## CHAPTER 3

### neurological disorders

a public health approach

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This chapter consists of 10 sections that focus on the public health aspects of the common neurological disorders as outlined in the box. Although notable differences exist between relevant public health issues for each neurological disorder, most sections cover the following topics: diagnosis and classification; etiology and risk factors; course and outcome; magnitude (prevalence, incidence, distribution by age and sex, global and regional distribution); disability and mortality; burden on patients’ families and communities; treatment, management and rehabilitation; delivery and cost of care; gaps in treatment and other services; policies; research; and education and training.
3.1 Dementia

Dementia is a syndrome caused by disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgement. Consciousness is not clouded. Dementia mainly affects older people: only 2% of cases start before the age of 65 years. After this the prevalence doubles with every five-year increment in age. Dementia is one of the major causes of disability in later life.

There are very many underlying causes of dementia. Alzheimer’s disease (AD), characterized by cortical amyloid plaques and neurofibrillary tangles is the most common, accounting for one half to three quarters of all cases. Vascular dementia (VaD) is diagnosed when the brain’s supply of oxygenated blood is repeatedly disrupted by strokes or other blood vessel pathology, leading to significant accumulated damage to brain tissue and function. The distinction between AD and VaD has been called into question, given that mixed pathologies are very common. Perhaps vascular damage is no more than a cofactor accelerating the onset of clinically significant symptoms in people with AD. There are a few rare causes of dementia that may be treated effectively by timely medical or surgical intervention—these include hypercalcaemia, subdural haematoma, normal pressure hydrocephalus, and deficiencies of thyroid hormone, vitamin B12 and folic acid. For the most part, altering the progressive course of the disorder is unfortunately not possible. Symptomatic treatments and support can, however, transform the outcome for people with dementia and their caregivers.

Alzheimer and other dementias have been reliably identified in all countries, cultures and races in which systematic research has been carried out, though levels of awareness vary enormously. In India, for example, while the syndrome is widely recognized and named, it is not seen as a medical condition. Indeed, it is often regarded as part of normal ageing (1).

For the purpose of making a diagnosis, clinicians focus in their assessments upon impairment in memory and other cognitive functions, and loss of independent living skills. For carers and, arguably, for people with dementia, it is the behavioural and psychological symptoms of dementia (BPSD) that are most relevant. Nearly all studies indicate that BPSD are an important cause of caregiver strain. They are a common reason for institutionalization as the family’s coping reserves become exhausted. Problem behaviours may include agitation, aggression, calling out repeatedly, sleep disturbance (day–night reversal), wandering and apathy. Common psychological symptoms include anxiety, depression, delusions and hallucinations. BPSD occur most commonly in the middle stage of dementia (see also the section on Course and outcome, below). Despite their significance, there has been relatively little research into BPSD across cultures. One might anticipate that cultural and environmental factors could have a strong influence upon both the expression of BPSD and their treatment.
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of BPSD and their perception by caregivers as problematic (2). Behavioural and psychological symptoms appear to be just as common in dementia sufferers in developing countries (3). In some respects the developing country caregivers were more disadvantaged. Given the generally low levels of awareness about dementia as an organic brain condition, family members could not understand their relative’s behaviour, and others tended to blame the carers for the distress and disturbance of the person they were looking after.

ETIOLOGY AND RISK FACTORS

The main risk factor for most forms of dementia is advanced age, with prevalence roughly doubling every five years over the age of 65 years. Onset before this age is very unusual and, in the case of AD, often suggests a genetic cause. Single gene mutations at one of three loci (beta amyloid precursor protein, presenilin1 and presenilin2) account for most of these cases. For late-onset AD both environmental (lifestyle) and genetic factors are important. A common genetic polymorphism, the apolipoprotein E (apoE) gene e4 allele greatly increases risk of going on to suffer from dementia; up to 25% of the population have one or two copies (4, 5). However, it is not uncommon for one identical twin to suffer from dementia and the other not. This implies a strong influence of the environment (6). Evidence from cross-sectional and case–control studies suggests associations between AD and limited education (7) and head injury (8, 9), which, however, are only partly supported by longitudinal (follow-up) studies (10). Depression is a risk factor in short-term longitudinal studies, but this may be because depression is an early presenting symptom rather than a cause of dementia (11). Recent research suggests that vascular disease predisposes to AD as well as to VaD (12). Smoking seems to increase the risk for AD as well as VaD (13). Long-term follow-up studies show that high blood pressure (14, 15) and high cholesterol levels (15) in middle age each increase the risk of going on to develop AD in later life.

Reports from epidemiological studies of protective effects of certain prescribed medication, non-steroidal anti-inflammatory drugs, hormone replacement therapy (HRT) and cholesterol-lowering therapies are now being investigated in randomized controlled trials. The randomized controlled trial of HRT in postmenopausal women indicated, against expectation, that it increased rather than lowered the incidence of dementia.

Despite many investigations, far too little is still understood about the environmental and lifestyle factors linked to AD and other dementias. It may be that the focus on research in developed countries has limited possibilities to identify risk factors. Prevalence and incidence of AD seem to be much lower in some developing regions (see the section on Epidemiology and burden, below). This may be because some environmental risk factors are much less prevalent in these settings. For example, African men tend to be very healthy from a cardiovascular point of view with low cholesterol, low blood pressure and low incidence of heart disease and stroke. Conversely, some risk factors may only be apparent in developing countries, as they are too infrequent in the developed economies for their effects to be detected; for example, anaemia has been identified as a risk factor in India (16).

COURSE AND OUTCOME

Dementia is usually a progressive disease and can be cured only if a reversible condition is identified as a cause and treated effectively. This happens in a small number of cases in the developed world, but could be more common in developing countries, where relevant underlying physical conditions (including marked nutritional and hormonal deficiencies) are more common.

Dementia affects every person in a different way. Its impact can depend on what the individuals were like before the disease: their personality, lifestyle, significant relationships and physical health.

The problems linked to dementia can be best understood in three stages (see Box 3.1.1).
Times are given as guidelines only — sometimes people can deteriorate more quickly and sometimes more slowly. Dementia reduces the lifespan of affected persons. In the developed, high income countries, a person with dementia can expect to live for approximately 5–7 years after diagnosis. In low and middle income countries, diagnosis is often much delayed, and survival in any case may be shorter. Again, of course, there is much individual variation — some may live for longer, and some may live for shorter times because of interacting health conditions.

Symptoms of dementia in early, middle and late stage of the disease are given in Box 3.1.1. It should be noted that not all persons with dementia will display all the symptoms. Nevertheless, a summary of this kind can help caregivers to be aware of potential problems and can allow them to think about future care needs. At the same time, one must not alarm people in the early stages of the disease by giving them too much information.

**EPIDEMIOLOGY AND BURDEN**
In 2005, Alzheimer’s Disease International commissioned a panel of experts to review all available epidemiological data and reach a consensus estimate of prevalence in each region and the numbers of people affected. Evidence from well-conducted, representative epidemiological surveys was lacking in many regions. The panel estimated that, globally, 24.3 million people have dementia today, with 4.6 million new cases annually. Numbers of people affected will double every 20 years to 81.1 million by 2040. Most people with dementia live in developing countries: 60% in 2001 rising to an estimated 71% by 2040. Rates of increase are not uniform; numbers in developed countries are forecast to increase by 100% between 2001 and 2040, but by more than 300% in China, India and neighbouring countries in South-East Asia and the Western Pacific. The detailed estimates contained

### Box 3.1.1 Stages and symptoms of dementia (Alzheimer’s disease)

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<tr>
<th>Early stage</th>
<th>Middle stage</th>
<th>Late stage</th>
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<td>The early stage is often overlooked. Relatives and friends (and sometimes professionals as well) see it as “old age”, just a normal part of the ageing process. Because the onset of the disease is gradual, it is difficult to be sure exactly when it begins. The person may: ■ have problems talking properly (language problems) ■ have significant memory loss — particularly for things that have just happened ■ not know the time of day or the day of the week ■ become lost in familiar places ■ have difficulty in making decisions ■ become inactive and unmotivated ■ show mood changes, depression or anxiety ■ react unusually angrily or aggressively on occasion ■ show a loss of interest in hobbies and activities</td>
<td>As the disease progresses, limitations become clearer and more restricting. The person with dementia has difficulty with day-to-day living and: ■ may become very forgetful, especially of recent events and people’s names ■ can no longer manage to live alone without problems ■ is unable to cook, clean or shop ■ may become extremely dependent on family members and caregivers ■ needs help with personal hygiene, i.e. washing and dressing ■ has increased difficulty with speech ■ shows problems with wandering and other behaviour problems such as repeated questioning and calling out, clinging and disturbed sleeping ■ becomes lost at home as well as outside ■ may have hallucinations (seeing or hearing things that are not there)</td>
<td>The late stage is one of nearly total dependence and inactivity. Memory disturbances are very serious and the physical side of the disease becomes more obvious. The person may: ■ have difficulty eating ■ be incapable of communicating ■ not recognize relatives, friends and familiar objects ■ have difficulty understanding what is going on around them ■ be unable to find his or her way around in the home ■ have difficulty walking ■ have difficulty swallowing ■ have bladder and bowel incontinence ■ display inappropriate behaviour in public ■ be confined to a wheelchair or bed</td>
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in this document (17) constitute the best available basis for policy-making, planning and allocation of health and welfare resources.

There is a clear and general tendency for prevalence to be somewhat lower in developing countries than in the industrialized world (18), strikingly so in some studies (19, 20). This trend was supported by the consensus judgement of the expert panel convened by Alzheimer’s Disease International, reviewing all available evidence (17). It does not seem to be explained merely by differences in survival, as estimates of incidence are also much lower than those reported in developed countries (27, 22). It may be that mild dementia is underdetected in developing countries because of difficulties in establishing the criterion of social and occupational impairment. Differences in level of exposure to environmental risk factors might also have contributed. The strikingly different patterns of mortality in early life might also be implicated; older people in very poor countries are exceptional survivors — this characteristic may also confer protection against AD and other dementias.

Long-term studies from Sweden and the United States of America suggest that the age-specific prevalence of dementia has not changed over the last 30 or 40 years (23). Whatever the explanation for the current discrepancy between prevalence in developed and developing countries, it seems probable that, as patterns of morbidity and mortality converge with those of the richer countries, dementia prevalence levels will do likewise, leading to an increased burden of dementia in poorer countries.

Studies in developed countries have consistently reported AD to be more prevalent than VaD. Early surveys from South-East Asia provided an exception, though more recent work suggests this situation has now reversed. This may be due to increasing longevity and better physical health: AD, whose onset is in general later than that of VaD, increases as the number of very old people increases, while better physical health reduces the number of stroke sufferers and thus the number with VaD. This change also affects the sex distribution among dementia sufferers, increasing the number of females and reducing the number of males.

Disability, burden and cost

Dementia is one of the main causes of disability in later life. In a wide consensus consultation for the Global Burden of Disease (GBD) report, disability from dementia was accorded a higher weight than that for almost any other condition, with the exception of spinal cord injury and terminal cancer. Of course, older people are particularly likely to have multiple health conditions — chronic physical diseases affecting different organ systems, coexisting with mental and cognitive disorders. Dementia, however, has a disproportionate impact on capacity for independent living, yet its global public health significance continues to be underappreciated and misunderstood. According to the GBD estimates in The world health report 2003, dementia contributed 11.2% of all years lived with disability among people aged 60 years and over: more than stroke (9.5%), musculoskeletal disorders (8.9%), cardiovascular disease (5.0%) and all forms of cancer (2.4%). However, the research papers (since 2002) devoted to these chronic disorders reveal a starkly different ordering of priorities: cancer 23.5%, cardiovascular disease 17.6%, musculoskeletal disorders 6.9%, stroke 3.1% and dementia 1.4%.

The economic costs of dementia are enormous. These can include the costs of “formal care” (health care, social and community care, respite care and long-term residential or nursing-home care) and “informal care” (unpaid care by family members, including their lost opportunity to earn income).

In the United Kingdom, direct formal care costs alone have been estimated at US$ 8 billion, or US$ 13 000 per patient. In the United States, costs have been estimated at US$ 100 billion per year, with patients with severe dementia costing US$ 36 794 each (1998 prices) (23, 24). A more recent estimate is of US$ 18 billion annually in the United States for informal costs alone. In developed
countries, costs tend to rise as dementia progresses. When people with dementia are cared for at home, informal care costs may exceed direct formal care costs. As the disease progresses, and the need for medical staff involvement increases, formal care costs will increase. Institutionalization is generally the biggest single contributor to costs of care.

Very little work has been done on evaluating the economic costs of dementia in developing countries. Shah et al. (25) list five reasons for this: the absence of trained health economists, the low priority given to mental health, the poorly developed state of mental health services, the lack of justification for such services, and the absence of data sets. Given the inevitability that the needs of frail older persons will come to dominate health and social care budgets in these regions, more data are urgently needed.

Detailed studies of informal costs outside western Europe and North America are rare, but a careful study of a sample of 42 AD patients in Denizli, Turkey, provides interesting data (26). Formal care for the elderly was rare: only 1% of old people in Turkey live in residential care. Families therefore provide most of the care. The average annual cost of care (excluding hospitalization) was US$ 4930 for severe cases and US$ 1766 for mild ones. Most costs increased with the severity of the disease, though outpatient costs declined. Carers spent three hours a day looking after the most severely affected patients.

The 10/66 Dementia Research Group also examined the economic impact of dementia in its pilot study of 706 persons with dementia and their caregivers living in China, India, Latin America and Nigeria (27). The key findings from this study are summarized in Box 3.1.2.

TREATMENT AND CARE

Early diagnosis is helpful so that the caregiver can be better equipped to deal with the disease and to know what to expect. A diagnosis is the first step towards planning for the future. There is no simple test to make a diagnosis. The diagnosis of AD is made by taking a careful account of the person’s problems from a close relative or friend, together with an examination of the person’s physical and mental state. It is important to exclude other conditions or illnesses that cause memory loss, including depression, alcohol problems and some physical illnesses with organic brain effects.

Currently there are no treatments that cure dementia. There is, however, evidence that drugs (cholinesterase inhibitors), in some cases but not all, temporarily decelerate the progressive cognitive decline that occurs in AD, and maybe in other forms of neurodegenerative dementia. These drugs act on the symptoms but not on the disease itself; they make only a small contribution to maintaining function. Evidence-based drug therapies are available for psychological symptoms such as depression, anxiety, agitation, delusions and hallucinations that can occur in people with dementia. There are modestly effective drugs (neuroleptics) available for the treatment of associated behavioural problems such as agitation. All of these drugs should be used with caution (the doctrine being “start low, go slow”), particularly tricyclic antidepressants (because of anticholinergic side-effects, therefore SSRI antidepressants — selective serotonin reuptake inhibitors — should always be preferred) and neuroleptics (because of anticholinergic side-effects, sedation, and an increased risk of stroke and higher all-cause mortality).

It is important to recognize that non-drug interventions are often highly effective, and should generally be the first choice when managing behavioural problems. The first step is to try to identify and treat the cause, which could be physical, psychological or environmental. Psychosocial interventions, particularly the provision of information and support to carers, have been shown to reduce the severe psychological distress often experienced by carers. Carers are also greatly assisted by a network of community health and social services; self-help organizations, especially Alzheimer associations, can also help them to find appropriate help. Carers can be educated about
dementia, countering lack of understanding and awareness about the nature of the problems faced. They can also be trained to manage better most of the common behavioural symptoms, in such a way that the frequency of the symptoms and/or the strain experienced by the carer is reduced. Above all, the person with dementia and the family carers need to be supported over the longer term. People with dementia need to be treated at all times with patience and respect for their dignity and personhood; carers need unconditional support and understanding — their needs should also be determined and attended to.

**Resources and prevention**

Developing-countrу health services are generally ill-equipped to meet the needs of older persons. Health care, even at the primary care level, is clinic-based; the older person must attend the clinic, often involving a long journey and waiting time in the clinic, to receive care. Even if they can get to the clinic the assessment and treatment that they receive are orientated towards acute rather than chronic conditions. The perception is that the former are treatable, the latter intractable and not within the realm of responsibility of health services. The 10/66 Dementia Research Group’s caregiver pilot study in 2004 indicated that people with dementia were using primary and secondary care health services. Only 33% of people with dementia in India, 11% in China and South-East Asia and 18% in Latin America had used no health services at all in the previous three months. In all centres, particularly in India and Latin America, there was heavy use of private medical services. One may speculate that this reflects the caregivers’ perception of the relative unresponsiveness of the cheaper government medical services.

The gross disparities in resources within and between developed and developing countries are leading to serious concerns regarding the flouting of the central ethical principle of distributive justice. New drug treatments are very expensive. Anticholinesterase therapies for AD are beyond the reach of all but the richest families in most developing countries. The same would be true for most SSRI antidepressants and “atypical” antipsychotic drugs, both of which are generally favoured in the West for use in older patients over the older and cheaper tricyclic antidepressants and “typical” antipsychotic drugs because of their better safety and side-effect profiles. The advent of a disease-modifying, as opposed to symptomatic, treatment for AD would introduce similar ethical concerns regarding accessibility to those that have arisen in relation to the management of HIV/AIDS in low income countries. Equity is also an important issue within developing countries. Access to care is often entirely dependent upon means to pay. Quite apart from economic constraints, health-care resources are grossly unevenly distributed between rural and urban districts. Most specialists, indeed most doctors, work in cities. Provision of even basic services to far-flung rural communities is an enormous challenge.

**Box 3.1.2 The 10/66 Dementia Research Group: key findings**

From the development perspective, one of the key findings from the study was that caregiving in the developing world is associated with substantial economic disadvantage. A high proportion of caregivers had to cut back on their paid work in order to care. Many caregivers needed and obtained additional support, and while this was often informal unpaid care from friends and other family members, paid caregivers were also relatively common.

People with dementia were heavy users of health services, and associated direct costs were high. Compensatory financial support was negligible; few older people in developing countries receive government or occupational pensions, and virtually none of the people with dementia in the 10/66 study received disability pensions.

Caregivers were commonly in paid employment, and almost none received any form of caring allowance. The combination of reduced family incomes and increased family expenditure on care is obviously particularly stressful in lower income countries where so many households exist at or near subsistence level. While health-care services are cheaper in low income countries, in relative terms families from the poorer countries spend a greater proportion of their income on health care for the person with dementia. They also appear to be more likely to use the more expensive services of private doctors, in preference to government-funded primary care, presumably because this fails to meet their needs.

Source: (?).
Future development of services for older people needs to be tailored to suit the health systems context. “Health systems” here can be taken to include macroeconomic factors, social structures, cultural values and norms, and existing health and welfare policy and provision.

Specialists — neurologists, psychiatrists, psychologists and geriatricians — are far too scarce a resource to take on any substantial role in the first-line care for people with dementia. The focus must be upon primary care. Many developing countries have in place comprehensive community-based primary care systems staffed by doctors, nurses and generic multipurpose health workers. The need is for:

- more training in the basic curriculum regarding diagnostic and needs-based assessments;
- a paradigm shift beyond the current preoccupation with prevention and simple curative interventions to encompass long-term support and chronic disease management;
- outreach care, assessing and managing patients in their own homes.

For many low income countries, the most cost-effective way to manage people with dementia will be through supporting, educating and advising family caregivers. This may be supplemented by home nursing or paid home-care workers; however, to date most of the growth in this area has been that of untrained paid carers operating in the private sector. The direct and indirect costs of care in this model therefore tend to fall upon the family. Some governmental input, whether in terms of allowances for people with dementia and/or caregivers or subsidized care would be desirable and equitable. The next level of care to be prioritized would be respite care, both in day centres and (for longer periods) in residential or nursing homes. Such facilities (as envisaged in Goa, for example) could act also as training resource centres for caregivers. Day care and residential respite care are more expensive than home care, but nevertheless basic to a community’s needs, particularly for people with more advanced dementia.

Residential care for older people is unlikely to be a priority for government investment, when the housing conditions of the general population remain poor, with homelessness, overcrowding and poor sanitation. Nevertheless, even in some of the poorest developing countries (e.g. China and India), nursing and residential care homes are opening up in the private sector to meet the demand from the growing affluent middle class. Good quality, well-regulated residential care has a role to play in all societies, for those with no family support or whose family support capacity is exhausted, both as temporary respite and for provision of longer-term care. Absence of regulation, staff training and quality assurance is a serious concern in developed and developing countries alike.

