of disability and in social and economic costs, as in the following examples:

- 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 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 3.1 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-3.2 provides a summary of these interventions classified on two axes. The horizontal axis distinguishes whether the intervention would accomplish primary, secondary, or



Source: Authors.

Figure 3.1 Causal Pathways for LDD

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.
- 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.

Table 3.2 Classification of Interventions to Prevent LDD

	Primary (prevention of condition that can lead to disability)	Secondary (prevention of disability once condition has occurred)	Tertiary (rehabilitation or prevention of further disability once disability has occurred)
Evidence for cost-effectiveness available for LMICs	Food fortification (*folic acid* and iodine[a]) Rubella vaccine[a] 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		*Prenatal screening for DS and prevention of DS births* *Newborn screening for metabolic disorders followed by interventions to prevent disability*	
Evidence for cost-effectiveness not available, but cost-effectiveness can be estimated from existing data	Malaria prevention[b]	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	*Community-based rehabilitation*

Note: Italicized text represents somewhat detailed consideration of cost-effectiveness included in this chapter.
a. Covered in chapter 56 of DCP2, but chapter emphasis is not on implications for preventing developmental disabilities.
b. Covered in detail in chapter 21 of DCP2.

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 μg 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 μg 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_{12} 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 μg of FA per 100-grams of the food item) should be adjusted for storage and other losses so that a daily dose of 400 μg 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 μg 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 μg to 240-μg per 100 grams of cereal. So that women receive a daily dose of 400 μg, 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.

Table 3.3 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.

Life Expectancy and Quality of Life. Life expectancy for children with DS is substantially lower than that of the general 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 3.3 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 3.4. 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 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 Tompkinison 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

Table 3.4 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
East Asia and the Pacific										
Indonesia	10	5.61	7,546,188	1,345,851	5.05	7,556,281	1,497,390	14.88	36.0	7.13
Europe and Central Asia										
Hungary	56	31.40	7,574,655	241,237	28.26	7,631,174	270,041	38.31	35.98	1.27
High-income countries										
Canada	120.79	67.73	7,614,750	112,433	60.95	7,736,658	126,926	36.09	35.96	0.59
Latin America and the Caribbean										
Argentina	160	89.71	7,639,014	85,150	80.74	7,800,496	96,612	22.50	35.94	0.45
Middle East and North Africa										
Israel	100	56.07	7,601,884	135,579	50.46	7,702,810	152,643	22.14	35.96	0.71
South Asia										
Pakistan	440	246.71	7,812,290	3,1666	222.04	8,256,364	37,185	4.12	35.84	0.16
Sub-Saharan Africa										
South Africa	210	117.75	7,669,956	65,139	105.9	7,881,901	74,377	16.46	35.92	0.34

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.

Table 3.5 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$)	Cost savings (US$)
East Asia and the Pacific						
Thailand	23.94	22.74	2,236,661	98,366	4,342,987	2,106,326
Europe and Central Asia						
Estonia	34.97	33.22	2,407,937	72,492	6,344,406	3,936,468
High-income countries						
United States	25.00	23.75	2,253,200	94,872	4,536,250	2,283,050
Latin America and the Caribbean						
Mexico	40.7	38.67	2,496,991	64,580	7,385,022	4,888,032
Middle East and North Africa						
Saudi Arabia	36.25	34.43	2,427,813	70,509	6,576,658	4,148,845
South Asia						
Pakistan	100.00	95.00	3,417,801	35,977	18,145,000	14,727,199
Sub-Saharan Africa						
South Africa	24.13	22.93	2,239,768	97,686	4,379,292	2,139,524

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 3.5 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 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 3.5 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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Chapter **4**

Alcohol

Jürgen Rehm, Dan Chisholm, Robin Room, and Alan D. Lopez

This chapter provides an overview of epidemiology of alcohol-use and health consequences as well as introducing cost-effectiveness interventions to reduce alcohol-related harm.

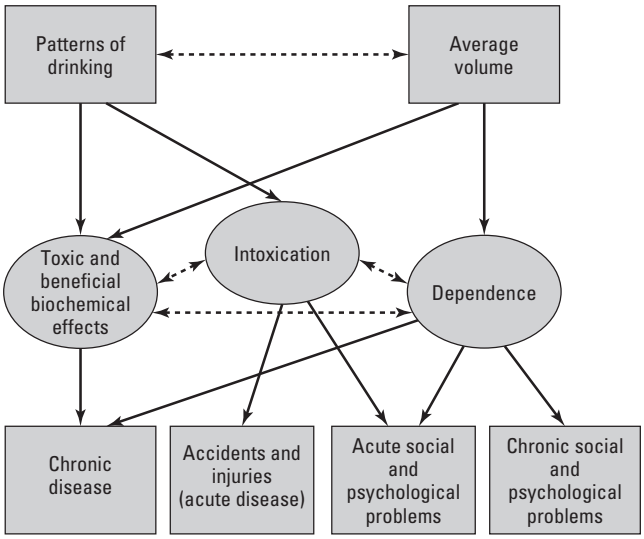
EPIDEMIOLOGY OF ALCOHOL USE AND ALCOHOL-RELATED DISEASE CONDITIONS

Alcoholic beverages and the problems they engender have been familiar fixtures in human societies since the beginning of recorded history. Because alcohol is causally related to more-than 60 International Classification of Diseases codes (Rehm, Room, Graham, and others 2003), disease outcomes are among the most important alcohol-related problems. Depending on the pattern of consumption, alcohol is also protective against diseases, most important among them, coronary heart disease (Rehm, Sempos, and Trevisan 2003). However, the net effect is negative, and 4 percent of the global burden of disease is attributable to alcohol, or about as much death and disability globally as is attributable to tobacco and hypertension (Ezzati and others 2002; WHO 2002). Alcohol thus constitutes a serious public health problem (Room, Babor, and Rehm 2005). Evidence-based preventive measures are available at both the individual and the population levels, with alcohol taxes, restrictions on alcohol availability, and drinking-and-driving countermeasures among the most effective policy options (Babor and others 2003). This chapter reviews the cost-effectiveness of different interventions in developing regions of the world.

Dimensions of Alcohol Related to Disease

The relationship between alcohol consumption and health and social outcomes is complex and multidimensional (Rehm and others 2004). As figure 4.1 shows, alcohol consumption is linked to acute and long-term health and social consequences through three intermediate mechanisms—toxic and beneficial biochemical effects, intoxication, and dependence (Babor and others 2003; Rehm, Room, Graham, and others 2003)—as follows:

- *Toxic and beneficial biochemical effects.* These effects of alcohol consumption may influence chronic disease in either beneficial or harmful ways. Accepted beneficial effects include the influence of moderate drinking on coronary heart disease through reduction of plaque deposits in arteries, protection against blood clot formation, and promotion of blood clot dissolution (Zakhari 1997). Examples of harmful effects include increased risk for high blood pressure and for liver damage (Rehm, Room, Graham, and others 2003) and direct toxic effects on acinar cells triggering pancreatic damage (Apte, Wilson, and Korsten 1997) or hormonal disturbances (Emanuele and Emanuele 1997). These are just examples, because alcohol exposure is associated with a multitude of toxic effects on different organs.
- *Intoxication.* Alcohol intoxication is a powerful mediator for acute health outcomes, such as accidental or intentional injuries or deaths, although intoxication can also be implicated in chronic health and social problems and in certain forms of heart disease. The subjective feeling of intoxication is mainly caused by the effects of alcohol on the central nervous system, and these effects are felt and can be measured even at light to moderate consumption levels (Eckardt and others 1998).
- *Dependence.* Alcohol dependence is a clinical disorder in its own right, but it is also a powerful mechanism sustain-



Source: Adapted from Babor and others 2003.

Figure 4.1 Model of Alcohol Consumption, Intermediate Outcomes, and Long-Term Consequences

ing alcohol consumption and mediating its impact on both chronic and acute physiological and social consequences of alcohol (Drummond 1990). In the quantitative analyses reported in this chapter, alcohol dependence—and alcohol-use disorders (AUDs) in general—will be considered only as a health outcome related to high-risk alcohol use.

This chapter, including the section on the cost-effectiveness of interventions, focuses primarily on health consequences, although later it briefly discusses the social consequences of high-risk drinking and recommended interventions. The epidemiological calculations are taken from Ezzati and others' (2002) comparative risk analysis (CRA) and the World Health Organization (WHO) assessment of the global burden of disease (WHO 2002). (For further information, see Mathers and others 2003; Rehm, Rehn, and others 2003; Rehm, Room, Graham, and others 2003; Rehm, Room, Monteiro and others 2003; Rehm and others 2004). The CRA defines alcohol exposure using two measures: the average volume of alcohol consumption and patterns of drinking (figure 4.1). It then relates these exposure measures to disease outcomes.

The average volume of consumption has been the conventional measure of exposure in alcohol epidemiology (Bruun and others 1975) and has been linked to many disease categories following the seminal work of English and others (1995; see also Rehm, Room, Graham, and others 2003). Patterns of drinking have been linked mainly to two categories of disease outcome: acute effects of alcohol (such as accidental and intentional injuries) and cardiovascular outcomes (mainly coronary heart disease). The CRA defines patterns of drinking primarily in terms of high-risk drinking occasions and also in terms of drinking in public settings and the proportion of drinking that occurs outside of meals (for further details, see Rehm and others 2004).

Epidemiology of High-Risk Alcohol Use

The intervention analyses presented in this chapter focus on average high-risk drinking, although patterns of drinking were also incorporated into the disease burden calculations. High-risk drinking is defined in sex-specific terms as drinking 20-grams per day or more of pure alcohol on average for females and 40 grams per day or more of pure alcohol on average for males (a bottle of table wine contains about 70 grams of pure alcohol). This definition of high-risk drinking is fairly standard in alcohol epidemiology and was first introduced by English and others (1995) on the basis of Australian guidelines. Originally, English and others (1995) used two categories: *hazardous drinking* (defined as drinking between 20 and 40 grams per day of pure alcohol on average for females and between 40 and 60 grams per day of pure alcohol for males) and *harmful drinking* (defined as drinking 40 grams per day or more of pure alcohol on average for females and 60 grams per day or more of pure alcohol on average for males). These categories have been used in almost every comprehensive meta-analysis on alcohol and disease since 1995 (see Rehm, Room, Graham, and others 2003 for an overview). However, critics asserted that the terms *hazardous drinking* and *harmful drinking* were not neutral; thus, the CRA uses drinking categories II and III, referring to the term *high-risk drinking* when both categories are considered together. High-risk drinking thresholds differ by sex because the risk for chronic disease is related to lower volumes of drinking for women than for men; thus, the thresholds for high-risk drinking were set to reflect an approximately similar risk of chronic disease.

Table 4.1 shows the distribution of high-risk drinking by age and by World Bank region. The table excludes the Middle East and North Africa because prevalence rates of high-risk drinking are considerably lower than 1 percent and this situation is unlikely to change in the near future.

Calculating the burden of high-risk alcohol use that is avertable by means of effective interventions requires additional epidemiological data—in particular, rates of incidence to and remission from high-risk alcohol use and the relative fatality of high-risk alcohol users compared with non-high-risk alcohol users. We derived remission rates from studies of natural recovery from alcohol problems, which found an average of 10.9 years to remission (Sobell, Ellingstad, and Sobell 2000), with an adjustment of plus 20 percent for older age groups and minus 20 percent for younger age groups. We set the relative risk of mortality for high-risk alcohol users age 15 to 44 at 2.5 and the relative risk for older age groups at 1.3 for men and 1.4 for women (Gmel, Gutjahr, and Rehm 2003; Rehm, Gutjahr, and Gmel 2001). Using WHO disease-modeling software, we derived an internally consistent epidemiological profile of current high-risk alcohol use in each region, including specifications of incidence and the relative risk of mortality, with currently observed rates of prevalence, remission, and risk of mortality as inputs. A final input parameter is the disability level for high-risk alcohol use, which we estimated at 0.154 (where zero equals no disability); this is a weighted

Table 4.1 Prevalence of High-Risk Drinking by Gender, Age Group, and Region, 2000
(percentage of the population)

Region	Gender	Age group (years)				
		15–29	30–44	45–59	60–69	70+
Europe and Central Asia	Male	20.8	18.7	21.4	15.2	8.1
	Female	11.2	10.4	11.5	7.9	5.7
Latin America and the Caribbean	Male	9.7	11.1	10.6	7.9	3.4
	Female	6.8	7.5	6.5	5.8	3.1
Sub-Saharan Africa	Male	10.4	14.3	12.9	11.3	8.4
	Female	3.1	4.7	5.1	3.2	2.2
East Asia and the Pacific	Male	6.2	7.5	7.1	6.5	5.0
	Female	0.3	0.2	0.1	0.1	0.0
South Asia	Male	0.8	2.5	0.3	0.1	0.0
	Female	1.2	0.4	0.4	0.0	0.0
High-income countries	Male	18.0	17.9	16.2	10.9	7.6
	Female	10.9	8.7	9.8	6.8	5.4

Source: Authors' calculations based on Rehm, Rehn, and others 2003 and Rehm and others 2004.
Note: The criteria for high-risk drinking were set sex specific (for details see text).

average based on the severity breakdown of high-risk drinkers from the CRA (80 percent category II, or hazardous; 20-percent category III, or harmful). The preference values for these health states of 0.11 and 0.33, respectively, are derived from Stouthard, Essink-Bot, and Bonsel (2000).

Relationship between High-Risk Drinking and AUDs

Assessing the relationship between high-risk drinking and AUDs is not a straightforward exercise. Even though high-risk drinking over a long period entails the risk of AUDs, that all people with AUDs are also high-risk drinkers does not automatically follow. First, neither the definition of alcohol dependence nor WHO's (1993) definition of harmful use includes actual consumption levels. An individual is considered dependent if at least three of the following criteria apply:

- strong desire or compulsion to take the substance
- impaired control and physiological withdrawal if the substance is reduced or ceased
- tolerance to the effects of the substance
- preoccupation with use of the substance
- persistent use despite clear evidence of harmful consequences.

By contrast, harmful alcohol use is defined as a pattern of use that is causing damage to physical or mental health. Thus, whereas many of these criteria are associated with high-risk alcohol use, no strict classificatory rule indicates that people with AUDs are a subcategory of high-risk drinkers.

Second, the prevalence of AUDs is often derived from surveys, where the operationalization usually requires that three symptoms be present in a lifetime and at least one of these criteria be present within the past 12 months (see, for example, Demyttenaere and others 2004, table 2). Thus individuals may be categorized as alcohol dependent even if they are currently abstaining from alcohol.

Third, qualitative studies across a wide range of cultures have found that the criteria used for diagnosing AUDs often have different meanings and implications in different cultural settings (Room and others 1996; Schmidt and Room 1999). For instance, in the United States over the past decade, the level of reported AUDs increased despite decreases in high-risk drinking (Grant and others 2004). This fact has been explained in terms of changes in drinking norms and social attitudes during a period when the United States has become a "drier" culture. Thus, the measurement of AUDs is quite complex and culturally dependent. Moreover, AUDs are only one outcome of alcohol consumption and, in many parts of the world, not the most important one. As a result, we decided to focus on high-risk alcohol consumption rather than AUDs.

Relationship between Alcohol Use and Disease Categories

The exact procedures for quantifying the risk of disease attributable to alcohol are described in detail elsewhere (Rehm, Room, Graham, and others 2003; Rehm and others 2004). For-most chronic disease categories, investigators have derived alcohol-attributable fractions of disease by combining prevalence and relative risk estimates based on meta-analyses (Corrao and others 2000; English and others 1995; Gutjahr, Gmel, and Rehm 2001; Ridolfo and Stevenson 2001; Single and-others 1996, 1999). For depression, we drew alcohol-attributable fractions from mental health surveys, looking at the rates of comorbidity and the order of onset of depression and alcohol disorders. For coronary heart disease, we modeled the interaction of average volumes and patterns of drinking based on multilevel analyses that include temporal information as covariates (Gmel, Rehm, and Frick 2003; Rehm and others 2004). For the final estimates, we based alcohol-attributable fractions on these multilevel results for all countries, except for developed countries with relatively

favorable drinking patterns (Australia, Japan, and countries in North America and Western Europe), which are not discussed here because the focus is on developing countries. For injuries, we took a similar multilevel approach to quantify the interaction of the average volume of consumption and patterns of drinking in determining alcohol-attributable fractions (Rehm and others 2004).

Thus the analysis includes the following major disease categories:

- chronic disease
  - cancer (mouth and oropharyngeal, esophageal, liver, female breast)
  - neuropsychiatric diseases (AUDs, unipolar major depression, epilepsy)
  - diabetes
  - cardiovascular diseases (hypertensive diseases, coronary heart disease, stroke)
  - gastrointestinal diseases (cirrhosis of the liver)
  - conditions arising during the perinatal period (low birthweight)
- injury
  - unintentional injury (motor vehicle accidents, drowning, falls, poisonings, other unintentional injuries)
  - intentional injury (self-inflicted injuries, homicide, other intentional injuries).

We did not include other disease categories that are clearly alcohol-related, such as fetal alcohol syndrome, because the current analysis was based on the CRA and was, thus, limited to the global burden-of-disease categories.

Social Determinants of Exposure and Risk

Alcohol-specific risks to health are in part determined and modified by social determinants. For example, Harrison and Gardiner (1999) find that for men age 25 to 69 in England and Wales in 1988–94, those in the lowest socioeconomic status category, unskilled labor, had a 15-fold greater risk for alcohol-related mortality than professionals in the highest category had. These differences cannot be explained by the overall volume of drinking, which actually tended to be greater for those in higher socioeconomic groups. Rather, the differences can be explained by the fact that more of the drinking of those in lower socioeconomic status categories is in high-risk patterns; that is, depending on the use values for drinking in the culture, poor drinkers may see little point in wasting resources on drinking that is not to intoxication. Poorer drinkers are also likely to be less protected physically and socially from possible harm arising from drinking, such as injuries and chronic and infectious diseases. Mäkelä (1999) finds that multiple dimensions of socioeconomic status are required to capture all the adverse interactions of socioeconomic status with alcohol-related mortality.

A critical macroeconomic question is how a country's level of economic development is related to alcohol-related risks to health. The impact of alcohol on disease and mortality may be more potent in countries with greater poverty and nutritional deficiencies (Isichei, Ikwuagu, and Egbuta 1993; Room and others 2002, 119–30). However, most of the risk relationships between alcohol and disease have been derived from studies in established market economies, and the extent of systematic research is currently insufficient to allow quantification of this phenomenon. As a result, the estimated disease burden cited here may be considered as a lower-bound estimate of the actual alcohol-attributable disease burden in developing countries.

BURDEN OF DISEASE RELATED TO HIGH-RISK ALCOHOL USE

In the following sections, the procedures to estimate alcohol-related burden of disease are described, as well as the limitations of the used approach.

Determining the Alcohol-Related Burden of Disease

Table 4.2 breaks down alcohol-attributable disability-adjusted life years (DALYs) by disease category and World Bank region using a constant 3 percent per year discount rate, but with no age weighting. Results differ from those of the CRA (Ezzati and others 2002; Rehm and others 2004; WHO 2002) because of the use of non-age-weighted DALYs.[1]

Determining the Burden of Disease Related to High-Risk Alcohol Consumption

In determining the burden of disease related to high-risk alcohol consumption, we first divided the burden of disease between chronic and acute disease. For chronic disease, we assume that almost the entire disease burden reported in the CRA is associated with high-risk alcohol use. Indeed, the overall disease burden in the CRA is an underestimate, because drinking up to 20 grams per day of pure alcohol by females and up to 40 grams per day of pure alcohol by males is globally associated with a net beneficial effect in relation to chronic disease. However, this effect occurs mainly in countries with moderate drinking patterns (Rehm, Sempos, and Trevisan 2003), which tend to be high-income countries (Rehm, Rehn, and others 2003). Although high-risk but regular drinking patterns may also have some beneficial effects, such effects are not important in countries with binge drinking patterns. (For the association between alcohol and coronary heart disease, see McKee and Britton 1998; Puddey and others 1999; Rehm, Sempos, and Trevisan 2003; for consequences on modeling the regional burden of disease, see Rehm and others 2004.)

