EPILEPSY

A public health imperative

World Health Organization

ILAE International League Against Epilepsy

IBE International Bureau for Epilepsy

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Contents

Foreword

Epilepsy is one of the most common neurological diseases worldwide, affecting around 50 million people of all ages around the world. The risk of premature death in people with epilepsy is up to three times that of the general population. The lives of people with epilepsy are often impacted by stigma, discrimination and human rights violations.

We know that while 80% of people with epilepsy live in low- and middle-income countries, most of them do not have access to treatment. This is despite the availability of effective antiseizure medicines, which can cost as little as US$ 5 per year. A lack of action to address the epilepsy treatment gap has dire consequences for people's lives and well-being, and impacts social and economic development.

This report presents encouraging evidence that almost a quarter of epilepsy cases are preventable and 70% of people with epilepsy can live seizure free with low-cost and effective medicines. As evidence from multiple countries shows, it is feasible to integrate epilepsy into primary health care and thereby ensure that all people with epilepsy have access to quality and affordable treatment and services.

If we are to achieve the health-related Sustainable Development Goals (SDGs), it is imperative that we substantially scale up global efforts to address epilepsy. The SDGs include the targets of reducing premature deaths from noncommunicable diseases and promoting mental health and well-being; as well as achieving universal health coverage with access to quality services and effective, affordable essential medicines. The importance of addressing epilepsy was also underlined in a World Health Assembly (WHA) resolution on the global burden of epilepsy in 2015. The resolution requests that WHO provide technical support to countries for epilepsy management, especially those with the lowest access to services and resources, where the burden of epilepsy is greatest.

This is the first global report on epilepsy produced by WHO and key partners. It highlights the available evidence on the burden of epilepsy and the public health response required at global, regional and national levels. The report is also an important milestone in re-energizing and translating the WHA resolution into action as it provides guidance to governments, policy-makers and stakeholders as they seek to reduce the disease burden as part of the universal health coverage agenda.

I encourage all WHO Member States and partners to build on the findings and recommendations of this report and to share it widely.

Dr Ren Minghui
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Preface

Epilepsy is a brain disease characterized by abnormal electrical activity causing seizures or unusual behaviour, sensations and sometimes loss of awareness. It carries neurological, cognitive, psychological and social consequences and accounts for a significant proportion of the world's burden of disease. Despite availability of effective and low-cost antiseizure medicines, more than 75% of people with epilepsy in low-income countries do not have access to treatment.

This report is the product of a long-standing collaboration between WHO and leading nongovernmental organizations working in the area of epilepsy, the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Together we have made substantial progress in encouraging countries to prioritize epilepsy in public health agendas.

Epilepsy: a public health imperative presents a comprehensive picture of the impact that the condition has on people with epilepsy, their families, communities and societies. Epilepsy has a high risk of disability, psychiatric comorbidity, social isolation and premature death. Across the world, people with epilepsy and their families suffer from stigma and discrimination. Many children with epilepsy do not go to school; adults are denied work, the right to drive or marriage. The human rights violations faced by people with epilepsy around the world are unacceptable.

It is time to highlight epilepsy as a public health imperative, to strongly encourage investment in reducing its burden, and to advocate for actions to address gaps in epilepsy knowledge, care and research.

Raising epilepsy on the global public health agenda cannot be done alone. The adoption of the World Health Assembly resolution on epilepsy by Member States drew attention to the need for coordinated action at country level. The resolution provides a powerful tool to engage governments and civil society in taking concrete action to promote access to care and to protect the rights of people with epilepsy.

Epilepsy: a public health imperative is a call for sustained and coordinated action to ensure that every person with epilepsy has access to the care and treatment they need, and the opportunity to live free from stigma and discrimination in all parts of the world.

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Acronyms and abbreviations

ADA	Americans with Disabilities Act
ADHD	attention deficit hyperactivity disorder
AEDs	antiepileptic drugs
AES	American Epilepsy Society
ASD	autism spectrum disorder
CDEs	common data elements
CHW	community health workers
CNS	central nervous system
CRPD	Convention on the Rights of Persons with Disabilities
CT	computerized axial tomography
CURE	Citizens United for Research in Epilepsy
DALYs	disability-adjusted life years
EAE	Epilepsy Alliance Europe
EEG	electroencephalography
EU	European Union
GBD	global burden of disease
GCAE	Global Campaign Against Epilepsy
GDP	gross domestic product
HIC	high-income countries
HIV	human immunodeficiency virus
IBE	International Bureau for Epilepsy
ICARE	Interagency Collaborative to Advance Research in Epilepsy (USA)
ILAE	International League Against Epilepsy
LMIC	low- and middle-income countries
mhGAP	WHO mental health Gap Action Programme
MRI	magnetic resonance imaging
NCD	noncommunicable disease
NGO	nongovernmental organization
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health (USA)
PAHO	Pan American Health Organization
SDG	Sustainable Development Goal
SMR	standardized mortality ratio
SUDEP	sudden unexpected death in epilepsy
TBI	traumatic brain injury
UHC	universal health coverage
USA	United States of America
WHA	World Health Assembly
WHO	World Health Organization

Overarching messages

BURDEN

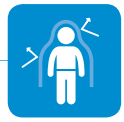
The burden of epilepsy is high and often neglected in public health agendas. Epilepsy is one of the most common neurological diseases, affecting around 50 million people of all ages around the world. The risk of premature death in people with epilepsy is up to three times that of the general population. Roughly half of adults with epilepsy have at least one other health condition. Psychiatric conditions, such as depression and anxiety, make seizures worse and reduce quality of life. Epilepsy has significant economic implications in terms of health care needs and lost productivity at work.

STIGMA AND DISCRIMINATION

In all parts of the world, people with epilepsy are the target of discrimination and human rights violations. The stigma of epilepsy can discourage people from seeking treatment and has consequences for quality of life and social inclusion. Improving knowledge and raising awareness of epilepsy in schools, work places, and communities is needed to reduce stigma. Legislation based on internationally accepted human rights standards can prevent discrimination and rights violations, improve access to health care services, and raise the quality of life for people with epilepsy.

TREATMENT GAP

Three-quarters of people living with epilepsy in low-income countries do not get the treatment they need. Yet, up to 70% of people with epilepsy could become seizure free with appropriate use of cost-effective antiseizure medicines. A significant proportion of the burden of epilepsy could be avoided by scaling up routine availability of antiseizure medicines, possible at an annual cost as low as US$ 5 per person. It is feasible to integrate epilepsy treatment into primary health care – training nonspecialist providers, investing in continuous supplies of antiseizure medicines and strengthening health systems can substantially reduce the epilepsy treatment gap.



PREVENTION

An estimated 25% of epilepsy cases are preventable. The major modifiable risk factors for epilepsy are: perinatal insults, central nervous system infections, traumatic brain injury and stroke. Preventing epilepsy is an urgent unmet need. Effective interventions for prevention are available and delivered as part of broader public health responses in maternal and newborn health care, communicable disease control, injury prevention and cardiovascular health.

THE TIME TO ACT IS NOW

Sustained and coordinated action to prioritize epilepsy in public health agendas is required at global, regional and national levels. World Health Assembly resolution WHA68.20 on the global burden of epilepsy and the need for coordinated action at the country level to address its health, social and public knowledge implications sets the framework for increasing investment in epilepsy. There is a pressing need for increased investment in research and to address the burden of epilepsy through integration in primary health care, ensuring that all people with epilepsy have access to quality and affordable care.

Executive summary

Introduction

Epilepsy is a brain disease characterized by abnormal brain activity causing seizures or unusual behaviour, sensations and sometimes loss of awareness. It carries neurological, cognitive, psychological and social consequences and **accounts for a significant proportion of the world's burden of disease, affecting around 50 million people worldwide.** The number of people with epilepsy is expected to increase further due to rising life expectancy worldwide and an increasing proportion of people surviving insults which often lead to epilepsy, such as birth trauma, traumatic brain injury (TBI), infections of the brain and stroke. The physical, psychological and social consequences of epilepsy impose significant burdens on people living with the condition and their families. Around the world, people with epilepsy and their families suffer from stigma and discrimination, often facing serious difficulties in education, employment, marriage and reproduction. Nearly 80% of people with epilepsy live in low- and middle-income countries (LMIC), where treatment gaps exceed 75% in most low-income countries and 50% in most middle-income countries. This is despite the effectiveness and low cost of antiseizure medicines.

The Sustainable Development Goals (SDGs), which seek to achieve global economic, social and environmental sustainable development by 2030, will not be realized without investment in physical and mental health for all people, including those living with epilepsy. This report calls for accelerated action to highlight epilepsy as a public health priority and support investment in reducing the burden it places.

At the Sixty-eighth World Health Assembly (WHA) in 2015, 194 Member States unanimously adopted resolution WHA68.20 on epilepsy which called for the need for coordinated action at the country level to address its health, social and public knowledge implications. The third High-level Meeting on the prevention and control of noncommunicable diseases (NCDs) in 2018 highlighted the importance of mental health conditions, drawing the attention of policy-makers to integrate epilepsy into action on NCDs and mental health. This report represents a collaborative effort between the World Health Organization (WHO), the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) to provide technical support to countries in addressing the needs of people with epilepsy.

The objective of this report is to raise the prioritization of epilepsy on the global agenda; to describe a public health approach that addresses its high burden; and to advocate for crucial actions that address gaps in epilepsy knowledge, care and research. It is written for not only policy-makers and public health experts and health care providers, but also for people living with epilepsy, their families and civil society organizations.

Global burden of epilepsy

Epilepsy accounts for over 13 million disability-adjusted life years (DALYs) and is responsible for more than 0.5% of the global burden of disease (GBD). It affects people of all ages, sexes, races, income groups and geographical locations. Around 7.6 per 1000 persons have epilepsy during their lifetime. It has a bimodal distribution according to age with peaks in the youngest individuals and in those over 60 years of age. Epilepsy has a variety of causes, ranging from genetic, metabolic, infectious, structural, immune and unknown. There is a higher incidence of epilepsy in LMIC (139 per 100 000 person-years) compared with high-income countries (HIC) (48.9).

Epilepsy carries a significantly increased risk of premature mortality, compared with the general population. Among deaths directly attributable to epilepsy, important immediate causes include sudden unexpected death in epilepsy (SUDEP), status epilepticus – characterized by seizure duration of over 30 minutes or seizures occurring close together without recovery in between, unintentional injuries, and suicide.

In LMIC, early death among people with epilepsy is significantly higher than in HIC. Excess mortality in LMIC is more likely to be associated with causes attributable to lack of access to health facilities and preventable causes such as drowning, head injuries, and burns. This could be substantially reduced with education about the risk of death and improved access to treatments, including antiseizure medicines.

Roughly half of the people with epilepsy have coexisting physical or psychiatric conditions. Physical and psychiatric comorbidities in people with epilepsy are associated with poorer health outcomes, increased health care needs, decreased quality of life and greater social exclusion. The most prevalent psychiatric comorbidities are depression (23%) and anxiety (20%). Intellectual disability is the most common comorbidity in children with epilepsy (30–40%). Epilepsy is also commonly associated with neurodegenerative diseases.

Epilepsy is a treatable condition. Up to 70% of people with epilepsy could become seizure free with appropriate diagnosis and use of cost-effective, and commonly available, antiseizure medicines. This can lead people with epilepsy to continue, or return to, a full and productive life. Despite the very low cost of antiseizure medicines, more than 75% of people with epilepsy in low-income countries do not receive treatment. Left untreated, **people living with epilepsy face devastating social consequences,** including stigma, discrimination and human rights violations.

Leadership and governance for epilepsy

Given the burden of epilepsy, **a broad public health approach is needed to improve the care and quality of life of people with epilepsy.** This requires governments to provide universal coverage through health and social care services, as well as policies and legislation to address stigma, discrimination and barriers to civil rights.

In many countries, laws impacting the lives of people with epilepsy are outdated and fail to protect and promote their human rights. Legislation for epilepsy, where it exists, sometimes actively violates the rights of people with epilepsy. This leads to unmet needs in the areas of education, employment, residential and community services, and access to appropriate and affordable health care.

Leadership and governance are critical levers for addressing these challenges and to improve care and support for people with epilepsy. **The implementation of policies and plans for epilepsy requires strong leadership and intersectoral collaboration.**

While significant steps forward have been made in recent years under the leadership of WHO/ILAE/IBE, more action is needed globally as well as oversight for implementation in every country, to reduce the burden of epilepsy. Legislative initiatives, public campaigns and social programmes are needed to guarantee the social and human rights of people with epilepsy. These should align with international human rights standards and global health agendas such as SDGs. Appropriate and integrated treatment of people with epilepsy requires that governments allocate sufficient funds towards epilepsy care and adopt a public health approach. Better data and information systems are needed to make the case for prioritizing epilepsy in global public health agendas.

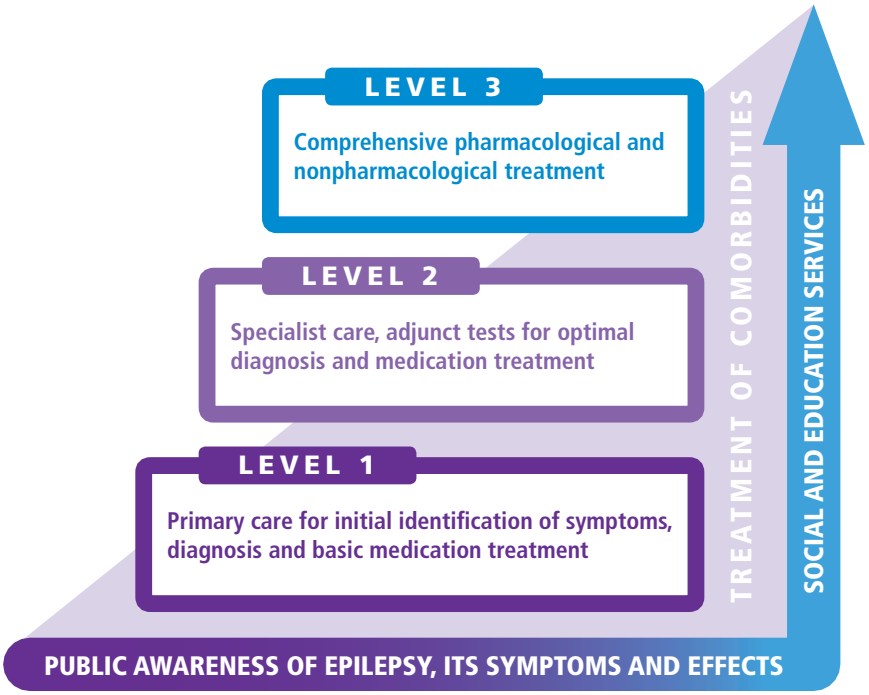
Comprehensive health care response to epilepsy

Health care for people with epilepsy involves providing health care and social services to decrease morbidity, premature mortality and adverse psychosocial outcomes associated with the condition. Providing quality epilepsy care is a challenge because of its complexity, chronicity and considerable comorbidity.

The care needs of people with epilepsy are multifaceted and should be a matter of great concern for policy-makers in all countries, as there are considerable gaps in policies and care available for epilepsy worldwide. **Access to care for people with epilepsy varies considerably across and within countries and unmet needs exist in every country, but particularly in LMIC.**

The spectrum of health care needs for people with epilepsy and their families can be viewed as a stepped model: starting with the initial diagnosis and continuing, as necessary, through to nonpharmacological therapies (e.g. surgery) for drug-resistant epilepsy (see figure below). **The management of comorbidities should be an essential component at all levels of care.** Multidisciplinary health care teams that emphasize person-centred care are also important in the stepped model (e.g. physicians, nurses, pharmacists, therapists and social workers). Community-based care should be emphasized to increase access to all people in need of epilepsy services. Social and educational services should provide individualized support to people with epilepsy, throughout the levels of care and should continue, as needed, even when the person is no longer having seizures.

Stepped model to improve quality of care for people with epilepsy



Policy-makers need to ensure that there are sufficient population and health care system data to determine the need for and evaluation of epilepsy care, identify appropriate training for providers, provide guidelines for quality health care, and allocate the required resources to ensure those living with epilepsy have access to adequate health and social services.

Country examples of comprehensive care for epilepsy do exist. The WHO Programme on reducing the epilepsy treatment gap has shown that epilepsy care can be cost-effectively integrated into the primary health system in low-resource settings. Through pilot projects in Ghana, Mozambique, Myanmar and Viet Nam the programme has meant that 6.5 million people now have access to health facilities where epilepsy care is available.

Access to antiseizure medicines

Various terms are used to describe medicines used to manage acute seizures (e.g. antiseizure, anticonvulsant, and antiepileptic medicines/drugs); antiseizure medicines is the broadest possible term for this class of medicines (not all seizures are convulsive, nor do all seizures constitute epileptic conditions).

People with epilepsy require treatment with antiseizure medicines for many years, sometimes for a lifetime. The abrupt withdrawal of antiseizure medicines may result in life-threatening consequences, including status epilepticus. Therefore, it is essential to ensure that access to these medicines is sustained over time to ensure uninterrupted treatment.

The imperative to increase access to essential medicines was highlighted in the United Nations SDGs in goals 3.4 and 3.8. The key components of access are: **rational selection, availability, affordability and appropriate use of essential medicines** (see figure below).