Similarly, low income countries lack the economic and human capital to contemplate widespread introduction of more sophisticated services; specialist multidisciplinary staff and community services backed up with memory clinics and outpatient, inpatient and day care facilities. Nevertheless, services comprising some of these elements are being established as demonstration projects. The ethics of health care require that governments take initial planning steps, now. The one certainty is that “in the absence of clear strategies and policies, the old will absorb increasing proportions of the resources devoted to health care in developing countries” (28). This shift in resource expenditure is, of course, likely to occur regardless. At least, if policies are well formulated, its consequences can be predicted and mitigated.

Prevention, where it can be achieved, is clearly the best option, with enormous potential benefits for the quality of life of the individual, the family and carers, and for society as a whole. Primary preventive interventions can be highly cost effective, given the enormous costs associated with the care and treatment of those with dementia (see the section on Disability, burden and cost, above). The primary prevention of dementia is therefore a relatively neglected area. Evidence from the developed world suggests that risk factors for vascular disease, including hypertension, smoking, type II diabetes, and hypercholesterolaemia may all be risk factors for AD as well as VaD. The epidemic of smoking in developing countries (with 13% of African teenagers currently
smoking), and the high and rising prevalence of type II diabetes in South-East Asia (a forecast 57% increase in prevalence between 2000 and 2010, compared with a 24% increase in Europe) should therefore be particular causes of concern. It is as yet unclear whether the improvements in control of hypertension, diet and exercise, and particularly the decline in smoking seen in developed Western countries that has led to rapid declines in mortality from ischaemic heart disease and stroke, will lead to a later decline in the age-specific incidence of AD and other dementias. Many of these preventive measures are also likely to improve general health (29).

Delivery of care
All over the world the family remains the cornerstone of care for older people who have lost the capacity for independent living, whether as a result of dementia or other mental disorder. However, stereotypes abound and have the potential to mislead. Thus, in developed countries with their comprehensive health and social care systems, the vital caring role of families, and their need for support, is often overlooked. This is true for example in the United Kingdom, where despite nuclear family structures and contrary to supposition, there is a strong tradition that persists today for local children to provide support for their infirm parents. Conversely, in developing countries the reliability and universality of the family care system is often overestimated. Older people are among the most vulnerable groups in the developing world, in part because of the continuing myths that surround their place in society (30). It is often assumed that their welfare is assured by the existence of the extended family. Arguably, the greatest obstacle to providing effective support and care for older persons is the lack of awareness of the problem among policy-makers, health-care providers and the community. Mythologizing the caring role of the family evidently carries the risk of perpetuating complacency.

The previously mentioned 10/66 Dementia Research Group’s multicentre pilot study was the first systematic, comprehensive assessment of care arrangements for people with dementia in the developing world, and of the impacts upon their family caregivers (27). As in the EUROCare study with data from 14 European countries (31), most caregivers in developing countries were older women caring for their husbands or younger women caring for a parent. Caring was associated with substantial psychological strain as evidenced by high rates of psychiatric morbidity and high levels of caregiver strain. These parameters were again very similar to those reported in the EUROCare study. Some aspects, however, were radically different. People with dementia in developing countries typically live in large households, with extended families. Larger families were associated with lower caregiver strain; however, this effect was small and applied only where the principal caregiver was co-resident. Indeed, it seemed to operate in the opposite direction where the caregiver was non-resident, perhaps because of the increased potential for family conflict.

In many developing countries, traditional family and kinship structures are widely perceived as under threat from the social and economic changes that accompany economic development and globalization (30). Some of the contributing factors include the following:

- Changing attitudes towards older people.
- The education of women and their increasing participation in the workforce (generally seen as key positive development indicators); tending to reduce both their availability for caregiving and their willingness to take on this additional role.
- Migration. Populations are increasingly mobile as education, cheap travel and flexible labour markets induce young people to migrate to cities and abroad to seek work. In India, Venkoba Rao has coined an acronym to describe this growing social phenomenon: PICA — parents in India, children abroad. “Push factors” are also important. In the economic catastrophe of the 1980s, two million Ghanaians left the country in search of economic betterment; 63% of older persons have lost the support of one or more of their children who have migrated to distant places in Ghana or abroad. Older people are particularly vulnerable after displacement as a result of war or natural disaster.
Declining fertility in the course of the final demographic transition. Its effects are perhaps most
evident in China, where the one-child family law leaves increasing numbers of older people,
particularly those with a daughter, bereft of family support.

In sub-Saharan Africa, changing patterns of morbidity and mortality are more relevant; the
ravages of the HIV/AIDS epidemic have “orphaned” parents as well as children, as bereaved
older persons are robbed of the expectation of economic and practical support into later life.

A PUBLIC HEALTH FRAMEWORK

At its 20th annual conference held in Kyoto, Japan, Alzheimer’s Disease International released a Kyoto
Declaration, benchmarking progress in ten key areas using a public health framework developed by
WHO (see Table 3.1.1). The framework addresses treatment gaps, policies, research and training and
identifies three levels of attainment for countries with low, medium and high levels of resources, hence
suggesting a feasible, pragmatic series of actions and objectives for health systems at all levels of
development.

Table 3.1.1 Minimum actions required for dementia care

<table>
<thead>
<tr>
<th>Ten overall recommendations</th>
<th>Scenario A Low level of resources</th>
<th>Scenario B Medium level of resources</th>
<th>Scenario C High level of resources</th>
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<tbody>
<tr>
<td>1. Provide treatment in primary care</td>
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<td>Recognize dementia care as a component of primary health care</td>
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<td>Include the recognition and treatment of dementia in training curricula of all health personnel</td>
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<td>Provide refresher training to primary care physicians (at least 50% coverage in five years)</td>
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<td>Develop locally relevant training materials</td>
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<td>Provide refresher training to primary care physicians (100% coverage in five years)</td>
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<tr>
<td>Improve effectiveness of management of dementia in primary health care</td>
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<tr>
<td>Improve referral patterns</td>
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<tr>
<td>2. Make appropriate treatments available</td>
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<tr>
<td>Increase availability of essential drugs for the treatment of dementia and associated psychological and behavioural symptoms</td>
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<tr>
<td>Develop and evaluate basic educational and training interventions for caregivers</td>
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<td>Ensure availability of essential drugs in all health-care settings</td>
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<td>Make effective caregiver interventions generally available</td>
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<tr>
<td>Provide easier access to newer drugs (e.g. anticholinesterase agents) under public or private treatment plans</td>
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<td>3. Give care in the community</td>
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<td>Establish the principle that people with dementia are best assessed and treated in their own homes</td>
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<td>Develop and promote standard needs assessments for use in primary and secondary care</td>
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<td>Initiate pilot projects on development of multidisciplinary community care teams, day care and short-term respite care</td>
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<td>Move people with dementia out of inappropriate institutional settings</td>
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<td>Initiate pilot projects on integration of dementia care with general health care</td>
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<tr>
<td>Provide community care facilities (at least 50% coverage with multidisciplinary community teams, day care, respite and inpatient units for acute assessment and treatment)</td>
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<td>According to need, encourage the development of residential and nursing-home facilities, including regulatory framework and system for staff training and accreditation</td>
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<td>Develop alternative residential facilities</td>
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<td>Provide community care facilities (100% coverage)</td>
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<td>Give individualized care in the community to people with dementia</td>
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<td>Ten overall recommendations</td>
<td>Scenario A Low level of resources</td>
<td>Scenario B Medium level of resources</td>
<td>Scenario C High level of resources</td>
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<td>4. Educate the public</td>
<td>Promote public campaigns</td>
<td>Use the mass media to promote</td>
<td>Launch public campaigns for</td>
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<td>against stigma and discrimination</td>
<td>awareness of dementia, foster</td>
<td>early help-seeking, recognition</td>
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<td></td>
<td>Support nongovernmental</td>
<td>positive attitudes, and help</td>
<td>and appropriate management of</td>
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<td></td>
<td>organizations in public education</td>
<td>prevent cognitive impairment</td>
<td>dementia</td>
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<td>5. Involve communities,</td>
<td>Support the formation of self-</td>
<td>Ensure representation of</td>
<td>Foster advocacy initiatives</td>
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<tr>
<td>families and consumers</td>
<td>help groups</td>
<td>communities, families, and</td>
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<td>Fund schemes for</td>
<td>consumers in policy-making,</td>
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<td>nongovernmental organizations</td>
<td>service development and implementation</td>
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<td>6. Establish national</td>
<td>Revise legislation based on</td>
<td>Implement dementia care</td>
<td>Ensure fairness in access to</td>
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<td>policies, programmes and</td>
<td>current knowledge and human</td>
<td>policies at national and</td>
<td>primary and secondary health</td>
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<td>legislation</td>
<td>rights considerations</td>
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<td>care services, and to social</td>
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<td>Formulate dementia care</td>
<td>Establish health and social care</td>
<td>welfare programmes and</td>
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<td>programmes and policies:</td>
<td>budgets for dementia care</td>
<td>benefits</td>
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<td>— Legal framework to support</td>
<td>Increase the budget for mental</td>
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<td>and protect those with</td>
<td>health care</td>
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<td>— Inclusion of people with</td>
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<td>— Inclusion of caregivers in</td>
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<td>compensatory benefit schemes</td>
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<td>Establish health and social care</td>
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<td>budgets for older persons</td>
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<td>7. Develop human resources</td>
<td>Train primary health-care</td>
<td>Create a network of national</td>
<td>Train specialists in advanced</td>
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<td>workers</td>
<td>training centres for physicians,</td>
<td>treatment skills</td>
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<td>Initiate higher professional</td>
<td>psychiatrists, nurses,</td>
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<td>training programmes for</td>
<td>psychologists and social</td>
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<td>Develop training and resource</td>
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<td>8. Link with other sectors</td>
<td>Initiate community, school and</td>
<td>Strengthen community programmes</td>
<td>Extend occupational health</td>
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<td>workplace dementia awareness</td>
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<td>services to people with early</td>
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<td>Encourage the activities of</td>
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<td>Provide special facilities in the</td>
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<td>nongovernmental organizations</td>
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<td>Initiate evidence-based mental</td>
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<td>health promotion programmes</td>
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<td>in collaboration with other sectors</td>
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<td>9. Monitor community</td>
<td>Include dementia in basic health</td>
<td>Institute surveillance for early</td>
<td>Develop advanced monitoring</td>
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<td>health</td>
<td>information systems</td>
<td>dementia in the community</td>
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<td>Survey high-risk population</td>
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<td>Monitor effectiveness of</td>
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<td>groups</td>
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<td>preventive programmes</td>
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<td>10. Support more research</td>
<td>Conduct studies in primary</td>
<td>Institute effectiveness and cost-</td>
<td>Extend research on the causes of</td>
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<td></td>
<td>health-care settings on the</td>
<td>effectiveness studies for</td>
<td>dementia</td>
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<td>prevalence, course, outcome and</td>
<td>community management of dementia</td>
<td>Carry out research on service</td>
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<td>impact of dementia in the</td>
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<td>prevention of dementia</td>
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</tbody>
</table>

* Based on overall recommendations from *The world health report 2001* (32).
# CONCLUSIONS AND RECOMMENDATIONS

<table>
<thead>
<tr>
<th>1</th>
<th>Dementia is a disease and not a part of normal ageing.</th>
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<tbody>
<tr>
<td>2</td>
<td>Dementia affects some 24 million people, most of them elderly, worldwide. Up to two thirds live in low and middle income countries.</td>
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<td>3</td>
<td>Awareness of dementia is very low in all world regions, a problem leading to stigmatization and inefficient help-seeking.</td>
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<td>4</td>
<td>No cure is currently available for the most common causes of dementia, but much can and should be done to improve the quality of life of people with dementia and their carers.</td>
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<td>5</td>
<td>Governments should be urged to take account of the needs of people with dementia, as an integral part of a comprehensive programme of health and welfare services for older people.</td>
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<td>6</td>
<td>The priority should be to strengthen primary care services, through training and reorientation from clinic-based acute treatment services to provision of outreach and long-term support.</td>
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<td>7</td>
<td>Governments, nongovernmental organizations working in the area of Alzheimer and other dementias, professionals and carers need to work together to raise awareness, counter stigma and improve the quality and coverage of care services.</td>
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</tbody>
</table>
REFERENCES

Brazil has among the 11 largest populations of elderly people in the world; eight of these populations are in developing countries. According to the Brazilian 2000 census, there are 10 million people aged 65 years and over, corresponding to about 6% of the whole population. It is predicted that by 2050 the elderly population will have increased by over 300%, whereas the population as a whole will have increased only by over 30%. Brazil has also one of the highest rates of urbanization in the world with almost one third of the whole population living in only three metropolitan areas (São Paulo, Rio de Janeiro and Belo Horizonte), as well as one of the highest levels of inequality between the rich and the poor with almost 50% of the national income concentrated among the richest 10% of the population. Most elderly people live in large cities in poverty.

According to a recent consensus on the global prevalence of dementia, Brazil has today 729,000 people with dementia; this number is estimated to increase to 1.4 million by 2020 and to 3.2 million by 2040. Dementia in Brazil is still a hidden problem and there is little awareness of it. Most elderly people live with their spouses or extended family (only 15% live alone and fewer than 1% live in institutions). Families with one or more elderly members are relatively advantaged because of the means-tested non-contributory pension benefits for older Brazilians, introduced in the 1990s. However, the informal support that family caregivers can offer to their relations in more need is still difficult because of impoverishment.

RECOMMENDED READING

For professionals

For carers and non-medical readers

Box 3.1.3  Case-study: Brazil

The majority of Brazilians (75%) are cared for by the federal programme SUS (Unified Health System) while the remainder are in the hands of a private system. Primary care is provided primarily by the Family Health Programme, in which health professionals go to the patient’s home for periodic health evaluation and management; however, this programme covers only 40% of the population. Specialists (geriatricians, psychiatrists and neurologists) see referred patients as outpatients and inpatients. Long-term care is scarce and is mostly provided by religious organizations for those with severe disability and limited family support. Community care is generally available in metropolitan areas, but only from private providers for those who can afford the charges. Home care provided by SUS is being introduced but still covers only a small proportion of the elderly population.

While the current health system does not meet the needs of older people, there are encouraging developments. The Brazilian Psychiatric Association has a Geriatric Psychiatry section promoting training in dementia assessment and care; the geriatricians and neurologists see referred patients as outpatients and inpatients. Several universities have research programmes in dementia. Several regional nongovernmental organizations work to support people with dementia and their caregivers; these are united in a federation — Federação Brasileira de Associações de Alzheimer (FEBRAZ) — which is a member of Alzheimer’s Disease International.
Box 3.1.4 Case-study: India

In India, life expectancy has gone up from 20 years at the beginning of the 20th century to 62 years at present. Better medical care and low fertility have made the elderly population the fastest growing section of society. India has over one billion people, 16% of the world's population: it is estimated that the growth in the elderly population is 5–8% higher than growth in the total population. The consequence is that, while in 2001 there were 70 million people aged over 60 years, by 2025 there will be an estimated 177 million.

According to a recent consensus, the prevalence of dementia in India is 1.9% over the age of 60 years. In the context of the large population and demographic transition, the total numbers are estimated to more than treble in the next 35 years, reaching over six million by 2040. The public health and socioeconomic implications are enormous.

The joint family system — the traditional support system for frail elderly people — is crumbling because of the migration of the younger generation to the cities in search of better prospects. The women who traditionally took on the role of caregivers are also working and cannot spend as much time caring for the elderly. Dementia is considered as a normal part of ageing and is not perceived as requiring medical care. Thus primary health-care physicians rarely see this condition in their clinical work. Private medical care (which includes home visits) is preferred and this leads to a higher out-of-pocket cost for dementia care. Carers experience significant burdens and health strain. More than 80% of carers are female and around 50% are spouses who are themselves quite old. People with dementia are often neglected, ridiculed and abused. Old-age homes do not admit people with dementia.

These research findings led to the implementation of the Dementia Home Care Project which was supported by WHO. In this project, a flexible, stepped-care intervention was adopted to empower the carers with knowledge and skills to manage the person with dementia at home. The intervention was implemented by locally trained home care advisers under supervision. This not only helped in decreasing the stress of looking after a person with dementia, but also helped the caregivers to manage behavioural problems and thus reduced the number of deaths in the intervention group.

Evidence from research has helped the advocacy campaign in India. There is a need to make dementia a public health priority and create a network of home care advisers to provide supportive and educational interventions for the family caregivers through the primary health-care system in India.

Box 3.1.5 Case-study: Nigeria

Nigeria is the most populous African country, with about 130 million inhabitants. According to United Nations estimates, it is likely that the figure of 0.5 million (4.7% of the whole population) people over 60 years of age in 2000 will have more than trebled by 2040 (1.8 million people, i.e. 7.5% of the population). Old people have traditionally been cared for within the extended family. Social and economic changes have disrupted this system, however, especially by young people moving into the towns and leaving the old people to cope on their own. No effective alternatives have been provided for their care.

Specialist health services are in short supply. In 2005 there were only about 77 psychiatrists and three occupational therapists in the country. Industrial therapy was not offered anywhere. Specialist social workers are few and work under severe limitations. There are no specialist services for the elderly (geriatric or psychogeriatric services, meals on wheels, respite care or drop-in centres) and few nursing homes. There is no insurance cover for medical services for elderly people.

Usually record-keeping, accountability and political will are poor, so that many elderly people who retire do not receive their benefits. Recently the Federal Government has introduced a contributory pension scheme, but in the past elderly people found it difficult to learn about and access their entitlements. Elderly Nigerians are among the poorest groups in the country.

A national policy on elderly care was published in 2003, and a National Implementation Plan is now under way, but is being piloted only among certain Federal civil servants.

Assessing the extent of dementia among this huge, varied and shifting population is not easy, but what little research has been done suggests prevalence rates for dementia may be low. Interest in the mental health of elderly Nigerians is only just beginning: for example in the past three years, old-age mental health clinics have been established at two universities. There is no formal training for geriatric medicine and psychiatry. Anti-dementia drugs are rarely available.
### 3.2 Epilepsy

Epilepsy is a chronic neurological disorder affecting both sexes and all ages, with worldwide distribution. The term is also applied to a large group of conditions characterized by common symptoms called “epileptic seizures”, which may occur in the context of a brain insult that can be systemic, toxic or metabolic. These events (called provoked or acute symptomatic seizures) are presumed to be an acute manifestation of the insult and may not recur when the underlying cause has been removed or the acute phase has elapsed.

Epilepsy has been defined as “a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure” (1). An epileptic seizure is defined as “a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain” (1). These definitions recognize that a diagnosis of epilepsy implies the existence of a persistent epileptogenic abnormality that is present whether seizures occur or not, as well as that there may be consequences of this persistent abnormality other than the occurrence of seizures that can cause continuous disability between seizure occurrence (interictally). Because it is often difficult to identify definitively an enduring predisposition to generate epileptic seizures, a common operational definition of epilepsy is the occurrence of two or more non-provoked epileptic seizures more than 24 hours apart.

Differential diagnosis of transient events that could represent epileptic seizures involves first determining that the events are epileptic, then distinguishing between provoked epileptic seizures and a chronic epileptic condition. Febrile seizures in infants and young children and withdrawal seizures in alcoholics are common examples of provoked seizures that do not require a diagnosis of epilepsy. If seizures are recurrent, it is next necessary to search for an underlying treatable cause. If such a cause cannot be found, or if it is treated and seizures persist, then treatment of seizures is guided by diagnosis of the specific seizure type(s), and syndrome if present (see Box 3.2.1).

**Etiology and risk factors**

Epileptic conditions are multifactorial disorders, and it is useful to discuss three important factors. The first factor is predisposition, or threshold. Anyone with a functioning brain is capable of having a seizure; however, seizures occur more easily in some people than in others. The ease with which a seizure can be provoked, or an epileptic condition can be induced, is referred to as a threshold. Individual differences in threshold are largely attributable to genetic variations but could also be acquired, such as certain types of perinatal injuries, which can alter threshold. Threshold is a dynamic phenomenon; it varies throughout the day, it also changes in relation to hormonal influences.
during the menstrual cycle in women. Stimulant drugs lower seizure threshold and sedative drugs increase it; however, withdrawal from sedative drugs can lower threshold and provoke seizures. Antiepileptic drugs work by increasing seizure threshold.

The second important factor for epilepsy is the epileptogenic abnormality itself. Epilepsies attributable to identifiable brain defects are referred to as symptomatic epilepsies. Symptomatic epilepsies can be caused by a variety of disorders, including brain malformations, infections, vascular disturbances, neoplasms, scars from trauma, including strokes, and disorders of cerebral metabolism. Treatment for symptomatic epilepsy is most effective if it is directed at the underlying cause. The most common symptomatic epilepsy is temporal lobe epilepsy, usually associated with a characteristic lesion called “hippocampal sclerosis”. Hippocampal sclerosis appears to be caused by cerebral injury within the first few years of life in individuals with a genetic predisposition to this condition. Some forms of epilepsy are unassociated with identifiable structural lesions or diseases and are usually unassociated with other neurological or mental deficits. These are genetically transmitted, generally easily treated with medications without sequelae, and referred to as idiopathic epilepsies.