For injuries, which are considered to be acute outcomes, we started by separating out the proportion of injury not caused by high-risk drinking, which we accomplished by assuming that injuries are linearly related to per capita

Table 4.2 Alcohol-Attributable DALYs by Disease Category and World Bank Region, 2001
(thousands of DALYs)

Disease category	Europe and Central Asia	Latin America and the Caribbean	Sub-Saharan Africa	Middle East and North Africa	East Asia and the Pacific	South Asia	High-income countries	World
Chronic disease								
Maternal and perinatal conditions	12	7	39	1	2	29	6	105
Cancer	526	296	635	25	2,820	189	1,103	5,594
Neuropsychiatric	2,159	3,315	1,035	89	4,726	1,444	4,752	17,600
Vascular	2,639	926	556	40	1,751	1,199	–2,488	5,209
Other noncommunicable diseases	1,175	739	504	27	997	306	1,153	5,126
Subtotal chronic disease	6,511	5,283	2,769	182	10,296	3,167	4,526	33,634
Injury								
Unintentional	4,127	1,984	2,308	135	3,613	2,222	1,753	15,619
Intentional	1,822	1,872	1,074	9	927	567	571	6,755
Subtotal injury	5,949	3,856	3,382	144	4,540	2,789	2,324	22,374
Total DALYs attributable to alcohol	12,460	9,139	6,151	326	14,836	5,956	6,850	56,008
Total DALYs from all diseases	116,502	104,287	344,754	65,570	346,225	408,655	149,161	1,535,871
Proportion of DALYs attributable to alcohol (percent)	10.7	8.8	1.8	0.5	4.3	1.5	4.6	3.6

Source: Authors' calculations based on Rehm and others 2004 and WHO 2002.
Note: Negative DALYs can occur because certain patterns of alcohol have cardio-protective effects.

consumption (Rehm and others 2004).[2] This assumption is probably conservative, because high-risk drinkers in countries with binge drinking patterns are likely to have more frequent and intensive drinking occasions, and the risk of injury usually rises logarithmically with the amount of drinking on a specific occasion (see, for example, National Highway Traffic Safety Administration 1992). Following this initial calculation, we could calculate the proportion of per capita consumption related to high-risk drinking in each region, thereby determining the proportion of injury caused by high-risk drinking (table-4.3). Together with our calculation of the chronic disease burden attributable to high-risk alcohol use, this percentage enabled us to estimate the overall disease burden attributable to high-risk alcohol use: whereas 3.6 percent of the global burden was attributable to alcohol drinking generally, 2.8 percent was attributable to high-risk drinking.

Limitations of the CRA Approach

The CRA's estimates of the global and regional alcohol-related burden of disease are based on a number of assumptions, of which the following are the most crucial:

- The estimates of per capita consumption and unrecorded consumption for different countries do not contain substantial measurement error.
- The distribution of consumption as derived from surveys is similar to actual distribution in the population.
- The relationships between alcohol and chronic disease derived from meta-analyses of cohort and case-control studies are stable among countries and regions.

Some evidence indicates that per capita consumption can be reliably estimated, and information on this indicator is available for the vast majority of countries (Rehm, Rehn, and others 2003). With respect to survey information, reliability and worldwide coverage are lower. However, because the overall volume of consumption and, thus, the average volume per capita are based on production and sales estimates, the measure of the volume of drinking overall can be considered reliable. These factors leave the stability of relationships between alcohol and chronic disease as the most crucial part of our estimates. Some indications suggest that relative risks may not be the same in developing countries as in developed countries (for example, for tobacco and lung cancers, see Liu and others 1998). Thus, the CRA's estimates may be biased, most likely toward an overestimation of the impact of alcohol.

One additional problem pertains to the usual epidemiological approach as applied to alcohol. Most information about alcohol and chronic disease is derived from cohorts. Because cohorts are frequently not representative of the population as a whole, specific patterns of consumption such as binge drinking are often not represented, and thus their influence cannot be analyzed (Rehm, Gmel, and others 2003). Unfortunately, the patterns most often missing are those that are the most detrimental with respect to health; thus, the impact of alcohol on chronic diseases that are influ-

Table 4.3 DALYs Attributable to High-Risk Average Alcohol Consumption by Disease Category and Region, 2001
(thousands of DALYs)

Disease category	Europe and Central Asia	Latin America and the Caribbean	Sub-Saharan Africa	East Asia and the Pacific	South Asia	High-income countries	World
Total chronic disease	6,510	5,283	2,770	10,296	3,167	4,526	33,634
Total injury	3,149	1,500	1,693	1,532	514	1,092	9,207
Total DALYs attributable to high-risk alcohol consumption	9,659	6,783	4,463	11,828	3,681	5,618	42,841
Total DALYs from all diseases	116,502	104,287	344,754	346,225	408,655	149,161	1,535,871
Proportion of DALYs attributable to high-risk alcohol consumption	8.3	6.5	1.3	3.4	0.9	3.8	2.8

Source: Authors' calculations based on Rehm and others 2004 and WHO 2002.

enced by patterns of drinking other than average volumes is underestimated.

INTERVENTIONS FOR REDUCING HIGH-RISK DRINKING

The next two sections estimate the burden of disease attributable to high-risk alcohol consumption that is currently being averted or could be averted by a range of personal and nonpersonal intervention strategies and calculate the expected costs and cost-effectiveness of such interventions. Methods and analyses draw on Chisholm and others (2004), adjusted as necessary to conform to the analytical standards of this volume, including the specification of all costs in U.S. dollars rather than international dollars.

Population Model

We determined intervention effectiveness using a state transition population model (Lauer and others 2003), which traces the development of a regional population taking into account births, deaths, and the specified risk factor—in this case, high-risk alcohol use. In addition to population size and structure, the population model uses a number of epidemiological parameters (incidence and prevalence, remission, and cause-specific and residual rates of mortality) and assigns age- and gender-specific health state valuations to both the disease in question and to the nondiseased population. The output of the model is an estimate of the total healthy life years experienced by the population over a lifetime period (100 years).

We ran the model for a number of possible scenarios, including no intervention at all (natural history), current intervention coverage, and scaled-up coverage of current and possible new interventions. For the intervention scenarios, we used an implementation period of 10 years for an intervention program (after which epidemiological rates return to their natural history levels), from which we derived the number of additional DALYs averted each year compared with the case for no intervention at all. We discounted DALYs at 3 percent but did not age weight them.

Effectiveness

A number of interventions have been evaluated and shown to-be effective in reducing alcohol use, yet their level of implementation remains low in all but a handful of countries and their potential effect on population-level health has rarely been assessed. By contrast, some interventions without clearly established effects continue to be widely used, including, for example, mass media public information campaigns and school-based education aimed at reducing alcohol consumption. Recent reviews of measures to reduce alcohol misuse have assessed the quality of the evidence for four types of interventions specifically aimed at reducing high-risk alcohol use (Babor and others 2003; Ludbrook and others 2002):

- policy and legislative interventions, including taxation of alcohol sales, laws on drunk driving, restrictions on retail outlets, and controls on advertising
- measures to better enforce these interventions, such as random breath testing of drivers
- mass media and other awareness campaigns
- brief interventions with individual high-risk drinkers.

On the basis of these reviews, we included the following strategies and intervention effects in our analysis: drinking-and-driving legislation and random breath testing, taxation of-alcoholic beverages, reduced hours of sale in retail outlets, and advertising bans (included as population-based interventions) and so-called brief interventions (included as interventions aimed at personal behavior). We considered including one other intervention strategy—mass media or school-based awareness campaigns—but omitted it in the final analysis on the grounds that evidence for its effectiveness was weak, both in terms of methodological quality and in terms of its effect on consumption (as opposed to

transfer of information or knowledge alone) (Babor and others 2003; Edwards and others 1994; Foxcroft and others 2003; Foxcroft, Lister-Sharp, and Lowe 1997; Ludbrook and others 2002).

Drunk-Driving Legislation and Random Breath Testing. Drunk-driving laws and reinforcement policies, such as random breath testing of drivers, influence fatal and nonfatal traffic injuries among both high-risk alcohol users and other members of the population, such as passengers and pedestrians. We assessed two independent effects on alcohol-related traffic injuries, but note that evidence for these effects comes from the developed countries, where road infrastructures and driving patterns may differ significantly from those in the developing world. The first intervention was drunk-driving laws, estimated to reduce traffic fatalities by 7 percent if widely implemented across a region. The second was enforcement by random breath testing, estimated to reduce fatalities by 6 to 10 percent in regions partially implementing such a strategy and by 18 percent with wide implementation. The effect on nonfatal injuries was estimated to be a reduction of 15 percent (Peek-Asa 1999; Shults and others 2001). In each region, we applied these estimated effects to the proportion of total deaths and of years lived with a disability attributed to alcohol-related traffic accidents (table 4.4).

Taxation on Alcoholic Beverages. Excise taxation on alcoholic beverages primarily affects the incidence of drinking through reduced consumption. Effects are measured in terms of price elasticity, which relates the change in consumption to the size of the price increase (table 4.5). We derived price elasticities, adjusted downward by one-third to reflect possible reduced price responsiveness among high-risk drinkers, with reference to preferred type of alcoholic beverage (beer, wine, or spirits) by region, built up from country-level data (WHO 2003b). This downward adjustment of price elasticities for high-risk drinkers is a conservative approach; most of the literature found similar effects on high-risk and dependent drinkers as on social users (Babor and others 2003; see also Farrell, Manning, and Finch 2003).

Price elasticities ranged from –0.3 for the most preferred beverage category to –1.5 for the least preferred (Babor and others 2003; Levy and Ornstein 1983). For a beer-drinking region where wine is the second-most preferred beverage type, for example, elasticities were set as follows: beer –0.3, wine –1.0, distilled spirits –1.5. We performed sensitivity analysis around these elasticities. We evaluated three rates of excise tax on alcoholic beverages: the current rate of tax, a 25 percent increase over the current rate, and a 50 percent increase over the current rate. We adjusted estimated reductions in the incidence of high-risk alcohol use by the observed or expected level of unrecorded consumption resulting from illicit production and smuggling (for instance, an estimated 35 percent of alcohol consumption in Eastern Europe and Central Asia is unrecorded, a proportion that was modeled to increase by 10 to 15 percent with the tax increases). In regions with rates of unrecorded consumption already greater than 50 percent (South Asia and Sub-Saharan Africa), tax increases can actually have a regressive impact on incidence if accompanied by a rise in the already high level of unrecorded (and therefore untaxed) consumption.

Reduced Hours of Sale in Retail Outlets. Access to and availability of alcohol can be dramatically reduced by prohibition or rationing, but implementing and sustaining such strategies without adverse effects, such as black markets and poisonings from home-produced alcohol, present considerable challenges. A more modest strategy is to reduce the hours of sale of retail outlets selling alcoholic beverages (for example, no sales for off-premise consumption for a 24-hour period at the weekend), which in Scandinavia has reduced consumption and alcohol-related harm (Leppänen 1979; Nordlund 1984; Norström and Skog 2003). On the basis of these studies, we modeled a modest reduction of 1.5 to 3.0 percent in the incidence of high-risk drinking and 1.5 to 4.0 percent in alcohol-related traffic fatalities, depending on the regional pattern of drinking, with the largest effects in regions with the highest levels of high-risk drinking occasions.

Advertising Bans. Public health specialists are becoming increasingly interested in the effect of a comprehensive ban on alcohol advertising, including advertising on television and through radio and billboards. However, available evidence from econometric studies suggests a modest effect on consumption at best, even for a comprehensive ban, arguably because of the continuing presence of other alcohol marketing strategies, such as product placement or event sponsorship (Grube and Agostinelli 2000; Saffer 2000; Saffer and Dave 2002). Here we consider the potential effects of a comprehensive advertising ban (television, radio, and billboards) by modeling a 2 to 4 percent reduction in the incidence of high-risk alcohol use, depending on regional drinking patterns.

Brief Interventions. We modeled brief interventions (such as physician advice provided in primary health care settings), which involve a small number of education sessions and psychosocial counseling, to influence the prevalence of high-risk drinking by increasing remission and reducing disability. Efficacy reviews of brief interventions reveal an estimated 13 to 34 percent net reduction in consumption among high-risk drinkers (Higgins-Biddle and Babor 1996; Moyer and others 2002; Whitlock and others 2004), which, if applied to the total population at risk, would reduce the overall prevalence of high-risk drinking by 35 to 50 percent, equivalent to a 14 to 18-percent improvement in the rate of recovery over no treatment at all. After taking into account adherence (70 percent) and potential treatment coverage in the population (50 percent of high-risk drinkers), however, we estimated remission rates to be between 4.9 and 6.4 percent higher than natural history rates.

Table 4.4 Effectiveness of Drinking-and-Driving Legislation and Its Enforcement
(per 100,000 population)

World Bank region	WHO subregion	Sex	Attributable fractions (per 100,000 deaths)		Effectiveness of drinking-and-driving laws and random breath testing	
			Deaths attributed to traffic accidents[a]	Deaths attributed to alcohol-related traffic accidents[a]	Reduced deaths (per 100,000)	Reduced years lost due to disability (per 100,000)
Europe and Central Asia	Europe B	Male	1,473	657	141	77
		Female	542	74	16	6
	Europe C	Male	2,197	1,396	299	193
		Female	799	223	48	30
Latin America and the Caribbean	Americas B	Male	4,358	2,053	439	148
		Female	1,514	220	47	12
	Americas D	Male	2,599	861	184	64
		Female	1,093	101	22	6
Sub-Saharan Africa	Africa D	Male	2,159	417	89	43
		Female	1,079	90	19	9
	Africa E	Male	2,075	803	172	107
		Female	1,027	123	26	17
East Asia and the Pacific	Southeast Asia B	Male	7,809	1,993	427	164
		Female	2,343	127	27	8
	Western Pacific B	Male	3,629	723	155	66
		Female	1,790	157	34	12
South Asia	Southeast Asia D	Male	3,689	591	126	45
		Female	1,451	53	11	3

Source: Deaths attributed to traffic accidents: WHO 2003a; deaths attributed to alcohol-related traffic accidents: Rehm and others 2004.
B = low child mortality, low adult mortality; C = low child mortality, high adult mortality; D = high child mortality, high adult mortality; E = high child mortality, very high adult mortality.
a. Percentages for all age groups combined shown here.

Costs

Costs covered in the analysis include program-level costs associated with running the intervention (such as administration, training, and media costs) and patient-level costs (such as costs of primary care visits). Program-level costs include resource inputs used in the production of an intervention at a level above that of the patient or providing facility, such as central planning, policy, and administration functions, as well as resources devoted to preventive programs, such as the enforcement of drunk-driving legislation by police officers (Johns and others 2003). We derived estimated quantities of resources required to implement each intervention for 10 years at the national, provincial, and district levels with reference to the region's prevailing characteristics—for example, the stability and efficiency of tax systems, the volume of traffic (for breath testing), and the strength of antidrinking sentiment as indicated by existing alcohol controls (advertising bans, restricted sales). In this analysis, patient-level resource inputs used in the provision of a given health care intervention (for example, hospital inpatient days, outpatient visits, medications, and laboratory tests) are relevant only to brief interventions. We estimated an average of four primary care visits per year for the intervention itself, plus an additional 0.33 outpatient visits (20 percent ×1.67 visits) and 0.25 inpatient days (5 percent × 5 days) (see, for example, Fleming and others 2000). We applied these patient-level resource inputs to the 50 percent of prevalent high-risk alcohol users in receipt of brief advice in year 1 and (because we model an enduring effect for 10 years) year 6 and to the 50 percent of incident cases in years 2 to 5 and 7 to 10. Note that, throughout, the costing does not include possible offsetting revenues for the government, for instance, from drunk-driving convictions and, in particular, from the revenues likely to result from increased alcohol taxes.

Unit costs and prices of program- and patient-level resource inputs include the salaries of central administrators; the capital costs of vehicles, offices, and furniture; and the cost per outpatient visit (see chapter 7 of DCP2 for an overview of the costing methodology, plus prices by World Bank region). All costs are expressed in U.S. dollars for 2001 and are discounted at an annual rate of 3 percent.

COST-EFFECTIVENESS OF INTERVENTIONS

In the following section, we provide results relating to the population-level health effects, costs, and cost-effectiveness of the evidence-based interventions previously reviewed.

Table 4.5 Effect of Taxation on the Incidence of High-Risk Alcohol Use

World Bank region	WHO subregion[a]	Prevalence by preferred beverage (percent)			Rate of taxation by preferred beverage (percent)				Price increases (percent)[b]			Nonrecorded or untaxed consumption (percent)	Effect (percent)[c]		
		Most preferred	Next preferred	Least preferred	Most preferred	Next preferred	Least preferred		Elasticity –0.3, most preferred	Elasticity –1.0, next preferred	Elasticity –1.5, least preferred		Baseline	Lower[d]	Upper[e]
Europe and Central Asia	Europe B	0.45 (spirits)	0.30 (beer)	0.25 (wine)	0.29	0.13	0.12	(current rate)	–0.04	–0.08	–0.11	0.34 (current rate)	–0.05	–0.03	–0.06
					0.36	0.16	0.15	(25 percent increase)	–0.05	–0.09	–0.13	0.37 (10 percent increase)	–0.05	–0.04	–0.07
					0.44	0.20	0.18	(50 percent increase)	–0.06	–0.11	–0.15	0.39 (15 percent increase)	–0.06	–0.04	–0.08
	Europe C	0.68 (spirits)	0.21 (beer)	0.11 (wine)	0.65	0.13	0.25	(current rate)	–0.08	–0.08	–0.20	0.36 (current rate)	–0.06	–0.04	–0.08
					0.81	0.16	0.31	(25 percent increase)	–0.09	–0.09	–0.24	0.40 (10 percent increase)	–0.06	–0.05	–0.09
					0.98	0.20	0.38	(50 percent increase)	–0.10	–0.11	–0.27	0.42 (15 percent increase)	–0.07	–0.05	–0.09
Latin America and the Caribbean	Americas B	0.53 (beer)	0.30 (spirits)	0.17 (wine)	0.16	0.49	0.22	(current rate)	–0.03	–0.22	–0.18	0.29 (current rate)	–0.08	–0.06	–0.10
					0.20	0.61	0.28	(25 percent increase)	–0.03	–0.25	–0.22	0.32 (10 percent increase)	–0.09	–0.06	–0.12
					0.24	0.74	0.33	(50 percent increase)	–0.04	–0.28	–0.25	0.34 (15 percent increase)	–0.10	–0.07	–0.13
	Americas D	0.58 (spirits)	0.39 (beer)	0.03 (wine)	0.26	0.21	0.25	(current rate)	–0.04	–0.12	–0.20	0.22 (current rate)	–0.06	–0.04	–0.08
					0.33	0.26	0.31	(25 percent increase)	–0.05	–0.14	–0.24	0.24 (10 percent increase)	–0.07	–0.05	–0.09
					0.39	0.32	0.38	(50 percent increase)	–0.06	–0.16	–0.27	0.25 (15 percent increase)	–0.08	–0.05	–0.10
Sub-Saharan Africa	Africa D	0.79 (beer)	0.16 (spirits)	0.05 (wine)	0.36	0.41	0.35	(current rate)	–0.05	–0.19	–0.26	0.77 (current rate)	–0.02	–0.01	–0.03
					0.45	0.51	0.44	(25 percent increase)	–0.06	–0.23	–0.30	0.85 (10 percent increase)	–0.01	–0.01	–0.02
					0.54	0.62	0.53	(50 percent increase)	–0.07	–0.25	–0.34	0.89 (15 percent increase)	–0.01	–0.01	–0.02
	Africa E	0.49 (beer)	0.30 (spirits)	0.21 (wine)	0.28	0.50	0.38	(current rate)	–0.04	–0.22	–0.28	0.47 (current rate)	–0.08	–0.06	–0.10
					0.35	0.63	0.48	(25 percent increase)	–0.05	–0.26	–0.32	0.52 (10 percent increase)	–0.08	–0.06	–0.11
					0.42	0.75	0.57	(50 percent increase)	–0.06	–0.29	–0.36	0.55 (15 percent increase)	–0.09	–0.06	–0.11
East Asia and the Pacific	Southeast Asia B	0.88 (spirits)	0.12 (beer)	0.00 (wine)	0.30	0.40	0.00	(current rate)	–0.05	–0.19	0.00	0.36 (current rate)	–0.04	–0.03	–0.05
					0.38	0.50	0.00	(25 percent increase)	–0.05	–0.22	0.00	0.39 (10 percent increase)	–0.05	–0.03	–0.06
					0.45	0.60	0.00	(50 percent increase)	–0.06	–0.25	0.00	0.41 (15 percent increase)	–0.05	–0.03	–0.07
	Western Pacific B	0.88 (spirits)	0.11 (beer)	0.01 (wine)	0.17	0.09	0.11	(current rate)	–0.03	–0.06	–0.10	0.27 (current rate)	–0.02	–0.02	–0.03
					0.21	0.11	0.14	(25 percent increase)	–0.04	–0.07	–0.12	0.32 (10 percent increase)	–0.03	–0.02	–0.04
					0.26	0.14	0.17	(50 percent increase)	–0.04	–0.08	–0.14	0.31 (15 percent increase)	–0.03	–0.02	–0.04
South Asia	Southeast Asia D	0.89 (spirits)	0.11 (beer)	0.00 (wine)	0.40	0.25	0.00	(current rate)	–0.06	–0.13	0.00	0.79 (current rate)	–0.01	–0.01	–0.02
					0.50	0.31	0.00	(25 percent increase)	–0.07	–0.16	0.00	0.87 (10 percent increase)	–0.01	–0.01	–0.01
					0.60	0.38	0.00	(50 percent increase)	–0.08	–0.18	0.00	0.91 (15 percent increase)	–0.01	–0.01	–0.01

Source: WHO 2003b.

a. B = low child mortality, low adult mortality; C = low child mortality, high adult mortality; D = high child mortality, high adult mortality; E = high child mortality, very high adult mortality.

b. Price rise caused by tax = [percentage of tax/(1 + percentage of tax)] × elasticity × 2/3 (high-risk drinkers less responsive).

c. Effect = sum of (prevalence × price increase) for each beverage × (1 – percentage of unrecorded consumption).

d. Lower-range elasticities = –0.2, –0.7, –1.2.

e. Upper-range elasticities = –0.4, –1.3, –2.0.