Framework for understanding access to medicines for epilepsy

RATIONAL SELECTION

The process of interpreting best practice evidence in the creation of medicine lists

- There are 11 antiseizure medicines currently included in the *WHO Model List of Essential Medicines*
- Some complex epilepsy syndromes may require treatments not on this list

AVAILABILITY

The extent to which quality medicines can be found in the health system and accessible to those in need

- Inadequate availability of antiseizure medicines and trained health care providers is a major public health concern
- In LMIC, antiseizure medicines may be available less than 50% of the time in the public sector

AFFORDABILITY

A metric evaluated by the cost burden of medicines across levels of the health system (including for people with epilepsy)

- Barriers to affordability of medicines can lead to financial hardship for people in need
- Generic medicines may improve affordability but quality must be ensured

APPROPRIATE USE

People should be provided with an uninterrupted supply of inexpensive and appropriate medicines at doses, and for durations, suitable for their clinical conditions

- Ensuring appropriate access to antiseizure medicines is one of the highest priorities
- Provider level barriers (e.g. training and supervision) and community and user-level barriers (e.g. awareness of epilepsy as a treatable condition) should be addressed to ensure appropriate use

Ensuring uninterrupted supply of appropriate access to antiseizure medicines is one of the highest priorities. Policies should be in place to monitor supply chains and stock-outs in health facilities and address possible disruptions.

Access to antiseizure medicines offers the potential for approximately 70% of people with epilepsy to live seizure free (on medicines), with an opportunity to impact their quality of life and participation in society. Understanding the myriad of financial, educational and sociocultural barriers to accessing antiseizure medicines is crucial for the adequate planning of financial, health system and clinical interventions to help improve access to treatment for people with epilepsy.

Actions to improve access to medicines should be addressed at the international, national, district, community and individual levels. There are different options when establishing health policies impacting access to antiseizure medicines. The optimal model to be adopted depends on the local context, and opportunities to integrate an epilepsy action plan within broader public health objectives. Transparent policies that involve all stakeholders – from suppliers to government acquisition – need to be developed.

The social response: misconceptions and stigma in epilepsy

Stigma is a significant contributor to poor physical and mental health in people with epilepsy and will not be improved with a single approach. A multipronged strategy, which is culturally appropriate, multisectoral and collaborative, is needed.

Misconceptions and poor understanding about the nature of epilepsy contribute to the burden of disease and lead to stigma. This includes the perception of epilepsy as a form of insanity, ruining people's lives, and being untreatable or contagious. Misconceptions and negative attitudes cause people with epilepsy to feel shame, embarrassment and disgrace. The impact of feeling socially excluded contributes to the physical, psychological and social burden of epilepsy. **Stigma can delay appropriate health care seeking, access to care, health financing and availability of treatment.**

Institutionalized discrimination in epilepsy affects employment, education, marriage and childbearing, and driving regulations. Discriminatory laws exist in a number of countries. Most were repealed decades ago, but the legacy of these laws can still lead to misconceptions and discrimination.

Direct investments in health care do not necessarily lead to improvements in epilepsy-related stigma. To reduce stigma, funds need to be directed toward epilepsy awareness and stigma-reduction programmes. Policy-makers can reduce stigma by changing laws that are punitive to people with epilepsy. A multisectoral public health response needs to include interventions that improve the knowledge of individuals and their families, teachers, employers, health care providers, disability service providers, care providers, first responders, traditional healers, media, community and policy-makers.

Prevention of epilepsy

The high global burden of epilepsy requires prevention where possible. The major modifiable risk factors for epilepsy are: perinatal risk factors, central nervous system (CNS) infections, TBI and stroke, which, together, account for an estimated 25% of epilepsy cases.

- **Perinatal risk factors** related to epilepsy include gestational age at delivery, birth weight, maternal health conditions such as nutritional status, pre-eclampsia, the presence and skill of birth attendants,

method of delivery, perinatal infection (e.g. human immunodeficiency virus [HIV]), and other adverse events and conditions.

- **Central nervous system infections,** according to population-based studies, comprise three main categories: bacterial meningitis, viral encephalitis and neurocysticercosis. Bacterial meningitis and viral encephalitis combined account for approximately 2–3% of epilepsies in HIC and about 5% of epilepsies in LMIC. In some LMIC where the *Taenia solium* (pork tapeworm) is endemic, roughly one-third of epilepsies are attributed to neurocysticercosis. Malaria is one of the most common parasitic diseases worldwide. Its neurological form, known as cerebral malaria, is a potential cause of epilepsy in malaria-endemic regions of the world.

- **Traumatic brain injury** is the cause of epilepsy in 4% of cases in LMIC and 5% of cases in HIC. Road traffic injuries, falls and violence are the most common causes of TBI. The risk of epilepsy is higher in people with severe versus mild TBI (increased almost 20-fold).

- **Stroke,** including ischaemic and haemorrhagic types, is also a common potentially preventable cause of epilepsy, representing 12% of epilepsies in HIC and 2.7% in LMIC. Seizures after stroke are associated with increased premature mortality, disability, and higher resource allocation and costs. In population-based studies, stroke was identified as a common cause of status epilepticus (12–40% in HIC, 5–15% in LMIC).

Estimates of the burden of epilepsy attributable to preventable causes are at best approximate and the true burden undoubtedly varies between regions and localities. The **primary prevention** of these causes has a substantial impact on the development of epilepsies and requires improving maternal health care and obstetrical services, communicable disease control, injury prevention, and cardiovascular and cerebrovascular health with reduction of the major risk factors of NCDs. An understanding of the development of epilepsy after a brain insult or parasitic infection is critical to the development of **secondary preventive strategies.**

Epilepsy research

Epilepsy research has enabled remarkable progress in deepening our understanding of the etiologies and mechanisms leading to epilepsy and associated comorbidities. It has also brought interventions and treatments to improve the management of seizures and their comorbid conditions or consequences. There remains, however, a **dramatic inequality in access to and utilization of research resources and expertise across the globe.**

Investment in research for epilepsy is insufficient. Even in HIC, where significant investments in epilepsy research have been made, funding for epilepsy only represents a small proportion of overall funding. In the United States of America, the National Institutes of Health (NIH) support for epilepsy research accounted for less than 0.09% of the total NIH budget dedicated to research and has stagnated over the last 3 years, unlike other neurological conditions which have attracted increasing research support, e.g. Alzheimer disease research, autism and rare diseases.

The **barriers in funding epilepsy research are higher in LMIC,** where financing comes from domestic organizations and most funding is directed towards communicable diseases and little towards epilepsy. Whether research is preclinical, clinical or at the population level, it is important to engage and sustain the best pool of researchers in the field, at all career stages, and enrich the available resources by maintaining collaborations within and beyond the epilepsy community to facilitate this.

Developing epilepsy research priorities around the world may be a vehicle to improve research support and advocacy. Recognizing the need to determine possible areas of research priority, and as a response to regional declarations on epilepsy, taskforces combining regional expertise from ILAE and IBE were established to address research priorities in their region. A significant role in the advocacy for epilepsy research has also been played by organizations led by families that have experienced epilepsy, e.g. Citizens United for Research in Epilepsy (CURE).

The way to advance epilepsy research is through capacity building, especially research partnerships between HIC and LMIC; increased funding and infrastructure for epilepsy research; optimization of research process standardization; establishment of global, regional and national research priorities; enhanced efforts to translate research findings into policies and programmes; and fostering stakeholder collaboration and partnership.

The way forward

Major gaps in awareness, diagnosis and treatment of epilepsy impose a significant global burden on the lives of people with epilepsy. *Epilepsy: a public health imperative* raises epilepsy as a public health priority to address these gaps through a cost-effective, coordinated response. People with epilepsy and their families are asking that this unique opportunity not be lost, and that global action be taken.

EPILEPSY
A public health imperative

The time to act is NOW.

Urgent actions are needed, and these include:

- **Promote** epilepsy as a public health priority to reduce its burden.
- **Improve** public attitudes, reduce stigma and promote protection of the rights of people with epilepsy.
- **Invest** in health and social care systems to improve accessibility to epilepsy care.
- **Enhance** access to cost-effective antiseizure medicines globally.
- **Prevent** acquired epilepsies through improved care for common causes, such as perinatal injury, central nervous system infections, stroke and traumatic brain injuries.
- **Increase** priority given to epilepsy in research agendas.

EPILEPSY: A PUBLIC HEALTH IMPERATIVE

Introduction

Introduction

A public health concern

Epilepsy accounts for a significant proportion of the world's disease burden *(1)*. It accounted for over 13 million disability-adjusted life years (DALYs; a summary measure of health loss defined by the sum of years of life lost for premature mortality and years lived with disability) in 2016 or 0.5% of the overall global burden of disease *(2)*. More than 5 million new cases are diagnosed every year and the number of people with epilepsy is expected to increase further *(1)*. This is due to the rising life expectancy worldwide and the increasing proportion of people surviving epilepsy-provoking insults, such as birth injury, head trauma, brain infection and stroke.

Epilepsy is a devastating global health concern and can develop at any time in one's life. It is characterized by an enduring predisposition to generate epileptic seizures, and results in neurobiological, cognitive, psychological and social consequences. Epilepsy carries an overall increased risk of premature mortality *(3)*. SUDEP, status epilepticus, accidents, drowning, unintentional injuries and suicide are the most important and potentially preventable causes of death in people with epilepsy. People with epilepsy may have one or more coexisting physical or psychiatric conditions *(4, 5)*. These comorbidities are associated with poor health outcomes, such as increased health care needs, decreased quality of life and higher mortality *(6)*.

People with epilepsy and their families can be the target of discrimination and human rights violations, affecting their quality of life and social inclusion, which often dissuades them from seeking treatment *(7)*. Epilepsy is often related to conditions of poverty, and epilepsy results in poverty from lost earnings due to disability, time seeking care, and stigma around employability *(8)*. This affects people with epilepsy as well as family members, especially those caring for children with epilepsy.

People with epilepsy, their families, and the community need to be aware that seizures can be controlled. Up to 70% of people with epilepsy could become seizure free with appropriate use of antiseizure medicines *(9)*.

Major gaps in awareness, diagnosis and treatment are devastating the lives of millions of people with epilepsy throughout the world. Unfortunately, the areas with the highest burden of epilepsy are often those with the lowest coverage of health services. The epilepsy treatment gap is defined as the proportion of people with epilepsy who require treatment but do not receive it, expressed as a percentage *(10)*. It is estimated to exceed 75% in most low-income countries *(10)*. This disparity exists despite epilepsy treatment being inexpensive and effective in the majority of cases.

Epilepsy is not often recognized as a global public health priority. This is despite the high global prevalence and burden of disease for people with epilepsy and their families, the economic impact, and the associated stigma and social exclusion. The Sustainable Development Goals (SDGs), which seek to achieve global economic, social and environmental sustainable development by 2030 *(11)*, will not be achieved without investment in physical and mental health for all people, including those living with epilepsy.

To support investment in reducing the burden of epilepsy, this report calls for accelerated action to make epilepsy a public health priority. At the Sixty-eighth World Health Assembly (WHA) in

Sixty-eighth World Health Assembly (WHA) in 2015, a resolution on epilepsy (WHA68.20) was adopted *(12)*; calling for the "need for coordinated action at the country level to address its health, social and public knowledge implications." This report represents a collaborative effort between the World Health Organization (WHO), the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) to guide governments, policy-makers and a range of stakeholders to take actionable steps towards defeating epilepsy.

Epilepsy defined

WHAT IS EPILEPSY?

Epilepsy is a brain disease characterized by an enduring predisposition to generate epileptic seizures *(13)*. It carries neurological, cognitive, psychological and social consequences. People with epilepsy have recurring seizures that often occur spontaneously and without warning. The definition and the classification of seizures and epilepsy were recently revised by the ILAE to meet advances in scientific knowledge.

Definitions

Epilepsy: A brain disease defined by any of the following conditions:

- at least two unprovoked (or reflex) seizures occurring > 24 hours apart;
- one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years;
- diagnosis of an epilepsy syndrome *(13)*.

Drug-resistant epilepsy: Failure of adequate trials of two antiseizure medicine schedules to achieve sustained seizure freedom *(14, 15)*.

Antiseizure medicines: Although various terms are used to describe medicines used to manage acute seizures (e.g. antiseizure, anticonvulsant, and antiepileptic medicines); antiseizure medicines is the broadest possible term for this class of medicines (not all seizures are convulsive, nor do all seizures constitute epileptic conditions).

Epilepsy, in remission: When there is resolution of an age-dependent syndrome or no seizures for the last 10 years and no antiseizure medicine for the last 5 years *(13)*.

Seizure: Transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain *(16)*.

Unprovoked seizure: A seizure occurring in a person aged one month or older, occurring in the absence of precipitating factors *(17)*.

Acute symptomatic seizure: Also known as a provoked seizure, occurring at the time of a systemic insult or in close temporal association with a documented brain insult *(17)*.

Reflex epilepsy: Rare epileptic syndromes with seizures induced by specific triggering factors (either by visual, auditory, somato-sensitive or somato-motor stimulation, or by higher cortical function activities) *(13)*.

Sudden unexpected death in epilepsy (SUDEP): Sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death of an individual with epilepsy. SUDEP is determined with or without evidence of a terminal seizure and excluding status epilepticus, in which investigation and postmortem examination, including toxicology, do not reveal a cause of death other than epilepsy *(18)*.

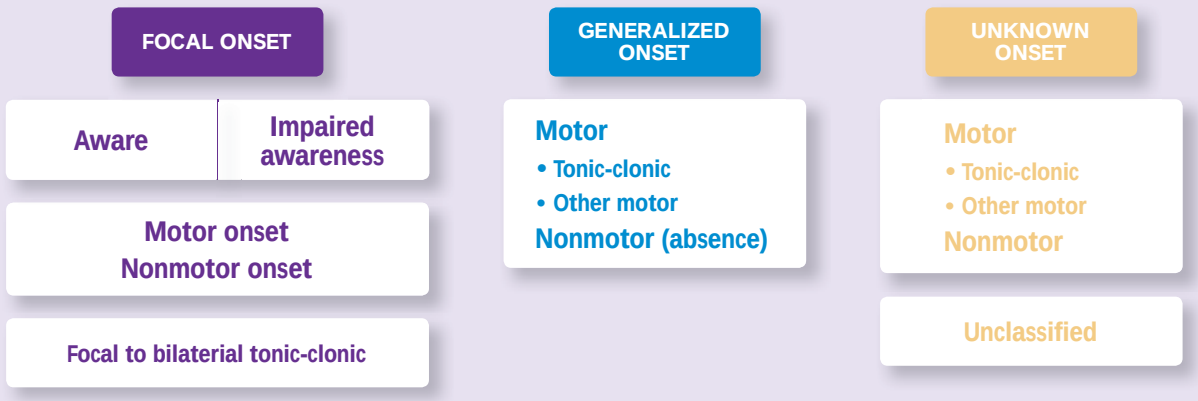
Status epilepticus: Seizure duration ≥ 30 minutes or seizures without recovery in between *(19)*.

HOW ARE SEIZURES AND EPILEPSY CLASSIFIED?

Classification of seizure types is important for the selection of appropriate therapies and offers a common language for providing good quality care. The classification of seizures, originally based on the 1981 classification *(20)*, was revised by the ILAE (Fig. I.1) *(21)* with modifications in terminology and recognition of new seizure types based on advances in scientific knowledge.

A fundamental distinction is made between seizure onset that is focal (seizures arise in one hemisphere of the brain); generalized (originates in both hemispheres simultaneously); and seizures of unknown onset *(21)*. Focal seizures are subclassified according to whether awareness (a marker for consciousness) is intact or impaired. Next, focal seizures are divided into motor or nonmotor. A seizure that begins focally (in one part of the body) and then spreads bilaterally is termed focal to bilateral tonic-clonic. Tonic refers to stiffening, and clonic to rhythmical jerking. Generalized seizures are categorized as motor and nonmotor (absence).

Fig. I.1 Classification of seizures

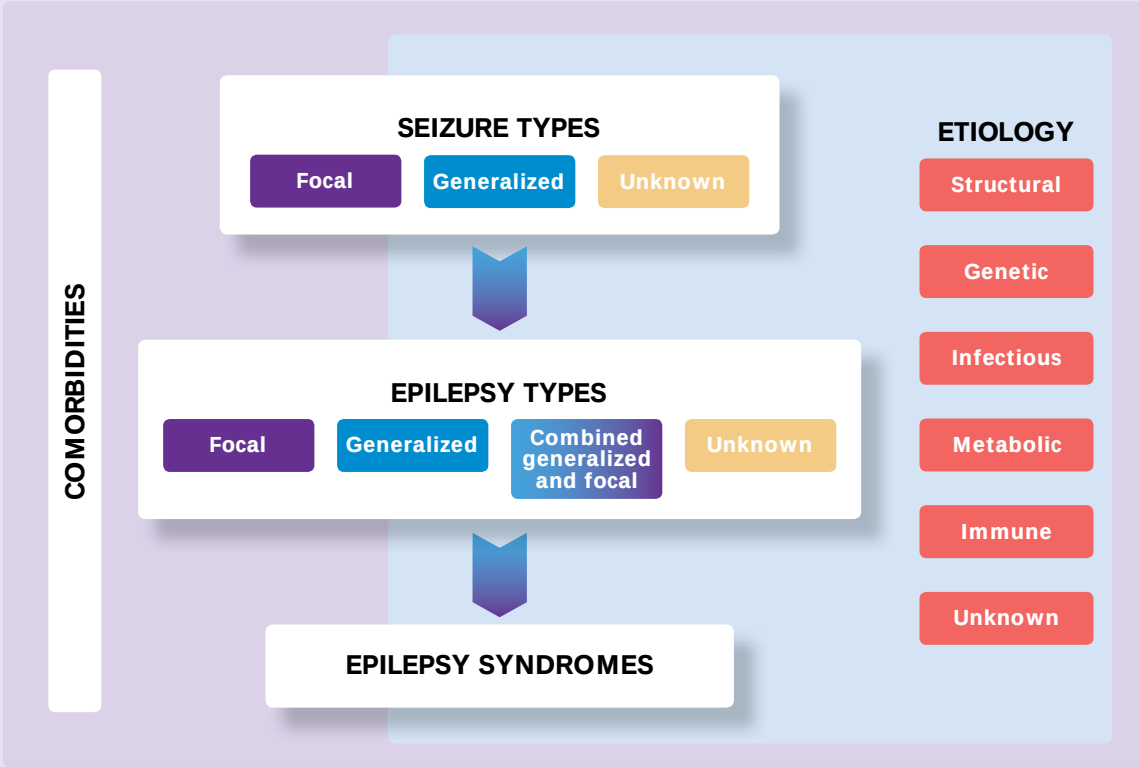


Source: Fisher, 2017 *(21)*.