The third important factor is the precipitating condition, which determines when seizures occur. Common precipitating factors include fever for children with febrile seizures, alcohol and sedative drug withdrawal, sleep deprivation, stimulant drugs and — in some patients — stress. Reflex seizures are precipitated by specific sensory stimuli. The most common are photosensitive seizures induced by flickering light, but some patients have very specific reflex epilepsy with seizures precipitated by such stimuli as being startled, particular types of music, certain visual patterns, reading, eating and hot-water baths. Identification of precipitating factors is helpful if they can be avoided, but in most patients specific precipitating factors are not apparent, and may not exist at all.

Patients with a high seizure threshold can experience severe epileptogenic brain injuries and precipitating factors but never have seizures, while those with low seizure thresholds can develop epilepsy with minimal insults and, in many, from precipitating factors alone (provoked seizures).

**COURSE AND OUTCOME**

Because there are many types of seizures and epilepsy, there is no single course or outcome. Prognosis depends on the seizure type, the underlying cause, and the syndrome when this can be determined. Approximately one in 10 individuals will experience at least one epileptic seizure in their lifetime, but only one third of these will go on to have epilepsy. There are a number of idiopathic epilepsy syndromes characterized by onset at a certain age, and specific seizure types. Those that begin in infancy and childhood, such as benign familial neonatal seizures, benign childhood epilepsy with centroteemporal spikes, and childhood absence epilepsy, usually remit spontaneously, while those that begin in adolescence, the juvenile idiopathic epilepsies, are often lifelong. Most of these are easily treated with antiepileptic drugs (AEDs), with no neurological or

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**Box 3.2.1  Types of epileptic seizure**

<table>
<thead>
<tr>
<th>I. Generalized onset</th>
<th>II. Focal onset</th>
<th>III. Neonatal</th>
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<tbody>
<tr>
<td>A. Clonic and tonic seizures</td>
<td>A. Local</td>
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<td>B. Absences</td>
<td>1. Neocortical</td>
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<tr>
<td>C. Myoclonic seizure types</td>
<td>2. Limbic</td>
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<tr>
<td>D. Epileptic spasms</td>
<td>B. With ipsilateral propagation</td>
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<td>E. Atonic seizures</td>
<td>C. With contralateral spread</td>
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<td></td>
<td>D. Secondarily generalized</td>
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*Source: adapted from (2).*
mental sequelae. Slowly, the genetic basis of these idiopathic epilepsies is being revealed, and there appears to be considerable diversity in that single-gene mutations can give rise to more than one syndrome, while single syndromes can be caused by more than one gene mutation.

The prognosis of symptomatic epilepsies depends on the nature of the underlying cause. Epilepsies attributable to diffuse brain damage, such as West syndrome and Lennox–Gastaut syndrome, are characterized by severely disabling medically refractory “generalized” seizures, mental retardation and often other neurological deficits. Epilepsies resulting from smaller lesions may be associated with “focal” seizures that are more easily treated with drugs and can remit spontaneously as well. When pharmacoresistant focal seizures are due to localized structural abnormalities in one hemisphere, such as hippocampal sclerosis in temporal lobe epilepsy, they can often be successfully treated by localized resective surgery. Some patients with more diffuse underlying structural lesions that are limited to one hemisphere can also be treated surgically with hemispherectomy or hemispherotomy.

Whereas 80–90% of patients with idiopathic epilepsies can expect to become seizure free, and many will undergo spontaneous remission, the figure is much lower for patients with symptomatic epilepsy, and perhaps only 5–10% of patients with temporal lobe epilepsy and hippocampal sclerosis will have seizures that can be controlled by pharmacotherapy. Of these patients, however, 60–80% can become free of disabling seizures with surgery. Advances in neurodiagnostics, particularly neuroimaging, are greatly facilitating our ability to determine the underlying causes of seizures in patients with symptomatic epilepsies and to design more effective treatments, including surgical interventions.

**Epidemiology**

**Incidence of epilepsy and unprovoked seizures**

The annual incidence of unprovoked seizures is 33–198 per 100 000, and the incidence of epilepsy is 23–190 per 100 000 (3). The overall incidence of epilepsy in Europe and North America ranges from 24 and 53 per 100 000 per year, respectively (4–6). The incidence in children is eventually higher and even more variable, ranging from 25 to 840 per 100 000 per year, most of the differences being explained by the differing populations at risk and by the study design (3). In developing countries, the incidence of the disease is higher than that in industrialized countries and is up to 190 per 100 000 (3, 7). Although one might expect a higher exposure to perinatal risk factors, infections and traumas in developing countries, the higher incidence of epilepsy may be also explained by the different structure of the populations at risk, which is characterized by a predominant distribution of young individuals and a short life expectancy.

**Incidence by age, sex and socioeconomic status**

In industrialized countries, epilepsy tends to affect mostly the individuals at the two extremes of the age spectrum. The peak in the elderly is not detected in developing countries, where the disease peaks in the 10–20-year age group (8). This may depend on the age structure of the population and on a relative under-ascertainment of the disease in older individuals.

The incidence of epilepsy and unprovoked seizures has been mostly reported to be higher in men than in women in both industrialized and developing countries, though this finding has rarely attained statistical significance. The different distribution of epilepsy in men and women can be mostly explained by the differing genetic background, the different prevalence of the commonest risk factors in the two sexes, and the concealment of the disease in women for sociocultural reasons.

The incidence of epilepsy is higher in the lower socioeconomic classes. This assumption is supported by the comparison between industrialized and developing countries and by the comparison, within the same population, of people of different ethnic origin (9).
Prevalence of epilepsy
The overall prevalence of epilepsy ranges from 2.7 to 41 per 1000 population, though in the majority of reports the rate of active epilepsy (i.e. at least one seizure in the preceding five years) is in the range 4–8 per 1000 (5, 10). The prevalence of active epilepsy is generally lower in industrialized countries than in developing countries, which may reflect a lower prevalence of selected risk factors (mostly infections and traumas), a more stringent case verification, and the exclusion of provoked and unprovoked isolated seizures.

Prevalence by age, sex and socioeconomic status
In industrialized countries, the prevalence of epilepsy is lower in infancy and tends to increase thereafter, with the highest rate occurring in elderly people (10). Where available, age-specific prevalence rates of lifetime and active epilepsy from developing countries tend to be higher in the second (254 vs 148 per 1000) and third decades of life (94 vs 145 per 1000) (8). The differences between industrialized and developing countries may be mostly explained by the differing distribution of the risk factors and by the shorter life expectancy in the latter.

As with incidence, prevalence of epilepsy tends to be higher in men. However, this finding is not consistent across studies and, with few exceptions, is not statistically significant.

Socioeconomic background has been found to affect the frequency of epilepsy reports in both industrialized and developing countries. In developing countries, prevalence rates have been shown to be greater in the rural compared with the urban context (11, 12) or in the lower compared with the higher socioeconomic classes. However, opposite figures were reported in a meta-analysis of epidemiological studies from India (13), which suggests that rural and urban environments should not be invariably used as proxies of lower vs higher socioeconomic conditions.

Mortality
The mortality rate of epilepsy ranges from 1 to 8 per 100 000 population per year, but international vital statistics give annual mortality rates of 1–2 per 100 000 (14). Based on a meta-analysis of studies investigating mortality in the past 100 years, the standardized mortality ratio (SMR) for epilepsy, which is the ratio between the deaths observed among patients with epilepsy and the deaths expected in a reference population with a similar age distribution, was found to range from 1.3 to 9.3 (15). The SMR for epilepsy ranges from 1.6 to 5.3 in children and adults and is inversely correlated with age (16). The higher SMRs may be partly explained by the inclusion of provoked seizures. The highest mortality risk in the youngest age groups can be interpreted in part in the light of the underlying epileptogenic conditions and the lower number of competing causes of death.

It is extremely difficult to analyse the epilepsy death rate in the general population of a developing country because incidence studies of epilepsy are difficult to perform, death certificates are unreliable and often unavailable, and the cause of death is difficult to determine. Based on available data, it seems that the mortality rate of epilepsy in developing countries is generally higher than that reported in developed countries. These data cannot be generalized, however, as they have been obtained from selected populations (17).

BURDEN ON PATIENTS, FAMILIES AND COMMUNITIES
Worldwide, 50 million people have epilepsy. Many more people, however — an estimated 200 000 000 — are also affected by this disorder, as they are the family members and friends of those who are living with epilepsy. Around 85% of people with epilepsy live in developing countries. There are two million new cases occurring in the world every year. Up to 70% of people with epilepsy could lead normal lives if properly treated, but for an overwhelming majority of patients this is not the case (18).
Epilepsy is among the disorders that are strongly associated with significant psychological and social consequences for everyday living (19). People with hidden disabilities such as epilepsy are among the most vulnerable in any society. While their vulnerability may be partly attributed to the disorder itself, the particular stigma associated with epilepsy brings a susceptibility of its own. Stigmatization leads to discrimination, and people with epilepsy experience prejudicial and discriminatory behaviour in many spheres of life and across many cultures (20).

People with epilepsy experience violations and restrictions of both their civil and human rights. Civil rights violations such as unequal access to health and life insurance or prejudicial weighting of health insurance provisions, withholding of the right to obtain a driving licence, limitations to the right to enter particular occupations and the right to enter into certain legal agreements, in some parts of the world even marriage, are severely aggravated by epilepsy. Discrimination against people with epilepsy in the workplace and in respect of access to education is not uncommon for many people affected by the condition. Violations of human rights are often more subtle and include social ostracism, being overlooked for promotion at work, and denial of the right to participate in many of the social activities taken for granted by others in the community. For example, ineligibility for a driving licence frequently imposes restrictions on social participation and choice of employment.

Informing people with epilepsy of their rights and recourse is an essential activity. Considering the frequency of rights violations, the number of successful legal actions is very small. People are often reluctant to be brought into the public eye, so a number of cases are settled out of court. The successful defence of cases of rights abuse against people with epilepsy will serve as precedents, however, and will be helpful in countries where there are actions afoot to review and amend legislation.

Epidemiological assessment of the global burden of epilepsy
Overall, epilepsy contributed more than seven million DALYs (0.5%) to the global burden of disease in 2000 (21, 22). Figure 3.2.1 shows the distribution of DALYs or lost years of healthy life attributable to epilepsy, both by age group and by level of economic development. It is apparent that close to 90% of the worldwide burden of epilepsy is to be found in developing regions, with more than half occurring in the 39% of the global population living in countries with the highest levels of premature mortality (and lowest levels of income). An age gradient is also apparent, with the vast majority of epilepsy-related deaths and disability in childhood and adolescence occurring in developing regions, while later on in the life-course the proportion drops on account of relatively greater survival rates into older age by people living in more economically developed regions.

Figure 3.2.1 Distribution of the global burden of epilepsy, by age group and level of economic development

![Figure 3.2.1](image-url)
Economic assessment of the national burden of epilepsy

Economic assessments of the national burden of epilepsy have been conducted in a number of high income countries (e.g. 23, 24) and more recently in India (25), all of which have clearly shown the significant economic implications the disorder has in terms of health-care service needs, premature mortality and lost work productivity. For example, the Indian study calculated that the total cost per case of these disease consequences for epilepsy amounted to US$ 344 per year (equivalent to 88% of average income per capita), and that the total cost for the estimated five million cases resident in India was equivalent to 0.5% of gross national product. Since such studies differ with respect to the exact methods used, as well as underlying cost structures within the health system, they are currently of most use at the level of individual countries, where they can serve to draw attention to the wide-ranging resource implications and needs of people living with epilepsy.

The avertable burden of epilepsy

Having established the attributable burden of epilepsy, two subsequent questions for decision-making and priority setting relate to avertable burden (the proportion of attributable burden that is averted currently or could be avoided via scaled-up use of proven efficacious treatments) and resource efficiency (determination of the most cost-effective ways of reducing burden). Figure 3.2.2 provides a schematic overview of these concepts.

As part of a wider WHO cost–effectiveness work programme (26), information has been generated concerning the amount of burden averted by the current or scaled-up use of treatment with AEDs, together with estimates of cost and cost–effectiveness (27). Effectiveness was expressed in terms of DALYs averted and costs were expressed in international dollars. Compared with a “do nothing” scenario (i.e. the untreated natural history of epilepsy), results from nine developing epidemiological subregions suggest that extending AED treatment coverage to 50% of primary epilepsy cases would avert 150–650 DALYs per million population (equivalent to 13–40% of the current burden), at an annual cost per case of International $ 55–192. Older first-line AEDs (phenoobarbitone, phenytoin) were most cost effective on account of their similar efficacy but lower acquisition cost (International $ 800–2000 for each DALY averted). In all nine developing regions, the cost of securing one extra healthy year of life was less than average per capita income. Extending coverage further to 80% or even 95% of the target population would evidently avert more of the burden still, and would remain an efficient strategy despite the large-scale investment in manpower, training and drug supply/distribution that would be required to implement such a programme. The results for one developing subregion in Africa — consisting of 20 countries with a high rate of child mortality and a very high level of adult mortality — are depicted in Figure 3.2.2

Figure 3.2.2 Attributable and avertable burden of epilepsy in an epidemiological subregion of Africa

* Each DALY averted costs less than average per capita income.

Source: schema (28); data (27).
(27, 28), which divides the total attributable burden of epilepsy into three categories: burden that is averted by AEDs at current levels of effective treatment coverage (19%); burden that is avertable via the scaling-up of AEDs (to a further 41% if complete coverage is reached); and burden that is not avertable via AEDs (estimated to be 40%, though this assumes that the current level of drug compliance would prevail).

**TREATMENT, REHABILITATION AND COST**

The primary focus of care for patients with epilepsy is the prevention of further seizures, which may, after all, lead to additional morbidity or even mortality (29). The goal of treatment should be the maintenance of a normal lifestyle, preferably free of seizures and with minimal side-effects of the medication. Up to 70% of people with epilepsy could become seizure free with AED treatment.

In 25–30% of people with epilepsy the seizures cannot be controlled with drugs. Epilepsy surgery is a safe and effective alternative treatment in selected cases. Investment in epilepsy surgery centres, even in the poorest regions, could greatly reduce the economic and human burden of epilepsy. There is a marked treatment gap with respect to epilepsy surgery, however, even in industrialized countries.

Attention to the psychosocial, cognitive, educational and vocational aspects is an important part of comprehensive epilepsy care (30). Epilepsy imposes an economic burden both on the affected individual and on society, e.g. the disorder commonly affects young people in the most productive years of their lives, often leading to avoidable unemployment.

Over the past years, it has become increasingly obvious that severe epilepsy-related difficulties can be seen in people who have become seizure free as well as in those with difficult-to-treat epilepsies. The outcome of rehabilitation programmes would be a better quality of life, improved general social functioning and better functioning in, for instance, performance at work and improved social contacts (31).

In 1990, WHO identified that the average cost of medication (phenobarbitone) could be as low as US$ 5 per person per year (32). From an economic point of view also, therefore, it is an urgent public health challenge to make effective epilepsy care available to all who need it, regardless of national and economic boundaries.

**Prevention**

Currently, epilepsy tends to be treated once the condition is established, and little is done in terms of prevention. In a number of people with epilepsy the cause for the condition is unknown; prevention of this type of epilepsy is therefore currently not possible (33, 34). A sizeable number of people with epilepsy will have known risk factors, but some of these are not currently amenable to preventive measures. These include cases of epilepsy attributable to cerebral tumours or cortical malformations and many of the idiopathic forms of epilepsy.

One of the most common causes of epilepsy is head injury, particularly penetrating injury. Prevention of the trauma is clearly the most effective way of preventing post-traumatic epilepsy, with use of head protection where appropriate (for example, for horse riding and motorcycling) (34).

Epilepsy can be caused by birth injury, and the incidence should be reduced by adequate perinatal care. Fetal alcohol syndrome may also cause epilepsy, so advice on alcohol use before and during pregnancy is important. Reduction of childhood infections by improved public hygiene and immunization can lessen the risk of cerebral damage and the subsequent risk of epilepsy (33, 34).

Febrile seizures are common in children under five years of age and in most cases are benign, though a small proportion of patients will develop subsequent epilepsy. The use of drugs and other methods to lower the body temperature of a feverish child may reduce the chance of having a febrile convulsion and subsequent epilepsy, but this remains to be seen.
Epilepsy may be a complication of various infections of the central nervous system (CNS), such as cysticercosis and malaria (35, 36). These conditions are more prevalent in the tropical belt, where low income countries are concentrated. Elimination of the parasite in the environment would be the most effective way to reduce the burden of epilepsy worldwide, but education concerning how to avoid infection can also be effective.

To sum up, currently the prevention of epilepsy may be possible in cases caused by head trauma and by infections and infestations of the CNS, but would require intensive efforts to improve basic sanitation, education and practice. Most cases of epilepsy at the current state of knowledge are probably not preventable but, as research improves our understanding of genetics and structural abnormalities of the brain, this may change.

**Treatment gap**

Worldwide, the proportion of patients with epilepsy who at any given time remain untreated is large, and is greater than 80% in most low income countries (33, 34). The size of this treatment gap reflects either a failure to identify cases or a failure to deliver treatment. In most situations, however, both factors will apply. Inadequate case-finding and treatment have various causes, some of which are specific to low income countries. They include people’s attitudes and beliefs, government health policies and priorities (or the lack of them), treatment costs and drug availability, as well as the attitude, knowledge and practice of health workers. In addition, there is clear scarcity of epilepsy-trained health workers in many low income countries. The lack of trained personnel and a proper health delivery infrastructure are major problems, which contribute to the overall burden of epilepsy. For instance, in most sub-Saharan countries there is no resident neurologist and there are no scanning facilities using magnetic resonance imaging (MRI) (35). This situation is found in many other resource-poor countries and is usually more acute in rural areas. The lack of trained specialists and medical facilities needs to be seen in the context of severe deficiencies in health delivery that apply not only to epilepsy but also to the whole gamut of medical conditions. Training medical and paramedical personnel and providing the necessary investigatory and treatment facilities will require tremendous effort and financial expenditure and will take time to achieve. The aim should be to provide high standards of epilepsy care with equitable access to all who need them throughout the world.

There is a dearth of epilepsy services, trained personnel and AEDs, which contributes to a massive diagnostic and treatment gap in epilepsy that is more pronounced in low income countries. A huge effort is required to equalize care for people with epilepsy around the world. Improvement of the care delivery system and infrastructure alone are not a sufficient strategy but need to be supplemented by education of patients, their families and the general public.

**RESEARCH**

Despite the significant advances in understanding epileptogenic mechanisms and in counteracting their pathological consequences, the problem still has to be faced of treating more effectively the severe epilepsies and of preventing their unfavourable evolution (37). So far, research has been unsuccessful in developing effective strategies capable of preventing the development of the pathogenic process, set in motion by different etiological factors, that leads ultimately to chronic epilepsies (38). To do so, it is important to take advantage of the results that are continuously being made available to the scientific community thanks to the synergy of basic and clinical multidisciplinary research. This means that the clinical applicability of neurobiological results should be evaluated, the way in which the new information can be translated into diagnostic and therapeutic terms should be assessed, and ad hoc guidelines and recommendations should be produced accordingly.

In elaborating their health-care strategies, regional and national communities should not simply refer to the available scientific information, but should also contribute to it by means of their own
original investigations. This is mandatory if they are to meet specific local requirements taking into account the socioeconomic situations in which health-care policy is to be formulated. Important actions have been undertaken by the International League Against Epilepsy (ILAE) through its various commissions (on genetics, neurobiology, psychobiology, epidemiology, therapeutic strategies, diagnostic methods and health-care policy) to help developing countries in establishing research projects oriented to their specific problems. Moreover, ILAE is active in promoting international collaborative research networks, facilitating partnerships between developed and developing countries, promoting fellowships and grant programmes and in sensitizing the relevant international institutions such as the World Bank, WHO and the United Nations Educational, Scientific and Cultural Organization (UNESCO) to epilepsy research (39). A specific project for collaborative studies involving developed and developing countries is part of the triennial action plan of the Global Campaign Against Epilepsy. The project aims to stimulate and facilitate the synergy between countries in different economic situations that is particularly important for epidemiological and genetic studies and clinical trials of new AEDs.

The main point here is that research is not a matter of technology; rather, it is the result of an intellectual attitude aimed at understanding and improving the principles upon which every medical activity should be based. Therefore, everybody whose work concerns epilepsy can and should contribute to the advancement of epileptology to the benefit of the millions of human beings suffering from epilepsy, no matter how advanced the technological context of his or her current work.