Population-Level Effects

Except for random breath testing, two-thirds of the total population-level health gain from these interventions was among males (the proportion for random breath testing rises to 80 to 90 percent because of the higher proportion of deaths and injuries attributed to traffic accidents among men). A clear difference is also apparent between regions with relatively high rates of high-risk alcohol use (that is, prevalence in the total population greater than 5 percent) and regions with generally low levels of high-risk drinking (that is, less than 2 percent).

As shown in table 4.6, in the three regions with a higher prevalence of high-risk alcohol use—Europe and Central Asia, Latin America and the Caribbean, and Sub-Saharan Africa—the most effective interventions were taxation and brief physician advice to individual high-risk drinkers, with each averting more than 500 DALYs per million population per year. The remaining control strategies—random breath testing, reduced access to alcoholic beverage retail outlets, and a comprehensive advertising ban—mainly produced effects in the range of 200 to 400 DALYs averted per million population per year. In the two regions with lower rates of high-risk drinking (particularly among the female population), by contrast, the burden that is avertable through taxation is very much reduced (10 to 100 DALYs averted per million population per year). In South Asia, the most effective intervention is enforcement of drinking-and-driving laws by means of random breath testing, because of the higher rate of traffic-related injuries than elsewhere as well as the low levels of high-risk drinking.

Population-Level Costs

Table 4.7 summarizes the costs and cost-effectiveness of each intervention and of two combination strategies by region. The most costly interventions to implement in all regions were random breath testing and brief physician advice in primary care. The higher costs of brief advice stem from a combination of patient-level costs in the provision of the intervention itself (an average annual cost of US$7 to US$20 per treated case), plus program costs associated with administration and training primary care providers (15 to 40 percent of total costs). Random breath testing is also a relatively resource-intensive intervention to implement because of the need for regular sobriety checkpoints administered by law enforcement officers. Other interventions, including taxation, had a per capita cost in the range US$0.02 to US$0.13, depending in part on the efficiency of the tax collection system and the degree of antidrinking sentiment.

Population-Level Cost-Effectiveness

Compared with doing nothing, taxation is the most cost-effective population-level strategy in Europe and Central Asia, Latin America and the Caribbean, and Sub-Saharan Africa, the three regions with a relatively high prevalence of high-risk drinking (table 4.7). At the current rate of tax, for example, each DALY averted costs US$104 to US$225, equivalent to 4,435 to 9,633 DALYs averted per US$1 million expenditure. Advertising bans had a cost per unit of effect similar to that of reduced access to sales outlets, US$134 to US$380, equivalent to 2,631 to 7,442 averted DALYs per US$1 million dollars expenditure, whereas random breath testing had the highest estimated cost per DALY averted: US$973 to US$1,856 per DALY, approximately 500 to 1,000 DALYs averted per US$1 million dollars expenditure. Brief physician advice provided in primary care settings had an average cost-effectiveness in the range of US$204 to US$502 per DALY averted, or close to 2,000 to 5,000 averted DALYs for every US$1 million expenditure.

Starting from the current situation in these regions, the most efficient strategies for reducing high-risk alcohol use would be tax increases (additional gains are obtained at virtually no extra cost because the costs of tax administration and enforcement remain relatively constant whatever the rate of tax), followed by the introduction or escalation of comprehensive advertising bans on alcohol products, reduced access to retail outlets, and the provision of brief interventions such as physician advice in primary care. Even a multifaceted strategy made up of an increase in taxation plus full implementation of the other interventions considered here has a favorable ratio of costs to health benefits.

In East Asia and the Pacific and South Asia, the two regions with lower rates of high-risk alcohol use, a comparison of intervention costs and effects to a no-intervention scenario reveals that current practice—namely, excise taxes on alcoholic beverages—is not the most efficient response to the existing burden of alcohol use. The reduced efficiency of taxation in these lower-prevalence regions is related both to the distribution of the fixed costs of administering and enforcing alcohol tax legislation across a smaller target population of drinkers and to underlying drinking patterns: more than 85 percent of all alcohol consumption falls into a single preferred drink category, spirits, which therefore diminishes the scope for reducing the consumption of less preferred but more elastic categories of alcoholic beverages. In South Asia, targeted strategies such as brief physician advice and random breath testing have the lowest cost per DALY averted (around US$500), while taxation policies are the most expensive at more than US$2,500 per DALY averted. In East Asia and the Pacific, the most cost-effective interventions are brief physician advice, a comprehensive ban on advertising, and reduced access to retail outlets (below US$250 per DALY averted).

Implications and Limitations of Sectoral Cost-Effectiveness Analyses

This cost-effectiveness analysis offers a new approach to generating economic evidence that can inform public health policy on alcohol in a wide range of cultural and epidemiological settings (Chisholm and others 2004). Resulting estimates of cost-effectiveness can inform policy makers not only by determining the efficiency of existing resource allocation and

Table 4.6 Population-Level Effects of Interventions to Reduce High-Risk Alcohol Use by World Bank Region

	Coverage[a] (percent)	Europe and Central Asia	Latin America and the Caribbean	Sub-Saharan Africa	East Asia and the Pacific	South Asia
Burden of disease (DALYs/million population)		20,241	12,894	6,685	6,263	2,652
Total effect (DALYs averted/ million population/year)						
Excise tax on alcoholic beverages (current situation)	*0.95*	685	586	697	83	13
Excise tax on alcoholic beverages (25 percent increase)	*0.95*	756	654	724	96	10
Excise tax on alcoholic beverages (50 percent increase)	*0.95*	828	719	764	109	8
Reduced access to alcoholic beverage retail outlets	*0.95*	441	287	386	203	32
Comprehensive advertising ban on alcohol	*0.95*	395	243	406	226	20
Random breath testing of motor vehicle drivers	*0.80*	284	307	197	181	125
Brief advice to heavy drinkers by a primary care physician	*0.50*	1,328	713	539	362	80
Combination: highest tax + brief advice		2,048	1,360	1,237	447	83
Combination: highest tax + advertising ban + random breath testing + brief advice		2,551	1,784	1,715	790	210
Reduction in current burden (percent)						
Excise tax on alcoholic beverages (current situation)	*0.95*	0.03	0.05	0.10	0.01	0.01
Excise tax on alcoholic beverages (25 percent increase)	*0.95*	0.04	0.05	0.11	0.02	0.00
Excise tax on alcoholic beverages (50 percent increase)	*0.95*	0.04	0.06	0.11	0.02	0.00
Reduced access to alcoholic beverage retail outlets	*0.95*	0.02	0.02	0.06	0.03	0.01
Comprehensive advertising ban on alcohol	*0.95*	0.02	0.02	0.06	0.04	0.01
Random breath testing of motor vehicle drivers	*0.80*	0.01	0.02	0.03	0.03	0.05
Brief advice to heavy drinkers by a primary care physician	*0.50*	0.07	0.06	0.08	0.06	0.03
Combination: highest tax + brief advice		0.10	0.11	0.19	0.07	0.03
Combination: highest tax + advertising ban + random breath testing + brief advice		0.13	0.14	0.26	0.13	0.08

Source: Chisholm and others 2004.

a. Refers to the modeled percentage of all high-risk drinkers exposed to the intervention.

practices, but also by identifying priorities for future alcohol control strategies. Furthermore, use of a common methodology enables comparison with cost per DALY estimates for other risk-factors or disease entities, which may constitute an important argument when considering priorities for the allocation of-scarce health care resources. However, the application of a broad sectoral approach using entire regions as the unit of analysis clearly limits the approach's use in specific country contexts, where demographic or epidemiological characteristics, as well as treatment costs and coverage, may not coincide with estimates for the region as a whole. In addition, extrapolation of the extent of intervention effects from relatively information-rich countries to other sociocultural settings lessens the precision of derived estimates of population-level health gains.

Although an ongoing analytical step is to calibrate results at-the country level, the primary purpose and utility of the sectoral approach is to identify interventions that are clearly

Table 4.7 Costs and Cost-Effectiveness of Interventions to Reduce High-Risk Alcohol Use by World Bank Region

	Coverage[a] (percent)	Europe and Central Asia	Latin America and the Caribbean	Sub-Saharan Africa	East Asia and the Pacific	South Asia
Total cost (US$ million/year/million population)						
Excise tax on alcoholic beverages (current situation)	*0.95*	0.10	0.13	0.07	0.04	0.04
Excise tax on alcoholic beverages (25 percent increase)	*0.95*	0.10	0.13	0.07	0.04	0.04
Excise tax on alcoholic beverages (50 percent increase)	*0.95*	0.10	0.13	0.07	0.04	0.04
Reduced access to alcoholic beverage retail outlets	*0.95*	0.10	0.10	0.06	0.03	0.03
Comprehensive advertising ban on alcohol	*0.95*	0.07	0.09	0.05	0.03	0.02
Random breath testing of motor vehicle drivers	*0.80*	0.53	0.47	0.19	0.18	0.07
Brief advice to heavy drinkers by a primary care physician	*0.50*	0.36	0.36	0.11	0.08	0.04
Combination: highest tax + brief advice		0.44	0.48	0.18	0.12	0.07
Combination: highest tax + advertising ban + random breath testing + brief advice		0.97	0.97	0.39	0.30	0.15
Cost-effectiveness relative to no intervention (US$/DALY averted)						
Excise tax on alcoholic beverages (current situation)	*0.95*	141	225	104	516	2,671
Excise tax on alcoholic beverages (25 percent increase)	*0.95*	127	202	100	447	3,654
Excise tax on alcoholic beverages (50 percent increase)	*0.95*	116	184	95	394	4,641
Reduced access to alcoholic beverage retail outlets	*0.95*	216	340	152	146	827
Comprehensive advertising ban on alcohol	*0.95*	185	380	134	123	1,123
Random breath testing of motor vehicle drivers	*0.80*	1,856	1,542	973	984	531
Brief advice to heavy drinkers by a primary care physician	*0.50*	270	502	204	224	462
Combination: highest tax + brief advice		216	350	143	269	845
Combination: highest tax + advertising ban + random breath testing + brief advice		381	546	229	383	707
DALYs averted/US$ million expenditure						
Excise tax on alcoholic beverages (current situation)	*0.95*	7,107	4,435	9,633	1,937	374
Excise tax on alcoholic beverages (25 percent increase)	*0.95*	7,847	4,953	10,007	2,239	274
Excise tax on alcoholic beverages (50 percent increase)	*0.95*	8,590	5,442	10,553	2,536	215
Reduced access to alcoholic beverage retail outlets	*0.95*	4,638	2,940	6,580	6,856	1,209
Comprehensive advertising ban on alcohol	*0.95*	5,417	2,631	7,442	8,139	891
Random breath testing of motor vehicle drivers	*0.80*	539	648	1,027	1,016	1,882
Brief advice to heavy drinkers by a primary care physician	*0.50*	3,705	1,992	4,891	4,460	2,163
Combination: highest tax + brief advice		4,627	2,859	7,016	3,718	1,184
Combination: highest tax + advertising ban + random breath testing + brief advice		2,621	1,833	4,364	2,612	1,415

Source: Chisholm and others 2004.

a. Refers to the modeled percentage of all high-risk drinkers exposed to the intervention.

cost-effective as opposed to those that clearly do not seem to offer good value for money. In this respect, the primary conclusion to be drawn from the analysis is that in regions with high or moderate rates of high-risk alcohol use, a number of intervention strategies can have a notable effect on population health, including both individual-based interventions, such as brief-physician advice at the primary care level, as well as population-wide measures, such as taxation of alcoholic beverages. Of these, taxation has the most sizable and least resource-intensive effect on reducing the avertable burden of high-risk alcohol use. In regions where high-risk alcohol use represents less of a public health burden, targeted approaches such as brief physician advice as well as other intervention strategies that restrict the supply or promotion of alcoholic beverages appear to be the most cost-effective mechanisms, although greater empirical support for the efficacy of these interventions in these localities is clearly needed before considering their widespread implementation.

Even though sectoral cost-effectiveness analysis pursues a societal perspective, considerable challenges remain in relation to the appropriate measurement of certain societal costs and effects that fall outside the boundaries of the health system. Therefore, this analysis has not been able to successfully capture potential reductions in workforce and household productivity losses among high-risk drinkers, nor does it incorporate the economic costs associated with alco-

hol-related crime, violence, and harm reduction. It also does not value the time spent by patients and informal caregivers in seeking or providing care and support. Including these modest additional costs and substantial incremental effects is likely to improve the cost-effectiveness ratios of all interventions, but to a variable and currently unknown extent.

ECONOMIC BENEFITS OF INTERVENTIONS

By design, estimates of the burden of alcohol do not include most social harm and harm to people other than the drinker; however, the burden of social problems from drinking can be at least as significant as the health burden. The burden attributable to alcohol in the CRA estimates is actually a substantial underestimate of the full harm alcohol imposes on human welfare. The estimates reported earlier reflect primarily the chronic disease and injury effects of drinking. Because the CRA focused on disease and disability, the estimates were not designed to take account of the social harm and problems that are particular to alcohol and that result for the drinker and for others as a consequence of a person's drinking (Klingemann and Gmel 2001). These problems are quite prevalent in many populations (Room and others 2003) and are also affected by the interventions listed earlier.

Some information on the relative burden of alcohol for social services versus health services is available for a handful of societies. In an estimate of the staffing and service costs attributable to alcohol in different service systems in Scotland for fiscal year 2001/02, for instance, health services accounted for only 21 percent of the estimated costs, whereas social services accounted for 19 percent, and criminal justice and fire services accounted for 60 percent (Catalyst Health Consultants 2001, 3). If those estimates are used as a rough gauge of the burden to society, the illness and disability burden of alcohol may thus constitute half or less of the total burden when social problems are also taken into consideration.

Thus, policies that affect the levels of alcohol-related health and social harm not only are a matter of intervening to save people from the detrimental effects of their own behavior, but also potentially have a broader effect on the health and well-being of families and of associates of drinkers. This issue is especially relevant for women: even though men predominate among high-risk drinkers worldwide (Rehm and others 2004; Room and others 2002), women bear much of the burden of harm from others' drinking, not only in such forms as domestic violence, but also in such forms as diversion of family resources from greater needs.

IMPLEMENTATION OF CONTROL STRATEGIES: LESSONS OF EXPERIENCE

The following paragraphs provide a few concrete examples of interventions or policy changes that illustrate the actual implementation and effects of control strategies in developing societies (the examples are taken from Room and others 2002).

Tax Rate Reduction and the Resulting Disease Burden in Mauritius

Mauritius, an island nation in the Indian Ocean, has a population of about 1 million. These people are of Indian, African, European, and Chinese origin. By religious affiliation, 53 percent are Hindu, 29 percent are Christian, and 17 percent are Muslim. Tourism is the third-ranked industry in terms of hard currency earnings. In June 1994, the government drastically lowered customs duties on imported alcoholic beverages to 80-percent from rates that had ranged from 200 percent for wine to 600 percent for whisky and other spirits (Abdool 1998). The government made the change under pressure from the hotel industry, which claimed that tourists were not purchasing enough alcohol because of its high prices (Lee 2001). Other reasons given for the change were to reduce unofficial imports from abroad and to make better, more refined alcoholic beverages available to the local population. Despite little evidence to support the view, there were claims in the public discussion that better-quality alcohol would result in fewer health problems.

The effects of the change were felt mainly by Mauritians rather than tourists, as follows:

- Arrests for driving with blood alcohol over the legal limit made primarily in connection with traffic crashes increased by 23 percent between 1993 and 1997.
- Admissions of alcoholism cases to the island's psychiatric hospital shot up in 1994. The 1995 rate was more than twice the 1993 rate, and the rate rose again slightly in 1996 and 1997. Medical specialists in Mauritius agree that patients with alcohol problems account for an increasing portion of-admissions in general medical wards and now represent between 40 and 50 percent of bed occupancy (Abdool 1998).
- Age-adjusted death rates per 100,000 population for chronic liver disease and cirrhosis rose from 32.8 for males and 4.0-for females in 1993 to 42.7 for males and 5.3 for females in 1996 (WHO 1999, 2000).

Even though available statistics are limited, the reduction in alcohol import taxes clearly had a substantial negative effect on the health of Mauritians. Thus, the government's 1997 call for control measures for alcohol—specifically, new permits for licensed premises, increased excise duties on alcohol, and limitations on bars' opening hours—was not surprising. Alcohol taxes were increased somewhat in the 1999/2000 budget (U.S. Department of State 1999). However, an analysis by World Bank staff that did not take health effects into account called for further reductions in maximum tariff rates, identifying Mauritius as having an antitrade bias on the basis of the structure of its alcohol and tobacco taxes (Hinkle and Herrou-Aragon 2001).

Wallace and Bird (2003) suggest the following general principles for setting and collecting alcohol taxes in the context of developing societies from the perspective of revenue generation rather than public health (see also Tax Policy Chief Directorate 2002):

- Countries around the world need revenues they can raise relatively efficiently, but this need is probably more critical in the case of developing nations. That said, alcohol taxes are probably a good bet for future revenues.
- Excise taxes on alcohol should be set by alcohol content, rather than as a percentage of the price.
- Tax rates should be logically defined so that alcoholic beverages with similar alcohol content are treated similarly, with stronger alcohol beverages taxed more heavily.
- Analyses of revenue-maximizing rates should be conducted to determine a range of tax rates that is likely to maximize government revenues.
- Tax systems should be designed to be as simple as possible to allow for the maximum efficiency of tax administration.

Reduced Access through Locational Prohibition in Brazil

The second example involves the institution of a new control on alcohol availability in an environment where it is likely to be combined with driving. Although we have modeled the effects of another, better studied availability control (namely, closing on a weekend day), a wide variety of possible measures is available to control the time and place of alcohol purchase or drinking (Babor and others 2003; Room and others 2002). Even though in this case the particular control was extremely limited in scope, it appears to have had measurable effects.

Traffic deaths are an important source of mortality in Brazil, amounting to 3.6 percent of overall mortality. The few available studies suggest that alcohol plays a significant role in traffic casualties. For instance, one study in São Paulo found positive blood alcohol levels in 72 percent of pedestrian deaths and 32 percent of driver and passenger deaths of persons age 13 and older (Carlini-Cotrim and Chasin 2000).