Epilepsy classification (Fig. I.2) aligns with the seizure classification *(22)*. Levels of classification include seizure type, epilepsy type and epilepsy syndrome. Indeed, epilepsy is really an umbrella term that includes many different types of epilepsies, some of which are recognized syndromes (e.g. childhood absence epilepsy) but many for which an epilepsy syndrome has not been defined. When a person first presents with seizures, a physician or other health care provider starts by classifying the type of seizure. Then, the person's type of epilepsy needs to be classified and, in many cases, a specific epilepsy syndrome diagnosis can be made. There is increasing awareness that many of the epilepsies are associated with comorbidities such as intellectual and psychiatric impairment, and behavioural problems (Fig. I.2, left side). Appropriate classification is critical for tailoring treatment strategies and recognizing associated comorbidities (see Chapter 1).

HOW ARE SEIZURES AND EPILEPSY CLASSIFIED? (continued)

Fig. I.2 Classification of the epilepsies



Source: Scheffer et al. *(22)*.

WHAT ARE THE CAUSES OF EPILEPSY?

The causes of epilepsy are divided into the following categories: structural, genetic, infectious, metabolic, immune and unknown *(22)*. Investigating the causes of epilepsy is crucial to ensure early detection and management of the various etiologies, but also to implement interventions aimed at decreasing the large portion of preventable epilepsies, for example, from traumatic brain injury (TBI), stroke, etc.

Causes of epilepsy

Structural: Abnormalities visible on structural neuroimaging which may be acquired (e.g. epilepsy from stroke, trauma and infection), or may be genetic (e.g. epilepsy from malformation in development of the cerebral cortex).

Genetic: A known or presumed genetic mutation in which seizures are a core symptom of the disorder.

Infectious: A known infection in which seizures are a core symptom (such as meningitis or encephalitis). Common examples are neurocysticercosis, tuberculosis, HIV, cerebral malaria, and congenital infections such as Zika virus and cytomegalovirus.

Metabolic: A known or presumed metabolic disorder in which seizures are a core symptom (e.g. porphyria, uraemia or pyridoxine-dependent seizures).

Immune: An immune disorder in which seizures are a core symptom. Autoimmune disorders affect multiple organ systems and frequently involve CNS inflammation.

Unknown: The cause of the epilepsy is not yet known.

Objectives of the report

The objective of this report is to raise epilepsy as a global public health priority, to emphasize a public health approach to addressing its high burden, and to advocate for actions that address gaps in epilepsy care, education and research.

The report provides an up-to-date review that can inform actions to improve the lives of those living with epilepsy worldwide. It outlines key information about epilepsy, ranging from its epidemiology and burden, health care financing and legislation, and the current state of research, to support countries as they embark on efforts to improve epilepsy care and outcomes globally.

The target audiences of this report are broad. They include policy-makers and public health experts, specialist and nonspecialist health care providers, people living with epilepsy and their families, and civil society organizations.

Methodology

The information sources for this report include:

- Reports from a large group of experts that reviewed existing literature (scientific evidence and reports) for each chapter and provided case examples to highlight challenges and lessons learned from all six WHO regions and across World Bank income groups.

- A survey, conducted by the ILAE/IBE, which addressed a broad range of information such as leadership, governance, policy, plans and programmes for epilepsy, health and social response to epilepsy, access to antiseizure medicines for epilepsy, misconceptions, stigmatization and discrimination around epilepsy, epilepsy prevention, epilepsy research, epilepsy partnerships and collaborations (the survey methodology can be found in Annex 1).

- Input from an advisory committee across all stages of the report's development, from early conceptualization to drafting of chapters with working groups and reviewing drafts during face-to-face meetings in 2018.

- International experts from a variety of stakeholder groups reviewed and provided feedback on the report; including nongovernmental organizations (NGOs) and epilepsy organizations, researchers and clinicians, as well as people living with epilepsy and their families.

Contents of the report

Chapter 1: Global burden of epilepsy – This chapter provides an overview of the epidemiology of epilepsy, focusing on its incidence, prevalence, premature mortality, cost, comorbidities and prognosis. Where feasible, the data are presented by age, sex, seizure type and epilepsy type.

Chapter 2: Leadership and governance for epilepsy – In this chapter, existing health policies, plans and legislation for people with epilepsy are discussed. Emphasis is placed on the importance of collaboration between WHO, multisectoral stakeholders in government, academia, and professional and advocacy organizations such as the ILAE and IBE.

Chapter 3: Comprehensive health care response to epilepsy – This chapter addresses the health care needs of people with epilepsy, including their access to care, quality of care, financial protection and information for surveillance and evaluation of epilepsy care. Previous global surveys are summarized and data from a new survey of 11 economically and geographically diverse countries are presented to illustrate how epilepsy care is being delivered.

Chapter 4: Access to antiseizure medicines – In this chapter, factors, including barriers and facilitators influencing access to antiseizure medicines, are explored such as cultural acceptability, affordability, availability and health policies to name a few.

Chapter 5: The social response: misconceptions and stigma in epilepsy – In this chapter, the dimensions of stigma are defined with their correlates. Concrete examples of stigma, its associated factors and its impact on the lives of those living with epilepsy are presented, along with suggestions of how to reduce it.

Chapter 6: Prevention of epilepsy – This chapter provides a synopsis of the major preventable causes of epilepsy, including pre- or perinatal brain insults, CNS infections, TBI and stroke, along with the effectiveness of prevention strategies to address them.

Chapter 7: Research on epilepsy – The current state of epilepsy research, barriers and facilitators to epilepsy research and research priorities for epilepsy around the world are described in this chapter. The importance of capacity building, standardization of research process, prioritization of epilepsy research, enhancement of research translation and stakeholder collaboration are emphasized.

Chapter 8: Way forward – Summarizing the chapters of this report, this section offers an overview of the issues – that epilepsy carries a great burden and requires action across stakeholder groups with interventions at individual, health system and societal levels.

In summary, this evidence- and experience-based report provides a strong foundation confirming that epilepsy is a serious public health issue and provides suggestions on how to move from information to a call for action. Examples of barriers to epilepsy care, well-being and research are provided along with successful initiatives that have already been implemented in various regions of the world. With the growing number of individuals affected by epilepsy globally, particularly as the population ages, there is an urgent need to implement policies, legislation and interventions to address this very disabling condition that can affect anyone around the globe.

CHAPTER 1

Global burden of epilepsy

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Global burden of epilepsy

Introduction

Epilepsy is a chronic noncommunicable disease (NCD), affecting all ages and sex, with a worldwide distribution. Epilepsy affects an estimated 50 million people *(1, 23)*, making it one of the most common neurological diseases globally. The prevalence of epilepsy may differ significantly if considering active prevalence or lifetime prevalence which includes cases in remission (for definitions, see opposite). Epilepsy is treatable, with approximately 70% of people responding to antiseizure medicines *(9, 24)*.

Nearly 80% of those with epilepsy reside in low- and middle-income countries (LMIC), where rates of epilepsy prevalence and incidence are higher than in high-income countries (HIC) *(10)*. The differences in rates of epilepsy are likely due to the causes of disease in these settings, including endemic infections (e.g. malaria or neurocysticercosis), higher incidence of injuries (e.g. related to motor vehicle accidents and birth), as well as lack of access to health care.

Epilepsy is often associated with physical and psychological comorbidities, affecting the ability to work and carrying social consequences (see Chapter 5). The risk of dying early is also higher for those living with epilepsy. Among deaths directly due to epilepsy or seizures, important immediate causes include SUDEP, status epilepticus, unintentional injuries and suicide *(25)* (for definitions of SUDEP and status epilepticus, see Introduction). Epilepsy in LMIC carries a significantly higher mortality, as in HIC. In LMIC the excess mortality is associated with lack of access to health facilities and preventable causes *(26)*.

DEFINITIONS AND CLASSIFICATIONS

Risk factors: Any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury (https://www.who.int/topics/risk_factors/en/).

Active epilepsy: Defined by regular treatment with antiseizure medicines or when the most recent seizure has occurred within the last 5 years *(27)*.

Incidence of epilepsy: The number of new cases of epilepsy over a specified period of time divided by the number of the population at risk.

Epilepsy, in remission: When there is resolution of an age-dependent syndrome or no seizures for the last 10 years and no antiseizure medicine for the last 5 years *(13)*.

Lifetime prevalence: The risk of having epilepsy at some point during the lifetime; it is used to estimate the cumulative incidence of epilepsy.

Point prevalence: The number of cases of active epilepsy cases, divided by the target population on that day (active cases per 1000 persons).

Standardized mortality ratio (SMR): The ratio of the observed deaths to the expected deaths in the target population.

Box 1.1 Factors that affect reported rates of incidence, prevalence and mortality of epilepsy

Consequence of the condition: Premature mortality, seizure remission, etiology of disease (due to brain infection, head injury), associated accidental deaths.

Individual and community-based differences: Age, ethnicity, socioeconomic and sociocultural factors, lack of adherence to medicine, stigma, local definitions of epilepsy, varying death rates (motor vehicle accidents, fractures).

Health care system: The treatment gap, limited availability of diagnostic tools and access to antiseizure medicines.

Survey methodology: Challenges with ascertainment due to diagnostic misclassification (acute symptomatic or isolated seizures), case source (health care data, recall bias), and study design (prospective vs retrospective)

Source: Beghi & Hesdorffer, 2014 *(28)*.

Epidemiological estimates of epilepsy are fraught with challenges. Given the differences in reported incidence, prevalence and mortality rates these data should be applied to individual countries with caution. Factors that affect reported rates of epilepsy include consequences of the condition itself, individual and community-based differences, health care system related challenges and survey methodologies. For examples of these factors, see Box 1.1. This chapter aims to present an overview of the epidemiology of epilepsy, spanning from incidence, prevalence and premature mortality, to etiology, comorbidities and outcomes.

Global incidence and prevalence of seizures and epilepsy

Incidence of acute symptomatic seizures

Having seizures does not constitute the diagnosis of epilepsy; epilepsy is a tendency for recurrent seizure activity. The median incidence of acute symptomatic seizures is 29–39 per 100 000 per year *(29)*. Acute symptomatic seizures predominate in the youngest age class (under 1 year of age) and in the elderly. Traumatic brain injury, cerebrovascular disease, medicine withdrawal, infection and metabolic insults are the commonest causes.

Incidence of epilepsy

In a systematic review and meta-analysis of incidence studies, the pooled incidence rate of epilepsy was 61.4 per 100 000 person-years (95% CI: 50.7–74.4) *(1)*. There is a higher incidence of epilepsy in LMIC compared with HIC, 139.0 (95% CI: 69.4–278.2) and 48.9 (95% CI: 39.0–61.1), respectively *(1)*. This can be explained by a greater exposure to perinatal risk factors, higher rates of infections and TBI and the different structure of populations (demographic distribution) at risk in LMIC (see Annex 2, Tables A2.1 and A2.2). The incidence of epilepsy is also higher in the lower socioeconomic classes in HIC, and, within the same population, people of differing ethnic origin *(28)*.

Prevalence of epilepsy

The overall lifetime prevalence of epilepsy is 7.60 per 1000 population (95% CI: 6.17–9.38) and is higher in LMIC (8.75 per 1000; 95% CI: 7.23–10.59) than in HIC (5.18 per 1000; 95% CI: 3.75–7.15) *(1)*. The point prevalence of active epilepsy is 6.38 per 1000 persons (95% CI: 5.57–7.30); in LMIC it is 6.68 (95% CI 5.45-8.10) and in HIC is 5.49 (95% CI: 4.16-7.26) *(1)*. Details on the prevalence of active epilepsy for HIC are given in Annex 2 (Table A2.3) and for LMIC in Annex 2 (Table A2.4). Differences can be explained by the prevalence of selected risk factors (mostly infection and trauma), structure of the population at risk, and the treatment gap (see Chapter 4). In addition, there are methodological issues, such as more stringent case verification, and the exclusion of isolated and acute symptomatic seizures, resulting in under reporting.

Incidence and prevalence of epilepsy by sex and age

In a number of studies, the incidence and prevalence of epilepsy is slightly higher in men than in women,

though not statistically significant *(1)*. The slight difference may be explained by the different prevalence of the most common risk factors, and the concealment of the condition in women for sociocultural reasons in certain regions *(30)*.

The incidence of epilepsy is generally higher in the youngest and oldest age groups *(1)*, with estimates in the United States of America of 86 per 100 000 per year in the first year of age, a trend to decrease to about 23–31 per 100 000 in those aged 30 to 59 years, and an increase thereafter, up to 180 per 100 000 in the over 85 age group *(31)*.

In LMIC, epilepsy peaks in children; this may be a result of under-ascertainment of the condition in older individuals as well as the demographic structure of the country. Age-specific incidence rates of epilepsy have decreased with time in the youngest age groups, probably due to improvements in perinatal care and better control of infectious diseases. In contrast, the incidence has increased in the elderly, likely due to increased life expectancy (with parallel increase of age-related epileptogenic conditions, such as stroke, tumours and neurodegenerative disorders), and increased ascertainment of the disease in this age group.

The incidence of epilepsy is highest in the first year of life and declines to adult levels by the end of 10 years of age *(32)*. Lifetime and active prevalence are slightly higher in LMIC than in HIC. Among particular populations, prevalence estimates also vary and tend to be higher in individuals of certain ethnicities (e.g. indigenous populations), drawing attention to current limited data and the need for additional study of at-risk groups.

Incidence and prevalence by seizure type

Focal seizures are the predominant seizure type *(33)*. The most common type of focal seizure is a focal impaired awareness seizure (accounting for approximately 36% of all people with seizures) *(31)*. In most LMIC, however, the predominant seizure type reported are generalized tonic-clonic seizures. This could be a reflection of under-ascertainment of the other seizure types, largely likely due to a lack of recognition and diagnostic tools.

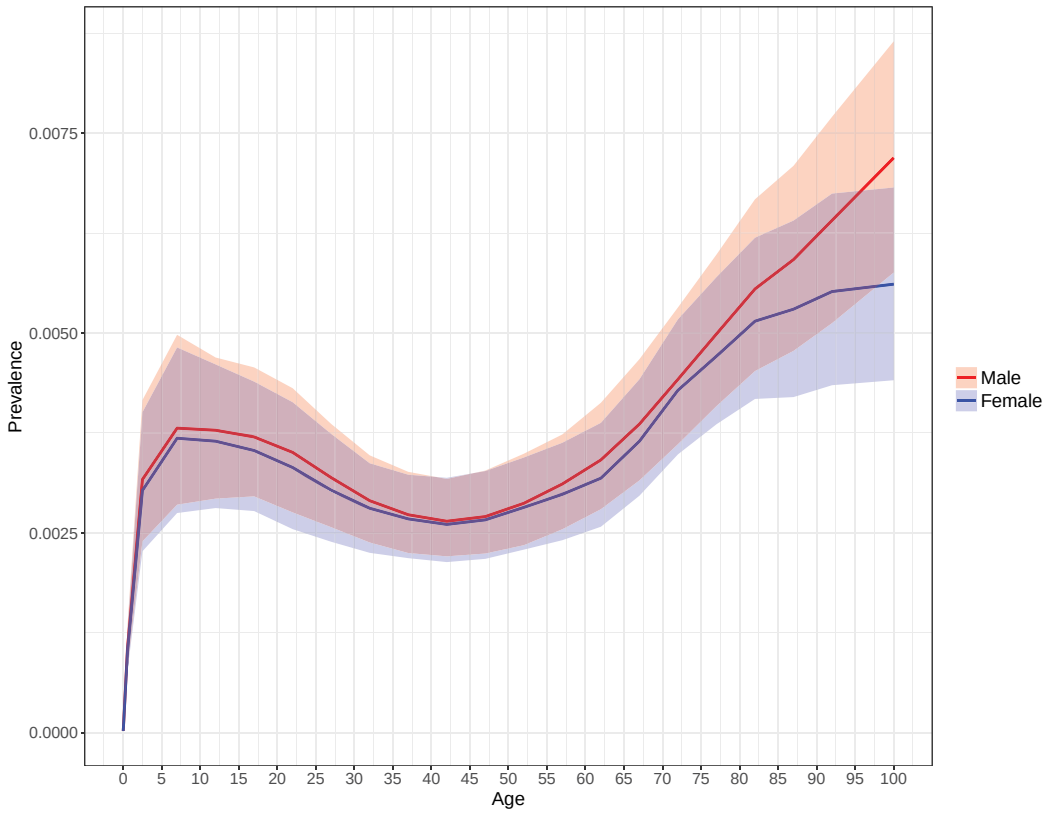
Incidence and prevalence by epilepsy type

Evidence-examining incidence and prevalence of epilepsy types is limited, but in a population-based study in Rochester, United States of America, focal epilepsies of unknown etiology were the most common group of epilepsies in people newly diagnosed with epilepsy (17.5 cases per 100 000 per year), followed by symptomatic partial epilepsies (focal epilepsies of structural or metabolic etiology) (17.2), unknown epilepsies (epilepsies of unknown etiology) (9.7), symptomatic/cryptogenic epilepsies (epilepsies of structural or metabolic etiology/ unknown etiology) (4.0), idiopathic generalized epilepsies (3.7), and idiopathic partial epilepsies (i.e. generalized and focal epilepsies of presumed genetic origin) (0.2) *(34)*.