**EDUCATION AND TRAINING**

Education and training programmes aimed at improving the expertise of health-care providers play an essential role in fostering epilepsy care throughout the world. The need for an integrated, multidisciplinary approach to epilepsy care prompted several countries to organize annual epilepsy courses for neurologists, general practitioners, technicians and nurses at national level.

Multinational programmes are being implemented on the basis of the pioneering experience of ILAE’s European Epilepsy Academy (EUREPA), which has developed two innovative educational models: train-the-trainers courses and European Epileptology Certification. The aim of the train-the-trainers courses is to turn experienced personnel into qualified teachers of epileptology. It significantly contributes to raising the profile of epilepsy care across Europe and is now being implemented in other regions. European Epileptology Certification can be obtained by completing an 18-month educational programme based on periods of training in selected institutions that allow the accumulation of credits.

EUREPA is also developing an important project of distance education in epileptology. Some modules have been completed and successfully tested: the course on genetics of epilepsy has already been evaluated (40). An annual residential Epilepsy Summer School for young epileptologists from all over the world exists at Venice’s International School of Neurological Sciences; since 2002, it has trained students from 64 countries. The interaction between students and teachers and among the students themselves resulted in several ongoing international collaborative projects that are further contributing to raising the profile of epilepsy care in several developing areas (41).

The philosophy on which the educational initiatives of ILAE and EUREPA are based is an interactive relationship that stimulates the active participation of students. The theoretical teaching, based either on residential courses or distance education systems, includes an interactive discussion of clinical cases and practical training programmes in qualified epilepsy centres. A further effort is needed to expand exchange programmes for visiting students from economically disadvantaged countries.
PARTNERSHIPS WITHIN AND BEYOND THE HEALTH SYSTEM

Partnerships within and beyond the health system are essential in order to achieve a world in which no person’s life is limited by epilepsy. As the President of ILAE put it, “we all have a shared interest in that we want to improve epilepsy care throughout the world”. Such partnerships include:

- nongovernmental organizations, which are themselves partnerships as they are made up of individuals who have common goals and interests;
- patients and professionals at national, regional and global levels, in order to raise awareness of epilepsy and stimulate research;
- patient and professional nongovernmental organizations and WHO, in order to decrease the treatment gap;
- patients, professionals and politicians, for example to develop national health-care programmes;
- foundations and charitable organizations, who support the work of the nongovernmental organizations both financially and with human resources;
- health-care providers, to try to improve the availability, accessibility and affordability of treatment;
- the private sector, especially the pharmaceutical industry.

ILAE/IBE/WHO Global Campaign Against Epilepsy

The problems related to provision of care and treatment to people with epilepsy are too complex to be solved by individual organizations, therefore the three leading international organizations working in the field of epilepsy (ILAE, the International Bureau for Epilepsy (IBE) and WHO) joined forces to create the Global Campaign Against Epilepsy. The Campaign aims to provide better information about epilepsy and its consequences and to assist governments and those concerned with epilepsy to reduce the burden of the disorder. Its strategy, specific objectives and activities are summarized in Box 3.2.2.

To date, over 90 countries are involved in the Campaign. As part of general awareness-raising, regional conferences on public health aspects of epilepsy have been organized in all six regions of WHO with the participation of over 1300 delegates from the epilepsy organizations (IBE and

Box 3.2.2  ILAE/IBE/WHO Global Campaign Against Epilepsy

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Strategy</th>
<th>Activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>To increase public and professional awareness of epilepsy as a universal and treatable brain disorder</td>
<td>To provide a platform for general awareness</td>
<td>Organization of regional conferences followed by Regional Declarations</td>
</tr>
<tr>
<td>To raise epilepsy to a new plane of acceptability in the public domain</td>
<td>To assist departments of health in the development of national programmes on epilepsy</td>
<td>Assessment of country resources for epilepsy worldwide</td>
</tr>
<tr>
<td>To promote public and professional education about epilepsy</td>
<td></td>
<td>Assistance with the development of regional reports</td>
</tr>
<tr>
<td>To identify the needs of people with epilepsy at national and regional levels</td>
<td></td>
<td>Development of educational materials</td>
</tr>
<tr>
<td>To encourage governments and departments of health to address the needs of people with epilepsy, including awareness, education, diagnosis, treatment, care, services and prevention</td>
<td></td>
<td>Coordination of demonstration projects</td>
</tr>
</tbody>
</table>
ILAE), public health experts from governments and universities and representatives from WHO headquarters and regions.

The goals of the conferences were to review the present situation of epilepsy care in the region, to identify the country’s needs and resources to control epilepsy at a community level, and to discuss the involvement of countries in the Campaign. As a result of these consultations, Regional Declarations summarizing perceived needs and proposing actions to be taken were developed and adopted by the conference participants.

In order to make an inventory of country resources for epilepsy worldwide, a questionnaire was developed by an international group of experts in the field. On the basis of the data collected through this questionnaire, regional reports were developed. These reports provide a panoramic view of the epilepsy situation in each region, outline the various initiatives that were taken to address the problems, define the current challenges and offer appropriate recommendations (32, 42).

The next logical step in the assessment of country resources was the comprehensive analysis of the data. Within the framework of the WHO Atlas Project, launched by WHO in 2002 to provide information about health resources in different countries, the analysis was summarized in the Atlas of Epilepsy Care in the World (30). The epilepsy atlas has been produced in collaboration with the ILAE/IBE/WHO Global Campaign Against Epilepsy using ILAE and IBE chapters and WHO networks. The atlas provides global and regional analyses on epilepsy resources and is another result of the fruitful collaboration between ILAE, IBE and WHO (43).

One of the main activities aiming to assist countries in the development of their national programmes on epilepsy is the initiation and implementation of demonstration projects. The ultimate goal of these projects is the development of a variety of successful models of epilepsy control that may be integrated into the health-care systems of the participating countries and regions. In general terms, each demonstration project has four aspects:

- assessing whether knowledge and attitudes of the population are adequate, correcting misinformation and increasing awareness of epilepsy and how it can be treated;
- assessing the number of people with epilepsy and estimating how many of them are appropriately treated;
- ensuring that people with epilepsy are properly served by health personnel equipped for their task;
- analysing the outcome and preparing recommendations for those who wish to apply the findings to the improvement of epilepsy care in their own and other countries.

In summary, it may be concluded that the collaboration of ILAE, IBE and WHO within the frame of the Global Campaign has been very successful and led to significant achievements in various areas such as raising public and professional awareness and education, development of effective modules for epilepsy control, and assessment and analysis of epilepsy resources in all countries of the world.
CONCLUSIONS AND RECOMMENDATIONS

1. Epilepsy is one of the most common serious neurological disorders worldwide with no age, racial, social class, national or geographic boundaries.

2. Worldwide, 50 million people have epilepsy. Around 85% of these live in developing countries.

3. Up to 70% of people with epilepsy could lead normal lives if properly treated, but for an overwhelming majority of patients this is not the case.

4. The worldwide incidence, prevalence and mortality of epilepsy are not uniform and depend on several factors, which include the structure of the local population, the basic knowledge of the disease, the socioeconomic and cultural background, the presence of environmental risk factors, and the distribution of infrastructure, financial, human and material resources.

5. Some forms of epilepsy, particularly those associated with CNS infections and trauma, may be preventable.

6. As epileptic seizures respond to drug treatment, the outcome of the disease depends on the early initiation and continuity of treatment. Difficulties with availability of or access to treatment (the treatment gap) may seriously impair the prognosis of epilepsy and aggravate the social and medical consequences of the disease.

7. In low income countries the treatment gap needs to be seen in the context of the local situation, with inadequate resources for all forms of health delivery as well as education and sanitation.

8. The treatment gap is not only a matter of the lack of availability of AEDs, but encompasses the lack of infrastructure, training and public awareness of the condition. All these areas need to be confronted.

9. Integration of epilepsy care in national health systems needs to be promoted by developing models for epilepsy control worldwide.

REFERENCES

RECOMMENDED READING

3.3 Headache disorders

Headache is a painful feature of a relatively small number of primary headache disorders, some of which are widespread and are often life-long conditions. Headache also occurs as a characteristic symptom of many other conditions; these are termed secondary headache disorders. Collectively, headache disorders are among the most common disorders of the nervous system, causing substantial disability in populations throughout the world.

Figure 3.3.1 Population-based epidemiological studies of migraine

Note: All studies used International Headache Society criteria (or reasonable modifications of these criteria) for diagnosing migraine and were conducted in general population or community-based adult samples of at least 500 participants. Numbers are estimated 1-year prevalences.

Source: (3).
Despite the widespread and incapacitating nature of headache, it is underestimated in scope and scale, and headache disorders remain under-recognized and under-treated everywhere (1). Table 3.3.1 classifies headache disorders into primary, secondary, and neuralgias and other headaches, with their symptoms (2).

The worldwide epidemiology of headache disorders is only partly documented. Population-based studies have mostly focused on migraine (Figure 3.3.1) which, though the most frequently studied, is not the most common headache disorder. Others, such as the more prevalent tension-type headache and the more disabling so-called chronic daily headache syndromes, have received less attention. Furthermore, few population-based studies exist for developing countries, where limited funding and large and often rural (and therefore less accessible) populations, coupled with the low profile of headache disorders compared with communicable diseases, prevent the systematic collection of information.

Nevertheless, despite regional variations, headache disorders are thought to be highly prevalent throughout the world, and recent surveys add support to this belief. Sufficient studies have been conducted to establish that headache disorders affect people of all ages, races, income levels and geographical areas (Figure 3.3.2). Four of them — three primary headache disorders and one secondary — have particular public health importance.

**Figure 3.3.2 Population-based epidemiological studies of headache disorders**

<table>
<thead>
<tr>
<th>Region</th>
<th>Prevalence</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>21.6%</td>
<td>2 studies</td>
</tr>
<tr>
<td>Asia</td>
<td>58.6%</td>
<td>5 studies</td>
</tr>
<tr>
<td>Europe</td>
<td>56.1%</td>
<td>8 studies</td>
</tr>
<tr>
<td>N. America</td>
<td>53.5%</td>
<td>3 studies</td>
</tr>
<tr>
<td>Oceania</td>
<td>50.0%</td>
<td>1 study</td>
</tr>
<tr>
<td>S. America</td>
<td>41.3%</td>
<td>4 studies</td>
</tr>
</tbody>
</table>

*a all headache disorders or unspecified headache.

Note: All studies were conducted in general population or community-based adult samples of at least 500 participants. Numbers are estimated 1-year prevalences.

Source: (3).
### Table 3.3.1 Classification of headache disorders

<table>
<thead>
<tr>
<th>Type</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td>1. Migraine</td>
</tr>
<tr>
<td></td>
<td>2. Tension-type headache</td>
</tr>
<tr>
<td></td>
<td>3. Cluster headache and other trigeminal autonomic cephalalgias</td>
</tr>
<tr>
<td></td>
<td>4. Other primary headaches</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td>5. Headache attributed to head and/or neck trauma</td>
</tr>
<tr>
<td></td>
<td>6. Headache attributed to cranial or cervical vascular disorder</td>
</tr>
<tr>
<td></td>
<td>7. Headache attributed to non-vascular intracranial disorder</td>
</tr>
<tr>
<td></td>
<td>8. Headache attributed to a substance or its withdrawal</td>
</tr>
<tr>
<td></td>
<td>9. Headache attributed to infection</td>
</tr>
<tr>
<td></td>
<td>10. Headache attributed to disorder of homoeostasis</td>
</tr>
<tr>
<td></td>
<td>11. Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses,</td>
</tr>
<tr>
<td></td>
<td>teeth, mouth or other facial or cranial structures</td>
</tr>
<tr>
<td></td>
<td>12. Headache attributed to psychiatric disorder</td>
</tr>
<tr>
<td>**Neuralgias and</td>
<td>13. Cranial neuralgias, central and primary facial pain and other headaches</td>
</tr>
<tr>
<td>other headaches</td>
<td>14. Other headache, cranial neuralgia, central or primary facial pain</td>
</tr>
</tbody>
</table>

Source: (1).

### TYPES OF HEADACHE DISORDERS

**Migraine**

Migraine is a primary headache disorder. It almost certainly has a genetic basis (4), but environmental factors play a significant role in how the disorder affects those who suffer from it. Pathophysiologically, activation of a mechanism deep in the brain causes release of pain-producing inflammatory substances around the nerves and blood vessels of the head. Why this happens periodically, and what brings the process to an end in spontaneous resolution of attacks, are uncertain.

Usually starting at puberty, migraine is recurrent throughout life in many cases. Adults with migraine describe episodic disabling attacks in which headache and nausea are the most characteristic features; others are vomiting and dislike or intolerance of normal levels of light and sound. Headaches are typically moderate or severe in intensity, one-sided and pulsating, aggravated by routine physical activity; they usually last from several hours to 2–3 days. In children, attacks tend to be of shorter duration and abdominal symptoms more prominent. Attack frequency is typically once or twice a month but can be anywhere between once a year and once a week, often subject to lifestyle and environmental factors that suggest people with migraine react adversely to change in routine.

Migraine is most disabling to people aged 35–45 years, but it can trouble much younger people, including children. Studies in Europe and the United States have shown that migraine affects 6–8% of men and 15–18% of women (5, 6). A similar pattern probably exists in Central America: in Puerto Rico, for example, 6% of men and 17% of women were found to have migraine (7). In South America, prevalences appear only slightly lower (8).

A recent survey in Turkey suggested even greater prevalence in that country: 9% in men and 29% in women (9). Similarly, in India, although major studies are still to be conducted, anecdotal evidence suggests migraine is very common. High temperatures and high light levels for more than eight months of the year, heavy noise pollution and the Indian habits of omitting breakfast, fasting frequently and eating rich, spicy and fermented food are thought to be common triggers (10). Migraine appears less prevalent, but still common, elsewhere in Asia (around 8%) and in Africa (3–7% in community-based studies) (3). In these areas also, major studies have yet to be carried out.

The higher rates in women everywhere (2–3 times those in men) are hormonally driven.
Tension-type headache
The mechanism of tension-type headache is poorly understood, though it has long been regarded as a headache with muscular origins (11). It may be stress related or associated with musculoskeletal problems in the neck.

Tension-type headache has distinct subtypes. As experienced by very large numbers of people, episodic tension-type headache occurs, like migraine, in attack-like episodes. These usually last no more than a few hours but can persist for several days. Chronic tension-type headache, one of the chronic daily headache syndromes, is less common than episodic tension-type headache but is present most of the time: it can be unremitting over long periods. This variant is much more disabling.

Headache in either case is usually mild or moderate and generalized, though it can be one-sided. It is described as pressure or tightness, like a band around the head, sometimes spreading into or from the neck. It lacks the specific features and associated symptoms of migraine.

Tension-type headache pursues a highly variable course, often beginning during the teenage years and reaching peak levels around the age of 30–40 years. It affects three women to every two men. Episodic tension-type headache is the most common headache disorder, reported by over 70% of some populations (12), though its prevalence appears to vary greatly worldwide (3). In Japan, for example, Takeshima et al. (13) found 22% of the population to be affected, while Abduljabbar et al. (14) recorded only 3.1% with tension-type headache in a rural population of Saudi Arabia (though it was still the most common headache type). Lack of reporting and under-diagnosis were thought to be factors here, and it may be that cultural attitudes to reporting a relatively minor complaint explain at least part of the variation elsewhere. Chronic tension-type headache affects 1–3% of adults (3).

Cluster headache
Cluster headache is one of a group of primary headache disorders (trigeminal autonomic cephalalgias) of uncertain mechanism that are characterized by frequently recurring, short-lasting but extremely severe headache (1).

Cluster headache also has episodic and chronic forms. Episodic cluster headache occurs in bouts (clusters), typically of 6–12 weeks’ duration once a year or two years and at the same time of year. Strictly one-sided intense pain develops around the eye once or more daily, mostly at night. Unable to stay in bed, the affected person agitatedly paces the room, even going outdoors, until the pain diminishes after 30–60 minutes. The eye is red and watery, the nose runs or is blocked on the affected side and the eyelid may droop. In the less common chronic cluster headache there are no remissions between clusters. The episodic form can become chronic, and vice versa.

Though relatively uncommon, probably affecting no more than 3 per 1000 adults, cluster headache is clearly highly recognizable. It is unusual among primary headache disorders in affecting six men to each woman. Most people developing cluster headache are 20–30 years of age or older; once present, the condition may persist intermittently for 40 years or more.

Medication-overuse headache
Chronic excessive use of medication to treat headache is the cause of medication-overuse headache (15), another of the chronic daily headache syndromes.

Medication-overuse headache is oppressive, persistent and often at its worst on awakening in the morning. A typical history begins with episodic headache — migraine or tension-type headache. The condition is treated with an analgesic or other medication for each attack. Over time, headache episodes become more frequent, as does medication intake. In the end-stage, which not all patients reach, headache persists all day, fluctuating with medication use repeated every few hours. This evolution occurs over a few weeks or much, much longer. A common and
probably key factor at some stage in the development of medication-overuse headache is a switch to pre-emptive use of medication, in anticipation of the headache.

All medications for the acute or symptomatic treatment of headache, in overuse, are associated with this problem, but what constitutes overuse is not clear in individual cases. Suggested limits are the regular intake of simple analgesics on 15 or more days per month or of codeine- or barbiturate-containing combination analgesics, ergotamine or triptans on more than 10 days a month (1). Frequency of use is important: even when the total quantities are similar, low daily doses carry greater risk than larger weekly doses.

In terms of prevalence, medication-overuse headache far outweighs all other secondary headaches (16). It affects more than 1% of some populations (17), women more than men, and children also. In others for whom there are no published data, in Saudi Arabia for example, clinical experience suggests this disorder is not uncommon, with a tendency to be more evident in affluent communities.

Serious secondary headaches
Some headaches signal serious underlying disorders that may demand immediate intervention (see Box 3.3.1). Although they are relatively uncommon, such headaches worry nonspecialists because they are in the differential diagnosis of primary headache disorders. The reality is that intracranial lesions give rise to histories and physical signs that should bring them to mind.

Over-diagnosed headaches
Headache should not be attributed to sinus disease in the absence of other symptoms indicative of it. Many patients with headache visit an optician, but errors of refraction are overestimated as a cause of headache. Dental problems may cause jaw or facial pain but rarely headache.

EPIDEMIOLOGY AND BURDEN
Taken together, headache disorders are extraordinarily common. In developed countries, tension-type headache alone affects two thirds of adult males and over 80% of females (12). Extrapolation from figures for migraine prevalence and attack incidence suggests that 3000 migraine attacks occur every day for each million of the general population (6). Less well recognized is the toll of chronic daily headache: up to one adult in 20 has headache on more days than not (17, 18). Further...
thermore, several (though not all) follow-up studies in developed countries suggest that headache prevalence and burden are increasing (19).

No significant mortality is associated with headache disorders, which is one reason why they are so poorly acknowledged. Nevertheless, among the recognizable burdens imposed on people affected by headache disorders are pain and personal suffering, which may be substantial, impaired quality of life and financial cost. Above all, headache disorders are disabling: worldwide, WHO ranks migraine alone at 19th among all causes of years of life lost to disability (YLDs) (20). Collectively, all headache disorders probably account for double this burden (3), which would put them among the top ten causes of disability. Repeated headache attacks, and often the constant fear of the next, damage family life, social life and employment (21). For example, social activity and work capacity are reduced in almost all people with migraine and in 60% of those with tension-type headache. Headache often results in the cancellation of social activities while, at work, people who suffer frequent attacks are likely to be seen as unreliable — which they may be — or unable to cope. This can reduce the likelihood of promotion and undermine career and financial prospects.

While people actually affected by headache disorders bear much of their burden, they do not carry it all: employers, fellow workers, family and friends may be required to take on work and duties abandoned by headache sufferers. Because headache disorders are most troublesome in the productive years (late teens to 60 years of age), estimates of their financial cost to society are massive — principally from lost working hours and reduced productivity because of impaired working effectiveness (22). In the United Kingdom, for example, some 25 million working or school days are lost every year because of migraine alone (6). Tension-type headache, less disabling but more common, and chronic daily headache, less common but more disabling, together cause losses that are almost certainly of similar magnitude.

Therefore, while headache rarely signals serious underlying illness, its public health importance lies in its causal association with these personal and societal burdens of pain, disability, damaged quality of life and financial cost. Not surprisingly, headache is high among causes of consulting both general practitioners and neurologists (23, 24). One in six patients aged 16–65 years in a large general practice in the United Kingdom consulted at least once because of headache over an observed period of five years, and almost 10% of them were referred to secondary care (25). A survey of neurologists found that up to a third of all their patients consulted because of headache — more than for any other single complaint (26).