In 1985, motivated by concern about alcohol and impaired driving and about the lax enforcement of drinking and driving laws, a conservative party politician from the state of São Paulo introduced legislation to prohibit alcohol sales in commercial facilities that had access to state highways. Even though the bill passed in the legislature, its implementation was delayed by the state's alcohol producers and commercial and industrial federations, which claimed that the law would be a barrier to improved facilities for travelers, would encourage people to carry bottles in their cars, and would restrict individual freedoms. Discussion in the press was also generally unsympathetic. In August 1988, however, a new state governor from the same party implemented the law. At that time, the press was slightly more supportive. Since then, the law has been on the books, although site visits to restaurants and snack bars along a state highway in 1997 suggested a low level of compliance. In 1995, another legislator from the same party proposed repealing the law on the grounds that no studies proved that it lowered traffic accidents. The repeal passed the legislature without significant public debate, but the state governor vetoed it. Undaunted, the same legislator then proposed a law to criminalize buying as well as selling alcohol along state highways. That law passed but has not yet been implemented.

A study by Carlini-Cotrim, Pinsky, and Serrano Barbosa (1998) assesses the effects of the intervention. Finding data for a controlled study comparing traffic casualties on state highways with casualties on federal highways, which were unaffected by the law, proved impossible. The best data available were on crashes and crashes resulting in injuries per 10,000 vehicles traveling on three short highway systems administered by a private agency. Linear regressions on those data for 1983–93 showed that the law had made a significant difference in the number of accidents resulting in injuries on all three roads and a significant difference in all accidents on two of the roads. A separate analysis on estimated accidents and accidents with injuries per 10,000 vehicles in two geographic areas of the state did not show significant effects of the law. Overall, the analyses do provide some support for the law having a beneficial effect on the rate of traffic casualties.

Drunk-Driving Enforcement in South Africa

No published studies are available of the implementation of random breath testing in a developing country. However, some data are available on a campaign to increase drunk-driving enforcement in South Africa, a strategy that has often shown some effects, although weaker and less lasting than those of random breath testing.

The minister of finance launched a short-term campaign, ARRIVE ALIVE, for the period October 1997 to January 1998, in response to the high rate of traffic fatalities and injuries. The campaign's main aim was to mobilize all available traffic policing, control, and education resources to reduce traffic accidents on South African roads by at least 5 percent, especially in the Western Cape, Gauteng, and KwaZulu Natal provinces, because 75 percent of all accidents occurred in those provinces. The ARRIVE ALIVE campaign targeted, in turn, what were considered the three critical factors having the greatest impact on injuries: failing to wear seat belts, drinking and driving, and speeding. Unofficially, the campaign came to be called "belts, booze, and bats out of hell."

As many of the parties interested in road safety as possible were involved, with funding drawn from a variety of government and business sources. The campaign included a number of components particularly relevant to alcohol use. New equipment purchased by the provinces included alcohol screening devices, alcohol evidentiary units, and so-called booze buses (vehicles containing all the technology needed to check breath and blood alcohol levels). Sentences were

increased to underline the point that traffic violations are serious offenses, with a three-month suspension of a driver's license and an increased maximum fine for a first conviction for drunk driving and with license suspension for one to five years for second offenders. Traffic supervisors underwent intensive training courses before the start of the campaign.

Because the aim of the campaign included educating road users, advertisements covering aspects of the campaign were run on the radio, on television, and in movie theaters throughout the country. Supplements were published in national and provincial newspapers. Private companies, such as a supermarket chain and an automobile manufacturer, also promoted the-campaign. A national transportation center, established to collect and collate data from local and provincial authorities, operated for 12 hours every day throughout the campaign. Traffic authorities staffed an additional 80 roadside communications points, and at selected points on certain routes, road signs were erected and updated to display the percentage of speed limit and drinking-and-driving violations and the rate of seat belt use in that area.

A total of 776 enforcement points were set up on 195 strategic routes in the selected provinces. Posters, pamphlets, key rings, and license decals were produced for distribution and display at roadblocks in the three provinces. Between October 1, 1997, and January 17, 1998, 6,674 notices of prosecution were issued for alcohol-related traffic offenses, 83 percent of which were issued in the intervention provinces.

Comparison studies showed a decrease in the drinking rate of drivers in the three provinces, whereas the other six provinces, as a group, showed an increase. KwaZulu Natal had the lowest drinking rate of all drivers throughout the campaign (3 to 7 percent), and the Western Cape had the most dramatic decrease (from 12.0 to 9.3 percent in October). Except for in Gauteng, the drinking rates for pedestrians decreased from more than 15 percent to less than 7 percent. Overall, during the months targeted, drinking-and-driving rates decreased by 2 to 4 percent, as measured by breath testing. The total number of crashes decreased by 8 percent, and fatalities dropped by 9 percent. The ratio of benefits to costs for the intervention was estimated as 4 to 1, based on an investment in the campaign of R50-million, or about US$4.4 million at 2002 rates (ARRIVE ALIVE Campaign 2000).

Despite the potential inconvenience of roadblocks and other enforcement activities, the public generally perceived the campaign positively. The liquor retail and hospitality industries complained about decreased sales, and tow truck operators complained about reduced business.

Even though driver behavior improved during the focus months, violations often increased after the focus was changed, for example, from drunk driving to seat belt use. This finding emphasizes the need for sustained enforcement as opposed to ad hoc campaigns. (This example was summarized from ARRIVE ALIVE Campaign 2000 and Cerff and Plüddemann 1998.)

Implementation of Brief Interventions in Several Developing Countries

In the first phase of the WHO Collaborative Project on Identification and Management of Alcohol Related Problems (Saunders and Aasland 1987), a screening measure suitable for use in both developing and developed countries—the alcohol-use disorders identification test—was developed to identify people at risk for alcohol problems among those attending primary health care services. In the second phase, a multicenter clinical trial of brief intervention procedures designed to reduce the health risks associated with hazardous alcohol use was carried out in primary health care settings in Australia, Bulgaria, Costa Rica, Kenya, Mexico, Norway, the Soviet Union, the United Kingdom, the United States, and Zimbabwe (Babor and others 1994).

The project's aims were to study the influence of simple advice and brief counseling, to examine the moderating role of reduced consumption on the prevention of alcohol-related problems, and to evaluate the cross-national generalizability of brief intervention techniques. The project's hypothesis was that the amount of change in alcohol consumption over a nine-month period would be proportional to the intensity of the intervention provided by a trained primary health care professional. The results showed a significant effect of interventions on both consumption and intensity of drinking among males, but the intensity of the intervention was not related to the amount of change in drinking behavior; 5 minutes of simple advice turned out to be as effective as 20 minutes of brief counseling (Babor and Grant 1992). The female sample was too small for the results to attain significance, and the intervention did not significantly affect men's frequency of dependence symptoms, problems related to alcohol, or concern expressed by others (WHO Brief Intervention Study Group 1996).

The findings suggest that in a population of high-risk drinkers, behavior change is more a function of motivational factors and social influence than of the moderation skills and social learning techniques that behavioral self-control training packages typically use. Changes in drinking were not attributable solely to the small number of patients who achieved an abstinence goal, nor to the small number who gave up daily or almost daily drinking. Rather, changes seem to have been distributed across a broad spectrum of the drinkers who reduced their consumption by small, but clinically meaningful, amounts.

RESEARCH AND DEVELOPMENT AGENDA

Research and development needs in the area of alcohol consumption are large and multidimensional. The work reported in this chapter represents best estimates from the available data, some of which were developed to fill the needs of the analysis; however, we cite few figures for the developing world for which we can say that the underlying data are so good that they could not usefully be improved. Nevertheless,

more and better data are available on alcohol than on many other health topics.

The health and social burdens of alcohol are clearly extremely large in most developing societies. Thus, the most urgent focus should be on development and evaluation projects to study the outcomes of various policy and program interventions. The projects must necessarily be attuned to what is politically feasible in a particular time and place. They are likely to include natural experiment studies, where the research tracks the effects of changes that governments undertake, whether those changes are expected to increase or to decrease the extent of alcohol problems. Where possible, the projects should include experimental and quasi-experimental studies, whereby the effects of a change at intervention sites are studied in comparison to outcomes at control sites, with random assignment where possible. Costing data should be included to permit cost-effectiveness analysis.

Also important are process studies—that is, research on how policy makers decide on policy changes, how they implement them, and what the reactions and sequelae are. For example, deciding to introduce a new alcohol tax may be the easiest part of an initiative, but actually implementing it in a developing society with a great deal of unrecorded alcohol in the informal market and with poorly guarded borders may be much more difficult. Currently, no international mechanism or nexus exists for developing and disseminating practical knowledge about implementing effective alcohol control strategies between developing countries.

At this time, nearly all studies of alcohol interventions come from a limited range of developed countries. Extending knowledge and experience in and between developing societies is urgently needed.

A secondary need, but one that is also important, is to extend the epidemiological database in developing societies on levels and patterns of drinking and on the health and social consequences of drinking. To this end, better estimation of unrecorded alcohol consumption is needed. Which dimensions of drinking patterns matter for what kinds of outcomes needs to be studied in the context of different kinds of developing societies. Studies of the effects that the interaction of drinking levels and patterns with poverty and social exclusion have on the extent of alcohol-related problems are also necessary. Because most of our knowledge about the health effects of drinking concerns mortality, studies of alcohol's role in various kinds of morbidity should be emphasized. Another area where data are lacking is the social harm arising from drinking, for which we cannot presently make the kinds of estimates that are possible to make for harm to health. Developing and reaching consensus on ways to measure the social harm caused by drinking is a substantial agenda for both the developed and the developing world.

Developing the epidemiological database can provide clues to etiology to be pursued further by biomedical and social researchers and, thus, offers hope for the development of new treatments or preventive interventions. It can provide information on the distribution of drinking patterns and problems in subpopulations that can be used to guide targeting and prevention and treatment priorities. However, from a short-term policy perspective, the most important function of developing the epidemiological database in a particular country may be providing a base for creating political will for action. For example, the development of devices to measure blood and breath alcohol and the collection of data on drinking and driving that they made possible were prerequisites for developing the political will and support for implementing drinking-and-driving countermeasures in industrial countries.

CONCLUSION

The burden of disease attributable to alcohol in the developing world is considerable, and the social harm not accounted for in this analysis increases the costs. However, known interventions can reduce the burden by up to 25 percent, depending on the region of the world. Compared with other interventions in the health care field, these interventions are quite cost-effective, but given the nature of many of the interventions, caution is needed. In particular, the following recommendations can be given:

- Interventions and research about their effectiveness are based mostly on experiences from established market economies; thus, the levels of effectiveness estimated in our analysis should be treated as broad indications. Depending on actual methods of implementation, individual interventions could be more or less effective.
- Interventions should ideally be modeled on the basis of the specific environment (that is, countries or provinces) and on the harm distribution in the respective environment, including social harm.
- General principles, such as restricting access to alcohol, should be attuned to local cultures and traditions when interventions are formulated.
- Population measures must take into account the complex interplay of public opinion and balance the interests of different groups and stakeholders with conflicting values. One of these stakeholders is, of course, the alcohol industry.

If policy makers keep these principles in mind, reducing the alcohol-related health burden could be one of the most cost-effective targets of population-level health programs in developing countries. This target is even more attractive because the measures discussed will also reduce the alcohol-related social burden, thereby further contributing to development.

NOTES

1. The global burden of disease attributable to alcohol is 4.0 percent using age-weighted DALYs and 3.6 percent using non-age-weighted DALYs. This difference can be explained by the many alcohol-attribut-

able outcomes occurring during adolescence and young adulthood, when age weights are higher.

2. The CRA defined *per capita consumption* as average consumption of pure alcohol per person 15 years old or older.

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Chapter **5**

Illicit Opiate Abuse

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Illicit drugs are those banned by international drug control treaties. They include cannabis products (for example, marijuana, hashish, and bhang); stimulant drugs (such as cocaine and methamphetamine); so-called dance-party drugs (such as 3, 4-methylenedioxymethamphetamine, also known as *ecstasy* or *MDMA*); and illicit opioids (for instance, heroin and opium) and diverted pharmaceutical opioids (such as buprenorphine, methadone, and morphine) (see annex 5.A).

Worldwide, 185 million people were estimated to have used illicit drugs during 1998–2002 (UNODC 2004; UNODCCP 2002). Cannabis was the most widely used illicit drug, with 146.2 million users in 2002, or 3.7 percent of the global population over age 15. The stimulant drugs were the next most widely used illicit drugs: 29.6 million people worldwide used amphetamines; 13.3 million used cocaine; and 8.3 million used ecstasy. An estimated 15.3 million, or 0.4 percent of the world population age 15 to 64, used illicit opioids; more than half used heroin and the remainder used opium or diverted pharmaceutical opioids. Illicit opioids continue to be the major illicit drug problem in most regions of the world in terms of impact on public health and public order (UNODC 2004).

Even though cannabis use accounts for about 80 percent of illicit drug use worldwide, the mortality and morbidity attributable to its use are not well understood, even in developed countries (W. Hall and Pacula 2003; Macleod and others 2004; WHO Programme on Substance Abuse 1997). The same is true of the morbidity and mortality attributable to cocaine and amphetamine-type stimulants (Macleod and others 2004). Dance-party drugs have been used for too short a time in most developed societies to enable a good assessment of their potential for harm (Boot, McGregor, and Hall 2000; Macleod and others 2004). The remainder of this chapter is concerned with disease control priorities for illicit opioid dependence, because dependent users account for most of the illicit opioids consumed and experience most of the harm such dependence causes (W. Hall, Degenhardt, and Lynskey 1999).

NATURE, CAUSES, AND HEALTH CONSEQUENCES OF ILLICIT OPIOID USE

Before considering interventions, we briefly summarize what is known about the antecedents, causes, and health consequences of illicit opioid use.

Antecedents of Heroin Use

Law enforcement efforts to reduce the availability of heroin aim to increase its price, deter illicit drug use, and promote social values that discourage heroin use (Fergusson, Horwood, and Lynskey 1998; Hawkins, Catalano, and Miller 1992; Newcomb and Bentler 1988). These gains may be at the cost of increasing harm among the minority who use opioids despite the prohibition—for example, by encouraging injecting use as the most efficient way to use an expensive drug and increasing needle sharing because clean injecting equipment is not freely available (Rhodes and others 2003; Strathdee and others 2003).

Two aspects of the family environment are associated with increased rates of both licit and illicit drug use in young people in developed countries. The first is exposure to a disadvantaged home environment, with parental conflict and poor discipline and supervision; the second is exposure to parents' and siblings' use of alcohol and other drugs (Hawkins, Catalano,

and Miller 1992). In developed countries, children who perform poorly in school because of impulsive or problem behavior and those who are early users of alcohol and other drugs are most likely to use illicit opioids (Fergusson, Horwood, and Swain-Campbell 2002). Affiliation with drug-using peers is a risk factor for drug use that operates independently of individual and family risk factors (Fergusson, Horwood, and Lynskey 1998; Hawkins, Catalano, and Miller 1992).

Health Consequences of Heroin Use

The following sections describe the major health consequences of heroin use. They include dependence, increased mortality and morbidity attributable to drug overdoses, and bloodborne viruses.

Heroin Dependence. In household surveys, 1 to 2 percent of adults in Australia, the United States, and Europe report using heroin at some time in their lives (Australian Institute of Health and Welfare 1999; EMCDDA 2002; SAMHSA 2002). The highest rates are typically among adults age 20 to 29. Self-reported heroin use in population surveys probably underestimates rates of use because heroin users are undersampled and those who are sampled underreport their use (W. Hall, Lynskey, and Degenhardt 1999).

In developed countries, one in four of those who report heroin use become dependent on it (Anthony, Warner, and Kessler 1994). People who are heroin dependent continue to use heroin in the face of problems that they know (or believe) to be caused by its use. These problems include being arrested or imprisoned, having interpersonal and family problems, catching infectious diseases, and suffering from drug overdoses. Many heroin users who seek treatment have typically been daily heroin injectors, although in Europe (EMCDDA 2002), North America (Office of National Drug Control Policy 2001), and parts of Asia, illicit opioid users also smoke or "chase" the drug (inhale the fumes released when heroin is heated) (UNODC 2004).

The American Psychiatric Association defines *drug dependence* as "a cluster of cognitive, behavioral, and physiologic symptoms indicating that the individual continues use of the substance despite significant substance-related problems" (American Psychiatric Association 1994, 176). In the fourth edition of the association's *Diagnostic and Statistical Manual of Mental Disorders* (1994,), a diagnosis of substance dependence requires that three or more of the following occur together:

At any time in the same 12-month period:

1. tolerance, as defined by either of the following:
   a. need for markedly increased amounts of the substance to achieve intoxication or desired effect
   b. markedly diminished effect with continued use of the same amount of the substance;
2. withdrawal, as manifested by either of the following:
   a. the characteristic withdrawal syndrome for the substance
   b. the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms;
3. the substance is often taken in larger amounts or over a longer period than was intended;
4. there is a persistent desire or unsuccessful efforts to cut down or control substance use;
5. a great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors, driving long distances), use the substance (e.g., chain smoking), or recover from its effects;
6. important social, occupational, or recreational activities are given up or reduced because of substance use;
7. the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

Indirect estimation methods suggest that in Australia, the United Kingdom, and the European Union fewer than 1 percent of adults age 15 to 54 are heroin dependent (EMCDDA 2002; W. Hall and others 2000). Research in the United States indicates that dependent heroin users who seek treatment or who come to the attention of the legal system may use heroin for decades (Goldstein and Herrera 1995; Hser, Anglin, and Powers 1993), with periods of use punctuated by abstinence (Bruneau and others 2004; Galai and others 2003), drug treatment, and imprisonment (Gerstein and Harwood 1990). When periods of abstinence are included, dependent heroin users use heroin daily for 40 to 60 percent of the 20 years that they typically are addicts (Ball, Shaffer, and Nurco 1983; Maddux and Desmond 1992).

Illicit opioid use increased in Asia, Europe, and Oceania and, to a lesser extent, in Africa and South America in the 1990s, but it has stabilized or declined since 2000 (UNODC 2004). Most illicit opioid users (7.8 million) live in Asian countries that surround the major opium-producing countries, Afghanistan and Myanmar. Europe accounts for about 25 percent of illicit opioid use (4 million users or 0.8 percent of the adult population age 15 to 64). Two-thirds of users are in Eastern Europe, which reported large increases in illicit opioid use during the second half of the 1990s (Atlani and others 2000; Hamers and Downs 2003; Kelly and Amirkhanian 2003; Rhodes and others 1999; Uuskula and others 2002).

Illicit opioid use stabilized in much of Asia between 2000 and 2002 (UNODC 2004) as a result of decreased opium production after the rapid expansion during the 1990s (Dorabjee and Samson 2000; Reid and Crofts 2000). After 2000, India and Pakistan reported stabilizing rates of illicit opioid use but increased injection of pharmaceutical opiates (Ahmed and others 2003; Dorabjee and Samson 2000; Strathdee and others 2003). China has reported a steady rate of growth in illicit opiate use in its southern and northern provinces (Beyrer 2003; Beyrer and others 2000; Yu and others 1998) and a 15-fold increase in the number of registered opioid addicts between 1990 and 2002, bringing the total to about 1 million (UNODC 2004).

Oceania experienced a marked rise in heroin use in the late 1990s, largely driven by a dramatic increase in the availability of heroin in Australia (Darke, Topp, and others 2002; W. Hall, Degenhardt, and Lynskey 1999). In late 2000, an abrupt heroin shortage resulted in a large reduction in fatal and nonfatal overdoses (Day and others 2004; Degenhardt, Day, and Hall 2004).

Mortality, Morbidity, and Heroin Dependence. In developed countries, dependent heroin users have an increased risk of premature death from drug overdoses, violence, suicide, and-alcohol-related causes (Darke and Ross 2002; Goldstein and Herrera 1995; Vlahov and others 2004). Heroin users treated before the HIV epidemic were 13 times more likely to die prematurely than their peers (Hulse and others 1999), with opioid overdose the most frequent cause of death (W. Hall, Degenhardt, and Lynskey 1999). In countries with a high prevalence of HIV infection, AIDS is a major cause of premature death among drug users (EMCDDA 2002; UNAIDS and WHO 2002). Fatal opioid overdose deaths increased in many developed countries during the 1990s before declining after 2000 (UNODC 2004).

In parts of Asia, Eastern Europe, and the United States, the sharing of contaminated injecting equipment accounts for a substantial proportion of new HIV infections (EMCDDA 2002; UNAIDS and WHO 2002; UNODC 2004). Injecting opioid use has been a major driver of HIV epidemics in China (Yu and others 1998), Myanmar (Beyrer and others 2000), the Russian Federation and former Soviet republics (Hamers and Downs 2003), and Vietnam (Beyrer and others 2000; Hien and-others 2001).