Different figures were reported in Iceland *(35)* where higher percentages were found for idiopathic partial epilepsies (focal epilepsies of presumed genetic origin) (5.4% vs 1.3% in Rochester) and idiopathic generalized epilepsies (generalized epilepsies of presumed genetic origin) (10.2% vs 5.7%) and lower percentages were found for symptomatic partial epilepsies (epilepsies of structural or metabolic etiology) (25.2% vs 33.8%), cryptogenic partial epilepsies (focal epilepsies of unknown etiology) (26.5% vs 34.4%), and generalized symptomatic epilepsies (generalized epilepsies of structural or metabolic etiologies) (0.3% vs 3.8%). The differences can be explained by difficulties with use of the syndrome classification in studies done in primary care facilities.

In a population-based study in children in the Rochester, United States of America, population, age at onset was significantly correlated with etiology. Approximately half of children had an unknown etiology for their epilepsy. Of the remainder, 28% were structural/metabolic, which predominated in children with seizure onset before 12 months of age; and 22% were genetic, which was more

Fig. 1.1 Global prevalence of idiopathic epilepsy by age and sex, 2016



Note: Shaded areas show 95% uncertainty intervals.
Source: GBD 2016 Epilepsy Collaborators, 2019 *(2)*.

likely with older age at onset *(33)*. A specific epilepsy syndrome could be detected in 28% of cases at initial diagnosis. Although both of these studies were carried out before the modern era of neuroimaging, the proportion of epilepsies in which a documented etiology could be detected roughly overlapped these figures.

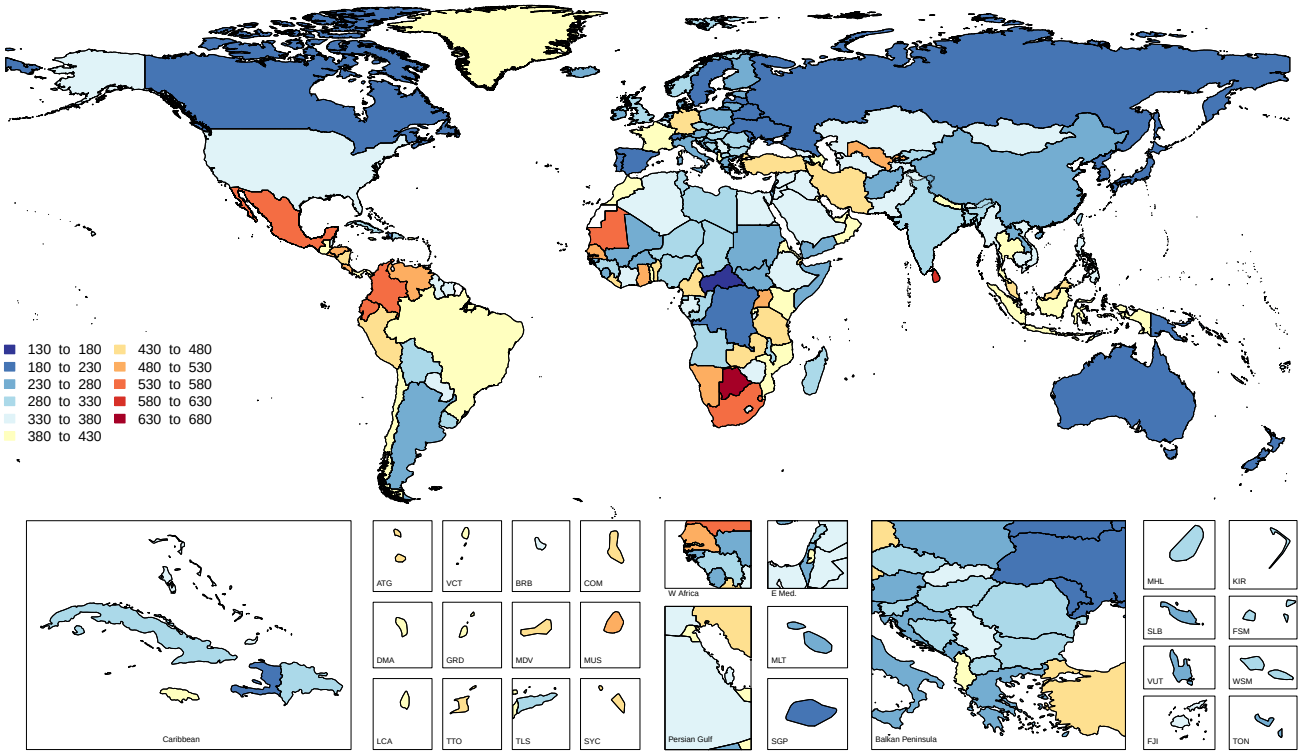
The 2016 GBD analysis estimated there were nearly 50 million individuals with active epilepsy of idiopathic or secondary nature globally; of these individuals, 24 million had active idiopathic epilepsy and prevalence was similar in men and women (see Fig. 1.1) *(2)*.

Burden of epilepsy

Epilepsy is one of the most common neurological diseases and affects people of all ages, races, social classes and geographical locations. In 2016, epilepsy accounted for more than 13 million DALYs, and was responsible for 0.5% of the total disease burden *(2)*. In children and young adults, epilepsy caused the most burden compared with any other neurological condition as estimated by the GBD study *(23)*. Ranking of age-standardized DALY rates (the sum of years of survival with disability) for all neurological disorders by GBD region in 2016 ranked epilepsy as second to eighth depending on the geographical region *(2)*. The highest prevalence of idiopathic epilepsy (due to a genetic cause or when diagnostic assessment did not reveal a causative factor) was found in eastern, western, and southern sub-Saharan Africa, central Asia, central and Andean Latin America, and southeast Asia (see Fig. 1.2).

The suffering and disability caused by epilepsy place a huge burden not only on individuals with epilepsy, but also on their families and indirectly on the community *(36)*. Its impact may be due to the physical and psychological consequences of seizures; the social exclusion faced by individuals and their families; and the stigma, as children may be barred from school, and adults may be banned from marriage, driving and employment (see Chapters 2 and 5).

Fig. 1.2 Age-standardized prevalence per 100 000 population of idiopathic epilepsy for both sexes, 2016



Source: GBD 2016 Epilepsy Collaborators, 2019 *(2)*.

Mortality and morbidity of epilepsy

People with epilepsy have a higher risk of death from various causes compared with the general population, up to three times higher *(37)*. Among deaths attributable to epilepsy or seizures, important immediate causes include SUDEP, status epilepticus, unintentional injuries and suicide *(25)*.

SUDEP incidence rate among people with epilepsy is 1.2 per 1000 person-years (95% CI: 0.9–1.5), ranging from 1.1 (95% CI: 0.5–2.3) in those under age 16 to 1.3 (95% CI: 0.9–1.8) in those more than 50 years of age *(38)*. The major risk factors for SUDEP are the presence and frequency of generalized tonic-clonic seizures (generalized more than focal), nocturnal seizures and lack of seizure freedom. Freedom from seizures, particularly freedom from generalized tonic-clonic seizures, is strongly associated with decreased SUDEP risk; and nocturnal supervision is protective *(39)*.

Epilepsy in LMIC carries a significantly greater mortality than in HIC *(26)*. In LMICs the excess mortality is more likely to be associated with causes attributable to lack of access to health facilities such as status epilepticus, and preventable causes such as drowning, head injuries, and burns.

In population-based studies in HIC, SMR calculations (i.e. the ratio between deaths in people with epilepsy and deaths expected in the general population) are 1.6 to 3.0 (Annex 2, Table A2.5) *(25)*. In LMIC (Annex 2, Table A2.6), the annual mortality rate in people with epilepsy is higher than in HIC, 19.8 (95% CI: 9.7–45.1) *(26)*. SMRs are slightly higher in men than in women and in children and adolescents, in people with epilepsies due to documented etiology, and those reporting less adherence to treatment.

As with prevalence and incidence, the epidemiological approach to epilepsy mortality depends on the quality of case ascertainment, the accuracy of the information on causes of death and the survey methods *(27)*. Significant differences in mortality rates are expected when comparing incidence-based

and prevalence-based studies, children and adults, and people with acute symptomatic seizures and with unprovoked seizures *(25, 40)*.

Economic burden of epilepsy

Epilepsy imposes direct costs on individuals and society due to the expense of health care and social services used for assessment, treatment and rehabilitation. It also creates indirect costs due to disabling side-effects and premature mortality that prevent a person from reaching their full potential in school, employment or household activities. Direct costs include the costs of health care (medicines, diagnostic investigations, surgery, hospitalization) and non-medical services such as social support, health education and transportation. Indirect costs are the monetary value of lost output due to an individual's reduced productivity and that of care providers *(8)*, as well as a result of epilepsy-related morbidity or premature mortality. Costs vary according to the severity of the condition, response to treatment, length of time since diagnosis and associated comorbidities.

Although the high-cost burden of epilepsy is well recognized, it has been poorly quantified around the globe, particularly in LMIC. Three recent reviews of studies estimating the cost of epilepsy (summarized in Table 1.1) report enormous variation in annual epilepsy costs per capita that are difficult to compare and explain. There is an urgent need for studies that evaluate the direct and indirect costs in a standardized fashion at country, region and global levels.

Common comorbidities with epilepsy

Roughly 50% of adults with active epilepsy have one or more coexisting physical or psychiatric conditions *(4, 5)*. These comorbidities are associated with poor health outcomes, such as increased health care needs, decreased quality of life, poorer response to treatment and higher mortality *(6)*. Epilepsy is comorbid with several NCDs, including stroke and TBI, which increase the burden of disease (see Chapter 6).

Psychiatric comorbidities

Psychiatric comorbidities are the most prevalent comorbidities with a reported prevalence of 29–40%, which is 7- to 10-fold higher than that of mental health conditions in the general population *(44)*. The most prevalent psychiatric comorbidities were depression (23.1%) and anxiety (20.2%) *(45, 46)*, as compared with 4.4% and 3.6% in the general population globally *(47)*. Alcohol abuse (8.7%), drug abuse (7.8%) and interictal psychosis (5.2%) are less prevalent psychiatric comorbidities in epilepsy *(48–50)*. Attempted and completed suicides are estimated to occur in 5–14.3% of people with

Table 1.1 Cost of epilepsy: reviews

Sources	Study period	Design/countries	Direct cost per person per year	Indirect cost per person
Kotsopoulos et al, 2001 *(41)*.	1996–2000	9 prevalence-based cost studies from 6 countries	US$ 680–5272 (1996)	NA
Strzelczyk et al, 2008 *(42)*.	Prior to 2007	22 prevalence-based cost studies from 14 countries	Ranged from US$ 40–4748 (2006)	Ranged from 12% to 85% of total costs
Allers et al, 2015 *(43)*.	Prior to July 2014	22 incidence-based direct cost studies from 16 different countries; 10 incidence-based indirect cost studies from 9 countries	Ranged from US$ 1736–5848 (2014)	Ranged from US$ 2037– 8587 (2014)

epilepsy *(51)* and the suicide-specific SMR among those with epilepsy is estimated to be 3.3 (95% CI: 2.8–3.7) *(52)*. Epilepsy is associated with an increased onset of psychiatric conditions (depression, suicidal behaviour, psychosis) before and after epilepsy diagnosis *(53)*. This points to potential underpinning mechanisms that both lower seizure threshold and increase risk for psychiatric conditions.

Neurodegenerative comorbidities

Epilepsy can be a part of progressive neurodegenerative diseases. These account for 6% of new epilepsy cases with the proportion increasing to 10% in people older than 65 years of age *(54)*. Epilepsy in Alzheimer disease usually presents at more advanced or severe stages of the disease, but can also occur early, particularly in early onset familial Alzheimer disease.

Other medical comorbidities in adults

Migraine occurs in approximately 19% of people with epilepsy *(55)*. Intellectual disability is relatively common in people with epilepsy, with an overall prevalence of around 26% *(56)*. Epilepsy in adults with intellectual disability has a worse prognosis than epilepsy in the general population, with lower rates of seizure freedom and high rates of mortality, including SUDEP *(57)*. Obstructive sleep apnea is present in up to 33% of people with drug-resistant focal epilepsy and can be associated with seizure occurrence or seizure worsening in older adults *(4)*.

Comorbidities in children and adolescents

Due to the significance of birth injuries as a cause of childhood epilepsy, as high as 70% of children with epilepsy have a comorbidity (depending on the reference population) *(58, 59)*. Comorbidities in children with epilepsy can be categorized as neurological/cognitive, psychological/behavioural and physical *(60)*.

Neurological comorbidities in children with epilepsy are variable, including intellectual disability, language impairment, migraine and sleep problems. Intellectual disability (full-scale intelligence quotient < 70 and deficits in adaptive behaviour) is the most common comorbidity in children with epilepsy (30–40%) *(60)*. Cognitive deficits associated with childhood-onset epilepsy may remain throughout adulthood. Children with epilepsy may also have significantly lower language scores in word knowledge, category fluency and response to commands of increasing length and complexity, especially in those with an earlier age of onset. The occurrence of speech disorders may be as high as 27.5% in children with epilepsy. There is a higher prevalence of migraine in children with epilepsy (14.7%) than in the general population (2.7–11%). Children with epilepsy have significantly more sleep problems. These include parasomnias, parent/child interaction during the night, sleep fragmentation, daytime drowsiness and bedtime difficulties *(60)*.

The most common psychiatric/behavioural disorders among children who have epilepsy include autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), depressive and anxiety disorders. Although infrequent, psychosis, oppositional defiant and tic disorders may occur in children who have epilepsy. Children with ASD have an increased prevalence of seizures, which is estimated to be 20–25% of the whole spectrum. The prevalence of ADHD is estimated to be between 12% and 39% in children with epilepsy and is much higher than the 3–7% in the general population of children. Mood disorders (depression and anxiety) are reported in 12–26% of children with epilepsy. Emotional disorders can be found in about 16% of children with epilepsy compared with 4.2% in the general population *(60)*.

Children with epilepsy may experience physical comorbid conditions resulting from the condition or adverse effects of treatment (see Chapter 4). Most well-known adverse effects of antiseizure medicines are notable and probably reversible after ceasing medication use. These include allergic reaction, thrombocytopenia, electrolyte imbalance, renal or

hepatic impairment, and neurobehavioural side-effects, such as concentration, mood disturbance and somnolence (drowsiness). Some physical comorbidities related to antiseizure medicines, including disturbances of hormonal balance, may potentially have a long-term impact on the physical health and quality of life of children with epilepsy *(60)*. Abnormal bone health was found in 58.3% of people with epilepsy aged 3 to 25 years old *(61)*. Female teens with epilepsy usually have a high prevalence of polycystic ovary syndrome, independent of the types of antiseizure medicines or the characteristics of the epilepsy *(62)*.

Epilepsy prognosis

With appropriate recognition and treatment, the overall prognosis of epilepsy is favourable in the majority of individuals when measured by seizure freedom. Reports from LMIC (where people with epilepsy are largely untreated) give prevalence and remission rates that overlap those of HIC *(63)*. Studies completed in the last 30 years in people with newly diagnosed epilepsy and long-term population-based studies have consistently shown that up to 70% of cases tend to achieve prolonged seizure remission (Annex 2, Table A2.7). However, one-third had persistent seizures after remission or without any remission *(64)*. These patterns have been partly confirmed by other studies *(9, 65–67)*. Etiology of epilepsy is by far the strongest prognostic predictor for seizure recurrence.

Prognosis after first-time seizure

In population-based studies, the risk of relapse of a first unprovoked seizure without treatment is reported as 36–37% at 1 year and 43–45% at 2 years. In a systematic review, the average recurrence risk at 2 years was 51% (95% CI: 49–53%) *(68)*. After a first unprovoked seizure, the probability of a relapse decreases with time. About 50% of recurrences occur within 6 months of the initial seizure and 76–96% within 2 years. A documented etiology of the seizure and an abnormal (epileptiform and/or slow) electroencephalography (EEG) pattern are the two most consistent predictors of recurrence. Interictal (between event) epileptiform EEG abnormalities tend to be associated with a higher risk of seizure recurrence than non-epileptiform abnormalities. Seizures during sleep and focal seizures are associated with a higher risk of recurrence. A positive correlation between seizure relapse and family history of seizures is also confirmed in people with first seizures of (presumed) genetic or unknown etiology. History of prior acute symptomatic seizures is occasionally found to increase the risk of relapse, while evidence is inconclusive or lacking for sex, age and status epilepticus as risk factors.

Prognosis of untreated epilepsy

The prognosis of untreated epilepsy has been observed by implication in low-income countries where the treatment gap is more than 75% *(10)*. Evidence arising mostly from low-income countries where antiseizure medicine is not readily available, indicates that spontaneous remission may occur in at least 30% of cases *(69)*. In a population-based study conducted in Ecuador, the cumulative annual incidence rate was 190 per 100 000 and the prevalence rate of active epilepsy was 7 per 1000, where a remission rate of 46% was shown *(10, 70)*. A survey was carried out in rural regions of China where 41% of 130 people with inactive epilepsy identified, which had never been treated, experienced spontaneous remission *(71)*. A study in the Plurinational State of Bolivia of 103 people with epilepsy found that at least 30% entered into remission during the follow-up period *(72, 73)*. The crude mortality rate in this population was 10 per 1000 person-years at risk; a three-fold increase in mortality was found in people with remote symptomatic epilepsy.