Far less is known about the public health aspects of headache disorders in developing and resource-poor countries. Indirect financial costs to society may not be so dominant where labour costs are lower but the consequences to individuals of being unable to work or to care for children may be severe. There is no reason to believe that the burden of headache in its personal elements weighs any less heavily where resources are limited, or where other diseases are also prevalent.

**BARRIERS TO CARE**

Headache ought to be a public health concern, yet there is good evidence that very large numbers of people troubled, even disabled, by headache do not receive effective health care (2). For example, in representative samples of the general populations of the United States and the United Kingdom, only half the people identified with migraine had seen a doctor for headache-related reasons in the last 12 months and only two thirds had been correctly diagnosed (27). Most were solely reliant on over-the-counter medications, without access to prescription drugs. In a separate general-population questionnaire survey in the United Kingdom, two thirds of respondents with migraine were searching for better treatment than their current medication (28). In Japan, awareness of migraine and rates of consultation by those with migraine are noticeably lower (29). Over
80% of Danish tension-type headache sufferers had never consulted a doctor for headache (30). It is highly unlikely that people with headache fare any better in developing countries. The barriers responsible for this lack of care doubtless vary throughout the world, but they may be classified as clinical, social, or political and economic.

**Clinical barriers**
Lack of knowledge among health-care providers is the principal clinical barrier to effective headache management. This problem begins in medical schools where there is limited teaching on the subject, a consequence of the low priority accorded to it. It is likely to be even more pronounced in countries with fewer resources and, as a result, more limited access generally to doctors and effective treatments.

**Social barriers**
Poor awareness of headache extends similarly to the general public. Headache disorders are not perceived by the public as serious since they are mostly episodic, do not cause death and are not contagious. In fact, headaches are often trivialized as “normal”, a minor annoyance or an excuse to avoid responsibility. These important social barriers inhibit people who might otherwise seek help from doctors, despite what may be high levels of pain and disability. Surprisingly, poor awareness of headache disorders exists among people who are directly affected by them. A Japanese study found, for example, that many patients were unaware that their headaches were migraine, or that this was a specific illness requiring medical care (31). The low consultation rates in developed countries may indicate that many headache sufferers are unaware that effective treatments exist. Again, the situation is unlikely to be better where resources are more limited.

**Political and economic barriers**
Many governments, seeking to constrain health-care costs, do not acknowledge the substantial burden of headache on society. They fail to recognize that the direct costs of treating headache are small in comparison with the huge indirect cost savings that might be made (for example by reducing lost working days) if resources were allocated to treat headache disorders appropriately.

**MANAGEMENT AND PREVENTION**
Successful management of headache disorders follows five essential steps:

- the sufferer must seek medical treatment;
- a correct diagnosis should be made;
- the treatment offered must be appropriate to the diagnosis;
- the treatment should be taken as directed;
- the patient should be followed up to assess the outcome of treatment, which should be changed if necessary.

Therefore the key to successful health care for headache is education (31), which first should create awareness that headache disorders are a medical problem requiring treatment. Education of health-care providers should encompass both the elements of good management (see Box 3.3.2) and the avoidance of mismanagement.

**Diagnosis**
Committing sufficient time to taking a systematic history of a patient presenting with headache is the key to getting the diagnosis right. The history-taking must highlight or elicit description of the characteristic features of the important headache disorders described above. The correct diagnosis is not always evident initially, especially when more than one headache disorder is present, but the history should awaken suspicion of the important secondary headaches. Once it is established that there is no serious secondary headache, a diary kept for a few weeks to record
the pattern of attacks, symptoms and medication use will usually clarify the diagnosis. Physical examination rarely reveals unexpected signs after an adequately taken history, but should include blood pressure measurement and a brief but comprehensive neurological examination including the optic fundi; more is not required unless the history is suggestive. Examination of the head and neck may find muscle tenderness, limited range of movement or crepitation, which suggest a need for physical forms of treatment but do not necessarily elucidate headache causation.

Investigations, including neuroimaging, rarely contribute to the diagnosis of headache when the history and examination have not suggested an underlying cause.

**Realistic objectives**
There are few patients troubled by headache whose lives cannot be improved by the right medical intervention with the objective of minimizing impairment of life and lifestyle (32). Cure is rarely a realistic aim in primary headache disorders, but people disabled by headache should not have unduly low expectations of what is achievable through optimum management.

Medication-overuse headache and other secondary headaches are, at least in theory, resolved through treatment of the underlying cause.

**Predisposing and trigger factors**
Migraine, in particular, is said to be subject to certain physiological and external environmental factors. While predisposing factors increase susceptibility to attacks, trigger factors may initiate them. The two may combine. Attempts to control migraine by managing either are often disappointing. A few predisposing factors (stress, depression, anxiety, menopause, and head or neck trauma) are well recognized but not always avoidable or treatable. Trigger factors are important and their influence is real in some patients, but generally less so than is commonly supposed.

Dietary triggers are rarely the cause of attacks: lack of food is a more prominent trigger. Many attacks have no obvious trigger and, again, those that are identified are not always avoidable. Diaries may be useful in detecting triggers but the process is complicated as triggers appear to be cumulative, jointly overflowing the “threshold” above which attacks are initiated. Too much effort in seeking triggers causes introspection and can be counter-productive. Enforced lifestyle change to avoid triggers can itself adversely affect quality of life.

In tension-type headache, stress may be obvious and likely to be etiologically implicated. Musculoskeletal involvement may be evident in the history or on examination. Sometimes, neither of these factors is apparent. An interesting variation in the Muslim world is the marked rise, observed in people ordinarily susceptible to headache, in tension-type headache incidence on the first day of fasting (33).

**Box 3.3.2 Seven elements of good headache management**

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<tr>
<td>1</td>
<td>Evident interest and investment of time to inform, explain, reassure and educate</td>
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<td>2</td>
<td>Correct and timely diagnosis</td>
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<td>3</td>
<td>Agreed high but realistic objectives</td>
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<td>4</td>
<td>Identification of predisposing and/or trigger factors and their avoidance through appropriate lifestyle modifications</td>
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<td>5</td>
<td>Intervention (optimal management of most primary headaches combines adequate but not excessive use of effective and cost-effective pharmaceutical remedies with non-pharmacological approaches; secondary headaches generally require treatment of the underlying cause)</td>
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<tr>
<td>6</td>
<td>Follow-up to ensure optimum treatment has been established</td>
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<td>7</td>
<td>Referral to specialist care when these measures fail</td>
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Cluster headache is usually but not always a disease of smokers, many of them heavy consumers of tobacco. However, patients with cluster headache who still smoke cannot be promised that giving up will end or even improve their headaches. Alcohol potently triggers cluster headache and most patients have learnt to avoid it during cluster periods.

**THERAPEUTIC INTERVENTIONS**

The purpose of pharmacotherapy of primary headache, once non-drug measures have been fully exploited, is to control symptoms so that the impact of the disorder on each individual patient’s life and lifestyle is minimized. This requires a therapeutic plan tailored for each patient, and patients with two or more coexisting headache disorders are likely to require separate plans for each disorder.

**Migraine**

Most people with migraine require drugs for the acute attack. These may be symptomatic or specific. The desirable goal of acute therapy with drugs currently available — resolution of symptoms and full return of function within two hours — is not attainable by all. When symptom control with best acute therapy is inadequate, it can be supplemented with prophylactic medication (34), usually for 4–6 months, aiming to reduce the number of attacks.

General population surveys indicate that large numbers of people with migraine manage themselves, with no more than symptomatic over-the-counter remedies (27). For many this appears adequate. Simple oral analgesia — acetylsalicylic acid or ibuprofen — is used to best advantage in soluble formulations taken early because gastric stasis develops as the migraine attack progresses and this impedes absorption. A prokinetic antiemetic — metoclopramide or domperidone — enhances the analgesic effect by promoting gastric emptying and is most suitable for nausea and vomiting. When oral symptomatic therapy fails, it is logical to bypass the gut using a non-steroidal anti-inflammatory drug such as diclofenac, with or without domperidone, given as rectal suppositories (35).

Specific drugs — triptans and, in certain circumstances, ergotamine tartrate — should not be withheld from those who need them. There are specific contraindications to these drugs, particularly coronary disease (and multiple risk factors thereof) and uncontrolled hypertension, but triptans as a class show higher efficacy rates than symptomatic treatments. Population-based needs assessments suggest many more people with migraine should receive triptans than currently do. Cost has much to do with this, and this constraint must be more evident in resource-poor countries where triptans are unlikely to be available. Denial of the best treatment available is difficult to justify for patients generally, however, and therefore for individuals: unnecessary pain and disability are the result. In addition, increasingly it is being demonstrated in developed countries that under-treatment of migraine is not cost effective: the time lost by sufferers and their carers is expensive, as are repeated consultations in the search for better therapy. On this basis some specialists believe that disability assessment should be the means to select patients to receive triptans. Where disability is the basis of choice, however, it should be noted that over 80% of people with migraine report disability because of it (36).

Which triptan to choose is an individual matter because different patients respond differently to them: one may work where another does not. In countries where more than one is available, patients may reasonably try each in turn to discover which suits them best. Relapse (return of headache within 6–48 hours) in 20–50% of patients who have initially responded is a troublesome limitation of triptans. A second dose is usually effective for relapse but, occasionally in some patients and often in a few, induces further relapse. This problem may underlie medication-overuse headache attributable to triptan overuse (37).

Drugs in a range of pharmacological classes have limited but often useful prophylactic efficacy against migraine through mechanisms that are presumably not identical but are unclear. The choice
of agent is guided by comorbidities and contraindications. Because poor compliance is a major factor impairing effectiveness, drugs given once daily are preferable, all else being equal. Beta-blockers without partial agonism (such as atenolol, metoprolol, and propranolol in a long-acting formulation) are likely to be first-line prophylactics in many countries. Cardioselectivity and hydrophilicity do not affect efficacy but both improve the side-effect profile, so atenolol may be preferred. Certain antiepileptic drugs (AEDs), notably divalproex or sodium valproate and topiramate, have good evidence of efficacy. Amitriptyline is useful especially when migraine and tension-type headache occur together. Relatively low doses are often sufficient. Among calcium channel blockers, only flunarizine has efficacy. Methysergide, a synthetic ergot alkaloid, is effective but recommended for use only under specialist supervision, and not for more than six months continuously.

In some women, hormonal influences are important in driving attack frequency, and a special approach may be taken to menstruation-related migraine (38).

**Tension-type headache**
Reassurance and over-the-counter analgesics (acetylsalicylic acid or ibuprofen rather than paracetamol) (39) are sufficient for infrequent episodic tension-type headache. Most people with this condition manage themselves: episodic tension-type headache is self-limiting and, though it may be temporarily disabling, it rarely raises anxieties. If medication usage is on fewer than two days per week there is little risk of escalating consumption.

People consult doctors because of episodic tension-type headache when it is becoming frequent and, in all likelihood, is no longer responding to painkillers. Long-term remission is then the objective of management, as it is for chronic tension-type headache. Symptomatic medication is contraindicated for tension-type headache occurring on more than two days per week: where it is already being taken at high frequency a diagnosis of chronic tension-type headache rather than medication-overuse headache cannot be made with confidence. Whichever condition is present (and it can be both), frequently taken symptomatic medication must be withdrawn as the first step (see below).

Physiotherapy is the treatment of choice for musculoskeletal symptoms accompanying frequent episodic or chronic tension-type headache. In stress-related illness, lifestyle changes to reduce stress, and relaxation and/or cognitive therapy to develop stress-coping strategies, are the treatment mainstays. Prophylactic medication has a limited role. Amitriptyline is first-line in most cases, withdrawn after improvement has been maintained for 4–6 months. Long-term remission is not always achievable, especially in long-standing chronic tension-type headache. A pain management clinic may be the final option.

**Cluster headache**
Because of its relative rarity, cluster headache has a tendency to be misdiagnosed, sometimes for years. It is the one primary headache that may not be best managed in primary care, but the primary care physician has an important role not only in recognizing it at once but also in discouraging inappropriate “treatments” (tooth extraction is not infrequent).

**Medication-overuse headache**
Prevention is the ideal management of medication-overuse headache, which means avoidance of acute medication for headache on more than 2–3 days per week on a regular basis. Education is the key factor: many patients with medication-overuse headache are unaware of it as a medical condition (40). Once this disorder has developed, early intervention is important since the long-term prognosis depends on the duration of medication overuse (41).

Treatment is withdrawal of the suspected medication(s). Although this will lead initially to worsening headache and sometimes nausea, vomiting and sleep disturbances, with forewarning and explanation it is probably most successful when done abruptly (42).
Serious secondary headaches
All the serious secondary headaches described above require specialist referral. In most cases, this should be immediate or urgent.

FOLLOW-UP AND REFERRAL
Neither the first diagnosis, nor the first proposed treatment plan, may be correct. Follow-up is essential, at intervals balanced on the one hand to allow time for treatment interventions to achieve observable effect and on the other to meet patients’ natural desires for a quick solution to a painful and often debilitating problem.

For migraine and episodic tension-type headache, attack frequency is likely to be the principal determinant. For chronic tension-type headache, follow-up provides the psychological support that is often needed while recovery is slow.

In medication-overuse headache, early review is essential once withdrawal from medication has begun, in order to check that it is being achieved: nothing is less helpful than discovering, three months later, that the patient ran into difficulties and gave up the attempt. During later follow-up, the underlying primary headache condition is likely to re-emerge and require re-evaluation and a new therapeutic plan. Most patients with medication-overuse headache require extended support: the relapse rate is around 40% within five years (41).

Urgent referral for specialist management is recommended at each onset of cluster headache. Weekly review is unlikely to be too frequent and allows dosage incrementation of potentially toxic drugs to be as rapid as possible. Patients commencing lithium therapy, or changing their dose, need levels checked within one week.

In all other cases, specialist referral is appropriate when the diagnosis remains (or becomes) unclear or these standard management options fail.

HEALTH-CARE POLICY
The volume of headache referrals to neurologists seen in developed countries is difficult to justify, and should not be repeated in countries where headache-related health services are being developed. The common headache disorders require no special investigation and they are diagnosed and managed with skills that should be generally available to physicians. Management of headache disorders therefore belongs in primary care for all but a very small minority of patients. Models of health care vary but, in most countries, primary care has an acknowledged and important role. It is a role founded on recognition that decisions in primary care take account of patient-related factors — family medical history and patients’ individual expectations and values — of which the continuity and long-term relationships of primary care generate awareness (43) while promoting trust and satisfaction among patients (44).

Even in primary care, however, the needs of the headache patient are not met in the time usually allocated to a physician consultation in many health systems. Nurses and pharmacists can complement the delivery of health care.

The evident burden of headache disorders on individuals and on society is sufficient to justify a strategic change in the approach to headache management (31, 45). In order to implement beneficial change, public health policy in all countries must embrace the following elements.

- The prevalence of the common headache disorders in each region of the world needs to be known, through further epidemiological research where necessary, in order to gain a complete picture of headache disorders and their clinical, social and economic implications locally.
- This information, as it is accumulated, should be employed to combat stigma and increase public awareness of headache as a real and substantial health problem.
Education, as the key to effective headache management, needs improving at all levels. In the case of the medical profession, this should begin in medical schools by giving headache disorders a place in the undergraduate curriculum that matches their clinical importance as one of the most common causes of consultation. Nowhere is this the case at present.

The health economics of headache disorders and their effective treatment generally support investment of health-care resources in headache management programmes, set up in collaboration with key stakeholders to create services appropriate to local systems and local needs. Their outcomes should be evaluated in terms of measurable reductions in population burden attributable to headache disorders.

**PARTNERSHIPS WITHIN AND BEYOND THE HEALTH SYSTEM**

The elements listed above form the framework of WHO’s Global Campaign to Reduce the Burden of Headache Worldwide (45). Launched in March 2004, this campaign — known as “Lifting the Burden” — is a formal partnership between WHO and the international nongovernmental organizations for headache: the lay World Headache Alliance and the professional International Headache Society and European Headache Federation. The objectives of Lifting the Burden are, region by region throughout the world, to:

- measure the burden of headache disorders;
- raise awareness of headache disorders among local health policy-makers;
- work with people and agencies locally to plan locally appropriate health-care solutions;
- put these solutions in place, providing clinical management supports;
- test them, and modify and re-test if necessary, for optimal beneficial change.

Aside from this partnership, lay and professional groups in countries around the world play important, though often less formal, roles in education and in sharing information and experience.

**RESEARCH**

Five research fronts are currently important in the field of headache medicine.

- Basic research concentrates on elucidating disease mechanisms, particularly those that respond to environmental influences and those with a genetic basis. The findings will guide the development of new treatments.
- Pharmaceutical research and clinical trials support the translation of new discoveries into better treatments for people with headache disorders.
- Epidemiological research will establish the scope and scale of headache-related burden of illness around the world. The results will guide appropriate allocation of health-care resources by policy-makers. Epidemiological studies may also identify preventable risk factors for headache disorders.
- Health services research, backed by health economics studies, may show that the reallocation of resources towards improving health-care delivery offers greater benefits for people with headache disorders — by more effectively using treatments already available — than the search for new pharmacological interventions. This is particularly so given the prevalence of medication misuse (both underuse and overuse). Community intervention studies may lead to better prevention of headache disorders.
- Outcomes research is needed to guide optimal health care and its delivery through organized health services.

The importance of patient and public involvement in defining research objectives should be emphasized: lay people have experience and skills that complement those of researchers.
CONCLUSIONS AND RECOMMENDATIONS

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<td>but headache rarely signals serious underlying illness. The huge public health</td>
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<td>Headache disorders have many types and subtypes, but a very small number of</td>
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<td>Although headache disorders can be treated effectively, globally they are not,</td>
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<td>Management of headache disorders everywhere in the world has low priority,</td>
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<td>Effective management of headache disorders can be provided in primary care for</td>
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<td>all but a very small minority of patients. Nurses and pharmacists can complement</td>
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<td>Good management, at whatever level, requires education of doctors and of people</td>
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<td>affected by headache disorders. Mismanagement, and overuse of medications to</td>
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<td>treat acute headache, are major risk factors for disease aggravation.</td>
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<td>Every government should acknowledge the humanitarian arguments for effective</td>
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<td>health care for headache disorders.</td>
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<td>Every government should be aware of the financial cost to the country of</td>
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<td>headache disorders in its population. Cost-of-illness studies will create</td>
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<td>may achieve through mitigated productivity losses.</td>
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<td>9</td>
<td>Partnerships between health policy-makers, health-care providers and people</td>
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<td>affected by headache disorders and their advocacy groups may be the best</td>
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REFERENCES


**RECOMMENDED READING**

3.4 Multiple sclerosis

Multiple sclerosis affects around 2.5 million people worldwide: it is one of the most common neurological disorders and cause of disability of young adults, especially in Europe and North America. There is a lack of epidemiological studies from Asia where the prevalence is reported to be low, though, with the availability of more neurologists and magnetic resonance imaging, a larger number of patients are being diagnosed. Although some people experience little disability during their lifetime, up to 60% are no longer fully ambulatory 20 years after onset, with significant implications for their quality of life and the financial cost to society.

Multiple sclerosis (MS) is an inflammatory demyelinating condition of the central nervous system (CNS) that is generally considered to be autoimmune in nature. In people with MS, the immune trigger is unknown, but the targets are myelinated CNS tracts. In regions of inflammation, breakdown of the blood–brain barrier occurs and destruction of myelin ensues, with axonal damage, gliosis and the formation of sclerotic plaques.

Plaques (MS lesions) may form in the CNS white matter in any location (and also in grey matter); thus, clinical presentations may be diverse. Continuing lesion formation in MS often leads to physical disability and, not infrequently, to cognitive decline.

DIAGNOSIS AND CLASSIFICATION

As the above definition suggests, MS can lead to a wide variety of symptoms, affecting different parts of the body and with varying severity. Diagnosis of MS has always been clinically based, but many tests — notably magnetic resonance imaging (MRI) and more specific diagnostic criteria — are now available to assist the clinician. MRI, the examination of the cerebrospinal fluid (CSF) and visual evoked potentials are helpful in confirming the clinical suspicion of MS. In Asia, where the prevalence is reported to be low (1–5 per 100 000), the clinical presentation may be similar to that seen in Europe and North America, with manifestations suggesting cerebral, brainstem, cerebellar, optic nerve and spinal cord involvement (western type of MS) or may present with more restricted recurrent optic nerve and spinal cord involvement (opticospinal form or the Asian variant). The reason for this variation is not known.