The prevalence of infection with hepatitis B and C viruses among injecting drug users is greater than 60 percent in Australia (National Centre in HIV Epidemiology and Clinical Research 1998), Canada (Fischer and others 2004), China (Ruan and others 2004), the United States (Fuller and others 2004), and the European Union (EMCDDA 2002). Chronic infection occurs in 75 percent of infections, and 3 to 11 percent of chronic hepatitis C virus carriers develop liver cirrhosis within 20 years (Hepatitis C Virus Projections Working Group 1998).

Heroin-related deaths primarily occur among young adults and account for a large number of life years lost in developed societies. In Australia in 1996, for example, such deaths accounted for 2.2 percent of life years lost, with each death accounting for 22 years of life lost (Mathers, Vos, and Stephenson 1999). In Scotland and Spain, opiate-related deaths account for 25 to 33 percent of deaths of young adult males (EMCDDA 2002).

Economic Costs of Illicit Opioid Use. In Canada, Xie and others (1996) calculate the costs of illicit drugs as 0.2 percent of-gross domestic product (GDP). In Australia, Collins and Lapsley (1996) estimate the economic costs of illicit drug abuse at 2 percent of GDP.

CONTRIBUTION OF OPIOID DEPENDENCE TO THE GLOBAL BURDEN OF DISEASE

Degenhardt, Hall, and others (2004) estimate the contribution of illicit opioid dependence to the global burden of disease using data on deaths caused by opioid and other drug overdoses, suicides and accidents, and HIV/AIDS. When estimates of morbidity attributable to illicit drug use were added in, illicit opioid use accounted for 0.7 percent of global disability-adjusted life years (DALYs) in 2000 (WHO 2003).

These estimates suggest that illicit opioid use is a significant global cause of premature mortality and disability among young adults. Even so, they probably underestimate the disease burden attributable to illicit opioids, because they omit differences across subregions in the quality of data on causes of mortality and estimates of mortality and morbidity attributable to hepatitis and violence (Degenhardt, Hall, and others 2004).

INTERVENTIONS FOR ILLICIT OPIOID DEPENDENCE

Methods adopted to control the problems arising from illicit opioid dependence include source-country control; interdiction of supply into end-use countries; enforcement by the police force and the criminal justice system of legal prohibitions on the supply, possession, and use of opioids; treatment of those who are opioid dependent, both voluntarily and under legal coercion from the criminal justice system; school-based and mass media preventive educational programs; and regulatory policies restricting the prescription of opioids (Manski, Pepper, and Petrie 2001).

Prevention of Heroin Use

Countries use a variety of interventions in attempts to prevent the initiation of use of illicit drugs such as cannabis (Manski, Pepper, and Petrie 2001; Spooner and Hall 2002), in the belief that early initiation of cannabis use leads to an increased risk-of-using illicit opioids (Fergusson, Horwood, and Swain-Campbell 2002). These interventions include legal prohibitions on the manufacture, sale, and use of opioid drugs for-nonmedical purposes; enforcement of these sanctions by law enforcement officials by means of fines and imprisonment; and enforcement of restrictions on medically prescribed opioids to prevent their diversion (Manski, Pepper, and Petrie 2001). Preventive measures also include mass media and school-based educational campaigns about the health risks of opioid and other illicit drug use (Spooner and Hall 2002). It is unclear how effective these interventions are in preventing cannabis use and even less clear whether they reduce the initiation of opioids (Caulkins and others 1999; Manski, Pepper, and Petrie 2001).

The most popular interventions against illicit opioid use in many developed societies have been the interdiction of

drug supply and the enforcement of legal sanctions against the possession, use, and sale of opioid drugs (Manski, Pepper, and Petrie 2001). As a consequence, imprisonment is the most common intervention to which many illicit opioid users have been exposed (Gerstein and Harwood 1990). In Asia and Eastern Europe, high rates of imprisonment of drug users have been a factor in HIV transmission, because drug users engage in high-risk injecting while imprisoned (Beyrer and others 2000).

Interventions to Reduce Heroin-Related Harm

The most effective intervention to reduce bloodborne virus infection arising from illicit injecting of opioids and other drugs is the provision of clean injecting equipment to reduce users' risks of contracting or transmitting bloodborne viruses. This intervention has been widely supported in most developed countries, but it has been incompletely adopted in developing countries that have problems with the concept of facilitating the injection of illicit drugs (UNAIDS and WHO 2002). Vaccinations are available against hepatitis B but not hepatitis C. These important interventions are covered in chapter 18 of DCP2.

A number of strategies can potentially reduce deaths from opioid overdoses (Darke and Hall 2003; Sporer 2003). First, injecting drug users can be educated about the dangers of combining the use of opioids with alcohol and benzodiazepines (McGregor and others 2001), both of which heighten the risk of a fatal opioid overdose (Darke and Zador 1996; Warner-Smith and others 2001). Heroin users also need to be discouraged from injecting in the streets or alone, thereby denying themselves assistance in the event of an overdose. These interventions have yet to be evaluated.

A second strategy is to encourage drug users who witness overdoses to seek medical assistance and to use simple resuscitation techniques until help arrives. A more controversial option is to distribute the opioid antagonist naloxone to high-risk heroin users (Darke and Hall 1997; Strang and others 1996). Neither of these interventions has been evaluated.

A third strategy is to provide supervised injecting facilities in areas with high rates of injecting opioid use (Dolan and others 2000; Kimber and others 2003). Supervised injecting facilities have been introduced in Germany, the Netherlands, and Switzerland (Dolan and others 2000; Kimber and others 2003), but their effect on overdose deaths has not been rigorously evaluated to date. A supervised injecting facility was evaluated in Australia, but the evaluation was limited by the concurrent onset of a heroin shortage that resulted in a 40 percent decline in overdose deaths (Kaldor and others 2003).

A fourth strategy is to increase methadone maintenance among older, high-risk opioid-dependent people, because individuals enrolled in methadone maintenance treatment (MMT) are substantially less likely to suffer from a fatal overdose (Caplehorn and others 1994; Gearing and Schweitzer 1974; Langendam and others 2001).

Treatment Interventions for Dependent Opioid Users

The range of treatment interventions includes voluntary programs such as detoxification, abstinence-oriented treatments, and oral Methadone maintenance treatment, as well as involuntary options imposed by criminal justice systems.

Detoxification. Detoxification is supervised withdrawal from a drug of dependence that attempts to minimize withdrawal symptoms. It is not a treatment for heroin dependence; it provides a respite from opioid use and may be a prelude to abstinence-based treatment (Mattick and Hall 1996).

Naltrexone is a longer-acting opiate antagonist than naloxone; it can be used to accelerate the opioid withdrawal process. Ultra-rapid opioid detoxification accelerates withdrawal by giving the patient naltrexone under general anesthetic. There is no evidence that accelerated withdrawal in itself reduces the high rate of relapse to heroin use in the absence of further treatment (W. Hall and Mattick 2000).

Abstinence-Oriented Treatments. Abstinence-oriented treatments aim to achieve enduring abstinence from all opioid drugs by providing some type of intervention after withdrawal to reduce the high rate of relapse to opioids (Mattick and Hall 1996). The interventions may include social and psychological support only or such support supplemented by pharmacological methods.

Residential treatment in therapeutic communities and outpatient drug counseling may entail encouraging patients to become involved in self-help groups such as Narcotics Anonymous. These approaches share a commitment to achieving abstinence from all opioids, using group and psychological interventions to help dependent heroin users remain abstinent. Therapeutic communities and drug counseling are usually provided through specialist addiction or mental health services. The former are residential, and the latter are provided on an outpatient basis.

No randomized controlled trials of therapeutic communities or outpatient drug counseling have been carried out. Observational studies in the United Kingdom (Gossop, Marsden, and Stewart 1998; Gossop and others 1997) and the United States (Hubbard and others 1989; Simpson and Sells 1982) have found that therapeutic communities and drug counseling were less successful than MMT in attracting and retaining dependent heroin users, but they substantially reduced heroin use and crime among those who remained in treatment for at least three months (Gerstein and Harwood 1990; Gossop, Marsden, and Stewart 1998; Gossop and others 1997). Some evidence indicated that therapeutic communities may be more effective if they are used in combination with legal coercion to ensure that heroin users are retained in treatment long enough to benefit from it (Gerstein and Harwood 1990).

Recovering drug users run Narcotics Anonymous groups using an adaptation of the 12-step philosophy of Alcoholics Anonymous. Some individuals use these groups as their sole

form of support for abstinence, whereas for others these groups complement therapeutic communities that are based on the same principles. Such groups are usually not open to people who are in opioid substitution treatment programs.

The most extensive research on self-help has been in the treatment of alcohol dependence. Treated alcoholics who participate in Alcoholics Anonymous groups have higher rates of abstinence than those who do not (see, for example, Tonigan, Connors, and Miller 2003; Tonigan, Toscova, and Miller 1996). The good outcome in those who attend Alcoholics Anonymous meetings may reflect the self-selection of motivated participants into self-help groups. Recent studies that have attempted to control for this possibility using sophisticated statistical methods have produced mixed results, with some showing the persistence of an effect of self-help after correction (Tonigan, Connors, and Miller 2003) while others do not (Fortney and others 1998).

Shepard and others (forthcoming) evaluate the effect of self-help participation on substance abuse 24 months after treatment for members of a mixed population of substance abusers treated at two treatment facilities in the United States, some of whom had problems with heroin. They find that participation in self-help groups was associated with longer abstinence from all drugs. Correction for self-selection did not eliminate the association in one treatment setting, but it made the results much more equivocal in the other.

Oral Methadone Maintenance Treatment. This treatment substitutes a long-acting, orally administered opioid for the shorter-acting heroin, with the aim of stabilizing dependent heroin users so that they are amenable to rehabilitation (Marsh and others 1990; Ward, Hall, and Mattick 1998). When given in high or blockade doses, methadone blocks the euphoric effects of injected heroin, allowing the individual to take advantage of psychotherapeutic and rehabilitative services.

Every one of the small number of randomized controlled trials of MMT compared with placebo or no treatment has produced positive results (W. Hall, Ward, and Mattick 1998; Mattick and others 2003). Large observational studies show that MMT decreases heroin use and criminal activity and reduces HIV transmission while patients remain in treatment (Gerstein and Harwood 1990; Simpson and Sells 1990; Ward, Hall, and Mattick 1998). MMT is the best-supported form of opioid maintenance treatment (Farre and others 2002; Marsch 1998; Mattick and others 2003).

Buprenorphine is a mixed agonist-antagonist that also blocks the effects of heroin. When given in high doses, its effects can last for up to three days, while its antagonist effects substantially reduce overdose and abuse (Oliveto and Kosten 1997; Ward, Hall, and Mattick 1998). Meta-analyses have found that buprenorphine is effective in the treatment of heroin dependence (Mattick and others 2003) and is of equivalent efficacy to MMT when delivered in primary health care and specialist treatment settings in Australia (Gibson and others 2003).

Bammer and others (2003) have proposed injectable heroin maintenance as a way of attracting into treatment those heroin users who are not interested in or have failed to respond to MMT. This method has recently been evaluated in the Netherlands (Central Committee on the Treatment of Heroin Addicts 2002) and Switzerland (Perneger and others 1998; Uchtenhagen, Gutzwiller, and Dobler-Mikola 1998). Perneger and others (1998) report a randomized controlled trial of injectable heroin maintenance in people who had failed at MMT. Stabilizing and safely maintaining heroin addicts on injectable heroin (self-administered on-site in a comprehensive health and social service) proved feasible for six months and substantially improved their health and social well-being. The Swiss trials showed that it was possible to maintain opioid addicts on injectable heroin for up to two years (Rehm and others 2001; Uchtenhagen, Gutzwiller, and Dobler-Mikola 1998). A recent randomized controlled trial in the Netherlands (Central Committee on the Treatment of Heroin Addicts 2002) confirms the findings of Perneger and others (1998).

Criminal Justice Interventions for Dependent Illicit Opioid Users. The most common intervention for illicit opioid dependence in most developed societies is imprisonment (EMCDDA 2003; Gerstein and Harwood 1990). Imprisonment is not intended to be a health intervention. Nonetheless, it is an ineffective way of reducing opioid dependence, when judged by-the high recidivism in longitudinal studies of dependent heroin users (see, for example, Hser, Anglin, and Powers 1993; Manski, Pepper, and Petrie 2001).

Legally coerced treatment is treatment that is legally forced on those who have been charged with or convicted of an offense to which their drug dependence has contributed (W.-Hall 1997). It is most often provided as an alternative to imprisonment, under the threat of imprisonment if the person fails to comply with the treatment (W. Hall 1997; Manski, Pepper, and Petrie 2001; Spooner, Hall, and Mattick 2001). Its major justification is that it is an effective way of treating offenders' drug dependence that reduces the likelihood of their offending again (Gerstein and Harwood 1990). A consensus view prepared for the World Health Organization (WHO) (Porter, Arif, and Curran 1986) was that compulsory treatment was legally and ethically justified only if the rights of the individuals were protected by due process and if the treatment provided was effective and humane.

Research into the effectiveness of legally coerced treatment for opioid dependence has been limited to observational studies (W. Hall 1997; Manski, Pepper, and Petrie 2001; Wild, Roberts, and Cooper 2002). Anglin's (1988) quasi-experimental studies of the California Civil Addict Program provide the strongest evidence of efficacy. These studies compared heroin-dependent offenders who entered the program between 1962 and 1964 with a group of similar offenders who went through the criminal justice system during the same period. They found that compulsory hospital treatment fol-

lowed by close supervision in the community substantially reduced heroin use and crime.

The effectiveness of less coercive forms of treatment has been supported by analyses of the effectiveness of community-based treatment provided while on probation or parole (Hubbard and others 1989; Simpson and others 1986). These studies showed that individuals who entered community-based therapeutic communities and drug-free outpatient counseling under legal pressure did as well as those who did so voluntarily (Hubbard and others 1988; Simpson and Friend 1988). The recent creation of specialized drug courts in the United States to process those arrested for drug-related offenses awaits rigorous evaluation (Belenko 2002; Manski, Pepper, and Petrie 2001).

Legally coerced MMT is also effective. The strongest evidence comes from a study in which drug offenders were randomly assigned to parole with and without community-based MMT (Dole and others 1969). This study showed a greater reduction in heroin use and lower rates of incarceration among those enrolled in MMT in the year following their release from prison. These findings are supported by observational studies that found no major differences in response to MMT between those who enrolled under legal coercion and those who did not (Anglin, Brecht, and Maddahain 1989; Brecht, Anglin, and Wang 1993; Hubbard and others 1988).

Economic Evaluations of Interventions for Illicit Opioid-Dependence

The few published economic evaluations of treatment interventions for illicit opioid dependence indicate varying levels of cost-effectiveness.

Detoxification. The National Evaluation of Pharmacotherapies for Opioid Dependence Project in Australia conducted a cost-effectiveness analysis of five interventions:

- naltrexone-induced rapid opioid detoxification under anesthesia
- naltrexone-induced rapid opioid detoxification under sedation
- conventional inpatient detoxification
- conventional outpatient detoxification
- buprenorphine outpatient detoxification.

A successful outcome was defined as achieving abstinence from heroin for one week (Mattick and others 2001).

Rapid detoxification under sedation was the most cost-effective method of detoxification (US$2,355 for one week of abstinence) and conventional outpatient detoxification the least cost-effective (US$12,031). Rapid detoxification under anesthesia achieved high rates of abstinence in the first week, but its expense reduced its cost-effectiveness (Mattick and others 2001).

Doran and others (2003) compared the cost-effectiveness of detoxification from heroin using buprenorphine in a specialist Australian clinic and in a shared care setting. They conducted a-randomized controlled trial with 115 heroin-dependent patients receiving a five-day treatment regime of buprenorphine. The specialist clinic was a community-based treatment agency in Sydney. Shared care involved treatment by a general practitioner, supplemented by weekend dispensing and some counseling at the specialist clinic. They estimate that buprenorphine detoxification in the shared care setting was US$17 more expensive per patient than the costs of treatment at the clinic (US$236 per patient).

Drug-Free Treatment. The limited economic evaluations of drug-free treatment have used data from observational studies of treatment outcomes in samples of patients who have mixed substance abuse problems that include opioids. For example, Shepard, Larson, and Hoffmann (1999) calculate a range of estimated costs for achieving an abstinent year in 408 patients at two different treatment facilities in the United States. The cost-effectiveness depended on the severity of the problem and the intensiveness and cost of the intervention. For outpatients with the least severe drug problems, the cost of an abstinent year was US$7,000, whereas the same outcome in patients with more severe problems who received long-term residential treatment cost US$20,000.

Shepard and others (forthcoming) use these data to estimate the cost-effectiveness of involvement in mutual self-help-groups, such as Alcoholics Anonymous and Narcotics Anonymous, in sustaining abstinence for up to 24 months after treatment. They find a positive association between self-help involvement and abstinence 12 and 24 months after treatment.-Applying statistical methods to correct for the effects of self-selection into self-help, they find that in a Veterans Administration hospital, the effects of self-help on abstinence persisted after the statistical correction, but at the other site, the results depended on the method of analysis that was used. They estimate the cost of achieving an abstinent year by means of self-help in the year following treatment at US$13,000, all of that due to the costs that participants incurred in attending a-group.

Oral Opioid Maintenance Treatment. Goldschmidt's (1976) economic evaluation of MMT found that it was as effective as-a-therapeutic community intervention and twice as cost-effective. Cartwright's (2000) review of the literature since 1976 identified a number of studies, all of which reported positive benefit-cost ratios for MMT.

Gerstein, Harwood, and Suter's (1994) California Drug and Alcohol Treatment Assessment study is the most comprehensive cost-benefit analysis carried out to date. The authors examine the effects of treatment—residential programs, outpatient programs, and methadone programs—on alcohol and drug use, criminal activity, health and health care utilization, and source of income. For each treatment modality, they found that the benefits during the first year of treatment significantly exceeded the cost of delivering the care. The benefit-cost ratio was 4.8 for residential treatment

and 11.0 and 12.6 for outpatients and discharged methadone participants, respectively.

Doran and others (2003) compared the cost-effectiveness of-buprenorphine and methadone treatment for opioid dependence. In a randomized controlled trial, 405 subjects were randomly assigned to each treatment at one of three specialist outpatient drug treatment centers. The study found that treatment with methadone was less expensive and more effective than treatment with buprenorphine, but the difference in cost (US$143 per additional heroin-free day gained) had a wide range of uncertainty around it (–US$1,469 to US$1,284).

The National Evaluation of Pharmacotherapies for Opioid Dependence Project also provided a cost-effectiveness analysis of methadone, buprenorphine, LAAM (levo-alpha-acetylmethadol), and naltrexone maintenance treatments (Mattick and others 2001). The daily costs of these maintenance treatments were similar for methadone and LAAM, but naltrexone was slightly more expensive. Buprenorphine maintenance treatment (BMT) was more expensive, but its cost-efficiency could have been improved to make its cost similar to that for the other treatments. MMT was the most cost-effective treatment for opioid dependence because it achieved one of the highest rates of retention in treatment among the four pharmacotherapies examined. Naltrexone treatment was the least cost-effective.

The costs of injectable heroin maintenance in the Dutch study was between US$18,015 and US$23,243 per patient per year (Bammer and others 2003). Most of the costs arose from the supervision of heroin use and the security required to prevent the diversion of heroin to the black market. Injectable heroin maintenance needs to produce substantially greater benefits for each participant than MMT to make it as cost-effective as MMT.

Economic Modeling of the Cost-Effectiveness of Opioid Maintenance Treatment. Barnett (1999), using data on the efficacy of MMT in reducing mortality derived from Gronbladh, Ohlund, and Gunne's (1990) Swedish study and U.S. cost data, estimated that MMT saved an additional year of life at a cost of US$5,900. Barnett, Zaric, and Brandeau (2001), using a similar approach, estimated that the use of buprenorphine by patients who would not use methadone would cost less than US$45,000 per quality-adjusted life year. Overall, however, they found that BMT was much less effective and more costly than MMT. Zaric, Barnett, and Brandeau (2000) assessed the economic benefits of using MMT to reduce HIV transmission in heroin users. They found that for heroin users living in a community with a high prevalence of HIV infection, expanding MMT use produced an additional year of quality-adjusted life at a cost of US$8,200.