Conclusion and way forward

Epilepsy is one of the most common neurological diseases globally, and disproportionately affects those in LMIC. Insufficient evidence is available on the incidence, prevalence and mortality of epilepsy, particularly in LMIC. Despite the variety of methods and definitions, data available consistently show that the prevalence reported in LMIC is underestimated and does not reflect reality *(74)*. Additional resources should be allocated to appropriately measure and monitor rates of epilepsy globally.

CHAPTER 1

Global burden of epilepsy

KEY MESSAGES

- **Epilepsy is treatable and affects around 50 million people, including more individuals in low- and middle-income countries compared with high-income countries.**
- **Improved and harmonized metrics of collecting and reporting incidence and prevalence of epilepsy, particularly in different populations (varying by income, age, sex and ethnicity/ race), as well as associated premature mortality and sudden unexpected death in epilepsy, are needed to better understand the burden of disease and carry out service planning.**
- **Premature mortality associated with epilepsy is high.**
- **Comorbidities of epilepsy need to be considered, identified and brought into clinical management programmes.**

CHAPTER 2

Leadership and governance for epilepsy

Leadership and governance for epilepsy

Introduction

Given the burden of epilepsy on people with the condition and their families, the challenges facing governments to provide inclusive health and social care services are substantial. Inadequate policies and legislation, and insufficient resources and information systems exist in many countries (see Chapter 5).

People with epilepsy often encounter barriers in achieving their full potential due to unmet needs in the areas of civil rights, education, employment, residential and community services, and access to appropriate and affordable health care. Legislation can be an important means to addressing these challenges. In many countries, however, laws impacting the lives of people with epilepsy are outdated and fail to protect and promote their human rights.

This chapter starts with a brief history of leadership and governance for epilepsy. It analyses the current state of health policies, plans and legislation and offers guidance on the mechanisms that are needed to reduce the burden of epilepsy worldwide. Commitment at all levels of government, and multisectoral collaboration between WHO, government and scientific agencies, professional and advocacy organizations such as the ILAE, IBE and other NGOs are needed. It also requires adequate funds are raised for epilepsy, to ensure people can access good quality services and are protected from financial hardship. Generation and strategic use of data on epilepsy are described in the chapter as an integral part of the leadership and governance function. The chapter provides examples of successful leadership and governance and makes a call for the necessary resources and infrastructure needed to reduce the burden.

History of international leadership combating epilepsy

Leadership and governance are critical levers for health system strengthening and driving global public health agendas. This involves ensuring strategic policy frameworks exist with mechanisms of effective oversight, coalition building and multistakeholder engagement, as well as attention to health system design and accountability *(75)*. The partnership established between WHO, ILAE and IBE has been a leading force in addressing the burden of epilepsy. Fig. 2.1 provides an overview of key milestones achieved in the past two decades.

Global campaigns for epilepsy

Since 1997, WHO, ILAE and IBE have led the Global Campaign Against Epilepsy (GCAE) *(76)*. The three-partner strategy of the GCAE included two parallel tracks: raising public awareness and understanding of epilepsy; and supporting ministries of health to identify needs and promote education, training, treatment, services, research

Fig. 2.1 A history of initiatives in reducing the global burden of epilepsy

and prevention. Following this strategy, the GCAE provided a framework for action at a global, regional and national level to bring epilepsy "out of the shadows."

The GCAE made substantial progress in bringing this hidden condition to the attention of policy-makers. The GCAE goals were to ensure that epilepsy care was incorporated into national policies and plans, and to facilitate the work of stakeholder organizations (IBE) and professionals (ILAE) who are dedicated to promoting the well-being of people with epilepsy. The campaign demonstrated the power of partnership between WHO and civil society organizations in leading the advancement of a strategic vision.

A key publication that arose from the GCAE was the *Basic principles and guidance instrument for drafting, adopting and implementing epilepsy legislation (77)*. It identified basic human rights principles for people with epilepsy. These include the right to the highest attainable standard of epilepsy care; access to quality health care and information; protection of the doctor-patient privilege and confidentiality of medical records; to live independently in the community; protection against discrimination because of epilepsy; education, employment, rehabilitation, and a driver's licence or the use of public transportation; and social protections, including an adequate standard of living. The report included a blueprint of action from which advocates could draw direction and inspiration for their ongoing efforts to promote optimal social and rights laws in their own countries.

As part of the activities of the GCAE, a community-based project supported by WHO and organized by

Box 2.1 Demonstrating high-quality and cost-effective epilepsy treatment in rural China

As part of the GCAE, a large community-based project was implemented in five provinces of rural China. The project aimed to reduce the epilepsy treatment gap by training and educating health care providers; raising public awareness to reduce stigma; identifying prevention approaches; and integrating epilepsy care into the local health systems.

Before the project began, there were an estimated 9 million people with epilepsy in the country, and a treatment gap of 63% *(78)*. Door-to-door epidemiological surveys found a lifetime prevalence of 7.0/1000 population and a prevalence of active epilepsy at 4.6/1000 *(79)*. During the project, primary health care physicians were trained to diagnose and treat epilepsy. They treated over 2400 people with epilepsy. Two years later, 70% of people had improved outcomes (25% of whom were seizure free) *(71)*.

Community education programmes were found to be effective in raising awareness that epilepsy is a treatable condition and were attributed to increased help-seeking in health facilities. Epidemiological surveys at the end of the project estimated the treatment gap had reduced to 50% (down by 13% from the start).

Cost-outcome analyses found that by diagnosing epilepsy and treating seizures with phenobarbital significantly reduced costs to the health system (from US$ 216.22 to US$ 13.24 and from US$ 30.83 to US$ 6.64 per person per year in rural Shanghai and Ningxia, respectively).

Results from the project were used to advocate for a large-scale implementation, which was supported by the National Health Commission and Beijing Neurosurgical Institute. The China National Epilepsy Project has been scaled-up to 240 counties across 19 provinces, serving 120 million people in rural areas. Over 230 000 people with epilepsy have been screened by rural health workers. More than 110 000 people with epilepsy were managed by trained physicians and treated using antiseizure medicines. About two-thirds of those treated experienced a reduction in seizures and one-third were seizure free. The China National Epilepsy Project is now considered an international standard for integrating epilepsy care in rural areas and primary health care services.

the Beijing Neurosurgical Institute was conducted in China between 2001 and 2004 *(78)*. The project focused on training health care providers to diagnose and manage epilepsy in nonspecialized health settings, especially in rural areas. It was successful in reducing the treatment gap by about 13% and was shown to be cost-effective (Box 2.1).

Regional declarations paved the way for country action

As part of GCAE awareness-raising, regional efforts brought together stakeholders in all six WHO regions (African Region, Region of the Americas, South-East Asia Region, European Region, Eastern Mediterranean Region and Western Pacific Region). Regional declarations on epilepsy were adopted to encourage country cooperation towards a common goal of reducing the epilepsy treatment gap and were followed by action.

In Chile, a plan of action and national programme were established to minimize the impact of epilepsy for the entire family (Box 2.2). The plan of action was developed in consultation with a group of experts and with input from all ministries of health in the region. The achievements in Chile show that regional-level collaboration aimed at influencing policy-makers is a powerful tool to improve services for people with epilepsy.

Following the regional declaration for Africa, projects were initiated in 19 out of the 46 countries in the region *(80)*. A project in Senegal led to a comprehensive public health model to tackle the burden of epilepsy. This model has since been adapted and enhanced in four other countries as part of the WHO Programme on reducing the epilepsy treatment gap (Box. 2.3).

Box 2.2 Chilean National Programme

Description of the programme

The Chilean Ministry of Health is committed to diminishing the impact of epilepsy for the entire family.

The government developed a National Epilepsy Programme to improve access to treatment and care and to improve quality of life for people with epilepsy in Chile.

It recognizes the biological, psychological and social aspects of the condition. It works with multisectoral stakeholders to implement the regional Pan American Health Organization (PAHO) declaration at country level.

Key achievements

- Developed a **national survey to gather data** on urban, rural and regional prevalence and incidence of epilepsy.
- **Universal access to medicines** with seven antiseizure medicines now available.
- Established an **expert commission** consisting of stakeholders from the Ministry of Health, leaders in neurology, ILAE and IBE.
- Launched a **national programme with a plan of action** to deliver multidisciplinary care at the primary, secondary and tertiary care levels which includes funding for equipment, training and human resources, as well as inclusion of epilepsy in national insurance plans.
- Established **referral pathways** for task shifting and better management in the community. **Clinical practice guidelines** specified roles and procedures across levels of care.
- Outlined a **strategy to provide comprehensive psychosocial care** to improve quality of life and prevention of associated comorbidities.
- Developed an **outreach strategy** to increase community awareness and social inclusion for people with epilepsy.

Box 2.3 WHO Programme on reducing the epilepsy treatment gap

For more than 20 years, WHO has led the global movement against epilepsy. As part of this commitment, and to build on the activities of the GCAE, WHO launched the Programme on reducing the epilepsy treatment gap in 2012. The aim of the programme is to expand the skills of nonspecialist health care providers to diagnose, treat and follow up with people with epilepsy. Pilot projects have been implemented in Ghana, Mozambique, Myanmar and Viet Nam.

Project teams in these four countries work in collaboration with WHO and ministries of health to bring early detection and treatment closer to where people with epilepsy live. Across these four countries the programme has reached 6.5 million people who now have access to health facilities where epilepsy care is available.

GHANA

Coverage increased from **15% to 38%** in 4 years.

Covered five regions and built capacity across levels of the mental health workforce:

- **29 specialists** supervisors;
- **690 nonspecialist providers** to diagnose and treat;
- **770 community workers, traditional and faith healers and midwives,** raised awareness of epilepsy and identified cases.

MOZAMBIQUE

Reached five provinces, 16 districts, 56 health facilities **benefiting over 2 million people.**

4863 awareness-raising sessions reached more than **96 000 people.**

Launched a **National Epilepsy Plan** to train all psychiatric technicians in the country by 2022.

Improved **monitoring and evaluation** of epilepsy indicators in the health information system.

MYANMAR

Coverage increased from 2% to 47%.

Epilepsy **was integrated into NCD prevention and management.**

The Ministry of Health and Sports launched the **Five-year Strategic Plan for Epilepsy.**

An advocacy group for people with epilepsy and families was established; awareness raising reached **286 218 people.**

Now being **scaled up to reach full coverage in five states/regions.**

VIET NAM

Treatment gap was reduced by 38%.

The project was **implemented in 82 communes** over 4 years.

2443 health staff were trained including specialists to supervise, primary care providers to diagnose and treat, and village health workers to identify cases.

The project was successful in **reducing seizures** and helping **people with epilepsy return to work.**

Note: The programme received support from Sanofi Espoir Foundation and UCB.
Sources: WHO, 2018 and 2019 *(81–83)*.

The WHO Programme on reducing the epilepsy treatment gap initiative demonstrates that there are simple, cost-effective ways to treat epilepsy in low-resource settings at the community level. Lessons learned from pilot projects are now being used to scale up epilepsy treatment and care and can be applied to other efforts to treat epilepsy worldwide.

World Health Assembly resolution on epilepsy

Global action has been further spurred by the adoption of the WHA resolution 68.20 on the burden of epilepsy and the need for coordinated action at country level to address its health, social and public knowledge implications *(84)*. Unanimously adopted in 2015, the resolution urges governments to formulate, strengthen and implement national policies and legislation to promote access to care and protects the rights of people with epilepsy. It recognizes the essential role of governments in increasing access to epilepsy care to achieve better health for all people.

The resolution calls on the 194 Member States, with coordination by WHO, to:

- strengthen effective leadership and governance and improve provision of epilepsy care;
- integrate epilepsy management into primary health care and increase access to medicines;
- support strategies for the prevention of epilepsy;
- increase public awareness of and education about epilepsy;
- strengthen health information and surveillance systems; and
- increase investment in research and research capacity.

The resolution provides a powerful tool to engage governments in taking concrete action to improve epilepsy care, promote public awareness and allocate resources to epilepsy research *(85)*. But the global treatment gap remains high, especially in low-resource settings *(10)*. Many essential antiseizure medicines are not readily available in several regions, particularly in the public sector, and the price of these medicines in low-income countries is several times higher compared with HIC *(86)*. Most governments have not set up national epilepsy programmes or allocated funds to implement policies and plans for epilepsy despite recognizing its global burden *(87)*.

Action from governments is needed to sustain the momentum from the achievements of the GCAE, regional declarations and the WHA resolution.

Policies and plans for epilepsy

Governments are urged to have health policies and national plans of action to support people with epilepsy, signifying political commitment to reduce the burden of epilepsy. These may be stand-alone policies and plans for epilepsy and/or integrated into existing policies for general health, mental health and NCDs that include consideration of the specific needs of people with epilepsy. They also need to be accompanied by protective laws in accordance with international human rights norms and standards.

There is considerable variability in the approaches that countries take to address the needs of people with epilepsy. According to the ILAE/IBE survey results (see Annex 1), only 20 countries (18% of respondents) have a stand-alone policy for epilepsy. More commonly, epilepsy is included in the general health policy, and/or within the national mental health policy. In Kenya, a national plan for epilepsy was launched in 2014 *(88, 89)*. The major features of this plan include: mobilize and train health care staff; create awareness and provide training to the community; provide health care services and data collection; obtain funding for research and data collection in private and public facilities; design national plans to combat epilepsy; and provide ongoing lobbying and advocacy to policy-makers, financers and implementers to improve the system.

It is important that governments identify how and where they will support people with epilepsy. Eswatini's NCD prevention and control policy,

written in collaboration between the WHO Regional Office for Africa and the Ministry of Health, names epilepsy as one of nine priority conditions *(90)*. In Malawi, a national strategy and action plan for NCDs was developed as a response to global goals to reduce NCD deaths by 25% in people aged 30–70 years by 2025 *(91)* and the SDG 3.4 to reduce premature mortality from NCDs by one-third by 2030 *(92)*. The NCD action plan implemented the use of "chronic care clinics" to treat priority NCDs of epilepsy, hypertension, asthma and diabetes in primary health care *(93)*. In Australia, uncontrolled epilepsy is classified as a disability. The government has harmonized disability support via a federal system known as the National Disability Insurance Agency, which includes support for people with epilepsy *(94)* and also helps to inform access to specific government services (e.g. disability support pension).

Policies to improve the quality of health services include actions that establish care pathways, develop and implement a quality care framework and performance measures, and enhance the screening and referral options and protocols for early identification of epilepsy and comorbidities *(95)*. Examples of countries implementing epilepsy care guidelines can be found in Chapter 3.

Multisectoral policies and coordinated action

A person-centred approach is needed to address the complex needs of people with epilepsy. The condition is known to have adverse effects on education, employment, marriage and other social opportunities. Poor quality of life for people with epilepsy is further worsened by associated comorbidities (e.g. depression and anxiety). Thus, there is a need for integrated and multisectoral policies with coordinated efforts across all levels of the government – local, regional and national.

Strengthening leadership to address the burden of epilepsy is a system-wide reform, requiring collaboration within and outside the health system *(96)*. In the Philippines, the local ILAE chapter has advocated for access to care and improved quality of life for people with epilepsy for the past two decades, working across the health, education and other social sectors (Box 2.4).

Box 2.4 Multisectoral collaboration for epilepsy in the Philippines

Milestones achieved by the Philippines League Against Epilepsy advocating with government policy-makers across health, education and social welfare ministries:

- Presidential proclamation 230 on 24 August 2002 declaring the first week of September every year as "National Epilepsy Week".
- A "training of trainers" programme for epilepsy managers and physicians in primary care facilities.
- Department of Education approval to promote epilepsy awareness, reduce stigma and bullying among school-aged children with the Epilepsy School Caravan.
- Epilepsy was added to the publicly funded Mental Health Act. The Philippine Mental Health Act (RA 11036) calls for the protection and the promotion of the rights of persons with psychiatric, neurological and psychosocial health needs as well as their families. This Act establishes a national mental health policy for the purpose of enhancing the delivery of integrated mental health services, promoting and protecting the rights of persons utilizing psychiatric, neurological and psychosocial health services, and appropriating funds.

Source: Paragua-Zuellig, 2017 *(97)*.

In some countries where national policies and programmes for epilepsy do not yet exist, NGOs and private sector organizations provide essential services. For example, in Pakistan, the National Epilepsy Centre is an NGO-run institution designed exclusively for epilepsy care. It provides holistic management (medical, social and psychological support) for people with epilepsy. It is a training facility for primary care physicians managed by volunteer neurologists. The centre conducts public awareness-raising activities in collaboration with a community support group and the Comprehensive Epilepsy Control Programme – an outreach project launched as part of GCAE. Such services may be able to provide integrated care for people with epilepsy in collaboration with government programmes.

Protective legislation

Legislation is a key component of good governance. It concerns the specific legal provisions to implement epilepsy policies and plans that promote human rights and social inclusion, prevent the disease and its associated comorbidities, inform the provision of high-quality services and improve access to care, and offer social protection for people living with epilepsy.

Fewer than half (42%) of the countries surveyed for this report (see Annex 1) reported the existence of epilepsy legislation. Where it does exist, legislation is often outdated, fails to adequately promote and protect their human rights and, in some cases, even violates these rights *(98)*. In some countries, laws contain restrictions that lead to the violation of human rights.