Typically, the clinician takes a detailed neurological history and carries out a neurological examination to assess how the nervous system has been affected. To establish the diagnosis of MS, a neurologist must demonstrate that involvement of the CNS is disseminated in time and space and exclude any other diagnostic possibility. Defined criteria are used to conclude whether the features fulfil the clinical diagnosis and allow for more precision, thus lessening the likelihood of an incorrect diagnosis. Currently, the most widely accepted guidelines to the diagnosis of MS are the “McDonald criteria” (7). These criteria incorporate MRI to provide evidence of dissemination in
time and space and enable the clinician to make an early diagnosis of MS. They also facilitate the
diagnosis of MS after a first attack (a clinically isolated syndrome) and in disease with insidious
progression (the primary progressive form of MS), see below.

While these criteria have proved to be useful in a typical adult Caucasian population of western
European ethnic origin, their validity remains to be proven in other regions such as Asia where
some studies still use Poser’s criteria. As the experience with MRI in MS builds up, it is expected
that the McDonald criteria with minor modifications will become applicable worldwide. It is always
essential that other conditions mimicking MS (such as vascular disorders, Sjogren’s disease and
sarcoid) are excluded.

**COURSE AND OUTCOME**

Just as the symptoms of MS are varied, so too is the course of the disease. Although some people
with MS experience little disability during their lifetime, up to 60% are no longer fully ambulatory
20 years after onset. In rare cases MS is so malignantly progressive it is terminal, but most people
with MS have a normal or near-normal life expectancy.

Typical patterns of progression, illustrated in Figure 3.4.1, are explained below.

- **Relapsing/remitting MS.** Approximately 80% of patients will initially present this form of
  MS, in which there are unpredictable attacks (relapses) during which new symptoms appear
  or existing symptoms become more severe. The relapses can last for varying periods (days
  or months) and there is partial or total recovery (remission). The disease may appear to be
  clinically inactive for months or years, though MRI studies show that asymptomatic inflam-
  matory activity is usually more frequent. Over time, however, symptoms may become more
  severe with less complete recovery of function after each attack, possibly because of gliosis
  and axonal loss in repeatedly affected plaques. People with MS may then enter a progressive
  phase, characterized by a step-like downhill course.

![Figure 3.4.1 Patterns of progression of multiple sclerosis](image-url)

Source (2).
Secondary progressive MS is characterized by progression that is not relapse related. Approximately 50% of patients with relapsing/remitting MS will develop secondary progressive MS within 10 years, and 80% will have developed this form of MS within 20 years of disease onset.

Primary progressive MS, which affects around 10–15% of all MS patients, is characterized by a lack of distinct attacks, but with slow onset and then steadily worsening symptoms. There is an accumulation of deficits and disability which may level off at some point or continue over years.

Benign MS. A diagnosis of benign MS is retrospective, when the accumulated disability from relapsing/remitting MS is either mild or non-existent after a long period (usually considered to be 15–20 years). Given that follow-up studies show that most patients of this type will eventually enter a disabling secondary progressive phase, the term “benign” is somewhat misleading.

Prognostic factor
Although MS is an unpredictable condition, some studies have suggested that onset with sensory symptoms or optic neuritis may have a better outlook. It has also been shown that multisite presentations and poor recovery from an initial episode may indicate a worse outcome. Studies that have observed a difference by sex usually indicate that males experience a more severe course than females.

Epidemiology and Burden
The incidence and prevalence of MS have been studied extensively. Some features of the disease are generally accepted and are discussed further in this section.

- The frequency of MS varies by geographical region throughout the world, apparently increasing with distance from the equator in both hemispheres.
- The disease is more common among women than men.
- Peak onset is at around 30 years of age.
- The disease is less common among non-white individuals than whites.

Etiology and risk factors
The distributions of MS by geography, sex, age, and race or ethnicity have all been explored for clues to etiology. Most early research focused on the possible role of an environmental factor that varied with latitude. To date no such risk factor for the disease has been unequivocally identified, though researchers continue to believe that one exists. There is substantial evidence of a genetic predisposition to the disease based on familial aggregation, and some debate over whether genetics or exposure to an environmental trigger primarily accounts for its geographical distribution. Relatively little is known about factors that predict the course of MS.

The worldwide distribution of MS can be only an indirect reflection of its cause, implicating some environmental factor that varies with latitude, and can be interpreted in at least three different ways in the search for clues to a specific etiology. First, an environmental risk factor may be more common in temperate than tropical climates. Second, such a factor may be more common in tropical climates, where it is acquired at an earlier age and consequently has less impact. Third, this factor may be equally common in all regions, but the chance of its acquisition or of the manifestation of symptoms is either increased by some enhancing factor present in temperate climates or reduced by a protective factor present in tropical areas.

Among those factors that have been most closely scrutinized are:
- infections, including a number of viral infections such as measles and Epstein–Barr virus;
- climate and solar conditions;
- living conditions;
- diet and trace elements.
It is now generally accepted that the etiology of MS involves some interplay of genetic and environmental factors. Evidence of racial or ethnic resistance, the increased risk among MS family members, and elevated monozygotic twin concordance rate all favour a genetic contribution to acquisition of the disease. The studies from which this evidence is derived, however, also indicate that heredity cannot entirely explain the occurrence of MS. This is underlined by the fact that no population-based study of monozygotic twins has found a concordance rate in excess of 30%. Some environmental factor, such as a virus or toxin, must still play a role.

**Global and regional distribution**

The fact that there is an uneven geographical distribution of MS has been known since early in the 20th century. The prevalence of MS has been shown to vary with latitude, with rates broadly rising as distance from the equator increases, in both the northern and southern hemispheres. While there is some truth to this, it belies the complex interaction of geography, genes and environment that larger scale epidemiological studies have uncovered.

As a recent meta-analysis of the epidemiology of MS put it “The updated distribution of MS [in Europe], showing many exceptions to the previously described north-south gradient, requires more explanation than simply a prevalence-latitude relationship. Prevalence data imply that racial and ethnic differences are important in influencing the worldwide distribution of MS and that its geography must be interpreted in terms of the probable discontinuous distribution of genetic susceptibility alleles, which can however be modified by environment. Because the environmental and genetic determinants of geographic gradients are by no means mutually exclusive, the race versus place controversy is, to some extent, a useless and sterile debate” (4).

There is substantial literature on the relationship between migration and the prevalence and incidence of MS. Studies both between and within countries invariably show that immigrants moving from high-risk to low-risk areas have a higher rate than that in their new homeland, but often somewhat lower than that in their place of origin. (Note that if this observation were based only on prevalence data, it might simply reflect the fact that sick and disabled people are less likely to move, rather than less frequent exposure to a risk factor or more frequent exposure to a protective factor in the new place of residence. However, data for the United States are based primarily on incidence and document the same decline in risk as found in prevalence studies.)

There are fewer studies of immigrants from low-risk to high-risk areas, but most findings indicate that immigrants retain the same risk as in their countries of origin. This may be because they carry some protective factor with them, but these studies frequently involve non-white immigrants in whom the disease is known to be rare and who may be genetically resistant.

All areas at medium to high risk for MS throughout the world have predominantly white populations. In countries with both white and non-white populations, MS rates are lower among non-whites. For example, the disease is virtually non-existent among Australian Aborigines, New Zealand Maoris and Black people in South Africa. In the United States, incidence and prevalence rates are twice as high among whites as among African Americans regardless of latitude. Furthermore, MS is also less frequent among North American Indians, Latin Americans, and people of the Western Pacific Region than among whites.

**Childhood multiple sclerosis**

While MS is predominantly an illness of young to middle-aged adults, it is also increasingly apparent that the disease can occur in children. Interest in, and knowledge of, paediatric MS has been increasing, and as a consequence the number of children diagnosed has also risen considerably over the last 10 years. At least 2.5–5% of all patients with MS experience their first clinical attack prior to their 16th birthday, though this may be an underestimate.

Typically, with paediatric MS, the sex difference is not as marked as it is with adults, the ratio of female to male being closer to 1:1 than the 2:1 that is normally cited for adults. This suggests
that, while the genetic implication of being female may influence MS risk, it appears to do so much more after puberty.

Further evidence of the role that environmental factors play comes from the studies of children of migrants. For example, the prevalence rates among the British-born children of immigrants from India, Pakistan, and parts of Africa and the West Indies were very much higher than those recorded for their parents and approximately equal to the expected rate for England.

**IMPACT**

Multiple sclerosis has a profound impact on patients’ social roles and the well-being of their families. Varying degrees of functional decline typically accompany MS. Because the onset is usually at about 30 years of age, the loss in productivity of people with MS can be substantial. Such functional decline will often interfere with the opportunities for people with MS to perform their customary roles. For example, physical disability — complicated by fatigue, depression and possibly cognitive impairment — contributes to an unemployment rate as high as 70% among people with MS; to replace lost earnings, they frequently collect disability benefits and social welfare. People with MS use more health-care resources than the general population (5). Together with their family members, they may also bear a financial burden related to home and transport modifications and the need for additional personal services.

The socioeconomic impact of MS on the individual is well illustrated by a recent United Kingdom study (6). In this population-based survey of all known patients with MS and their relatives in the county of Hampshire, England, about 53% of those who were employed at the time of diagnosis gave up their jobs, and the standard of living of 37% of patients and their families declined as a direct result of the disease. The ability to continue in gainful employment or to maintain social contacts and leisure activities correlates with the course and severity of the disease and cognitive function. Most carers reported symptoms that clearly related to organic pathologies, anxiety and symptoms of depression. The occurrence of these symptoms was associated with disease severity. The professional careers of 57% of relatives were also adversely affected by the patient’s illness.

The economic cost to society is also great (7). A recent economic analysis for the Australian MS Society (Acting Positively) illustrated the impact of the disease, which is considered typical (so far no global economic impact studies have been published). The Australian study found that the burden of the disease is likely to grow. Prevalence is expected to grow by 6.7% in the next five years, faster than population growth attributable to demographic ageing. The total financial costs of MS in 2005 are estimated at more than US$ 450 m (0.07% of GDP) and US$ 29 070 per person with MS, or US$ 23 per Australian per year. Lost productive capacity and the replacement value of informal community care are the two largest cost components (8). The following key economic factors were highlighted by the Australian study:

- Informal care for people with MS in the community represents 43% of total costs, with an average of 12.3 hours per week of informal care required per person with MS.
- Aids and modifications for people with physical disability were estimated to represent a further 4.6% of total financial costs.
- Production losses stemming from reduced work hours, temporary absences, early retirement and premature death are responsible for around 26% of total economic costs.
- Pharmaceuticals for people with MS, mainly beta-interferons, are estimated to represent 14% of total costs.
- Nursing home accommodation accounts for around 4.3% of total economic costs. Of the estimated 730 people with MS in (high care) nursing homes 37% are under 65 years of age.
- Other health-care costs — including hospitalizations, specialist and primary care and allied health expenses — account for 4.4%. Research is 1.9% of health expenditure, below the aver-
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Age of 2.4%. Deadweight losses arising from taxation revenue foregone and welfare payment transfers are estimated as US$ 10.5 million or 2.3% of total costs in 2005.

- The burden of disease — the suffering and premature death experienced by people with MS — is estimated to cost an additional 8968 DALYs (years of healthy life lost), with two thirds attributable to disability and one third to premature death.
- Last but not least, in Australia MS causes more disability and loss of life than all chronic back pain, slipped discs, machinery accidents, rheumatic heart disease or mental retardation.

PREVENTION AND TREATMENT

Uncertainty over the cause or development of MS implies that prevention is not currently a realistic option. Furthermore, there are no curative treatments available for MS (9). A number of disease-modifying drugs have been developed in the past 20 years, however, which reduce the number of attacks in the relapsing/remitting form of the disease. The extent to which eventual disease burden and disability are limited by use of the drugs is less clear. The most widely used disease-modifying drugs for MS are the beta-interferons (1a and 1b) and glatiramer acetate, which reduce the frequency and perhaps the severity of relapses. Although these drugs have been introduced in the developing regions, their high cost means many patients are unable to have access to them. The United States National MS Society also has developed several guidelines and recommendations, mainly for medical treatment (such as changing therapy and early intervention). To date, no medical treatments for the progressive forms of the disease exist, and results from studies focusing on neuroprotection and repair are eagerly awaited.

Corticosteroids are the medications of choice for treating exacerbations and can be administered in the hospital or community setting (the latter is usually preferred) (10). In addition to strategies aimed at the impact of the disease, drugs to ameliorate common MS symptoms — such as urinary dysfunction, spasticity and neuropathic pain — are relatively well established and widely used. European guidelines have been developed for both the use of the established disease-modifying drugs and the treatment of symptoms (11, 12).

Even though drug treatment options are relatively limited, significant improvements in the quality of life of people with MS can be supported by improved rehabilitation approaches. For patients with relatively moderate disability, exercise (both aerobic and non-aerobic) has been found to be useful, as has physiotherapy. There have been few, if any, studies evaluating the rehabilitation needs of those with more severe disability.

Neurorehabilitation

The philosophy of neurorehabilitation, which emphasizes patient education and self-management, is well suited to meet the complex and variable needs of MS (13). Neurorehabilitation aims to improve independence and quality of life by maximizing ability and participation. It has been defined by WHO as “an active process by which those disabled by injury or disease achieve a full recovery or, if a full recovery is not possible, realize their optimal physical, mental and social potential and are integrated into their most appropriate environment”. Together with Rehabilitation in Multiple Sclerosis, the European Multiple Sclerosis Platform (EMSP) developed useful guidance on this issue in their recommendations on MS rehabilitation services (14), one of the reference guidelines for their European Code of Good Practice in MS.

The essential components of successful neurorehabilitation include expert multidisciplinary assessment, goal-oriented programmes and evaluation of impact on patient and goal achievement through the use of clinically appropriate, scientifically sound outcome measures incorporating the patient’s perspective (14).

While these principles are intuitively sound, the evidence underpinning multidisciplinary assessment and goal-orientated programmes is weak. Fundamental to the provision of robust
evidence of the benefits of rehabilitation interventions is the use of scientifically sound outcome measures. In the field of MS, the limitations of the Expanded Disability Status Scale have been well aired and it can be argued that the scale is even less relevant to neurorehabilitation as it fails to incorporate the views of the patient.

The issues relating to the management of symptoms that affect people with MS are identical to those concerning neurorehabilitation: the need for robust clinical trials based on scientifically sound outcome measures, multidisciplinary expertise and the involvement of patients. The frequency with which these symptoms affect people with MS has been documented for a range of symptoms including fatigue, spasticity, pain and cognitive impairment. The need for a multidisciplinary and multimodal approach to symptom management is described in a recent review (15) and is exemplified in the case of spasticity (16).

**Service delivery**

Evaluating service delivery may be considered the most important and relevant issue in the management of MS. This is because it incorporates acute hospital and neurorehabilitation services with community-based activities and has to bring together medical and social services in a way that meets the complex and ever-changing needs of the person with MS.

Ideally, most services should be community-based with supporting expertise from the acute hospital or rehabilitation centre at times of particular need (such as at diagnosis or during a severe relapse) or complexity (when multiple symptoms interact and intensive inpatient rehabilitation is required). The optimum method of service delivery has not yet been defined, and little comparison has been made of existing services.

A recently published study (17) compared two forms of service delivery in a randomized controlled trial. One group received what was described as “hospital home care”, in which patients remained in the community but had immediate access to the hospital-based multidisciplinary team when required, while the other group received routine care. No difference was seen in the level of disability between the two groups after 12 months, but the “hospital home care” patients, who were more intensely treated, had significantly less depression and improved quality of life.

There continue to be major problems worldwide in delivering a model of care that provides truly coordinated services. There is serious inequity of service provision both within and across countries, and an inordinate and unacceptable reliance on family and friends to provide essential care. Establishing guidance, such as has been done by the National Institute for Clinical Excellence (18), is a step forward but a global initiative such as that of the Multiple Sclerosis International Federation (MSIF) to promote the quality of life of people with MS may be more effective (19). The key challenge will be ensuring the translation of these guidelines into practice.

Delivery of care to people with MS varies significantly around the world. In part this reflects the differences in incidence and therefore the relative importance afforded to the disease within a country’s health system. Given the importance of expensive diagnostic equipment (scanners) and the cost of the existing treatments, however, the variation also reflects different national income levels. In the developed countries, the cost of the treatment is borne by the government or insurance companies but in some regions the patients have to pay for drugs, making it difficult for them to take advantage of emerging new treatments.

The delivery of care for people with long-term illnesses is becoming increasingly “patient centred”, and a culture of treatment by interdisciplinary teams is emerging. Within this model, the aim is to offer patients a seamless service, which typically involves bringing together various health professionals including doctors, nurses, physiotherapists, occupational therapists, speech and language therapists, clinical psychologists and social workers. Other professionals with expertise in treating neurologically disabled people cover dietetics, continence advisory and management services, pain management, chiropody, podiatry and ophthalmology services.
Quality of life issues

MS will usually have a substantial adverse effect on a person's quality of life. Improving quality of life should be a key goal for policy-makers as well as those who advocate on behalf of people with MS. A recent key step has been the publication by MSIF of its quality of life principles (19), as mentioned above. The development of these principles was based on a series of interviews, a literature review, the clinical, programmatic, and research experience of the authors, and review by a work group and a technical oversight group organized by MSIF.

The principles are designed to be used by international organizations, national MS societies, people with MS and their families, governments, health, social and continuing care providers, employers, researchers, businesses and others to evaluate existing and proposed services and programmes and to advocate for improvements. The areas covered include:

- independence and empowerment;
- medical care;
- continuing care (long-term or social);
- health promotion and disease prevention;
- support for family members;
- transport;
- employment and volunteer activities;
- disability benefits and cash assistance;
- education;
- housing and accessibility of buildings in the community.

Treatment gap

There is no doubt that a significant treatment gap exists in approaches to MS between countries (and possibly within countries). Until a cure is found, people with MS have to rely on reducing the inflammation during an acute phase by the use of corticosteroids and providing symptomatic relief. The disease-modifying agents such as beta-interferon and glatiramer acetate can be offered to decrease the relapses and disease burden. Ideally, this treatment programme requires early diagnosis and adequate human resources and equipment. The situation is especially problematic in the developing countries, as often equipment such as an MRI scanner is not available or is too expensive. The disease-modifying agents are also costly and beyond the reach of many patients. In addition, rehabilitation centres for people with MS are not available.

A further illustration of the treatment gap between rich and less developed countries in their treatment of MS is apparent from data currently being collected by WHO, the MSIF and the EMSP. These data, which will in time be integrated into an international comparative and interactive database (MSIF/WHO Atlas of MS and European Map of MS), have been sourced by surveying neurologists and patient organizations across 98 geographically and economically diverse countries.

For example, in response to the key treatment question “What percentage of people with MS who fulfil the clinical prescription criteria for disease-modifying drugs [in your country] receive treatment?” the average answer from 15 responding members of the European Union was 64%. This compares with (for example) 45% for Brazil, 50% for the Russian Federation, 10–15% for Turkey and less than 5% for India.

RESEARCH

As with many neurological diseases, MS is extremely difficult to study. Even after several decades of intense research activity, it remains a mysterious condition with no known pathogen or accepted determinants of its severity or course. Nonetheless, optimism amongst the MS research community is high. Advances in non-invasive investigative techniques, particularly MRI, have led
to significant improvements in the ability to create images and track the course of the disease. Key areas of current research encompass immunology, genetics, virology/bacteriology, and the biology of the cells that make, maintain and repair myelin in the CNS (including developments in neural stem cells). The key outcome of the research effort to date has been an improved understanding of the pathology and the evolution of the disease and, as a consequence, new approaches to treatment including repair and neuroprotection.

In addition to the advances being made at the therapeutic level, significant improvements are being made in the management of the disease. In large part this has been stimulated by researchers adopting a more patient-centred approach. Whereas MS research used to be conducted by physicians on behalf of people with MS, today’s research protocols are more likely to be driven by patient perspectives. This is leading to research being carried out into factors determining the quality of life of people with MS, such as health-care policy, employment and welfare matters and the wider familial impact of the disease. Fortunately, there are active multiple sclerosis support groups in several regions of the world that are involved in improving the quality of life of people with MS.

**TRAINING**

There is a specific lack of public and professional awareness of the dimension of MS in the domains of epidemiology and impact of disease on individuals, carers and society, including impact on individual loss of independence, and cost of long-term care. In particular, the chronic progressive nature of the condition must be better conveyed to all. MSIF, through its member organizations, has proven very effective and capable of concerted action in the field of patient and lay public education.