Comparing the Cost-Effectiveness of Different Interventions

Comparative cost-effectiveness analyses of these interventions face major obstacles because the small number of published studies used different methods to cost interventions and different endpoints to assess the outcome of treatment. The following list, therefore, only ranks treatment interventions in the approximate order of their cost-effectiveness. We believe that estimates of their likely contribution to DALYs worldwide would be too speculative.

- *Detoxification.* Buprenorphine and supervised naltrexone-accelerated withdrawal delivered on an outpatient basis are the most efficient and effective ways to achieve withdrawal from opioids.
- *Self-help groups*. These groups provide the simplest form of postwithdrawal support for enduring abstinence and are also a low-cost intervention, because patients bear most of the costs; however, they have a low rate of uptake, and their effectiveness is only modest.
- *Oral opioid agonist maintenance treatment*. This form of treatment is the most widely used intervention for illicit opioid dependence in developed societies. It has a better uptake than other interventions, and it is moderately effective under the usual delivery conditions.
- *Drug-free residential treatment*. This form of treatment has a relatively low rate of treatment uptake and is costly because of its residential character and the need for intensive staff-patient interaction. It is effective for the minority of people who are retained in treatment long enough to benefit from it (usually three months). Retention in treatment may be improved if patients enter treatment under some form of legal coercion.
- *Naltrexone maintenance treatment*. This form of treatment has not been rigorously evaluated.
- *Injectable opioid maintenance*. This intervention is a more expensive variant of agonist maintenance treatment that has been used for patients with more severe cases of dependency but for whom retention and treatment outcomes have been good.

Calculation of the Averted, Avertable, and Unavertable Burden

Assuming that the disease burden from opioid dependence is potentially avertable, we used the following approach to estimate the avoidable burden of opioid dependence. We initially modeled the avertable burden using MMT and used this model for BMT. The first step was to establish the base case for opioid dependence using 2002 as the baseline year. We established the model of the base case for opioid dependence for regions and subregions according to WHO country classifications. We used population estimates for each region for those age 15 to 59, the age range in which heroin dependence is most prevalent. We incorporated Degenhardt, Hall, and others' (2004, table 13.1) figures for the prevalence of opioid use by region, assuming that the prevalence was 30 percent higher among male users than female users.

We obtained population-attributable fractions related to opioid dependence from the editors of this volume. We used nine relevant WHO categories to estimate the burden of disease attributable to opioid dependence—namely HIV/

AIDS, drug-use disorders, road traffic accidents, poisonings, falls, fires, drownings, other unintentional injuries, and self-inflicted injuries.

We calculated the mortality rate for opioid deaths by dividing the number of deaths by the estimated number of users. We took estimates of years of life lost (YLLs) and years lived with disability (YLDs), by gender, for each region from data obtained from the editors of this volume. We then used those estimates to calculate the DALYs for male users, female users, and all users (YLL + YLD = DALY). We discounted the YLLs, YLDs, and DALYs using a 3 percent discount rate.

The second step was to estimate the avertable burden by treatment with methadone or buprenorphine. Using the population and prevalence data, we assumed, in the first instance, that 50 percent of those dependent on opioids entered treatment. In the sensitivity analysis, we varied this proportion from 25 to 75 percent coverage. On the basis of Caplehorn and others' (1994) meta-analysis, we assumed that MMT reduced mortality by 25 percent. In the sensitivity analysis, we varied the reduction from 15 to 35 percent (using the confidence intervals around the estimated reduction). We assumed that the reduction in mortality associated with BMT was 20 percent, which we varied in the sensitivity analysis from 10 to 30-percent. Finally, we assumed that those who were alive and in treatment experienced a 25 percent reduction in disability, consistent with the Dutch disability weights.

The third step was to estimate the burden for those not treated. For those users not in treatment, we calculated DALYs using the original mortality rates.

The fourth step was to estimate the total avertable burden from treatment with methadone or buprenorphine by (a) adding the results of the second and third steps, the revised DALYs for those in treatment, and the residual for those not in treatment and (b) subtracting those figures from the base case estimates.

The fifth step was to cost the interventions using data on MMT and BMT from Doran and others (2003). They estimated the cost of MMT at $A 1,415 and of BMT at $A 1,729 for six months of treatment. We converted these estimates into U.S. dollars and multiplied them by two to provide yearly estimates of-treatment costs of US$1,732 for MMT and US$2,117 for BMT.

We applied relative price weights for each region using the Western Pacific as the reference case (1.00). We calculated the relative price weights for each cost type using data provided by the World Bank. The prices are a reflection of the public health systems in each region, and as far as possible they reflect the opportunity cost of health care resources in these regions.

Results. Our results are presented in table 5.1. We explored various combinations of coverage and reductions in mortality for MMT and BMT. For each intervention, as coverage and reductions in mortality increased, the number of DALYs averted increased. The wide discrepancies in DALYs averted within regions primarily reflect differences in population-attributable fractions for HIV/AIDS. Costs increased as a consequence of increased coverage for both interventions, whereas results for cost-effectiveness differ by both intervention and mortality.

The cost-effectiveness analysis suggests that for MMT (with a coverage of 25, 50, or 75 percent and reductions in mortality of 35 percent) the cost in international dollars per DALY averted ranges from a low of $128 in Africa, with high child and adult mortality where the prevalence of illicit opioid dependence is low (0.01 percent), to a high of $3,726 in Eastern Europe, with low child and adult mortality where the prevalence of illicit opioid dependence is high (0.55 percent). Across all the regions, the average cost-effectiveness ratio for MMT (with 25, 50, and 75 percent coverage and 35 percent reduction in mortality) is estimated at $2,236 per DALY averted.

Assessment. The results shown in table 5.1 provide a first approximation of the potential avertable burden in DALYs if MMT and BMT were applied to 50 percent of the opioid-dependent population in each region. Because the methods and data used to estimate avertable DALYs are subject to certain limitations, those results should be considered preliminary.

RELEVANCE TO DEVELOPING COUNTRIES

Much of the epidemiological research on illicit opioid dependence, its disease burden, and its societal harm comes from Australasia, Europe, and the United States. The major exception is research on the role of injecting drug use in HIV transmission in developing countries (see, for example, Beyrer and others 2000; Yu and others 1998). In addition, research on the effectiveness and cost-effectiveness of interventions for illicit opioid dependence has been conducted primarily in developed countries (Ward, Hall, and Mattick 1998), with the exception of studies of the effectiveness of methadone treatment in Hong Kong, China (see, for instance, Newman and Whitehill 1979), and in Thailand (Vanichseni and others 1991), both of which showed comparable effectiveness to that found in developed countries (W. Hall, Ward, and Mattick 1998).

Translating findings on interventions for opioid dependence in developed countries into disease control priorities for opioid dependence in developing countries presents three major challenges. First, countries differ in the scale of illicit opioid use and in the resulting disease burden. This variation reflects the effects of differences in the prevalence of injecting and noninjecting opioid users; the dependent opioid users' access to treatment and health services for overdoses, bloodborne viruses, and other complications of drug use; the access to needle and syringe programs; the extent to which illicit opioid use is concentrated in socially disadvantaged minority groups; and the capacity of public health services

Table 5.1 Cost-Effectiveness Results

			Total effect (DALYs averted per 1 million population)													
			Africa		The Americas			Eastern Mediterranean		Europe			Southeast Asia		Western Pacific	
Treatment	Coverage (%)	Mortality (%)	AFR-D	AFR-E	AMR-A	AMR-B	AMR-D	EMR-A	EMR-D	EUR-A	EUR-B	EUR-C	SEAR-B	SEAR-D	WPR-A	WPR-B
MMT	25	15	125	79	153	107	158	179	105	117	48	198	63	48	39	26
MMT	50	15	251	158	306	214	316	358	210	234	96	397	126	97	77	53
MMT	75	15	376	237	459	321	474	538	315	352	144	595	190	145	116	79
MMT	25	25	150	81	184	121	173	217	151	141	59	264	93	70	51	35
MMT	50	25	300	163	369	243	347	435	303	283	117	527	185	140	102	70
MMT	75	25	450	244	553	364	520	652	454	424	176	791	278	211	152	105
MMT	25	35	174	84	216	136	189	256	198	165	69	329	122	92	63	43
MMT	50	35	349	167	432	272	378	511	396	331	139	657	244	184	126	87
MMT	75	35	523	251	648	408	566	767	594	496	208	986	367	276	189	130
BMT	25	10	113	78	137	100	150	160	82	105	43	166	48	38	32	22
BMT	50	10	226	156	274	199	301	320	163	210	85	331	97	75	65	44
BMT	75	10	339	234	412	299	451	480	245	315	128	497	145	113	97	67
BMT	25	20	138	80	169	114	166	198	128	129	53	231	78	59	45	31
BMT	50	20	275	160	337	228	332	397	256	258	107	462	156	119	89	61
BMT	75	20	413	240	506	342	497	595	384	388	160	693	234	178	134	92
BMT	25	30	162	82	200	129	181	237	175	153	64	296	107	81	57	39
BMT	50	30	324	165	400	258	362	473	350	307	128	592	215	162	114	78
BMT	75	30	487	247	601	386	543	710	524	460	192	888	322	243	171	117
Total costs (US$ per 1 million population)																
MMT	25	15, 25, 35	0.10	0.01	0.25	0.06	0.12	0.95	0.65	0.20	0.16	0.35	0.06	0.19	0.07	0.03
MMT	50	15, 25, 35	0.19	0.02	0.50	0.11	0.24	1.90	1.30	0.40	0.32	0.71	0.11	0.39	0.13	0.07
MMT	75	15, 25, 35	0.29	0.03	0.74	0.17	0.36	2.86	1.95	0.60	0.49	1.06	0.17	0.58	0.20	0.10
BMT	25	10, 20, 30	0.12	0.01	0.30	0.07	0.15	1.16	0.80	0.24	0.20	0.43	0.07	0.24	0.08	0.04
BMT	50	10, 20, 30	0.24	0.03	0.60	0.14	0.29	2.33	1.59	0.49	0.40	0.86	0.14	0.47	0.16	0.08
BMT	75	10, 20, 30	0.35	0.04	0.91	0.20	0.44	3.49	2.39	0.73	0.59	1.29	0.20	0.71	0.24	0.12
Cost-effectiveness (US$ per DALY averted)																
MMT	25, 50, 75	15	768	136	1,618	520	755	5,315	6,213	1,711	3,379	1,782	875	3,984	1,716	1,284
MMT	25, 50, 75	25	643	132	1,342	458	688	4,381	4,300	1,419	2,764	1,341	597	2,749	1,301	974
MMT	25, 50, 75	35	552	128	1,146	408	632	3,726	3,288	1,212	2,339	1,074	453	2,099	1,048	784
BMT	25, 50, 75	10	1,041	168	2,204	682	969	7,269	9,764	2,329	4,646	2,606	1,396	6,277	2,493	1,867
BMT	25, 50, 75	20	855	164	1,793	595	880	5,869	6,210	1,895	3,716	1,869	867	3,975	1,809	1,354
BMT	25, 50, 75	30	726	159	1,510	527	805	4,921	4,553	1,598	3,096	1,458	629	2,909	1,419	1,062
DALYs averted per US$1 million spent																
MMT	25, 50, 75	15	1,302	7,363	618	1,922	1,325	188	161	585	296	561	1,142	251	583	779
MMT	25, 50, 75	25	1,556	7,575	745	2,185	1,453	228	233	705	362	746	1,676	364	768	1,027
MMT	25, 50, 75	35	1,811	7,787	873	2,448	1,582	268	304	825	428	931	2,210	476	954	1,275
BMT	25, 50, 75	10	961	5,939	454	1,465	1,032	138	102	429	215	384	717	159	401	536
BMT	25, 50, 75	15	1,170	6,112	558	1,681	1,137	170	161	528	269	535	1,153	252	553	739
BMT	25, 50, 75	20	1,378	6,286	662	1,896	1,242	203	220	626	323	686	1,590	344	705	942

to monitor and respond to emerging infectious disease and drug-use epidemics. The burden is likely to be greatest in settings where the primary route of administration is injecting and where public and personal health services are poorly developed, as appears to be the case in Asia and in Eastern Europe.

Second, societal wealth and health care infrastructure affect-the capacity of developing societies to treat illicit opioid dependence. A country's capacity to provide opioid substitution treatment will be affected by the cost of oral opioid drugs, such as methadone, LAAM, and buprenorphine, and the existence of specialist drug treatment centers; trained medical, nursing, and pharmacy staff; and a drug regulatory system, which are required so as to deliver opioid substitution treatment safely and effectively. Few developing countries possess this infrastructure. However, examples exist of apparently successful drug substitution programs, using such tools as sublingual buprenorphine, that have been conducted with minimal resources in extremely poor settings (Crofts and others 1998).

Third, in societies with a sizable illicit opioid dependence problem, cultural attitudes and beliefs will affect societal responses, especially attitudes toward illicit opioid use and dependence (Gerstein and Harwood 1990). A critical determinant of the social response will be the relative dominance of moral and medical understandings of drug dependence in general and opioid dependence in particular. A moral model of addiction sees addiction as largely a voluntary behavior, in which case it is seen as an excuse for bad behavior that allows drug users to continue to take drugs without assuming responsibility for their conduct (Szasz 1985). In this view, drug users who offend against the criminal code should be imprisoned (Szasz 1985). This model is the dominant one in many developed societies, which imprison drug users at high rates without any effect on the prevalence of drug abuse. Countries that adopt punitive policies toward drug users are reluctant to embrace harm reduction measures, such as needle and syringe programs and opioid maintenance treatment (Ainsworth, Beyrer, and Soucat 2003). A medical model of addiction, by contrast, recognizes that dependent opioid users require specific treatment if the sufferer is to become and remain abstinent (see, for example, Leshner 1997).

These competing views will affect the societal acceptability of opioid maintenance and abstinence-oriented approaches to the treatment of opioid dependence (Cohen 2003). Those who have a moral view of addiction will tend to prefer drug-free and self-help approaches toward treatment. Supporters of medical models of addiction will favor some form of opioid substitution treatment and the provision of clean needles and syringes to reduce the transmission of bloodborne viruses by injecting opioid and other drug users. Stronger advocacy by international organizations and agencies is needed for the adoption of such harm reduction measures as needle and syringe programs and agonist substitution programs.

RESEARCH AND DEVELOPMENT

Two main areas are important for research and development. First, better estimates are needed of the prevalence of illicit opioid dependence and prospective studies of the morbidity and mortality that it causes in both developed and developing countries. These estimates are especially needed in countries where illicit opioid use is high because of their proximity to source countries. Second, we need evaluations of the effectiveness and cost-effectiveness of self-help, drug-free, and oral opioid substitution treatment in developing countries. A priority should be the identification of safe, innovative, and less expensive ways of effectively delivering culturally acceptable forms of opioid maintenance treatments in developing countries. This effort may require experimentation with a range of substitute opioids, such as buprenorphine, and cheaper options, such as codeine and opium tincture.

CONCLUSIONS: PROMISES AND PITFALLS

Illicit opioid use, especially injecting use, contributes to premature mortality and morbidity in many developed and developing societies. Fatal overdoses and HIV/AIDS resulting from the sharing of dirty injecting equipment are major contributors to-mortality and morbidity, and the economic costs of illicit opioid dependence are substantial. Illicit opioid dependence generates substantial externalities that are not included in burden-of-disease estimates, principally law enforcement costs incurred in handling drug dealing and property crime.

The most popular interventions for illicit opioid dependence in many developed societies have been law enforcement efforts to interdict the drug supply and enforce legal sanctions against the use of opioid drugs. One consequence of this strategy has been that most illicit opioid users have been exposed to-the least effective intervention: imprisonment for drug or property offenses. Prisons rarely take the opportunity to treat dependence using opioid maintenance or to reduce the harm caused by illicit opioid use by providing access to clean injecting equipment.

In treatment settings, the most popular interventions have been detoxification (which is not a treatment but a prelude to treatment) and drug-free treatment (which is the least attractive and the least effective in retaining opioid-dependent people in treatment). Opioid agonist maintenance treatment has been ambivalently supported in many developed societies despite its being the treatment for which there is the best evidence of effectiveness, safety, and cost-effectiveness. The range of opioid agonists available for maintenance treatment is increasing. A number of developed countries have approved the use of BMT, which the limited data suggest may be approximately equivalent to MMT in efficacy and cost-effectiveness. Opioid antagonists have a niche role in the treatment of opioid dependence because of poor compliance and an increased risk-of overdose on return to heroin use.

Their efficacy may improve with the development of long-acting injectable forms of the drug.

ANNEX 5.A: PREVALENCE OF USE, ADVERSE HEALTH EFFECTS OF AND INTERVENTIONS FOR-CANNABIS, COCAINE, AMPHETAMINES, AND-MDMA USE AND DEPENDENCE

Cannabis

Cannabis is the most widely used illicit drug globally, with about 150 million users, or 3.7 percent of the world's population age 15 and older (UNODCCP 2003). Patterns of cannabis use have been most extensively studied in Australia, Canada, the United States, and Europe (W. Hall and Pacula 2003). Europe generally has lower rates of use than Australia, Canada, and the United States, with the highest rates in Denmark, France and the United Kingdom (EMCDDA 2002; W. Hall and Pacula 2003). The limited data from developing countries suggest that, with some exceptions (for example, Jamaica and South Africa), rates of cannabis use are lower in Africa, Asia, the-Caribbean, and South America than they are in Europe and-in English-speaking countries (W. Hall, Johnston, and Donnelly 1999).

Surveys in the United States have found long waves of cannabis use among young people since 1975. Cannabis use increased during the 1970s to peak in 1979, before declining steadily between 1980 and 1991. Use rose sharply in 1992 and increased throughout the 1990s, before leveling off in the late 1990s (Johnston, O'Malley, and Bachman 1994a, 1994b). There was also a rise in cannabis use during the early 1990s in Australia, Canada, and some European countries (W. Hall and Pacula 2003).

The natural history of cannabis use in the United States typically begins in the mid to late teens and reaches its maximum in the early 20s before declining in the mid to late 20s. Only a minority of young adults continue to use cannabis into their 30s (Bachman and others 1997; Chen and Kandel 1995). Getting married and having children substantially reduces rates of cannabis use (Bachman and others 1997).

Cannibis use can have several adverse health effects, as discussed below.

Acute Effects of Cannabis Use. The most frequent unpleasant effects of cannabis use are anxiety and panic reactions, which most often occur in users who are unfamiliar with the drug's effects. Psychotic symptoms such as delusions and hallucinations may be experienced following very high doses. There are no cases of fatal cannabis poisoning in the medical literature, and the fatal dose in humans is likely to exceed what recreational users are able to ingest (W. Hall and Pacula 2003).

Cannabis intoxication impairs a wide range of cognitive and behavioral functions that are involved in driving an automobile or operating machinery (Beardsley and Kelly 1999; Jaffe 1985). It has been difficult to determine whether these impairments increase the risk of being involved in motor vehicle accidents (Smiley 1999). Studies of the effect of cannabis on driving performance on the road have found only modest impairments, because cannabis-intoxicated drivers drive more slowly and take fewer risks than drivers intoxicated by alcohol (Smiley 1999).

Cannabinoids are found in the blood of substantial proportions of persons killed in motor vehicle accidents (Bates and Blakely 1999; Chesher 1995; Walsh and Mann 1999), but these findings have been difficult to evaluate because they have not distinguished between past and recent cannabis use (Ramaekers and others 2004). More recent research using better indicators of recent cannabis use has found a dose-response relationship between cannabis and risk of motor vehicle crashes (Ramaekers and others 2004). Cannabis used in combination with alcohol substantially increases risk of accidents (Bates and Blakely 1999; Ramaekers and others 2004).

Health Effects of Chronic Cannabis Use. Cannabis smoke is a-potential cause of cancer because it contains many of the same carcinogenic substances as cigarette smoke (Marselos and Karamanakos 1999). Cancers have been reported in the aerodigestive tracts of young adults who were daily cannabis smokers (W. Hall and MacPhee 2002), and a case-control study has found an association between cannabis smoking and head and neck cancer (Zhang and others 1999). A prospective cohort study of 64,000 adults did not find any increase in rates of head and neck or respiratory cancers (Sidney and others 1997). Further studies are needed to clarify the issue.