One example is the right to drive, which is an important component of a person's quality of life and shown to have large inconsistencies across the world. Historically, legislation entailed lifelong bans from driving after a seizure, and in some countries such punitive legislation still exists. Some countries can provide examples of driving legislation that is inclusive and safe for persons who have seizures under control or in full remission *(99)*. In the European Union (EU), harmonization of driving legislation is under way, but implementation of the directive has been slow. Other examples of legislative restrictions include laws against employment (e.g. limitations related to risk professions). Legislation needs to be developed to address these shortcomings. A positive improvement in the new epilepsy definition (see Introduction) is that there is now the ability to declare an epilepsy as resolved, with should help those who were banned from employment as a result of having active epilepsy.

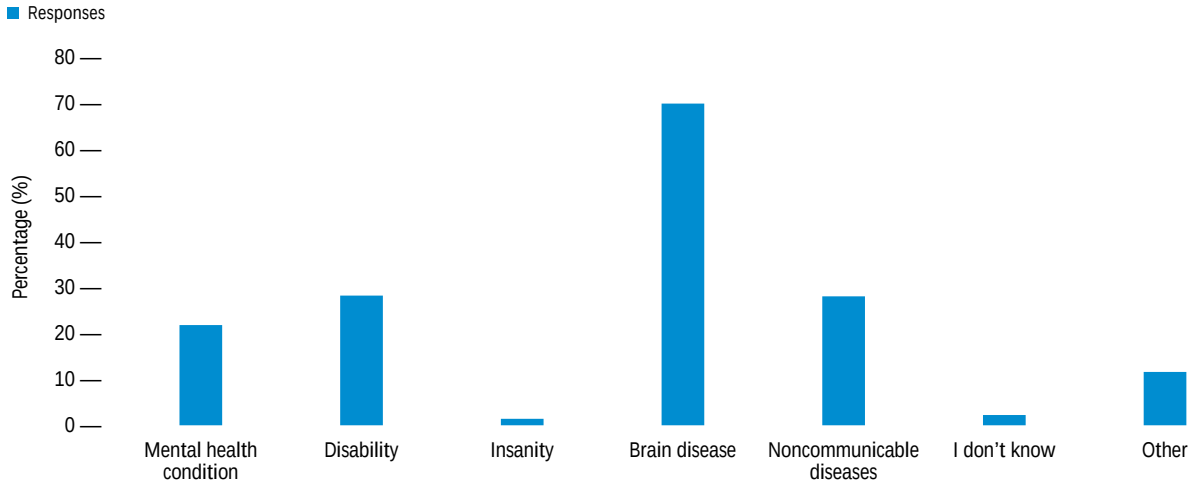
Legislation for protecting the rights of people with epilepsy may be either consolidated or dispersed *(100)*. In consolidated epilepsy legislation, all the relevant issues are incorporated in a single legislative document. The process of drafting, adopting and implementing such legislation provides a good opportunity for raising awareness with policy-makers and the public. The alternative is to insert provisions related to epilepsy into other legislation (e.g. protecting housing rights of people with epilepsy in existing legislation to provide subsidized housing by local authorities). Other legislative instruments, such as disability acts (see below, Pathways to epilepsy legislation), can provide powerful tools to support individuals against discrimination. This approach may increase beneficial provisions for people with epilepsy because they are included in legislation that benefits a wider range of people. A combined approach is also most likely to address the complexity of the needs of people with epilepsy.

Pathways to epilepsy legislation

There are many disease-specific programmes that have pathways in place where people with epilepsy could be included. For example: infectious disease portfolios, HIV/AIDS, clean and safe water programmes to reduce river borne infections, and agriculture portfolios to reduce neurocysticercosis (the result of accidental ingestion of eggs of *Taenia solium* – pork tapeworm in contaminated food). In LMIC, neurocysticercosis is the most common parasitic disease of the nervous system and is a leading cause of seizures *(101)* (see Chapter 6). By linking with other disease-specific programmes such as neurocysticercosis and agriculture and food safety legislation, epilepsy may be better treated and even prevented.

The way in which epilepsy is defined across countries in policies and legislation varies. Results from the ILAE/IBE survey indicate that 70% of countries define epilepsy as a brain disease, 28% a disability, 28% as an NCD, and 22% a mental health condition (respondents could select more than one) (Fig. 2.2). The varying definitions lead epilepsy policy to be dovetailed into agendas at different levels. The WHO *Global action plan for the prevention and control of noncommunicable diseases 2013–2020* provides a strategic framework for countries to improve prevention and management of epilepsy as an NCD.

Fig. 2.2 Integrating epilepsy into existing policies and legislation: defining epilepsy



Source: ILAE/IBE survey (Annex 1).

Frameworks for protecting human rights

The international human rights system provides an important framework for protecting the rights of all people, including those with epilepsy. The Universal Declaration of Human Rights *(102)*, the International Covenant on Economic, Social and Cultural Rights, and the International Covenant on Civil and Political Rights, form what is known as the International Bill of Human Rights *(103)*. It recognizes and protects the rights of people with disabilities even if these people are not explicitly mentioned. Many of the rights are relevant to people with epilepsy in light of the discrimination and human rights violations to which they are too often exposed (see Chapter 5).

The Convention on the Rights of Persons with Disabilities (CRPD), adopted by the United Nations in 2006 *(104)*, affirmed the rights of people with disabilities (including epilepsy) to health care, education, rehabilitation, employment and inclusion in the community. According to Article 19 of the CRPD, people have the right to live independently and to be included in the community. To do so, people with epilepsy need to be able to exercise a full range of civil, cultural, economic, political and social rights. A survey by the WHO, *Atlas: epilepsy care in the world 2005 (105)*, estimated that disability benefits for people with epilepsy were available in only 15% of low-income countries and in 82% of HIC. Legislation needs to ensure that people with epilepsy are included and have access to social service measures such as disability allowance, unemployment benefit, retirement benefits and access to health insurance.

Specific actions that countries can take to raise the issue within the political agenda include aligning epilepsy policies with international standards such as the CRPD and advocating for epilepsy to be included in disability benefits. Some countries have made progress in doing so. In Colombia, advocacy led to legislation that promotes the rights of people with epilepsy (Box 2.5).

In the United Kingdom of Great Britain and Northern Ireland, the Equality Act protects people in England, Scotland and Wales from unfair discrimination because of their disability, race, religion or belief, gender reassignment, marriage and civil partnership, pregnancy and maternity, sex, sexual orientation or age. Epilepsy is considered a protected disability under the Equality Act which means that people with the disease have the right to be treated fairly at work or when using services.

In the United States of America, legislation for people with disabilities has not always included epilepsy. The Americans with Disabilities Act (ADA) was signed in 1990 to ensure "equality of opportunity, full participation, independent living, and economic self-sufficiency" for individuals with

Box 2.5 Legislation to fight stigma of epilepsy in Colombia

Beginning in 2002, advocates for epilepsy, an impassioned senator and a group of parliamentarians drafted a law to illustrate the importance of protecting the human rights of people with epilepsy in Colombia. For this legislation to be passed in Colombia there were several steps of legalization (e.g. Ministry of Health, Parliament, the President of the Republic and the Constitutional Court). It was essential to ensure that from each of those institution's perspectives, the legal reform requested was consistent with existing legislation.

The law was passed in 2010 and since then campaigns have raised public awareness about the rights of people with epilepsy. Health care services better protect people with epilepsy to receive appropriate care and social programmes now enhance employment opportunities for people with epilepsy. Education for physicians, nurses, social workers, teachers and psychologists promotes the rights of people with epilepsy. These programmes are supported by the health system and have received funding from IBE under the "promising strategies" grants. The most important success of this legislation is that people with epilepsy in Colombia feel more respected and supported.

"If your medicine or any medical service is denied by the health office, show them the law, if you are fired from your job because of the epilepsy, show them the law, if you feel discriminated or stigmatized, show them the law."

Source: PAHO, 2013 *(106)*.

disabilities. After its enactment, several Supreme Court of the United States decisions narrowed its scope of coverage so that people with epilepsy were no longer protected against employment discrimination *(107)*. Advocates, including people with epilepsy and their families, worked to inform policy-makers of the need to expand the definition of a disability, and in 2008 the ADA was amended to ensure that people with treatable conditions like epilepsy were covered by the law. Despite the existence of these laws for 10 years, the full attainment of rights is still being implemented. For example, the right to employment for people with epilepsy, and who may have seizures on the job, is still being developed under the ADA.

Drafting appropriate legislation is vital to enhance inclusion, quality of care, and development of community-based services for people with epilepsy. Furthermore, involving people with epilepsy and their families in this process is an essential factor of success, ensuring the legislation meets the complex needs of this population.

Resource allocation

There is a critical need to increase funding around the world to support around 50 million people living with epilepsy. The heavy burden of morbidity and premature mortality translates into huge monetary costs to individuals and to society (see Chapter 1). Leaders throughout the global epilepsy community have for decades passionately advocated to secure funding for critically important epilepsy research, public health and other social programmes. Despite limited success, many countries have budgets that reflect grossly inadequate funding when compared with other health conditions with similar or in some cases, lower morbidity, premature mortality and prevalence (see Chapter 7). This is especially true in LMIC where 80% of people with epilepsy reside *(108)*.

Estimates suggest that some countries spend as little as 1% of their total national health care expenditure on epilepsy care and treatment *(43)*. The reasons for low public spending on epilepsy are many, but depend primarily on the priority given to epilepsy care by the government in health budget allocations. This requires intersectoral dialogue between ministries of health and finance, social welfare and education.

To achieve universal health coverage (UHC), epilepsy programmes will need to be publicly funded and governments in LMIC supported to develop such programmes (Box 2.6) (see Chapters 3 and 4). Existing programmes for NCDs and mental health may also need to be expanded to ensure they reach people with epilepsy.

The WHA resolution, in part, directs all Member States to make financial resources available as necessary to implement evidence-based plans and actions to improve care and reduce the burden of epilepsy. Some nations have responded to this call, developing funding mechanisms to support the needs of individuals with epilepsy. Limited governmental resources, tightening in many nations around the world, have resulted in more difficulties securing the needed funding for epilepsy research and public health programmes (see Chapters 3 and 7).

Some countries have developed innovative ways to increase funding. For example, in the Philippines, 80–90% of epilepsy services are in the private sector *(110)*. To increase access to services for those families who cannot afford private care, the Government's Philippine Charity Sweepstakes Office created the Individual Medical Assistance Program. It is a flagship programme to provide timely and responsive financial assistance to people with health-related problems, including those living with epilepsy. Such government assistance may be one way for LMIC to off-set the cost of epilepsy care.

Box 2.6 Towards universal health coverage with increased public spending for epilepsy

A reliance on public funding for health services is central to ensuring access to care whilst also protecting families from serious financial problems incurred by out-of-pocket spending. So, *how much public spending is enough*? No formula exists to estimate the level of public funding required to make progress towards UHC; although analyses suggest that even at low levels of public spending, countries can make significant steps.

Efforts have been made to estimate the level of public spending required to move towards UHC, including at least 5% of gross domestic product (GDP), and at least 15% of total government spending. What we know from the evidence is that when countries rely predominantly on private sources, many households forgo care or face serious financial problems.

Public funding for epilepsy in the health sector may be offset by reducing discretionary budget allocations resulting in little if any increase in total public funding available to extend coverage. Ensuring a stable and predictable flow of funds to epilepsy treatment and care is an important objective of revenue-raising policy, given its importance in avoiding disruptions in service delivery (e.g. stock-outs of antiseizure medicines and distribution of service providers). Evidence of improved and more efficient spending for epilepsy treatment and care is important to make the case for greater investment within the health system.

Source: Jowett et al., 2016 *(109)*.

Strengthening data and information systems to inform policy-making

The generation and strategic use of data and research on epilepsy is an integral part of the leadership and governance function. This requires considerably improving the quality of information on which epilepsy policies, strategies and plans are based; and for priority-setting informed by health-related SDGs; facilitating the adoption of a single country-led monitoring and evaluation framework; facilitating alignment of multisectoral stakeholders; and establishing mechanisms for accountability through performance reviews integrated with country planning processes. Such mechanisms need to be inclusive, independent, evidence-based, transparent, with adequate funding, and lead to action for improved outcomes.

The burden of epilepsy is determined by data collected through a variety of methods such as administrative and clinical records, population-based surveys and registries. Unfortunately, there is a lack of adequate epilepsy surveillance data and infrastructure in many countries *(111)*. Data collection systems for epilepsy exist in 40.1% of countries, according to WHO's *Atlas: epilepsy care in the world 2005 (105)* with great disparities among the regions, e.g. just 13.3% of countries in the Eastern Mediterranean Region. Many LMIC do not have any epidemiological data on epilepsy *(23)*. Limited data collection systems constitute a barrier to understanding the burden of epilepsy.

The 2016 GBD report ranked epilepsy as one of the most serious diseases of the brain, contributing to

5.0% of DALYs and 1.3% of deaths (see Chapter 1). Findings from the GBD study have important consequences for global public health assessments and health resource allocation; reinforcing the need for good quality data on epilepsy worldwide. There is a risk that policy debates ignore poorly documented or unrecognized challenges that could turn out to be of great relevance to the improvement of a population's health *(112)*.

Information gleaned from data is critical for health planning, management purposes and health policy *(95)*; diagnosis alone does not predict service needs, length of hospitalization, level of care or functional outcomes *(113)*. Data collected should be able to provide timely and accurate estimates of incidence and prevalence; etiology; risk factors and comorbidities; health status; quality of life outcomes; quality of care; access to and utilization of health care; and community services and costs. Comprehensive action is needed to provide more epilepsy-related data collection from a variety of sources. The following steps can improve the quality of epilepsy data available.

- **Step 1:** Standardize the collection of epilepsy data by using common definitions and terminology *(114)*.

- **Step 2:** Raise awareness of the need for data and encouraging the participation of people with epilepsy, as well as collaborative, international efforts needed to establish common methodologies.

- **Step 3:** Collect data from multiple sources including registries and disease-specific reporting systems, surveys and administrative and clinical data sets. Each data source has strengths and limitations in providing insights into the condition.

- **Step 4:** Link data within or across systems to generate a collection of data on large populations. In some countries, epilepsy needs to be included in public health surveillance systems as a mandatory service.

- **Step 5:** Adopt and expand use of linkable electronic health records systems to enhance the utility of this data for public health surveillance of the epilepsies *(115)*.

Examples of national and international data registries

One important source of data for action in the United States of America is Health and Human Services' Healthy People 2020 *(116)*. This is an initiative that provides objectives for improving the nation's health through monitoring and evaluation of key health indicators. It specifically addresses the needs of people with uncontrolled seizures to secure specialist care to manage their epilepsy. It guides public health activities at federal, state and local levels and demonstrates commitment to address the burden of epilepsy as part of nationwide health improvement priorities.

The European Epilepsy Academy established EURAP, an observational study that relies on the collaboration of investigators from 42 countries in the European region. The registry compares the safety of different antiseizure medicines during pregnancy with respect to the risk of birth defects. In one study, the most important risk factors for intrauterine death in pregnancies were determined to include maternal exposure to antiseizure medication polytherapy and the presence of major congenital malformations in at least one of the parents *(117)*. Data collected from this registry allowed the researchers to determine the best treatment for women with epilepsy and for policy-makers to develop international guidelines *(118)*.

In Australia, the Australian Pregnancy Register is an independent project governed by the Royal Melbourne Hospital Neuroscience Foundation. Since 2003, the observational register has been used to collect information about pregnant women with epilepsy to determine which antiseizure medicines are safest for babies while protecting mothers from seizures *(119)*.

Conclusion and way forward

Regardless of where they reside in the world, people living with epilepsy face barriers to accessing care and treatment. Reducing the burden of epilepsy requires strong leadership and the commitment of a range of stakeholders. It requires a commitment from governments at the local, regional, national and international level to develop strategic policy frameworks that recognize the needs of people living with epilepsy. It requires changes in health policies, plans and protective legislation, adequate funding and good quality data.

CHAPTER 2

Leadership and governance for epilepsy

KEY MESSAGES

- **Building on the achievements of the leadership from the World Health Organization, the International League Against Epilepsy and the International Bureau for Epilepsy, collaboration across a range of stakeholders is needed to support country action in raising awareness of epilepsy in political agendas and fulfilling the mandate of the World Health Assembly resolution on epilepsy and regional declarations.**
- **The implementation of policies and plans for epilepsy requires strong leadership and intersectoral collaboration. A joint effort of United Nations agencies, Member States, international and national nongovernmental organizations and civil societies aims to ensure the complex health and social care needs for people with epilepsy and their families are met.**
- **Legislative, public campaigns and social programmes are needed to guarantee the social and human rights of the people with epilepsy. These should align with international human rights standards and global health agendas such as the Sustainable Development Goals.**
- **Appropriate and integrated treatment of people with epilepsy requires that governments allocate sufficient funds to epilepsy care.**
- **Better data and information systems are needed to make the case for prioritizing epilepsy in global public health agendas.**

CHAPTER 3

Comprehensive health care response to epilepsy

Comprehensive health care response to epilepsy

Introduction

Health care for people living with epilepsy involves providing health care and social services to decrease morbidity, premature mortality and to improve psychosocial outcomes. Universal health coverage is necessary for people living with epilepsy and refers to the concept that "all people and communities can use the promotive, preventive, curative, rehabilitative and palliative health services they need, of sufficient quality to be effective, while also ensuring that the use of these services does not expose the user to financial hardship" *(120)*. Thus, UHC that ensures access to necessary care and financial protection should be a goal of all governments.