**CONCLUSIONS AND RECOMMENDATIONS**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>MS is the most prevalent inflammatory demyelinating disease of the central nervous system in young adults.</td>
</tr>
<tr>
<td>2</td>
<td>The cause is (as yet) unknown.</td>
</tr>
<tr>
<td>3</td>
<td>Initially, MS most often runs a relapsing/remitting course, later becoming progressive.</td>
</tr>
<tr>
<td>4</td>
<td>Depending on the site and extent of the lesions, a variety of symptoms may occur, often in parallel.</td>
</tr>
<tr>
<td>5</td>
<td>Many of the symptoms may be treated effectively with drugs and rehabilitation measures.</td>
</tr>
<tr>
<td>6</td>
<td>Immunomodulating therapies may reduce relapse frequency and progression of MRI abnormalities.</td>
</tr>
<tr>
<td>7</td>
<td>Rehabilitation is most important and aims at leading individuals to adapt their lifestyle.</td>
</tr>
<tr>
<td>8</td>
<td>Burden and costs, including the costs of treatment, are considerable for the persons affected, their relatives and society.</td>
</tr>
</tbody>
</table>
REFERENCES


RECOMMENDED READING

- Recommendations on rehabilitation services for persons with multiple sclerosis in Europe. Brussels, European Multiple Sclerosis Platform and Rehabilitation in Multiple Sclerosis, 2004 (European Code of Good Practice in Multiple Sclerosis).
neurological disorders: a public health approach

3.5 Neuroinfections

Infectious diseases that involve the nervous system affect millions of people around the world. They constitute the sixth cause of neurological consultation in primary care services and are reported globally by a quarter of WHO’s Member States and by half the countries in some parts of Africa and South-East Asia. Neuroinfections are of major importance since ancient times and, even with the advent of effective antibiotics and vaccines, still remain a major challenge in many parts of the world, especially in developing nations.

Approximately 75% of the world population live in developing countries where the worst health indicators are found. Their major health problems are generally related to warm climate, overcrowding, severe poverty, illiteracy and high infant mortality which induce a burden of illness from communicable diseases that differs drastically from the rest of the world. Added to these problems, the health budgets are low and opportunities for community interventions very small.

A demographic transition is under way throughout the world: as populations age, the burden of noncommunicable diseases (cardiovascular illnesses, stroke and cancer) increases, particularly in the least favoured regions. Thus, the majority of least-developed countries are facing a double burden from communicable and noncommunicable diseases. The global public health community is now faced with a more complex and diverse pattern of adult disease than previously expected and proposes a “double response” that integrates prevention and control of both communicable and noncommunicable diseases within a comprehensive health-care system (1).

Some diseases that used to be found in the developed world but have virtually disappeared, such as poliomyelitis, leprosy and neurosyphilis, are still taking their toll in developing regions. In addition, some of the protozoan and helminthic infections that are so characteristic of the tropics are now being seen with increasing frequency in developed countries owing to migration, large-scale military ventures and rapid means of transport that have the undesirable potential to introduce disease vectors. Although some infectious diseases have been nearly wiped out, the vast majority of them will not be eliminated in the foreseeable future. Indeed, WHO reports that at least 30 new diseases have been scientifically recognized around the world in the last 20 years (2). These emerging diseases include hantavirus (first identified in the United States in 1993), cryptosporidiosis (a waterborne cause of diarrhoea that recently affected more than 400 000 people in a single outbreak in the United States), the Ebola virus from Africa and the human immunodeficiency virus (HIV), among others. Re-emerging diseases are the infections once thought
The acquired immunodeficiency syndrome (AIDS) is caused by a retrovirus known as the human immunodeficiency virus (HIV), which attacks and impairs the body’s natural defence system against disease and infection. HIV is a slow-acting virus that may take years to produce illness in a person. During this period, an HIV-infected person’s defence system is impaired, and other viruses, bacteria and parasites take advantage of this “opportunity” to further weaken the body and cause various illnesses, such as pneumonia, tuberculosis and mycosis. When a person starts having such opportunistic infections, he or she has AIDS. The amount of time it takes for HIV infection to become full-blown AIDS depends on the person’s general health and nutritional status before and during the time of HIV infection. The average time for an adult is approximately 10 years without antiretroviral therapy (ART). Women are more likely to be infected with HIV than men. Children are also at risk (4). The number of people living with HIV globally has reached its highest level with an estimated 40.3 million people, rising from an estimated 37.5 million in 2003. More than three million people died of AIDS-related illnesses in 2005; more than 500 000 of them were children. Sub-Saharan Africa continues to be the most affected region globally, with 64% of new infections occurring there. HIV treatment has improved markedly, however, and hundreds of thousands of people are now living longer in better health because they are receiving ART: an estimated 250–350 000 deaths were averted in 2005 because of expanded access to HIV treatment (5).

Neurological complications occur in 39–70% of patients with AIDS and significantly impact on functional capacity, quality of life and survival. Neuropathological examination identifies abnormal neurological conditions in more than 90% of autopsies but is not always demonstrated clinically (6). The main etiological considerations include primary HIV-related syndromes, opportunistic conditions, inflammatory conditions, and medications (7) (see Table 3.5.1).
Table 3.5.1 Neurological diseases in the HIV-infected individual

<table>
<thead>
<tr>
<th>Type of condition</th>
<th>Examples</th>
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</thead>
<tbody>
<tr>
<td>Primary HIV-related syndromes</td>
<td>HIV-associated cognitive–motor complex</td>
</tr>
<tr>
<td></td>
<td>HIV-associated myelopathy</td>
</tr>
<tr>
<td></td>
<td>HIV-associated polyneuropathy</td>
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<tr>
<td></td>
<td>HIV-associated myopathy</td>
</tr>
<tr>
<td>Opportunistic conditions</td>
<td>Toxoplasma encephalitis</td>
</tr>
<tr>
<td></td>
<td>Cryptococcal meningitis</td>
</tr>
<tr>
<td></td>
<td>Cytomegalovirus encephalitis/polyradiculitis</td>
</tr>
<tr>
<td></td>
<td>Progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td></td>
<td>Primary central nervous system lymphoma</td>
</tr>
<tr>
<td>Inflammatory conditions</td>
<td>Acquired demyelinating neuropathies</td>
</tr>
<tr>
<td></td>
<td>Aseptic meningitis</td>
</tr>
<tr>
<td>Treatment-associated conditions</td>
<td>Zidovudine-induced myopathy</td>
</tr>
<tr>
<td></td>
<td>Nucleoside analog-induced neuropathy</td>
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</tbody>
</table>

Source: (7).

Multiple investigations in recent years suggest that the effects of neurological complications and opportunistic infections related to HIV have a clear trend to diminish since the introduction of new and more powerful antiretroviral agents. Nevertheless, prolonging the life of patients infected by the virus, attributable to therapeutic success, paradoxically favours the emergence of some neurological affections as treatment-associated neuropathy/myopathy; these affections can be more important than the benefits of therapy to achieve viral suppression.

Accurately diagnosing neurological disease in the HIV-infected individual is crucial for several reasons. First, many complications are treatable and their treatment can lead to either increased survival or improved quality of life. Second, identifying currently untreatable conditions provides the patient with the opportunity to participate in a growing number of therapeutic trials. Further, an accurate and focused diagnostic assessment and treatment plan will limit therapeutic misadventures and lead to cost-effective care delivery.

The worldwide use of highly active antiretroviral therapy (HAART) has played an important role in changing the incidence of neurological complications in AIDS patients. Recent studies have shown that HAART has produced both quantitative and qualitative changes in the pattern of HIV neuropathology: an overall decrease in the incidence of some cerebral opportunistic infections such as toxoplasmosis and cytomegalovirus encephalitis, for which successful treatment is available, whereas other uncommon types and new variants of brain infections, such as varicella-zoster encephalitis, herpes simplex virus encephalitis or HIV encephalitis, are being reported more frequently as ART promotes some immune recovery and increases survival (8). In developing countries, some endemic infections such as tuberculosis and Chagas disease have re-emerged in direct association with the spreading of HIV, and are now being considered as markers of AIDS.

Unfortunately, some patients may develop paradoxical clinical outcomes after starting treatment with HAART, known as neurological immune restoration inflammatory syndrome (NIRIS). Some treatment-related neurological disorders, like zidovudine-induced myopathy, nucleoside analog-induced neuropathy and efavirenz-induced neuropsychiatric disorders, can be more important than the benefits of the therapy of viral suppression (9).

Some therapies can prevent, treat or even cure many of the opportunistic infections and relieve the symptoms associated with them, but there is no cure for HIV/AIDS. The core benefit of HAART lies in its ability to reduce the rate of opportunistic infections by enhancing immune function,
slowing viral replication in the body and thereby improving patients’ quality of life and diminishing mortality. The cost of antiretroviral drugs is declining but, unfortunately, the treatments are still not affordable or accessible for most people.

Nevertheless, these important advances over the last decade have transformed HIV infection from a short-term, inevitably fatal disease to a chronic condition amenable to medical management, similar to diabetes or congestive heart failure.

It is important to integrate HIV prevention and care, and the challenges are immense: worldwide, fewer than one in five people at risk of becoming infected with HIV has access to basic prevention services. Of people living with HIV, only one in ten has been tested and is aware of the infection. For prevention interventions to achieve the results necessary to get ahead of the epidemic, projects with short-term horizons must translate into long-term programmatic strategies. In settings in which HIV is largely sexually transmitted, information and education campaigns can save lives. For example, intensive prevention programmes in the Mbeya region of the United Republic of Tanzania led to an increase in the use of condoms and the treatment of sexually transmitted infections between 1994 and 2000; those changes were accompanied by a decline in HIV prevalence among 15–24-year-old women from 21% to 15% in the same period (10). In settings in which HIV transmission is linked more closely to injecting drug use, harm-reduction strategies (for example, the provision of clean injecting equipment as well as adequate therapy for drug dependence) have proved to be effective. Other measures include voluntary counselling and testing, and improving women’s health — including access to family planning and safe childbirth — in order to prevent HIV transmission from mother to infant. There is no cure for HIV/AIDS.

**Viral encephalitis**

Acute viral encephalitis is often an unusual manifestation of common viral infections and most commonly affects children and young adults. Every day, more types of viruses are being associated with encephalitis (see Box 3.5.1), and its variable presence depends on the age group, geographical zone, season of the year and the state of health of patients. In the United States, epidemiological studies calculate the incidence of viral encephalitis approximately at 3.5–7.4 per 100 000 population. Estimates have been given for some causes of viral encephalitis: for example, it has been estimated that herpes simplex encephalitis (HSE) has an annual incidence of about one per million.

Herpes simplex encephalitis is the most important and common cause of **fatal sporadic viral encephalitis** in the industrialized world. At a global level, it seems that the most common cause of epidemic encephalitis is actually Japanese B encephalitis, with 10–15 000 deaths per year, markedly more than for herpes simplex encephalitis. It must be considered, however, that in up to about 50% of cases of viral encephalitis no specific cause can be found, so the predominant type is difficult to determine (11).

### Box 3.5.1 Causes of viral encephalitis

- **Herpes simplex virus** (HSV-1, HSV-2)
- Other herpes viruses:
  - varicella zoster virus (VZV)
  - cytomegalovirus (CMV)
  - Epstein–Barr virus (EBV)
  - human herpes virus 6 (HHV6)
- Adenoviruses
- Influenza A
- Enteroviruses, poliovirus
- Measles, mumps and rubella viruses
- Rabies
- Arboviruses, e.g.
  - Japanese B encephalitis virus
  - St Louis encephalitis virus
  - West Nile encephalitis virus
  - Eastern, Western, and Venezuelan equine encephalitis virus
  - Tick-borne encephalitis viruses
- Bunyaviruses, e.g. La Crosse strain of California virus
- Reoviruses, e.g. Colorado tick fever virus
- Arenaviruses, e.g. lymphocytic choriomeningitis virus
- Retroviruses, e.g. HIV-1
- Papovavirus, e.g. JC virus

Source: adapted from (11).
Viruses enter the central nervous system (CNS) through two distinct routes: hematogenous dissemination or neuronal retrograde dissemination. Hematogenous spread is the most common path. Humans are usually incidental terminal hosts of many viral encephalitides. Arbovirus encephalitides are zoonoses, with the virus surviving in infection cycles involving biting arthropods and various vertebrates, especially birds and rodents. The virus can be transmitted by an insect bite and then undergoes local replication in the skin.

Patients with viral encephalitis are marked by acute onset of a febrile illness and can experience signs and symptoms of meningeal irritation, focal neurological signs, seizures, alteration of consciousness and behavioural and speech disturbances. The diagnosis is made by immunological tests, neuroimaging techniques, electroencephalography and, sometimes, brain biopsy. No specific treatment is available for every encephalitis, and the illness often requires only medical support. The mortality rate and severity of sequelae depend largely on the etiological agent. Herpes virus encephalitis carries a mortality rate of 70% in untreated patients, with severe sequelae among survivors. Pharmacotherapy for herpes virus encephalitis consists of acyclovir and vidarabine. Effective preventive measures include control of vectors by removing water-holding containers and discarded tyres. Vaccines are available for eastern equine encephalitis, western equine encephalitis, and Venezuelan equine encephalitis in horses. Despite control efforts and disease surveillance, the 1999 outbreak of West Nile virus in New York with subsequent spread to other states showed that different viruses may spread because of increased international travel and trade (12).

Japanese encephalitis is a leading cause of viral encephalitis in Asia, with 30–50 000 clinical cases reported annually. It occurs from the islands of the Western Pacific in the east to the Pakistan border in the west, and from the Democratic People’s Republic of Korea in the north to Papua New Guinea in the south. Japanese encephalitis virus is transmitted by mosquitoes, which breed particularly in flooded rice fields. Pigs are the amplifying hosts. Distribution of the infection is thus very significantly linked to irrigated rice production combined with pig-rearing. An effective killed vaccine is available, but it is expensive and requires one primary vaccination followed by two boosters. It provides adequate protection for travellers but has limited public health value in areas where health service resources are scarce.

**Poliomyelitis**

Poliomyelitis is a crippling disease caused by any one of three related viruses, poliovirus types 1, 2 or 3. The primary way to spread poliovirus is through the faecal–oral route: the virus enters the body through the mouth when people eat food or drink water that is contaminated with faeces. The virus then multiplies in the intestine, enters the bloodstream, and may invade certain types of nerve cells which it can damage or destroy. Polioviruses spread very easily in areas with poor hygiene. In any child under 15 years of age with acute flaccid paralysis or any person of any age with paralytic illness, poliomyelitis always has to be suspected.

In 1963, Cuba began using an oral vaccine in a series of nationwide polio campaigns. Shortly thereafter, indigenous wild poliovirus transmission was interrupted. Through an extraordinary international effort that began 18 years ago, indigenous polioviruses have now been eliminated from all but four countries of the world, down from over 125 when the collaboration started (13). This progress is the result of a unique partnership forged between governments and the spearheading partners of the Global Polio Eradication Initiative — WHO, Rotary International, the United States Centers for Disease Control and Prevention (CDC) and UNICEF — to take up key challenges to reach all children, everywhere. The most visible element of the polio eradication initiative has been the National Immunization Days, as they require the immunization of every child under five years of age (nearly 20% of a country’s population) several times a year for a number of years in a row. As the result of an aggressive, deliberate and internationally coordinated effort, endemic
poliomyelitis has changed from being a devastating disease with a global distribution to one that is now endemic in four countries. In 2005, 1951 cases were reported worldwide.

**Rabies**
Rabies is one of the oldest and most feared diseases reported in medical literature. Rabies is a viral zoonosis (an animal disease transmissible to humans) caused by rhabdoviruses of the genus *Lyssavirus*. The disease is maintained in nature by several domestic and wild animal reservoir species, including dogs, foxes, mongooses, raccoons, skunks and many species of bat. Human infection is incidental to the epidemiology of rabies. In terms of risks to human health, dogs are the most dangerous reservoir: more than 99.9 % of human deaths from rabies worldwide result from the bite of a rabid dog. It is estimated that 50 000 persons die of rabies each year, mainly in Africa and Asia.

Human infection occurs when the virus, contained in the saliva of a rabid animal, is transmitted through penetrating bite wounds, open cuts in the skin, or contact with mucous membranes. The severity of the bite determines the risk of infection. The virus slowly travels up the nerve to reach the CNS where it replicates and then travels down nerves to the salivary glands where there is further replication. Man is occasionally infected, and once infection is established in the CNS the outcome is almost invariably fatal.

Second-generation vaccines consisting of highly purified vaccines prepared on primary and continuous cell lines and in embryonating eggs are available, though expensive, to prevent the occurrence of the disease in persons exposed to an animal suspected of rabies. The vaccines are usually administered according to regimens involving fewer doses (usually five or six) than those used for brain tissue vaccines. The regimens most commonly applied in the world are those recommended by WHO.

Control of rabies depends on education, vaccination of dogs, cats and farm animals and notification of suspected cases to local authorities (14).

**MYCOBACTERIAL AND OTHER BACTERIAL DISEASES**

**Tuberculosis**
With nine million new cases in 2004, resulting in 1.7 million deaths, tuberculosis is a leading infectious cause of morbidity and mortality worldwide (15). The resurgence of tuberculosis in many countries is attributable to its interaction with HIV infection, which has pernicious effects. Tuberculosis is the leading cause of death among people with HIV, while infection with HIV is the most potent risk factor for a latent tuberculosis infection to convert to active disease (16). Although tuberculosis most commonly affects the lungs (the usual site of primary infection), it can cause disease in any part of the body as a consequence of haematogenous spread from the lung. The proportion of all cases of tuberculosis that are extrapulmonary (i.e. in sites other than the lungs) varies between countries but is typically about 10–20%. Among extrapulmonary cases, the most common sites involved are the lymph nodes and the pleura, but the sites of tuberculosis associated with neurological disorders (meninges, brain and vertebrae) also constitute an important group. Meningeal tuberculosis has a high case-fatality rate, and neurological sequelae are common among survivors. Cerebral tuberculosis usually presents as a space-occupying lesion with focal signs depending on the location in the brain. Vertebral tuberculosis usually presents with local pain, swelling and deformity, and there is risk of neurological impairment because of spinal cord or cauda equina compression.

The diagnosis of nervous system tuberculosis is often difficult, because of its nature of great simulator and also because of limited access to methods to confirm it (17). Diagnosis depends on epidemiological and clinical data and findings during cerebrospinal fluid (CSF), neuroimaging and
bacteriological studies. Although not a direct consequence of tuberculosis, peripheral neuropathy can occur in tuberculosis patients as a side-effect of treatment with isoniazid, especially among patients who are malnourished, abuse alcohol, or are infected with HIV.

There are important public health approaches to the primary prevention of these tuberculosis-related conditions and to the secondary prevention of their adverse consequences. The most important overall approach to primary prevention consists of cutting the chain of transmission by case-finding and treatment. This approach is the basis of the international tuberculosis control strategy known as DOTS, which forms a central pillar of WHO’s new strategy for its Stop TB campaign (16). Although BCG vaccination has little impact in reducing the number of adults with infectious pulmonary tuberculosis, it is of crucial importance in preventing disseminated and severe cases of disease (including tuberculosis meningitis) in children. Therefore, in countries with high tuberculosis prevalence, WHO recommends a policy of routine BCG immunization for all neonates as part of the Expanded Programme on Immunization (EPI). It is estimated that the 100 million BCG vaccinations given to infants worldwide in 2002 will have prevented 30 000 cases of tuberculosis meningitis in children during their first five years of life (18). The primary prevention of isoniazid-induced peripheral neuropathy is by routine administration of pyridoxine to tuberculosis patients.

The main public health approach to the secondary prevention of the adverse consequences of tuberculosis disease of the meninges, brain and vertebrae is through promoting the application of the International Standards for Tuberculosis Care (19) to ensure prompt diagnosis and effective treatment. High-quality tuberculosis care will result not only in patients having the best possible outcome of treatment, but also in the public health benefit of decreased tuberculosis transmission by infectious cases and thereby, ultimately, an impact on the global burden of all tuberculosis cases, including those associated with neurological disorder. The key steps in diminishing the global burden of neurological disorder associated with tuberculosis are to promote: investment in full implementation of the Stop TB strategy and International Standards for Tuberculosis Care; full immunization coverage so that all neonates are protected by BCG from risk of disseminated and severe tuberculosis; and better understanding of the epidemiology of tuberculosis disease associated with neurological disorder through improved surveillance in countries with high tuberculosis prevalence.

Leprosy neuropathy
Leprosy is the cause of the most common treatable neuropathy in the world, caused by Mycobacterium leprae. The incubation period of the disease is about five years: symptoms, however, can take as long as 20 years to appear. The infection could affect nerves by direct invasion or during immunological reactions. In rare instances, the diagnosis can be missed, because leprosy neuropathy may present without skin lesions (neuritic form of leprosy). Patients with this form of disease display only signs and symptoms of sensory impairment and muscle weakness, posing difficulties for diagnosis, particularly in services where diagnostic facilities such as bacilloscopy, electroneuromyography and nerve biopsy are not available.