Three studies of different types of cancer have reported an-association with maternal cannabis use during pregnancy (W. Hall and MacPhee 2002). There have not been any increases in the rates of these cancers that parallel increases in rates of cannabis use (W. Hall and MacPhee 2002).

High doses of cannabinoids impair cell-mediated and humoral immunity and reduce resistance to infection by bacteria and viruses in rodents (Klein 1999). Cannabis smoke impairs the functioning of alveolar macrophages, the first line of the body's immune defense system in the lungs. The doses that produce these effects have been very high, and extrapolation to the doses used by humans is complicated by the fact that tolerance to these effects develops (Hollister 1992). There is as yet no epidemiological evidence that rates of infectious disease are higher among chronic heavy cannabis users. Several large prospective studies of HIV-positive homosexual men have not found that cannabis use makes it more likely that HIV-positive men develop AIDS (W. Hall and Pacula 2003).

Chronic administration of tetrahydrocannabinol (THC) disrupts male and female reproductive systems in animals, reducing testosterone secretion and sperm production, motility, and viability in males and disrupting ovulation in females (Brown and Dobs 2002). It is uncertain whether cannabis use has these effects in humans because of the limited research on human males and females (Murphy 1999).

The use of cannabis during pregnancy is associated with smaller birthweight (English and others 1997; Fergusson, Horwood, and Northstone 2002), but it does not appear to increase the risk of birth defects (W. Hall and Pacula 2003). In some studies, infants exposed to cannabis during pregnancy show behavioral and developmental effects during the first few months after birth; these effects are smaller than those seen after tobacco use during pregnancy (Fried and Smith 2001).

The changes that cannabis smoking causes in heart rate and-blood pressure are unlikely to harm healthy young adults, but-they may harm patients with hypertension, cerebrovascular disease, and coronary atherosclerosis (Chesher and Hall 1999; Sidney 2002). One controlled study suggests that cannabis use can precipitate heart attacks in middle-aged cannabis users who have atherosclerosis in the heart, brain, and peripheral blood vessels (Mittleman and others 2001).

Regular cannabis smoking impairs the functioning of the large airways and causes chronic bronchitis (Tashkin 1999; Taylor and others 2002). Given that tobacco and cannabis smoke contain similar carcinogenic substances, it is likely that chronic cannabis smoking increases the risks of respiratory cancer (Tashkin 1999).

Psychological Effects of Chronic Cannabis Use. Psychological effects of chronic cannabis use can include a dependence syndrome, cognitive effects, and psychotic disorders.

Dependence Syndrome A cannabis dependence syndrome occurs in heavy chronic users of cannabis (American Psychiatric Association 1994). Regular cannabis users develop tolerance to THC. Some experience withdrawal symptoms on cessation of use (Kouri and Pope 2000), and some report problems controlling their cannabis use (W. Hall and Pacula 2003). The risk of dependence is about 1 in 10 among those who ever use the drug, between 1 in 5 and 1 in 3 among those who use cannabis more than a few times, and about 1 in 2 among daily users (W. Hall and Pacula 2003).

Cognitive Effects Long-term daily cannabis use does not severely impair cognitive function, but it may more subtly impair memory, attention, and the ability to integrate complex information (Solowij 1998; Solowij and others 2002). It remains uncertain whether these effects are due to the cumulative effect of regular cannabis use on cannabinoid receptors in the brain or whether they are residual effects of THC that will disappear after an extended period of abstinence (W. Hall and Pacula 2003).

Psychotic Disorders There is now good evidence that chronic cannabis use may precipitate psychosis in vulnerable individuals (see, for example, Arseneault and others 2002; van Os and others 2002; Zammit and others 2002). It is less likely that cannabis use can cause psychosis de novo, because the incidence of schizophrenia has either remained stable or declined while cannabis use has increased among young adults (Degenhardt, Hall, and Lynskey 2003).

Effects of Cannabis Use on Adolescents. Cannabis use has a number of effects on adolescents.

Gateway Hypothesis Adolescents in developed societies typically use alcohol and tobacco before using cannabis, which in turn, they use before using hallucinogens, amphetamines, heroin, and cocaine (Kandel 2002). Generally, the earlier the age of first use and the greater the involvement with any drug in the sequence, the more likely a young person is to use the next drug in the sequence (Kandel 2002). The role played by cannabis in this sequence remains controversial (W. Hall and Lynskey forthcoming; W. Hall and Pacula 2003).

The simplest hypothesis is that cannabis use has a pharmacological effect that increases the risk of using drugs later in the sequence. Equally plausible hypotheses are that it is due to a combination of (a) early recruitment into cannabis use of nonconforming and deviant adolescents who are likely to use alcohol, tobacco, and illicit drugs; (b) a shared genetic vulnerability to dependence on alcohol, tobacco, and cannabis; and (c)-socialization of cannabis users within an illicit drug–using subculture, which increases the opportunity, and encouragement to use other illicit drugs (W. Hall and Pacula 2003).

Adolescent Psychosocial Outcomes Cannabis use is associated with early withdrawal from high school, early family formation, poor mental health, and involvement in drug-related crime. In the case of each of these outcomes, the strong associations in cross-sectional data are more modest when account is taken of the fact that cannabis users show characteristics before they use cannabis that predict these outcomes. For example, they have lower academic aspirations and poorer school performance than peers who do not use cannabis (Lynskey and Hall 2000; Macleod and others 2004). Nonetheless, the evidence increasingly suggests that regular cannabis use adds to the risk of these outcomes in adolescents already at risk (W. Hall and Pacula 2003).

Interventions for Cannabis Dependence. Although many dependent cannabis users may succeed in quitting without professional help, some are unable to stop on their own and will need assistance to do so. There has not been a great deal of research on pharmacological treatments for cannabis dependence, although a recent study trialed divalproex sodium with promising results (Levin and others 2004). Limited research exists on the effectiveness of different types of psychosocial treatments for dependent cannabis use (Budney and others 2000; Copeland and others 2001; Stephens, Roffman, and Simpson 1994). These approaches have involved short-term cognitive behavioral treatments modeled on similar treatments for alcohol dependence, usually given in three to six sessions on an outpatient basis.

In all of these studies, rates of abstinence at the end of treatment have been modest (20 to 40 percent), and subsequent high rates of relapse mean that rates of abstinence

after 12 months have been very modest (Budney and Moore 2002). Nonetheless, treatment does substantially reduce cannabis use and problems. These outcomes are not very different from those observed in the treatment for alcohol and other forms of-drug dependence (Budney and Moore 2002). Much more research is needed before sensible advice can be given about the best ways to achieve abstinence from cannabis.

Cocaine

After cannabis, cocaine is one of the most widely used illicit drugs in developed and developing societies. Some 14 million people were estimated to have used cocaine globally in 2003, with demand for treatment second only to heroin (UNODCCP 2003). The highest rates of reported cocaine use—and the best data on trends in cocaine use—come from the United States, the world's largest cocaine market. Rates of cocaine use in the United States increased from the mid 1970s until 1985, when 5.7 million Americans age 12 and older reported using cocaine in the preceding month. Rates of cocaine use in the preceding month have declined steadily since 1985. In 2000, 11.2 percent of Americans over age 12 reported that they had used cocaine at some time in their lives, and 0.4 percent (800,000 people) reported weekly cocaine use (SAMHSA 2001). Among young U.S. adults age 18 to 25, lifetime prevalence was 14.9 percent in 2001, rising slightly to 15.4 percent in 2002 (SAMHSA 2003). In 2002, annual prevalence figures from student surveys were 15 percent lower than 1998 figures and 60 percent lower than 1985 figures (UNODCCP 2003). A more recent study of U.S. adults age 35 years found that 6 percent of men and 3 percent of women had used cocaine within the preceding 12 months (Merline and others 2004).

The reported prevalence of cocaine use in other developed societies is much lower than that in the United States. In Europe, for example, rates of lifetime cocaine use range from 0.5 percent to 5 percent (EMCDDA 2003), compared with 12.3-percent among American adults in 2001 (SAMHSA 2001). Rates of cocaine use in Australia resemble those in Europe, with 4.3 percent of adults reporting lifetime use (Darke and others 2000).

The prevalence of cocaine use is likely to be lower in developing societies, but the poor quality of the available data makes it difficult to be sure (UNDCP 1997). There probably has been an increase in cocaine use in some developing countries in recent years, but it is difficult to estimate the size of the increase (United Nations Commission on Narcotic Drugs 2000). The region with the highest rates of cocaine use among developing societies is likely to be Central and South America. The botanical source is indigenous to the region and has traditionally been used by local populations. Moreover, several nations in Central and South America have a history of production and export to global markets. Recent reports indicate that cocaine abuse is increasing in South America (UNODCCP 2003), and a recent household survey on drug abuse in São Paulo, Brazil, estimated cocaine prevalence at 2.1 percent (Galduroz and others 2003).

Adverse Health Effects of Cocaine. Most cocaine use is infrequent; regular cocaine use (monthly or more frequently) can be-a major public health problem. Regular cocaine users who inject cocaine or smoke crack cocaine are especially likely to develop dependence and to experience problems related to their cocaine use (Platt 1997). In the United States, it has been estimated that one in six of those who ever use cocaine become dependent on the drug (Anthony, Warner, and Kessler 1994). High rates of cocaine dependence are found among people treated for alcohol and drug problems and among arrestees in the United States (Anglin and Perrochet 1998).

In large doses, cocaine may be harmful in both cocaine-naive and cocaine-tolerant individuals (Platt 1997; Vasica and Tennant 2002). The vasoconstrictor effects of cocaine in large doses place great strains on a number of the body's physiological systems (McCann and Ricaurte 2000). Effects on the cardiovascular system can result in a range of difficulties, from chest pain to fatal cardiac arrests (Lange and Hillis 2001). Neurological problems include cerebral vascular accidents such as strokes or seizures. Other effects of cocaine can include gastrointestinal problems such as vomiting, colitis, and bowel infarction and respiratory problems such as asthma, respiratory collapse, pulmonary edema, and bronchitis. Hyperthermia may occur because of the increased metabolism, peripheral vasoconstriction, and inability of the thalamus to control body-temperature (Crandall, Vongpatanasin, and Victor 2002). Obstetric complications can include irregularities in placental blood flow, premature labor, and low neonate birthweight (Majewska 1996; Platt 1997; Vasica and Tennant 2002).

Adverse health effects from cocaine are potentially fatal and can occur among healthy users irrespective of cocaine dose and frequency of use (Lange and Hillis 2001; Vasica and Tennant 2002). Although the likelihood of health problems may increase with dosage and frequency of use, there is wide individual variation in reactions to cocaine and, therefore, no specific combination of conditions under which adverse health effects can be predicted. There is no antidote to cocaine overdose as there is for an overdose of heroin (Platt 1997).

The impact of cocaine on mental health is also complex. Although cocaine can produce feelings of pleasure, it may also result in negative psychological symptoms such as anxiety, depression, paranoia, hallucinations, and agitation (American Psychiatric Association 1994). Regular cocaine users experience high rates of psychiatric disorders. In the United States, regular cocaine users report high rates of anxiety and affective disorders (Gawin and Ellinwood 1988; Platt 1997). The repeated use of large doses of cocaine can also produce a paranoid psychosis (Majewska 1996; Manschreck and others 1988; Platt 1997; Satel and Edell 1991). People

who are acutely intoxicated by cocaine can become violent, especially those who develop a paranoid psychosis (Platt 1997).

Animal studies suggest that cocaine use may be neurotoxic in large doses—that is, it can produce permanent changes in the brain and neurotransmitter systems (Majewska 1996; Platt 1997). It is unclear whether use is also neurotoxic in humans. Previous studies have documented a variety of neuropsychological effects of cocaine use, including deficits in memory and problem solving (Beatty and others 1995; Hoff and others 1996; O'Malley and others 1992). More recently, a twin study indicated that cocaine may lead to impaired attention and motor skills up to one year after the conclusion of heavy use (Toomey and others 2003).

The method by which cocaine is administered can result in adverse health effects (Platt 1997). Snorting cocaine through the nose can lead to rhinitis, damage to the nasal septum, and loss of the sense of smell. Smoking cocaine can lead to respiratory problems, and injecting cocaine leads to the risks of infections and bloodborne viruses associated with all injecting drug use.

Users who inject cocaine, either on its own or in combination with heroin ("speedballs"), inject much more frequently than other injecting drug users and, as a consequence, engage in more needle sharing, take more sexual risks, and have higher-rates of HIV infection (Chaisson and others 1989; Schoenbaum and others 1989; van Beek, Dwyer, and Malcolm 2001). Associations between cocaine use and HIV risk-taking have been reported in Europe (Torrens and others 1991), Australia (Darke and others 1992), and the United States (Chaisson and others 1989). Recent Australian research has-indicated that injecting cocaine users report more problems related to injecting drug use—such as vascular problems, abscesses, and infections—than other injecting drug users (Darke, Kaye, and Topp 2002).

The link between cocaine use and HIV risk is not restricted to those who inject cocaine. Crack smoking has been linked to higher levels of needle risk, sexual risk taking, and HIV infection (Chaisson and others 1989; Chirgwin and others 1991; Desjalais and others 1992; Grella, Anglin, and Wugalter 1995). Two mechanisms probably underlie the relationship between cocaine use and HIV infection. First, the short half-life of cocaine promotes a much higher frequency of injecting by users than that seen in heroin injectors. Second, cocaine itself disinhibits and stimulates users, encouraging them to take greater risks with sexual activity and needle use (Darke and others 2000).

Cocaine is associated with a risk of intentional injuries and injuries in general. A recent review reported that 28.7 percent of people with intentional injuries and 4.5 percent of injured drivers tested positive for cocaine (Macdonald and others 2003). Users are also at risk of death from an accidental overdose of cocaine. A recent study of accidental deaths from drug-overdose in New York between 1990 and 1998 found that 70 percent of deaths were caused by cocaine, often in combination with opiates (Coffin and others 2003). The causes of cocaine-related deaths are usually related to cardiovascular complications (Vasica and Tennant 2002), but death may also be due to brain hemorrhage, stroke, and kidney failure (Brands, Sproule, and Marshman 1998). Injection of cocaine is most likely to cause an overdose, followed by smoking it, with intranasal use involving the least risk (Pottieger and others 1992).

Much less is known about nonfatal cocaine overdose. A study in Miami, Florida, found that 40 percent of users had overdosed on cocaine at least once (Pottieger and others 1992). More recently, a study in Brazil found that 20 percent of users had experienced an overdose, with 50 percent knowing someone who had died from an overdose (Mesquita and others 2001). A study in Sydney, Australia, found that 17 percent of injecting cocaine users and 6 percent of noninjecting cocaine users had ever overdosed, with 9 percent and 3 percent, respectively, overdosing in the preceding 12 months (Kaye and Darke 2003). Frequency of cocaine use, severity of dependence, and route of administration did not predict an overdose, supporting the view that cocaine overdose is an unpredictable event.

Interventions for Cocaine Dependence. Efforts at intervention have included pharmacological treatments as well as psychotherapy and cognitive behavioral therapy.

Pharmacological Interventions Despite much research effort there are no effective pharmacological treatments for cocaine dependence (Kreek 1997; McCance 1997; Mendelson and Mellon 1996; Nunes 1997; Silva de Lima and others 2002; van den Brink and van Ree 2003). Attempts have been made to develop longer-acting agonist drugs that act on the same molecular targets as cocaine without producing its euphoric effects (for example, methylphenidate) (Kreek 1997) or that block its rewarding and euphoric effects (McCance 1997). There has also been a search for drugs that indirectly change the effects that cocaine has on the brain by acting on other neurotransmitter systems, such as the serotonergic system (for-example, fluoxetine) (McCance 1997). None of these approaches has produced an effective pharmacotherapy for cocaine dependence (Lima and others 2003; Platt 1997; Soares and others 2003).

Development of pharmacological therapies for cocaine dependence and their evaluation is complicated by the multiple interactive processes that may have contributed—for example, coexisting substance abuse or mental health issues (Mendelson and Mellon 1996). Many of the approaches to the-treatment of cocaine dependence have also been used in treating patients with alcoholism and other substance abuse disorders.

A number of drugs have been used to treat cocaine based on their relevance to the symptoms of cocaine dependence (Silva-de Lima and others 2002; van den Brink and van Ree 2003). The frequency of depressive symptoms has led to the exploration of the effectiveness of antidepressant drugs. Desipramine has been used with mixed effectiveness for

cocaine detoxification and the maintenance of abstinence (Covi and others 1994; Gawin, Kleber, and Byck 1989), but it appears to be most effective when there is evidence of previous or consequent symptoms of depression. Other antidepressants-have been used with mixed results: imipramine and trazodone have been found to have more adverse effects than desipramine, and fluoxetine has not been found to be effective (Mendelson and Mellon 1996). A recent systematic review found no current evidence to support the use of antidepressants in the treatment of cocaine dependence (Lima and others-2003).

Dopamimetic drugs have also been used to treat cocaine dependence; such treatments are based on the action of cocaine to block reuptake of dopamine. Unfortunately, although some of these drugs are relatively effective, they also result in quite severe adverse effects (Mendelson and Mellon 1996). Current evidence does not support the clinical use of dopamine agonists for cocaine dependence (Soares and others 2003). Opioid antagonists (for example, naltrexone) or opioid mixed agonist-antagonists (such as buprenorphine) have been explored, on the basis that cocaine dependence may be accompanied by dependence on opiates. Although there have been problems with compliance with naltrexone therapy (National Research Council Committee on Clinical Evaluation of Narcotic Antagonists 1978), buprenorphine has shown promising preclinical and clinical trial results (Kosten, Kleber, and Morgan 1989). Other promising directions include cannabinoid receptor antagonists and cortisol synthesis inhibitors (van den Brink and van Ree 2003) and vaccination against the effects of cocaine (Kantak 2003), but there is as yet no evidence on the effectiveness of any of these interventions.

Acupuncture has also been used to treat cocaine dependence. Auricular acupuncture is frequently used, but the small number of trials that have been conducted have not provided sufficient evidence of effectiveness (van den Brink and van Ree 2003).

Psychotherapy and Cognitive Behavioral Therapy The lack of evidence for pharmacological therapy means that treatment for-cocaine dependence currently relies on cognitive behavior therapies combined with contingency management strategies. Unfortunately, psychosocial treatments for cocaine dependence are also of limited effectiveness. Treatments such as therapeutic communities, cognitive behavioral treatments, contingency management, and 12 step–based self-help approaches benefit cocaine-dependent people by reducing their rates of cocaine use and improving their health and well-being, but rates of relapse to cocaine use after treatment remain high (Platt 1997).

Mendelson and Mellon (1996) conclude that there are no specific cognitive or behavioral interventions that are uniquely effective in treating cocaine dependence. However, some success has been demonstrated with incentive-based programs in which rewards are provided for urine samples that are free of cocaine, although there is doubt about whether results are sustained (Roozen and others 2004). Such programs are generally more effective when the patient's family and friends are involved (Higgins and others 1994). Petry and others (2004) suggested that contingency management was effective in reducing cocaine use in a community-based treatment setting. They found that the benefits of treatment depended on the magnitude of reward, with those earning up to US$240 obtaining better results than those earning up to US$80. They suggested that this form of intervention may work best for people with more severe dependence on cocaine.

A multicenter investigation examining the efficacy of four psychosocial treatments for cocaine-dependent patients concluded that individual drug counseling in combination with group drug counseling showed the most promise for effective treatment of cocaine dependence over two forms of traditional psychotherapy (Crits-Christoph and others 1999). Community reinforcement involving an intensive, biopsychosocial, multifaceted approach to lifestyle change has shown positive effects over four to six weeks and has the advantage of being tailored to individual goals (Roozen and others 2004).

The few studies of the long-term effects of treatment have not shown particularly encouraging results. A one-year follow-up of the U.S. Drug Abuse Treatment Outcome Studies reported that reductions in the use of cocaine in the year following treatment were associated with longer duration of treatment, particularly six months or more in long-term residential or outpatient treatments (Hubbard, Craddock, and Anderson 2003). A five-year national follow-up study of 45 U.S. treatment programs found that only 33 percent of the sample had highly favorable outcomes (Flynn and others 2003).