This chapter defines the health care needs of people living with epilepsy in terms of effective and cost-effective interventions, access to care, quality of care, epilepsy training, information for surveillance and evaluation of epilepsy care and financial protection for people with epilepsy. To illustrate how epilepsy care is being delivered around the world, previous global surveys are summarized and data from an expert-opinion assessment of 11 economically and geographically diverse countries are presented. Needs are compared with what is known about existing epilepsy care to identify key gaps and suggest potential solutions for improvement.

Overview of epilepsy health care needs

Epilepsy interventions and their cost–effectiveness

Despite the high prevalence of disability from epilepsy, there is increasing recognition that services and resources are disproportionately scarce, especially in LMIC. There are a variety of effective and cost-effective interventions for the prevention, management and care of epilepsy *(121)*. However, evidence of the cost–effectiveness of interventions to improve epilepsy care in these settings remains limited. Interventions are briefly described below.

Population based interventions include: (i) targeting epilepsy risk factors (e.g. improved perinatal care, particularly in LMIC and in rural areas with limited access to health care, can reduce the incidence and subsequent prevalence of epilepsy; prevention and control of neurocysticercosis and other infectious etiologies) (see Chapter 6); (ii) targeting stigma through legislation and advocacy, education and awareness raising to dispel myths and enhance seizure management, better support people with epilepsy to seek treatment and encourage social inclusion (see Chapter 5); (iii) policies and legislation needed to guarantee the availability of affordable and efficacious antiseizure medicines, separate budget lines for epilepsy services, and national funding support for epilepsy care (see Chapter 2). The

cost–effectiveness literature is focused on the pharmacological management of seizures, therefore economic evidence concerning population-based interventions is minimal.

Self-management interventions aim to support people to participate more actively in managing their care. Self-management can help those with epilepsy better identify and manage their seizure triggers, which can reduce frequency and decrease health services utilization and health care costs, as well as improve well-being *(121)*. A Cochrane review found that self-management interventions for children, adolescents and families affected by epilepsy are most effective when delivered in partnership between the person and the providers of services, as well as targeted services for specific groups (e.g. children or teenagers) *(122)*. However, the review also found there is currently a lack of evidence for the cost–effectiveness of self-management interventions.

Pharmacological interventions should be considered in those who present with seizures and can be classified as having epilepsy as per the ILAE definition (see Introduction). Most seizures can be well controlled with medicines and other types of treatments. A study in India showed that covering costs for both first- and second-line therapy and other medical costs alleviates the financial burden from epilepsy and is cost-effective across wealth quintiles and in all Indian states *(123)*.

A significant portion of the burden of epilepsy in LMIC can be averted by scaling up the routine availability of antiseizure medicines. A cost–effectiveness analysis of epilepsy treatment in nine WHO subregions found that first-line medicines, such as phenobarbital, represent a highly cost-effective use of resources for health *(124)*. Extending coverage of antiseizure medicines to 50% of primary epilepsy cases would avert 150–650 DALYs per million population, at an annual cost per capita of US$ 0.20–1.33. Older first-line medicines were most cost-effective on account of their similar efficacy but lower acquisition cost (US$ 800–2000 for each DALY averted).

Surgical management may be considered when those who are drug resistant (up to 40% of people with epilepsy overall, particularly those with focal epilepsy) and have failed two appropriate antiseizure medicine trials *(125)*. In those who have failed three antiseizure medicines, attempting to treat with additional medicines is unlikely to achieve sustained seizure freedom *(125)*. Surgery has been shown to be cost-effective in HIC, with health care costs declining significantly after successful surgery *(126, 127)*. A summary of health economic analyses of epilepsy surgery found that, in general, the costs per quality-adjusted life year are considered "very cost-effective" as recommended by the WHO *(128)*.

Alternative therapies for epilepsy include dietary therapies, medical marijuana and acupuncture; but only dietary therapies have been subjected to randomized trials (DCP-3). Despite their increased use, dietary therapies are resource intensive, costly and remain largely limited to HIC *(129)*.

Epilepsy has significant economic implications in terms of health care needs and costs, premature death and lost work productivity. The economic impact of epilepsy varies significantly depending on the duration and severity of the condition, response to treatment, and the health care system and setting. Out-of-pocket costs and productivity losses can create substantial burdens on households. Furthermore, poor knowledge and stigma, low prioritization within health systems, and lack of human resources, diagnostic facilities and medicine supply have led to a large number of untreated epilepsy cases, and consequently a high disease burden, particularly in LMIC. Table 3.1 indicates that a year of healthy life can be obtained for between US$ 600 and US$ 2500 by treating epilepsy with first-line antiseizure medicines. An assessment of the comparative cost–effectiveness analysis of 44 neuropsychiatric interventions in the WHO South-East Asia Region and sub-Saharan Africa subregion, estimated that the most cost-effective intervention was antiseizure medicine for epilepsy in primary care and that the annual cost of delivering a set of the most cost-effective interventions for schizophrenia, depression, epilepsy and alcohol use

Table 3.1 Regional cost–effectiveness of interventions for epilepsy (cost per DALY averted or healthy life year gained, 2012 US$)

	World Bank region					
	Sub-Saharan Africa	Latin America and the Caribbean	Middle East and North Africa	Europe and Central Asia	South Asia	East Asia and Pacific
EPI-1: older antiseizure medicines in primary care	694	1511	1450	2516	600	1057
EPI-2: newer antiseizure medicines in primary care	1884	2854	2877	4115	1639	2249

Sources: Patel et al., 2015 *(121)*; Chisholm and Saxena, 2012 *(130)*.

disorders would be US$ 3 to US$ 4 per capita *(130)*. Regarding the availability, price and affordability of antiseizure medicines, one study examined 46 countries and found that not only is the availability of these medicines lower in LMIC, but their costs are highest where the treatment gap is the greatest *(131)*. This study supports the view that availability and affordability of antiseizure medicines are likely major drivers in low-income countries (see Chapter 4).

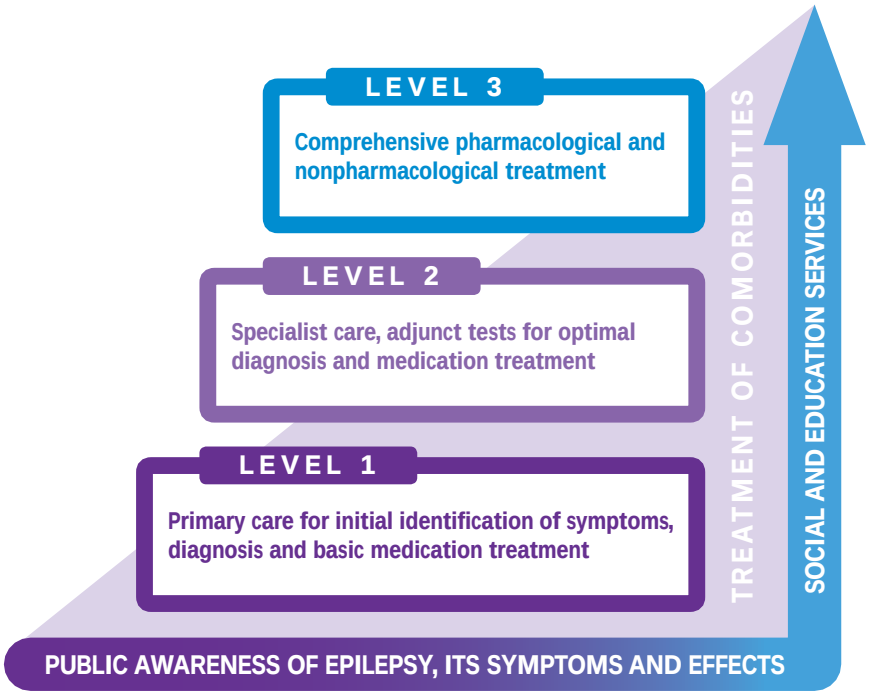
Health system and delivery of care

People with epilepsy, their families, and the community need to be aware that seizures can be stopped. Seizure control requires the correct diagnosis, initiation of appropriate treatment for the epilepsy and comorbidities, and careful follow-up, with the ultimate aim of suppressing seizures and improving quality of life. Deficits in quality care can include lack of, incorrect or late diagnosis; lack of or suboptimal care including insufficient attention to comorbidities; suboptimal adherence to therapy and self-management; and suboptimal availability or use of antiseizure medicines (see Chapter 4) and nonpharmacological therapies for drug-resistant epilepsy. Most people with epilepsy are able to be productive members of society and fulfil their potential with quality health care. Nevertheless, millions still need social support, either in terms of disability assistance, special education or workplace training and rehabilitation. The WHO Health Systems Framework can be used to guide health services development (Fig. 3.1).

Fig. 3.1 WHO Health Systems Framework

Source: WHO, 2010 *(132)*.

Fig. 3.2 Stepped model to improve quality of care for people with epilepsy



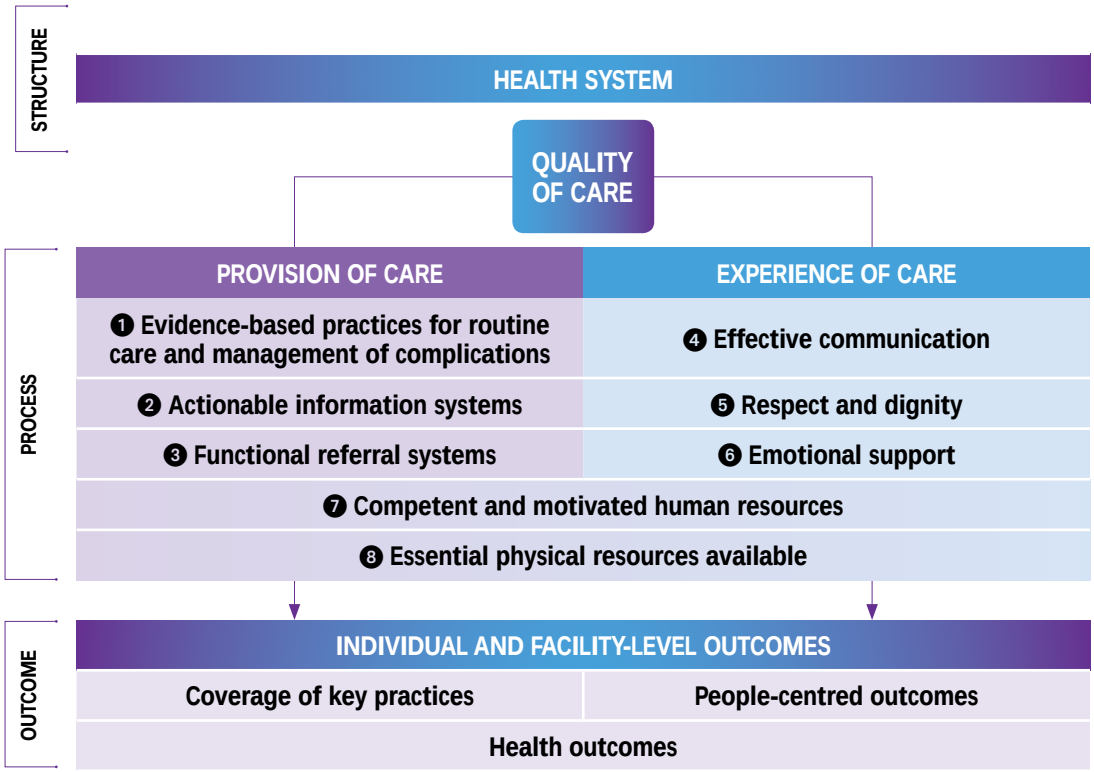
The spectrum of health care needs for people with epilepsy and their families can be viewed as a stepped model of care: beginning with the initial diagnosis and continuing, as necessary, through nonpharmacological therapies (e.g. surgery) for those with drug-resistant epilepsy. The management of comorbidities is an essential component at all levels of care. Community-based care should be emphasized to increase access to all people in need of epilepsy services. Multidisciplinary health care teams that emphasize person-centred care are also important in the stepped model (e.g. physicians, nurses, pharmacists, therapists, social workers, etc.). Social and educational services should provide individualized support, throughout the levels of care and continue, as needed, even after seizure freedom is reached. The stepped model, represented as three levels in Fig. 3.2, is useful for addressing the multifaceted needs of people with epilepsy, monitoring the quality and accessibility of care, and identifying treatment gaps across the spectrum of care and population groups (e.g. drug-responsive versus resistant groups, women related to reproductive health and epilepsy, disparities by rural/urban location).

Quality epilepsy care

WHO defines quality of care as the "extent to which health care services provided to individuals and populations improve desired health outcomes." It also proposes that quality of care should be "safe, effective, timely, efficient, equitable and people-centred." Poor-quality care can place people at greater risk and jeopardize the trust of communities in the health system. Therefore, improving quality alongside access to health services is essential to ensure the desired health outcomes are achieved. Epilepsy quality care should focus on improving diagnosis and providing optimal management that minimizes the impact of epilepsy on social, educational and employment activities. Establishing quality epilepsy care is based on:

- measuring the current standard of care;
- identifying gaps and areas for improvement;
- understanding how to improve care;
- demonstrating the provision of quality care; and
- ensuring access to high-quality services *(133)*.

Fig. 3.3 WHO Quality of care framework



Source: WHO, 2016 *(135)*.

Three main domains are suggested to assess the quality of care: structure (characteristics of the health care provider, facility, therapies (see Chapter 4) and procedures, organization and financing); process (measures arising from the interaction between the individual and health care provider, e.g. investigations ordered, treatments prescribed and delivered, communication); and outcomes (physical and mental health status, satisfaction with the care provided) *(134)*. WHO has proposed various quality of care frameworks, the best of which depend on the overall quality of care goal. The most commonly used one in recent years is irepresented in Fig. 3.3.

Epilepsy training

The level and type of training will be determined by the health care workforce situation in a country (availability of primary care and specialist clinicians), the resources available to investigate and manage epilepsy (diagnostic equipment, antiseizure medication and other treatments) and the availability of social and family support groups and services. Providers of epilepsy care need to: (i) be able to make an accurate diagnosis of epilepsy; (ii) have knowledge about available antiseizure medicines (see Chapter 4) and their indications and side-effects; (iii) recognize the common comorbidities in people with epilepsy (neurological and physical, e.g. sleep disturbances, migraine and bone health; psychological, e.g. anxiety, depression, low self-esteem; neuropsychological, e.g. memory, attention and concentration, and learning; and social, e.g. social isolation, stigma and discrimination); (iv) identify and discuss unique risks associated with epilepsy (e.g. SUDEP or cooking over an open fire); (v) communicate with people living with epilepsy and their families; and (vi) advise about reproduction in women living with epilepsy.

WHO, through the mental health Gap Action Programme (mhGAP), has produced guidelines for the management of mental, neurological and substance use disorders. These can be used by nonspecialists to provide epilepsy care (e.g. nurses or community health workers (CHW) in resource poor areas) *(136–139)*. This includes training of health care staff, from epilepsy nurses and pharmacists to neurologists with epilepsy expertise, to recognize

common comorbidities, including anxiety and depression and related risk factors. More detailed and extensive training is required for providers that have access to specialized investigations, e.g. EEG, neuroimaging such as magnetic resonance imaging (MRI), wider spectrum of antiseizure medicines and other nonpharmacological treatments, such as dietary therapies (e.g. ketogenic diets) or epilepsy surgery.

Information and data collection to inform epilepsy care

Population data

As discussed in Chapter 1, epidemiological data should be collected regularly and include prevalence, incidence, morbidity and premature mortality due to epilepsy (Table 3.2). Data should be available at regional and subregional levels, including urban and rural settings. This information, along with data on etiologies, risk factors and comorbidities, is important to understand the burden of epilepsy and monitor associated trends. Determination of epilepsy burden, often in terms of metrics combining morbidity and mortality, such as the DALY or the quality-adjusted life year, can inform policy-makers' decisions on resource allocation and priority setting. When regional or district health (as opposed to national level) planning and allocation takes place, understanding the epilepsy burden at the regional or district level is important, as differences between regions and urban and rural areas often exist.

Health care system data

Health care system data are important to monitor whether people are being diagnosed and able to access the care they need, to evaluate the quality of care, determine health care costs, and follow-up people to ascertain medicine adherence. Standardized data should include details about the health care provider, health care utilization and cost information (Table 3.3). Much of these data can be found in national registries, insurance systems and/or individuals' records. Additionally, collecting information on utilization may allow for the examination of accessibility and identify "bottlenecks" in care. Lastly, the aggregation of health care data of people living with epilepsy provides useful registries to analyse treatment patterns, costs and outcomes to inform treatment options, evaluate the cost–effectiveness of care and to determine best practices.

Table 3.2 Population data to monitor the burden of epilepsy

Incidence, prevalence and mortality	Number of all cases, number of new cases, mortality rates
Socio-demographic/economic characteristics	Age, sex, race/ethnicity, family status, household composition, educational attainment, employment status, income
Clinical characteristics	Age of onset, precipitating/underlying factors, seizure frequency and type
Comorbidities	Psychiatric and somatic
Knowledge and awareness about epilepsy and its management	Attitudes, knowledge, health-related behaviours and self-management skills
Health status	General and epilepsy-related health status and health behaviours

Table 3.3 Health care system data to monitor the level, type and cost of epilepsy care

Location and type of health care provider	Region (rural vs urban), outpatient vs inpatient, hospital vs clinic, level of provider training
Type of care provided	Diagnostics, treatment for epilepsy, treatment for comorbidities, social services
Utilization and cost of care	Hospital and community-based services, cost of diagnosis, cost of treatment, care modalities

Access to care and financial protection for epilepsy

Good access to care involves people with epilepsy being able to obtain appropriate and affordable health care in a timely manner to achieve the best possible health outcome. Although there are barriers as will be described below, this is the essence of accessible care and financial protection.