Delay in treatment is a major problem, because the disease usually progresses and the resulting disability if untreated may be severe, even though mycobacteria may be eliminated. Delay in treatment is, however, usually a result of delayed presentation because of the associated stigma. People with long-term leprosy may lose the use of their hands or feet because of repeated injury resulting from lack of sensation. Early diagnosis and treatment with the WHO-recommended multidrug therapy (MDT) is essential in order to prevent the disease from progressing and resulting in disability.

Bacterial meningitis
Bacterial meningitis is a very common cause of morbidity, mortality and neurological complications in both children and adults, especially in children. It has an annual incidence of 4–6
cases per 100 000 adults (defined as patients older than 16 years of age), and *Streptococcus pneumoniae* and *Neisseria meningitidis* are responsible for 80% of all cases (20). In developing countries, overall case-fatality rates of 33–44% have been reported, rising to over 60% in adult groups (21). Bacterial meningitis can occur in epidemics that can have a serious impact on large populations.

The highest burden of meningococcal disease occurs in sub-Saharan Africa, which is known as the “meningitis belt”, an area that stretches from Senegal in the west to Ethiopia in the east, with an estimated total population of 300 million people. The hyperendemicity in this area is attributable to the particular climate (dry season between December and June, with dust winds) and social habits: overcrowded housing at family level and large population displacements for pilgrimages and traditional markets at regional level. Because of herd immunity (whereby transmission is blocked when a critical percentage of the population had been immunized, thus extending protection to the unvaccinated), the epidemics occur in a cyclical fashion.

Meningitis is characterized by acute onset of fever and headache, together with neck stiffness, altered consciousness and seizures. The diagnosis can be confirmed by its clinical characteristics and bacteriological and immunological analyses of the CSF. Antibiotic treatment is effective in most cases but several neurological complications can remain, such as cognitive difficulties, motor disabilities, hypoacusia and epilepsy. In a recent review, treatment with corticosteroids was associated with a significant reduction in neurological sequelae and mortality (22).

Progress is more likely to come from investigations into preventive measures, especially the use of available vaccines and the development of new vaccines. Meningitis caused by *Haemophilus influenzae* type B has been nearly eliminated in developed countries since routine vaccination with the *H. influenzae* type B conjugate vaccine was initiated. The introduction of conjugate vaccines against *S. pneumoniae* may substantially reduce the burden of childhood pneumococcal meningitis and may even produce herd immunity among adults. The approval in 2005 of a conjugate meningococcal vaccine against serogroups A, C, Y and W135 is also an important advance that may decrease the incidence of this devastating infection. Local and nationwide surveillance, including the laboratory investigation of suspected cases, is critical for early detection of epidemics and the formulation of appropriate responses.

**Tetanus**

Tetanus is acquired through exposure to the spores of the bacterium *Clostridium tetani* which are universally present in the soil. The disease is caused by the action of a potent neurotoxin produced during the growth of the bacteria in dead tissues, e.g. dirty wounds or — for neonatal tetanus — in the umbilicus following non-sterile delivery. Tetanus is not transmitted from person to person: infection usually occurs when dirt enters a wound or cut. At the end of the 1980s, neonatal tetanus was considered a major public health problem. WHO estimated that, in 1988, 787 000 newborn children died of neonatal tetanus, a rate of 6.5 cases per 1000 live births. In 2004 the number of reported cases was 13 448. A worldwide total of 213 000 deaths were estimated to have occurred in 2002, 198 000 of them concerning children younger than five years of age (23).

Unlike poliomyelitis and smallpox, the disease cannot be eradicated because tetanus spores are present in the environment. Once infection occurs, mortality rates are extremely high, especially in areas where appropriate medical care is not available. However, this death toll can be prevented. Neonatal tetanus can be prevented by immunizing pregnant women and improving the hygienic conditions of delivery. Adult tetanus can be prevented by immunizing people at risk, such as workers manipulating soil; others at risk of cuts should be also included in the prevention measures. Some forms of toxoid are available (DTP, DT, TT or Td) and at least three primary doses should be given by the intramuscular route. Vaccination coverage with three doses of DTP is more than 80% for most countries around the world. The Maternal and Neonatal Tetanus elimination initiative was
neurological disorders: a public health approach

launched by UNICEF, WHO and the United Nations Population Fund (UNFPA) in 1999, revitalizing the goal of elimination of maternal and neonatal tetanus as a public health problem, defined as less than one case of neonatal tetanus per 1000 live births in every district of every country.

PARASITIC DISEASES

Neurocysticercosis

Cysticercosis is infection by the larvae of the pork tapeworm *Taenia solium*. The adult tapeworm (flat, ribbon-like, approximately 2–4 m long) lives only in the small intestine of humans, who acquire it (taeniiasis) by eating undercooked pork containing the viable larvae or cysticerci. A tapeworm carrier passes microscopic *Taenia* eggs with the faeces, contaminating the close environment and contacts and causing cysticercosis to pigs and humans. Human beings therefore acquire cysticercosis through faecal–oral contamination with *T. solium* eggs (24). Thus, vegetarians and other people who do not eat pork can acquire cysticercosis. Recent epidemiological evidence suggests that the most common source of infective eggs is a symptom-free tapeworm carrier in the household. Therefore, cysticercosis should be seen as a disease mostly transmitted from person to person (25). In the CNS, the larvae or cysticerci can cause epilepsy, hydrocephalus, spinal cord involvement, stroke, etc. (24, 26).

Cysticercosis is the parasitic disease that most frequently affects the CNS and is one of the major health problems of developing countries in Africa, Asia and Latin America. In addition, because of high immigration rates from endemic to non-endemic areas and tourism, neurocysticercosis is now commonly seen in countries that were previously free of the disease. Despite the advances in diagnosis and therapy, neurocysticercosis remains endemic in most low income countries, where it represents one of the most common causes of acquired epilepsy (27). Almost 50 000 deaths attributable to neurocysticercosis occur every year. Many more patients survive but are left with irreversible brain damage — with all the social and economic consequences that this implies (28). Seizures occur in up to 70% of patients. Several articles from different countries in Latin America consistently showed an association between around 30% of all seizures and cysticercosis (29).

Accurate diagnosis of neurocysticercosis is based on assessment of the clinical and epidemiological data and the results of neuroimaging studies and immunological tests (30). Therapy must be individualized according to the location of parasites and the degree of disease activity: this implies symptomatic therapy, anticysticidal drugs (albendazole/praziquantel), antiepileptic drugs and surgical treatment of complications such as hydrocephalus.

Neurocysticercosis is one of a few conditions included in a list of potentially eradicable infectious diseases of public health importance (31). The control strategy that seems promising at the moment is a combination of different available tools in order to interrupt or reduce the cycle of direct person-to-person transmission: mass human chemotherapy to eliminate the tapeworm stage, enforced meat inspection and control, improvement of pig husbandry and inspection, treatment of infected animals, surveillance, identification and treatment of individuals who are direct sources of contagion (human carriers of adult tapeworm) and their close contacts, combined with hygiene education and better sanitation. Animal vaccines are under development. Major obstacles include the lack of basic sanitary facilities in endemic areas, the extent of domestic pig-rearing, the costs of the interventions, and their cultural acceptability. Multiple genotypes of *T. solium* ramifications have been discovered in different regions, which could explain some of the possible differences in pathology of *T. solium* worldwide. Recently, a proposal was published to declare neurocysticercosis an international reportable disease (32). WHO suggests that all endemic countries should recognize the importance of taeniiasis and cysticercosis, collect epidemiological data and adopt policies and strategies for their control. So far, the infection has not been eliminated from any
region by a specific programme and no national control programmes are yet in place. Successful pilot demonstrations of control measures have been or are being conducted in Cameroon, Ecuador, Mexico and Peru, and a regional action plan developed in 2002 for eastern and southern Africa is now under way.

**Cerebral malaria**

Malaria remains a serious public health problem in the tropics, mostly in Africa. There exist four *Plasmodium* species that affect humans; of these, only *Plasmodium falciparum* can sequester in capillaries of the CNS and cause cerebral malaria. The infection is acquired when the parasite is inoculated through the skin during the sting of an infected *Anopheles* mosquito. Some patients with cerebral malaria present with diffuse cerebral oedema, small haemorrhages and occlusion of cerebral vessels by parasitized red cells. The burden of *falciparum* malaria is not only because of infection and mortality: the neurocognitive sequelae add significantly to this burden (33).

*P. falciparum* is identified by examination of blood smears with Giemsa stain. Since parasitaemia is cyclical, repeated examinations may be required. The CSF is normal in cerebral malaria. Neuroimaging studies may demonstrate brain swelling, cerebral infarcts, or small haemorrhages in severe cases. Artemisinin derivatives and quinine are the drugs of choice for cerebral malaria. Despite therapy, mortality remains high in severe or complicated malaria (34).

Preventive strategies relied upon are: the early treatment of malaria infections with effective medicines (artemisinin-based combination therapies) to prevent the progression of the disease to severe malaria; and vector control through different practices to reduce the rate of infection (use of insecticide-treated nets, bednets, insecticide sprays and mosquito coils). All these methods have been found to be highly cost effective. At present, multiple studies are under way to modify *Plasmodium* genes in order to diminish parasite virulence and consequently the morbidity and mortality attributable to malaria.

**Toxoplasmosis**

Toxoplasmosis is a disease caused by an obligate intracellular protozoal parasite termed *Toxoplasma gondii*. Human infection usually occurs via the oral or transplacental route. Consumption of raw or undercooked meat containing viable tissue cysts (principally lamb and pork) and direct ingestion of infective oocysts in other foods (including vegetables contaminated by feline faeces) are common sources of infection. Transplacental infection may occur if the mother acquires an acute infection or if a latent infection is reactivated during immunosuppression. In immunocompetent women a primary infection during early pregnancy may lead to fetal infection, with death of the fetus or severe postnatal manifestations. Later in pregnancy, maternal infection results in mild or subclinical fetal disease. In adults, most *T. gondii* infections are subclinical, but severe infection can occur in patients who are immunocompromised, such as those with AIDS and malignancies. Affected organs include both the grey and white matter of the brain, retina, alveolar lining of the lungs, heart, and skeletal muscle.

Patients with AIDS are at particular risk for developing disseminated toxoplasmosis, which more often manifests as CNS abnormalities. As many as 50% of patients with AIDS who are seropositive for *T. gondii* develop encephalitis. Toxoplasmosis is the most common cause of a focal brain lesion in patients with AIDS. The disease commonly localizes to the basal ganglia, though other sites in the brain and spinal cord may be affected. A solitary focus may be seen in one third of patients, but multiple foci are more common. In AIDS-related *Toxoplasma* encephalitis, a well-circumscribed indolent granulomatous process or features of diffuse necrotizing encephalitis occur.

For most people, prevention of toxoplasmosis is not a serious concern, as infection generally causes no symptoms or mild symptoms. High-risk groups, however, should consider being tested for *Toxoplasma* infection. HIV-infected individuals who test positive should receive drugs to prevent
development of toxoplasmosis when their CD4 count falls below 100 (35). Pregnant women, women who plan to become pregnant, and immunocompromised individuals who test negative for *Toxoplasma* infection should take precautions against becoming infected. Precautions consist in measures such as consuming only properly frozen or cooked meats, avoiding cleaning cats’ litter pans and avoiding contact with cats of unknown feeding history.

**American trypanosomiasis: Chagas disease**

Chagas disease is a serious problem of public health in Latin America, and is becoming more important in developed nations owing to the high flow of immigrants from endemic areas. Chagas disease is caused by *Trypanosoma cruzi*, a protozoan that it is transmitted by means of triatomin insects. Up to 8% of the population in Latin America are seropositive, but only 10–30% of them develop symptomatic disease (36).

The disease is a major cause of congestive heart failure, sudden death related to chronic Chagas disease, and cerebral embolism (stroke). Chagas disease can be diagnosed by demonstration of *T. cruzi* in blood smears and CSF samples or by serological testing. Neuroimaging usually demonstrates the location and extent of the cerebral infarct. Secondary prevention of stroke with long-term anticoagulation is recommended for all chagasic patients with stroke and heart failure, cardiac arrhythmias or ventricular aneurisms.

Traditional control programmes in Latin American countries have focused on the spraying of insecticides on houses, household annexes and other buildings. National programmes aimed at the interruption of the domestic and peridomestic cycles of transmission involving vectors, animal reservoirs and humans are feasible and have proved to be very effective. A prime example is the programme that has been operating in Brazil since 1975, when 711 municipalities had triatomin-infested dwellings: 10 years later only 186 municipalities remained infested, representing a successful accomplishment of the programme’s objectives in 74% of the originally infested areas (37).

**African trypanosomiasis: sleeping sickness**

African trypanosomiasis, also known as sleeping sickness, is a severe disease that is fatal if left untreated. The causative agents are protozoan parasites of the genus *Trypanosoma*, which enter the bloodstream via the bite of blood-feeding tsetse flies (Glossina spp.). The acute form of the disease attributable to *Trypanosoma brucei rhodesiense*, widespread in eastern and southern Africa, is closely related to a common infection of cattle known as N’gana, which restricts cattle-rearing in many prime areas of Africa. The chronic form caused by *T.b. gambiense* is found in western and central Africa.

Cattle and other wild mammals act as reservoir hosts of the parasites. Tsetse flies can acquire parasites by feeding on these animals or on an infected person. Incubation time usually varies from three days to a few weeks for *T.b. rhodesiense*, and several weeks to months for *T.b. gambiense*. Inside the human host, trypanosomes multiply and invade most tissues. Infection leads to malaise, lassitude and irregular fevers. Early symptoms, which include fever and enlarged lymph glands and spleen, are more severe and acute in *T.b. rhodesiense* infections. Advanced symptoms include neurological and endocrine disorders. As the parasites invade the CNS, mental deterioration begins, leading to coma and death.

Sleeping sickness claims comparatively few lives annually, but the risk of major epidemics means that surveillance and ongoing control measures must be maintained, especially in sub-Saharan Africa where 36 countries have epidemiological risk. Control relies mainly on systematic surveillance of at-risk populations, coupled with treatment of infected people. In addition, reduction of tsetse fly numbers plays a significant role, especially against the rhodesiense form of the disease. In the past, this has involved extensive clearance of bush to destroy tsetse fly breeding
and resting sites, and widespread application of insecticides. More recently, efficient traps and screens have been developed that, usually with community participation, can keep tsetse populations at low levels in a cost-effective manner (38).

**Schistosomiasis**

Schistosomiasis is an infection with a relatively low mortality rate but a high morbidity rate; it is endemic in 74 developing countries, with more than 80% of infected people living in sub-Saharan Africa. Infection is caused by trematode flatworms (flukes) of the genus *Schistosoma*: in freshwater, intermediate snail hosts release infective forms of the parasite. There are five species of schistosomes able to infect humans: *Schistosoma haematobium* (the urinary form) and *S. japonicum*, *S. mekongi*, *S. mansoni* and *S. intercalatum* (the “intestinal” forms).

If people are in contact with water where infected snails live, they become infected when larval forms of the parasites penetrate their skin. Later, adult male and female schistosomes pair and live together in human blood vessels. The females release eggs, some of which are passed out in the urine (in *S. haematobium* infection) or stools (*S. mansoni* and *S. japonicum*), but some eggs are trapped in body tissues. Immune reactions to eggs lodged in tissues are the cause of disease. Systemic complications are bladder cancer, progressive enlargement of the liver and spleen, intestinal damage due to fibrotic lesions around eggs lodged in these tissues, and hypertension of the abdominal blood vessels. Most cases of cerebral schistosomiasis are observed with *S. japonicum*, constituting 2–4% of all *S. japonicum* infections. However, CNS schistosomiasis also can occur with other species and involves seizures, headache, back pain, bladder dysfunction, paresthesias and lower limb weakness. Death is most often caused by bladder cancer associated with urinary schistosomiasis and by bleeding from varicose veins in the oesophagus associated with intestinal schistosomiasis. Children are especially vulnerable to infection, which develops into chronic disease if not treated. Diagnosis is made by using urine filtration and faecal smear techniques, antigen detection in endemic areas and antibody tests in non-endemic areas.

The disease is controlled through an integrated approach: drug treatment with praziquantel or oxamniquine (effective only against *S. mansoni*), provision of an adequate safe water supply, sanitation and health education (39).

**Hydatidosis**

Cystic hydatidosis/echinococcosis is an important zoonosis caused by the tapeworm *Echinococcus granulosus*. At present, four species of *Echinococcus* are recognized: *E. granulosus*, *E. multilocularis*, *E. oligarthrus* and *E. vogeli*. The parasite is distributed worldwide and about 2–3 million patients are estimated in the world (40). It causes serious human suffering and considerable losses in agricultural and human productivity. General lack of awareness of transmission factors and prevention measures among the population at risk, abundance of stray dogs, poor meat inspection in abattoirs, improper disposal of offal and home slaughtering practices play a role in the persistence of the disease.

The incidence of surgical cases ranges from 0.1 to 45 cases per 100 000 people. The real prevalence ranges between 0.22% and 24% in endemic areas. Ultrasounds have been very useful in large-scale prevalence surveys. Large prevalence studies have been conducted in many countries: in the Libyan Arab Jamahiriya, Morocco and Tunisia, the prevalence ranged from 1% to 2%.

In the normal life-cycle of *Echinococcus* species, adult tapeworms (3–6 mm long) inhabit the small intestine of carnivorous definitive hosts, such as dogs, coyotes or wolves, and echinococcal cyst stages occur in herbivorous intermediate hosts, such as sheep, cattle and goats. In most infected countries there is a dog–sheep cycle in which grazing sheep ingest tapeworm eggs passed in the faeces of an infected dog. Dogs ingest infected sheep viscera, mainly liver and lungs,
containing larval hydatid cysts in which numerous tapeworm heads are produced. These attach to the dog’s intestinal lining and develop into mature adult tapeworms. Humans become infected by ingesting food or drink contaminated with faecal material containing tapeworm eggs passed from infected carnivores, or when they handle or pet infected dogs. Oncospheres released from the eggs penetrate the intestinal mucosa and lodge in the liver, lungs, muscle, brain and other organs, where the hydatid cysts form. In the CNS, hydatidosis produces spinal disease and also is a potential cause of intracranial hypertension.

To control the parasite, a number of antihelmintic drugs have proved to be effective against adult stages of *E. granulosus* in the final host. The best drug currently available is praziquantel which exterminates all juvenile and adult echinococci from dogs. Several of the benzimidazole compounds have been shown to have efficacy against the hydatid cyst in the intermediate host. Echinococcosis can be controlled through preventive measures that break the cycle between the definitive and the intermediate host. These measures include dosing dogs, inspecting meat and educating the public on the risk to humans and the necessity to avoid feeding offal to dogs.

**IMPLICATIONS AND PREVENTION**

Infectious diseases that involve the nervous system affect millions of people around the world, especially in some regions in Africa and South-East Asia. Most of these diseases can cause high mortality rates in some populations and produce severe complications, disability and economic burden for individuals, families and health systems. Even with the advent of effective antibiotics and vaccines, they still remain a major challenge in many parts of the world, especially in developing countries where the worst health indicators are found. Some diseases that had been found in the developed world but have virtually disappeared, such as poliomyelitis, leprosy and neurosyphilis, are still taking their toll in developing regions. Conversely, some of the protozoan and helminthic infections that are so characteristic of the tropics are now being seen with increasing frequency in developed countries. Other major concerns are the development of drug-resistant organisms, the increasing number of immunocompromised populations and the rising number of diseases previously considered rare. Education, surveillance, development of new drugs and vaccines, and other policies are in constant evolution to fight against old and emerging infectious diseases of the nervous system.

Some preventive measures have a more rapid impact and are more cost effective than others. Regular, large-scale treatment to prevent disease is cheap, by treating carriers (i.e. humans or dogs) to prevent humans from getting infected as an intermediate host, or to regularly lower the worm load so that the person does not suffer from infection. Large-scale treatment in humans can be combined for several diseases (the “preventive chemotherapy” concept), and can be packaged in domestic animals — such as dogs — with other interventions such as rabies vaccination. The basic idea is to deliver such public health treatment packages regularly, to enable people to avoid the worst effects of infection, even with an ongoing lack of water, sanitation and hygiene. It has to be said that environmental measures would eventually solve the problem, but require a much more substantial investment and commitment. Some diseases are easily controlled and prevented with basic, inexpensive measures that are available worldwide, but their effectiveness entails a massive education effort and steady surveillance.
CONCLUSIONS AND RECOMMENDATIONS

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### RECOMMENDED READING