Amphetamines

According to WHO, amphetamines and methamphetamines are the most widely abused illicit drugs after cannabis, with an estimated 35 million users worldwide (Rawson, Anglin, and Ling 2002).

In Australia, the lifetime prevalence of amphetamine use is between 6 and 8 percent in the general population, making amphetamines the most commonly used illicit drug after cannabis during that period (Makkai and McAllister 1998). In 1998, the lifetime prevalence of amphetamine use was highest (25 percent) among male users age 20 to 29.

The use of amphetamines is generally less frequent than that of opioids (Darke and Hall 1995; Darke, Kaye, and Ross 1999; W. Hall, Bell, and Carless 1993; Hando, Topp, and Hall 1997; Vincent and others 1998). This pattern is no doubt due to the physical and psychological toll taken by regular amphetamine use. Although such use is less frequent overall, however, there is widespread bingeing on amphetamines, with frequent use over several consecutive days, which may be followed by benzodiazepine use to "come down." Polydrug use is particularly common among amphetamine users, who show a marked preference for stimulant drugs such as hallucinogens

and cocaine (Darke and Hall 1995; Hando and Hall 1994; Vincent and others 1998).

Globally, Europe is the main center of amphetamine production, particularly Belgium, the Netherlands, and Poland, with production increasing in Eastern Europe (UNODCCP 2003). Half of all Western European countries reported an increase in amphetamine abuse in 2000, but in 2001 the figure fell to 33 percent (UNODCCP 2003). Lifetime use of amphetamines is reported to be between 0.5 percent and 6 percent among European Union countries, with the exception of the United Kingdom, where the figure is 11 percent. Denmark and Norway also have relatively higher rates of use (EMCDDA 2003).

Adverse Health Effects of Amphetamine Use. Amphetamine users who inject the drug are at high risk of bloodborne infections through needle sharing. Amphetamine users are as likely as opioid users to share injection equipment (Darke, Ross, Cohen, and others 1995; Darke, Ross, and Hall 1995; W. Hall, Bell, and Carless 1993; Hando and Hall 1994; Kaye and Darke 2000; Loxley and Marsh 1991). In addition, the youth of amphetamine users places them at risk of sexual transmission of diseases such as HIV and hepatitis B virus (although not hepatitis C). Primary amphetamine users have been demonstrated to be a sexually active group, and small proportions engage in paid sex to support their drug use (Darke, Ross, Cohen, and others 1995; Hando and Hall 1994). Among gay and bisexual men, amphetamines may be used to enhance sexual encounters, which may lead to unprotected anal intercourse and increased risk of HIV infection (Urbina and Jones 2004).

High-dose amphetamine use, especially by injection, can result in a schizophreniform paranoid psychosis, associated with loosening of associations, delusions, and hallucinations (Gawin and Ellinwood 1988; Jaffe 1985). The psychosis could be reproduced by the injection of large doses in addicts (Bell 1973) and by the repeated administration of large doses to normal volunteers (Angrist and others 1974).

High proportions of regular amphetamine injectors describe symptoms of anxiety, panic attacks, paranoia, and depression. The emergence of such symptoms is associated with injecting the drugs, greater frequency of use, and dependence on amphetamines (W. Hall and others 1996; McKetin and Mattick 1997, 1998). Recent evidence also suggests that women may experience more emotional effects of amphetamine intoxication than men and higher rates of anorexia nervosa than women without amphetamine disorders (Holdcraft and Iacono 2004).

In sufficiently high doses, amphetamines can be lethal (Derlet and others 1989). However, the risk is low compared with the high risks of overdose associated with central nervous system depressants such as heroin. Typically, amphetamine-related deaths are associated with the effects of amphetamines on the cardiovascular system—for example, cardiac failure and cerebral vascular accidents (Mattick and Darke 1995).

There is evidence that amphetamines are neurotoxic (Robinson and Becker 1986). Evidence from animal studies indicates that heavy amphetamine use results in dopaminergic depletion (Ellison 1992; Fields and others 1991). The few studies of the neuropsychological effects of amphetamine abuse report findings similar to those found with cocaine abuse. Deficits in memory and attention have been attributed to amphetamine use (McKetin and Mattick 1997, 1998). More recently, a twin study indicated that amphetamine abuse might lead to impaired attention and motor skills up to one year after the conclusion of heavy use (Toomey and others 2003).

Interventions for Amphetamine Dependence. Treatment for methamphetamine abuse has been a relatively recent development and has generally been based on previous treatments for cocaine abuse (Huber and others 1997). Cretzmeyer and others (2003) reviewed treatments for methamphetamine abuse, noting that there has been little research on the effectiveness of drug treatment, probably because many amphetamine users use multiple drugs. The combination of methamphetamine use with use of marijuana or other sedating drugs indicates that effective treatments need to address the use of multiple drugs. A Cochrane Review concluded that evidence for success in treatment of amphetamine dependence is very limited, with no-pharmacological treatment demonstrated to be effective (Srisurapanont, Jarusuraisin, and Kittirattanapaiboon 2003).

An early study explored the use of aversion therapy in a multimodal treatment program using educational groups, individual counseling, occasional family counseling, and aftercare planning. The intervention paired an aversive stimulus (either chemical or electrical) with the act of using methamphetamines. Cocaine use was also treated in this way. After 12-months, 53 percent of patients were abstinent and the researchers noted that their results were promising, despite a number of limitations to the study (Frawley and Smith 1992).

An intervention combining imipramine, a tricyclic antidepressant, with intensive group counseling has been evaluated with cocaine and methamphetamine abusers. Patients received either a low or higher dose (as needed) of imipramine, as well as intensive group counseling and access to medical and psychiatric care. Those who received the higher dose stayed in treatment longer, but the results did not support the use of imipramine for methamphetamine abuse (Galloway and others 1994).

The Matrix Program for methamphetamine and cocaine abusers has also been evaluated. The Matrix Program uses a cognitive behavioral approach with an emphasis on relapse prevention (Huber and others 1997). The study evaluated the effectiveness of three conditions: Matrix treatment alone, Matrix treatment plus desipramine, and Matrix treatment plus placebo (Shoptaw and others 1994). The researchers concluded that those who received more Matrix treatment

had better abstinence rates than those who had less treatment but that desipramine had no effect on treatment outcome.

J. Hall and others (1999) conducted an evaluation of the effectiveness of the Iowa Case Management Project. The project was designed to supplement interventions provided by a drug abuse treatment agency and is a comprehensive social work intervention, including outreach activities and provision of limited emergency funds. The results of the evaluation showed that comprehensive case management was effective in improving employment status among amphetamine users subsequent to treatment. There was an almost significant lower incidence of depression among those who received the program compared with controls. Drug use decreased significantly for clients in both control and program conditions.

More recently, an Australian study evaluated the effectiveness of brief cognitive-behavioral interventions among regular users of amphetamines (Baker, Boggs, and Lewin 2001). The researchers found a clinically significant reduction in daily amphetamine use among the intervention groups compared with controls and concluded that further studies of brief cognitive-behavioral interventions are feasible and warranted. Although some promising interventions have been identified to assist methamphetamine abusers, no single treatment option has yet been established as better than any other in a randomized controlled trial (Cretzmeyer and others 2003).

Methylenedioxymethamphetamine

Methylenedioxymethamphetamine is more widely known as-*ecstasy* or *MDMA*. In Australia, the lifetime prevalence of MDMA use increased from 1 percent of the population in 1988 to 4.6 percent (about one in 20 persons) in 1998, with 2.3 percent reporting MDMA use in the preceding 12 months (Topp and others 1998). In 2001, 6.1 percent of Australians age 14 years or older reported lifetime use of MDMA, with 2.9 percent reporting use within the preceding year (Degenhardt, Barker, and Topp 2004). Rates of use are generally higher among males than females (3.1 percent versus 1.5 percent). MDMA use in the preceding 12 months is most common among those age 20-to 29 (5 percent of females and 12 percent of males) (Topp and others 1998).

The availability of MDMA has also increased, as indicated by the proportion of the population who have been offered MDMA (from 4 percent in 1988 to 7 percent in 1991) (Makkai and McAllister 1998), with 14 percent of those age 14 to 29 reporting that they had been offered MDMA in the preceding year.

Research suggests that the pattern of MDMA use changed during the 1990s (Topp and others 1998). Users of MDMA are commencing use at a younger age, and they appear to be using larger doses more frequently. The incidence of bingeing on MDMA appears to have increased, as does the prevalence of the parenteral use of this drug. The increase in the use of MDMA by injection has been noted among surveys of MDMA users and of injecting drug users generally.

An examination of trends in the United States suggested that, although the use of MDMA has increased over time, its prevalence is significantly less than that of other drugs of abuse (Yacoubian 2003b). A study of 14,520 U.S. college students indicated 6 percent lifetime use of MDMA, 3 percent within the preceding 12 months, and 1 percent within the preceding 30-days. Those who had used MDMA in the preceding 12-months were more likely to be white and a member of a fraternity or sorority and to have used a range of other drugs (Yacoubian 2003a). Rates of use are much higher in surveys of club attendees. A recent U.S. survey found 86 percent reporting lifetime use, 51 percent 30-day use, and 30 percent use within the preceding 2 days (Yacoubian and others 2003).

Abuse of MDMA had showed signs of decreasing in Western Europe but has recently shown signs of increase (UNODCCP 2003). Although MDMA use appears to be still diffusing, in 2003 only four countries (Ireland, the Netherlands, Spain, and the United Kingdom) reported a rate of more than 3 percent use among young adults in the preceding 12 months (EMCDDA 2003). In the United States, use declined in 2002 for the first time, but it increased in other regions, particularly the Caribbean, parts of South America, Oceania, Southeast Asia, the Near East, and southern Africa (UNODCCP 2003). Lifetime experience of MDMA is reported to range from 0.5-percent to 5 percent in European Union countries, with use more common in the Netherlands (EMCDDA 2003).

Population survey findings from New Zealand reported an increase in the preceding-year use of MDMA from 1.5 percent in 1998 to 3.4 percent in 2001. The increase was particularly evident among young men age 20 to 24 (from 4.3 percent to 12.5 percent) (Wilkins and others 2003).

Adverse Health Effects of MDMA. Early studies of MDMA use in Australia and the United States documented relatively few problems associated with the drug's use (Beck 1990; Beck and Rosenbaum 1994; Downing 1986; Solowij, Hall, and Lee-1992). A survey of 100 MDMA users (Solowij, Hall, and Lee-1992) found that the most common adverse effects were the side effects of acute use, such as appetite loss, dry mouth, palpitations, and bruxism (teeth grinding). Among the few heavy users in the study, only two reported feeling dependent on the drug.

With a change in the pattern of MDMA use in Australia, there has been an increase in the MDMA-related harms reported (Topp and others 1998). Some of the acute physical and psychological adverse effects that MDMA users have attributed to the use of this drug include energy loss, irritability, muscular aches, insomnia, and depression. More chronic adverse effects were also reported, including weight loss, depression, energy loss, insomnia, anxiety, and teeth problems. A recent U.K. study of 430 regular users of MDMA reported that 83 percent of participants reported low mood and 80 percent experienced impaired concentration. Long-term effects of-MDMA included the development of tolerance to MDMA

(59 percent), impaired ability to concentrate (38 percent), and depression (37 percent) (Verheyden and others 2003).

Physical symptoms that were perceived as being due to MDMA use alone (Topp and others 1998) included an inability to urinate, blurred vision, vomiting, numbness or tingling, loss of sexual urge, and hot and cold flushes. As with amphetamines, the use of MDMA to facilitate sexual encounters may lead to risky sexual behavior and risk of sexually transmitted infections such as HIV. Studies of gay and bisexual men have found an association between MDMA use and high-risk sexual behavior (Urbina and Jones 2004).

MDMA has been implicated in a growing number of deaths, both in Australia and in other countries (Henry, Jeffreys, and Dawling 1992; Solowij 1993; White, Bochner, and Irvine 1997). Although the reasons for extreme reactions have yet to be clearly determined, deaths have most often been attributed to hyperthermia when MDMA was used at dance venues. A combination of sustained exertion, high ambient temperatures, and inadequate fluid replacement appears to compound the effect of MDMA on thermoregulatory mechanisms, causing a rapid and fatal rise in body temperature (Topp and others 1998). Some deaths have been attributed to excessive water consumption, which causes cerebral edema (Cook 1996; Matthai and others 1996).

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Conclusion

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The disorders and conditions covered in the five chapters of this volume (mental and neurological disorders, learning and developmental disabilities, alcohol, illicit opiate abuse) are all characterized by low current levels of use of effective interventions. For common mental disorders (Chapter 1), primary care treatment is, at present averting only 3 to 8 percent of the existing disease burden. In the case of epilepsy (Chapter 2), 90% of people with this condition living in developing countries are inadequately treated (Meinardi and others 2001). The coverage of treatment interventions for severe mental disorders (Chapter 1) and alcohol use disorders (Chapter 4) is also low (Kohn and others 2004). While the low level of coverage with interventions underlines the need for substantial enhancement in resources, this also presents an opportunity in that the cost-effectiveness data can be used to focus enhanced resources to those interventions that are shown to give the best value for money. As mental, neurological developmental and substance use disorders move up in the public health agenda of developing countries the need and also the opportunity for making data-based decisions is substantial.

Developing countries face substantial challenges in providing services for these disorders. Recent data from WHO's Project Atlas (WHO 2005a; Saxena and others 2006; WHO 2005b; Belfer and Saxena 2006) clearly demonstrate the serious limitations of health care system in most developing countries in delivering care to people with mental, neurological and substance use disorders.

One-fifth of all countries and nearly half of all low income countries spend less than 1% of their health budget on mental health. More than half of all low and middle income countries have less than one psychiatrist and one psychiatric nurse per 100,000 population. The situation for neurological care is even worse - the corresponding figures for neurologists and neurological nurses being 61% and 71%. Training of fresh human resources is slow; 35% of all low income countries have no training facilities for psychiatrists, the corresponding percentage for neurologist training being 52%. Learning and developmental disabilities affect 10 to 20% of children in high income countries, this percentage may be even higher in low and middle income countries (Chapter 3). However, child and adolescent mental health resources are extremely rudimentary in most low and middle income countries (WHO 2005b). Most of the needs of individuals with learning and developmental disabilities consequently remain unmet in developing countries. Substance use disorders also remain seriously under-resourced in these countries. Thirty-four percent of all low and middle income countries have no substance abuse policy, in spite of the large and increasing prevalence and burden of these problems.

The gap in resources is not confined to their quantity. The quality of resources, the way they are allocated and the services provided are often extremely poor in not only low and middle income, but even in many high income countries. For example, in spite of years of debate and established consensus about the need for reducing the hegemony of psychiatric hospitals and increasing community-based mental health care, nearly two-thirds of all mental health beds still remain in large mental hospitals (WHO 2005a). The training of health care professionals in mental, neurological, developmental and substance abuse areas is rudimentary and often confined to drug treatment, leaving the psychosocial needs completely unmet.

Services systems for these conditions are often so poorly resourced that even the few professionals who staff them have little incentive to remain there. Migration is the result, further depleting the scare resources (Patel 2003; Ndetei, Karim, and Mubbashar 2004). This phenomenon, though a part of the larger picture of migration of health professionals in general (WHO 2006, Pond and McPake 2006) is especially disruptive to the mental health systems in countries already suffering an extreme scarcity of mental health professionals.

While the evidence for widespread use of several interventions against these disorders is strong, interventions can only be delivered by an effective health care system (Mills, Rasheed, and Tollman 2006). In view of the poorly organized and resourced service systems for mental, neurological, developmental and substance use disorders in developing countries, there is a need is to go beyond specific interventions and study service delivery in these settings. Policy-makers do not budget for interventions, they budget for facilities and services. And facilities and services are not established for delivering single interventions, but for a variety of them across disorder categories. Evaluation of a mental health care package (Chapter 1) is a step in the right direction, though the disorders and interventions included in this package are few and the regional estimates need to be further adapted to the specific situation in individual countries before these

estimations can be used for actual planning and resource allocation. Cost-effectiveness data on service packages in the area of neuro-psychiatric disorders will perhaps show higher gains due the inherent synergies of efforts.

The five chapters included in this volume provide a variety of extremely valuable information; however a few salient results, that have substantial policy implications are worth recapitulating here.

1. Community care is better than hospital care:
   Community-based services are more cost-effective than hospital-based services for severe mental disorders like schizophrenia and bipolar disorders. Community-based services are preferable to hospital-based services for many other reasons including far less possibilities of human rights violations. WHO has recommended community-based services as one of the basic strategies for expanding mental health services (WHO 2001). However, it should be noted that of the approximately 1.84 million psychiatric beds in the world, 68.6% are still in mental hospitals (WHO 2005a). This percentage is higher at 74.4% in low income countries compared to 55.0% of high income countries (WHO 2005a). Atlas data also show that more than half of all low and lower middle income countries do not have any community mental health care. Clearly, establishing or strengthening community mental health services is an urgent need for low- and middle-income countries.

2. Drugs are not a panacea:
   A combination of drug and psychosocial treatment is more cost-effective for schizophrenia and bipolar disorders than drug treatment alone. The effectiveness of psychosocial interventions for severe mental disorders has been recognized clinically for a long time and has also been demonstrated in research (Bustillo and others 2001; Roder and others 2006). Cost-effectiveness data further strengthen the case for psychosocial interventions being a core component of the care package for these disorders. Investment of resources into creating capacity for psychosocial interventions seems to be a sound strategy even in low- and middle-income countries.

3. Older drugs are relatively cost-effective:
   Clinicians as well as health services in developing countries are coming under increasing pressure by the pharmaceutical industry to use newer drugs for mental and neurological disorders. Cost-effectiveness data presented here clearly demonstrate that older drugs (antipsychotics, antidepressants and antiepileptics) are more cost-effective than newer drugs in developing countries, hence recommended for widespread use in public health care systems. Indeed Phenobarbital as an intervention for epilepsy is many-fold more cost-effective than any other intervention for it, clearly establishing it as the first choice for this common disorder. These results corroborate recommendations by WHO (WHO 2001) and observations made in other recent publications (Chisholm 2005; Kwan and Brodie 2004).

4. Population-level prevention can be cost-effective:
   The data presented in this volume demonstrate that population-level prevention can be cost-effective for some mental health and substance abuse conditions. The most persuasive examples come from the chapter on alcohol. Increased taxation on alcoholic beverages as a public health strategy has been shown to be cost-effective in many regions (Chisholm and others 2004). Other population level strategies that are cost-effective in some regions are advertising bans on alcoholic beverages, reduced access to alcoholic beverage retail outlets and random breath testing of motor vehicle drivers. The clear message to policy-makers is that population-level prevention of high-risk alcohol use and consequent problems is recommended on the cost-effectiveness evidence. This message is especially important for many developing countries where overall alcohol consumption or its high-risk use are increasing rapidly. Examples of population level interventions that prevent neurological disorders or disabilities include laws requiring motorcyclists to wear helmets, laws against drunk driving, public health policies to provide better perinatal care and folic acid fortification of the food supply though complete cost-effectiveness data for the last of these especially for developing countries are not yet available.

Overall, the evidence provided in the five chapters shows that interventions for prevention and treatment of mental, neurological, developmental and substance use disorders are moderately cost-effective, quite comparable to many interventions for other non-communicable chronic diseases. The evidence seems adequate to keep these interventions among the core public health strategies for decreasing disease burden in developing countries.

Though currently available evidence is adequate to take some policy steps and also to enhance the overall resources allocated to prevention and care of mental, neurological, developmental and substance use conditions and disorders, there are many unanswered questions. The chapters have identified a research agenda that needs to be pursued with vigour. One of the problems common to each of these areas is lack of data from developing countries. Much of the information that forms the basis for cost-effectiveness estimates comes from developed countries and is extrapolated and applied to developing countries. While this may be acceptable in the current state of the field, the margin of error is high in all such cases. The disability associated with mental, neurological, developmental and substance use disorders can be quite different across regions, countries and also across populations (e.g. urban versus rural) within the same country. The cost of providing an intervention also varies

substantially across countries and even within a country. Moreover, these costs are changing over time, sometimes rather quickly like when a medicine goes off-patent. These variations make generation of national and local data and its monitoring over time essential. In absence of such data, we may be using interventions that are of uncertain cost-effectiveness in a particular setting, but the bigger concern is that we may not be using interventions that have a high cost-effectiveness within that setting.

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