Difficulties in accessing health care occur when: services are not available to accurately diagnose epileptic seizures; antiseizure medicines cannot be obtained that could stop seizures and minimize frequency and severity of seizures and medication side-effects; therapies are unavailable to treat comorbidities or drug-resistant seizures; and support services are not available to build the capacity of individuals and families to manage their condition.

Given the heterogeneity of epilepsy, accessible care for people with epilepsy may require a wide range of health, social and educational services. It may also require assistance for individuals and family members in becoming knowledgeable about the condition, recognizing potential danger signs and supporting self-management. Ideally, basic knowledge about epilepsy would extend to the general public as well. Health and social service providers, people with epilepsy and families should work together to assess and treat the physical, psychological and social aspects of the condition, as well as coordinate clinical and community services.

Adequate financial protection means acquiring and keeping a public or private health insurance coverage that pays for the diagnostic and treatment services that may be needed *(140)*. These requirements arise as different care options may be needed from different health care providers (primary care providers including nurses and primary care workers, paediatricians and family practice providers, and specialists including neurologists, psychiatrists, specialist nurses, neuropsychologists and counsellors). Coverage may also be needed to pay for the services of other professionals, such as social workers, occupational specialists or nutritionists in different settings. There are a number of barriers that threaten the adequacy of financial protection, such as limited government funding for the needed spectrum of services, limited provision of public insurance plans or subsidies of premiums in private insurance plans, and limited coverage or provider payment by the plans. Such barriers may lead to high out-of-pocket payments that make services unaffordable.

Multi-country assessments of epilepsy care

The WHO *Atlas: epilepsy care in the world 2005* provided the first comprehensive summary of the global status of epilepsy care *(105)*. Key informants working in epilepsy care in 160 countries completed a survey in 2002–2004. Information on multiple aspects of care was obtained including: diagnostic services, primary care, inpatient care, specialist services, antiseizure medications, treatment gap, subspecialized care, surgery, and training and education. The report showed the enormous variation in the availability of resources, services and training in epilepsy care across and within countries. Available resources for epilepsy care were shown to be insufficient when correlated to the number of people needing such care and the known burden associated with this disorder. There were large inequities across groups of countries, with LMIC having extremely large treatment gaps indicating the need for urgent, substantial action to enhance resources for epilepsy care.

The PAHO *Report on epilepsy in Latin American and the Caribbean (106)* was the next multi-country assessment published in 2013. The report estimated that more than half of the population with epilepsy in Latin American and Caribbean countries were not receiving care. In most countries in the region, specialized services were non-existent or highly concentrated in urban centres. Two-thirds of countries did not have a health sector policy or programme addressing epilepsy care. These findings were based on survey data obtained from 25 of the 33 Latin American and Caribbean countries (76%) that responded. Other findings were:

- The basic antiseizure medicines on the *WHO Model list of essential medicines* at the time (phenytoin, sodium valproate, carbamazepine and phenobarbital) were included on national essential medicine lists by most of the countries. Only 62% of the countries reported that these medicines were available throughout the year at primary health care facilities.

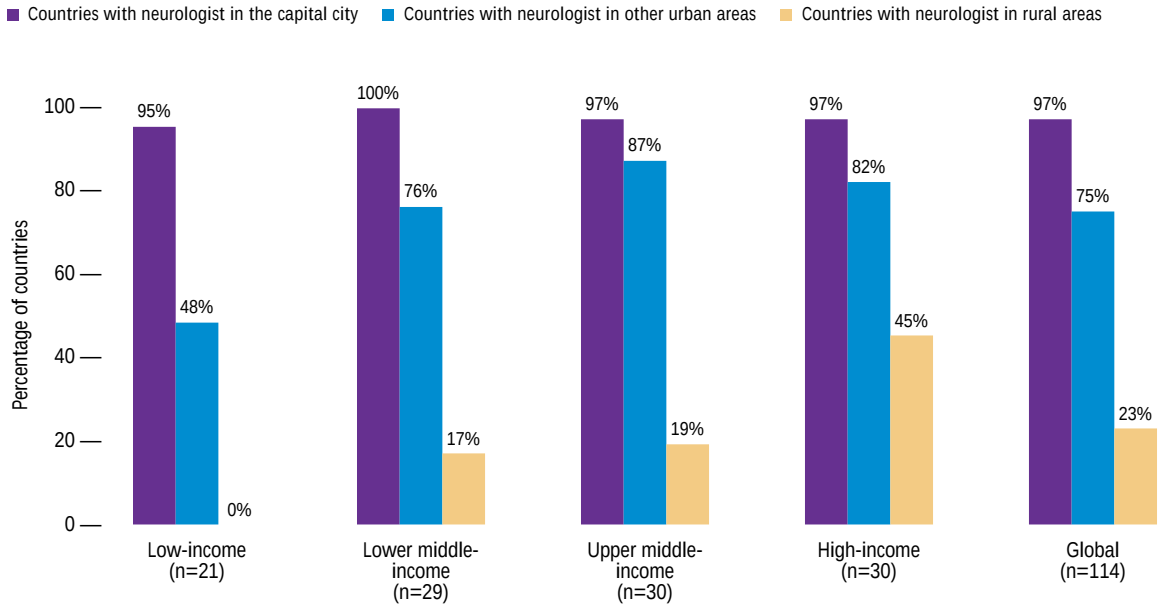
- Countries reported that problems with diagnosis (67%) and delays in initiation of treatment (63%) were the most frequent major difficulties in epilepsy care.

- Very low ratios of neurologists and neurosurgeons per capita were reported throughout the region. Only 12 Latin American and Caribbean countries reported having physicians with specialist training in epilepsy.

ILAE assessed the provision of epilepsy care in a regional survey of 33 European countries in 2017 and compared the results with a similar survey conducted 17 years earlier *(141)*. The total number of physicians involved in epilepsy care had increased since 2000, with the largest increase seen for neurologists. A lack of multidisciplinary teams to manage epilepsy across the region indicated that people may not have access to services needed to optimize treatment, consider comorbidity and give necessary psychosocial support. Such teams (e.g. that may include epilepsy nurse practitioners and other non-physician members) may lead to cost-effective ways of providing epilepsy care.

The latest global assessment of epilepsy care was part of WHO's *Atlas: country resources for neurological disorders* (second edition) *(142)* compiling data from 132 countries and two territories for 2015. The atlas was administered through WHO regional offices and included input from experts and delegates from national neurological associations. The questionnaire assessed health care for people with neurological conditions (including epilepsy) across several aspects: policies and legislation, financing of care, social welfare support, neurological workforce and services, information systems and professional associations/NGOs providing care. Overall, the results confirm that there continues to be a substantial deficit in policies, programmes, resources, services and financial coverage for epilepsy care, particularly in LMIC. Findings show an absence of specialist care available outside urban centres in LMIC; primary health care providers manage the vast majority of neurologic conditions with little training and limited access to antiseizure medicine (Fig. 3.4).

Fig. 3.4 Countries with neurologists in urban and rural areas, by World Bank income group



Source: WHO, 2017 *(142)*.

Assessment of epilepsy care in 11 countries

To provide an updated perspective on the status of epilepsy care, a working group of experts led by chapter co-leads and co-authors provided information describing the major features of epilepsy care in their respective countries. The aim of this assessment was to provide a snapshot of the variation in epilepsy care in those countries. Each informant was asked to base their information on published sources when available and their knowledge and experience when this was not available. The requested information was developed based on prior questionnaires and the broader WHO/ILAE/IBE survey tool developed for this report (see Annex 1). Topics included financial coverage, care guidelines, epilepsy training, availability of neurologists and epilepsy specialists, availability of services, diagnosis and treatment patterns, treatment gap, and professional and patient advocacy.

While considering the results of this assessment, a number of limitations should be considered: the countries do not provide a comprehensive perspective of epilepsy care worldwide; the information based on key informants has not been validated and does not necessarily represent WHO, ministries of health, or ILAE/IBE chapters in the countries; some of the questions were open-ended and a coding scheme was developed to summarize the responses; data are missing from some countries as not all informants were able to answer all questions; and the informants were not selected randomly but are a convenience sample of experts from different regions of the world.

Health expenditure

The total amount spent on health care in these 11 countries varies enormously (Table 3.4). As a percentage of GDP devoted to health care, the range is 3.5% in Kazakhstan to 17.1% in the United States of America in 2016. Ten of the 11 countries included in the assessment spend between less than 10% of their GDP on health care. This translates into a wide range of health care spending per capita, from US$ 35 in the United Republic of Tanzania to US$ 9870 in the United States of America. Eight countries spend under US$ 1000 per person per year on health care. All the countries rely on a mix of sources of health expenditure that includes government provided schemes, compulsory health insurance schemes, voluntary health care payment schemes and household out-of-pocket payments.

Availability of resources and services

In general, and particularly in LMIC, epilepsy can be diagnosed and treated at the primary care level. In (most) cases specialists are not required. The number of neurologists in each country varies from as low as the United Republic of Tanzania 0.01 per 100 000 to 19.4 per 100 000 in the Russian Federation *(142)*. Neurologists are generally located in larger urban cities and often in private practice. In countries with few neurologists, e.g. Kenya and the United Republic of Tanzania, psychiatrists often assess people with epilepsy. In India, psychiatrists, medical graduates, physicians or paediatricians may provide care. In other countries, nurses, medical or paramedical health workers or physicians' assistants may be more available.

Diagnostic technology

Experts from all 11 countries reported the availability of basic diagnostic technology (included EEG including inpatient EEG monitoring, magnetic resonance imaging (MRI) and computed tomography (CT) scans), but in seven countries these are only available in urban areas (Annex 4, Table A4.1). Six countries – Chile, China, India, South Africa, the United Kingdom of Great Britain and Northern Ireland and United States of America – also have more advanced neuroimaging techniques, such as magnetoencephalography and single-photon emission computed tomography. The advanced technology is available in rural areas only in the United Kingdom of Great Britain and Northern Ireland and United States of America.

Pharmacological and nonpharmacological treatment

Experts from all 11 countries reported having essential antiseizure medicines available in urban areas: phenobarbital, phenytoin, sodium valproate and carbamazepine (Annex 4, Table A4.2). In rural parts of Chile, China, India and Kenya,

Table 3.4 An overview of countries included in the assessment of epilepsy care

Income group[a]	Country	WHO region	Population	Percentage of GDP	Health care spending (2016)					
					Current health expenditure	Government schemes	Compulsory health insurance schemes	Voluntary health care payment schemes	Household out-of-pocket payments	Other
					US$ per capita					
Low	Uganda	African	41.5 million	6.2%	38	6	0	16	15	0
Low	United Republic of Tanzania	African	55.6 million	4.1%	35	19	3	2	8	4
Lower middle	India	South-East Asian	1.40 billion	3.6%	62	13	2	6	41	0
Lower middle	Kenya	African	48.5 million	4.5%	66	25	3	20	18	0
Upper middle	China	Western Pacific	1.32 billion	5.0%	398	77	154	24	143	0
Upper middle	Kazakhstan	European	17.9 million	3.5%	262	154	0	12	93	3
Upper middle	Russian Federation	European	143.9 million	5.3%	469	100	167	12	190	0
Upper middle	South Africa	African	56.5 million	8.1%	428	184	0	211	33	0
High	Chile	Americas	17.9 million	8.5%	1191	27	669	80	414	0
High	United Kingdom of Great Britain and Northern Ireland	European	65.3 million	9.8%	3958	3142	5	212	598	0
High	United States of America	Americas	322.1 million	17.1%	9870	2611	5467	698	1094	0

[a] Based on World Bank classification. Expenditure for year 2016; US$ per capital values rounded to the nearest whole number.

Sources: WHO, 2019 *(143)*.

phenobarbital was the most common first-line therapy prescribed. Newer antiseizure medicines (such as lamotrigine, levetiracetam, oxcarbazepine and topiramate) are widely available in Kazakhstan, the Russian Federation, United Kingdom of Great Britain and Northern Ireland and United States of America, as well as in urban settings in Chile, China and South Africa. The survey responses did not consistently specify whether the medicines were available at affordable costs.

Eight of the 11 countries reported the availability of nonpharmacological treatment options in urban areas, including behavioural and dietary approaches, vagus nerve stimulation, neurosurgery (type of surgery was not consistently specified), and deep brain stimulation and neurostimulation (Annex 4, Table A4.3). These were found predominantly in secondary or tertiary level health facilities or specialized epilepsy centres. In most countries, these nonpharmacological treatments were not

accessible in rural areas. In South Africa, a 2000 report found that only one public facility and two private facilities provided epilepsy surgery *(144)* compared with at least 10 in the United Kingdom of Great Britain and Northern Ireland *(145)*. In Kenya, epilepsy surgery availability is limited to two urban centres. Nevertheless, the majority of cases are managed adequately with antiseizure medicine alone.

Guidelines for epilepsy care

This assessment found substantial variation in national guidelines for care of epilepsy across the 11 countries. Only one country, the United Republic of Tanzania, reported having no guidelines on the diagnosis or treatment of epilepsy. The other countries' policies ranged from general principles and objectives for care (Kenya and Uganda), to general and/or specific clinical protocols and standards for epilepsy care (Chile, China, India, Kazakhstan, Russian Federation, South Africa, United Kingdom of Great Britain and Northern Ireland and United States of America).

Chile appears to have the most explicit policies ensuring access to a defined standard of care. Under the Chilean government insurance system, adults with epilepsy have the right to one neurologist visit a year and two nurse visits a year *(146)*. Children can visit a nurse four times and a neurologist twice per year. The access standards stipulate a maximum timeframe to receive treatment from a neurologist and define limits to out-of-pocket co-payments for treatment. The programme guarantees in Chile do not cover pharmacologic or nonpharmacological care for drug-resistant epilepsy *(147)*.

In the United Kingdom of Great Britain and Northern Ireland, the most notable government initiative on quality of care that have included epilepsy were the National Institute for Health and Care Excellence (NICE) guidelines on the diagnosis and management of the epilepsies in adults and children in primary and secondary care *(148)*. The NICE guidelines were incorporated in the 2013 quality standards in epilepsy which provide a national blueprint for epilepsy care in the United Kingdom of Great Britain and Northern Ireland.

The success of the GCAE project in China (see Chapter 2, Box 2.1) led to the publication of clinical guidelines for diagnosis and treatment of epilepsy (2007 and 2015 revision) by the China Association Against Epilepsy, which have been recognized by the government and used widely throughout the country.

South Africa does not have specific national epilepsy guidelines or a national epilepsy plan. However, epilepsy care, namely diagnosis, treatment and referral for specialist care, is highlighted in general, primary and hospital care guidelines that are regularly updated and released by the National Department of Health. The guidelines are based on principles and practices developed by the South African Medical Association.

Workforce training

In eight of 11 countries, most physicians who diagnose and treat people with epilepsy receive advanced medical school training in neurology and/or in another relevant specialism (paediatrics, psychiatry, or internal medicine) (Annex 4, Table A4.4). In eight countries, most primary care providers who treat epilepsy also receive formal training in epilepsy. Formal training in epilepsy for non-medically trained health care providers is available in only three of the countries.

Delivery of care

In rural parts of China, India, Kenya and South Africa, people often present initially to traditional or non-professionally trained healers before eventually being seen by primary care providers (medical officers or nurses) who are able to diagnose a person with epilepsy (Annex 4, Table A4.5). Among the HIC sampled, people are typically (and, in some countries, required to be) referred to a neurologist to receive a diagnosis of epilepsy.

Almost all the countries have policies and guidelines for referrals. In countries with specific policies on levels of care, the role of the primary care provider is generally to recognize symptoms and refer to specialists for diagnosis and initiation of treatment. This is the case in Chile and most parts of China, where the neurologist is responsible for making the

diagnosis and treatment plan, and the primary care provider continues to assist in management until the person is discharged by the neurologist *(149)*. In both countries nurses are not authorized to diagnose or treat epilepsy, but primary care physicians may *(149)*, whereas in Kenya and South Africa, nurses are often the primary providers of epilepsy care in government clinics, particularly in rural areas. Nurses can initiate basic treatment, then refer to primary care physicians for a definitive diagnosis and supplementary treatment. Complex cases may be further referred to neurologists for further investigations (e.g. EEG or MRI) or combination therapy. Nurses and other primary care providers receive little or no training in epilepsy care in India, Kazakhstan, Kenya and the Russian Federation.

In the United Kingdom of Great Britain and Northern Ireland, neurologists and epilepsy specialists usually diagnose and treat epilepsy, although primary care providers are involved in management. Some epilepsy specialist nurses in the United Kingdom of Great Britain and Northern Ireland have received training to be able to prescribe antiseizure medicines *(150)*. The United Kingdom of Great Britain and Northern Ireland offers specific training in epilepsy to nurses nationwide and certifies nurse epilepsy specialists. The United States of America has epilepsy training opportunities for primary care providers sponsored by the government and private organizations but offers no specialty certification. The US Centers for Disease Control and Prevention has developed and is testing a training curriculum in epilepsy for community health workers *(151)*.

In most HIC, the diagnosis of epilepsy is often but not always made by a neurologist; however, the follow-up referral pathways of care vary. In the United Kingdom of Great Britain and Northern Ireland, general practitioners refer the person to a neurology clinic in a district general hospital, where consultants can then refer on to specialized services. This is in stark contrast to India where, although the health care system is organized into levels, there is no formal system of referrals. Differences in the referral pathways can even occur within a single country leading to misdiagnosis. A 2006 US National Academy of Medicine (formerly the Institute of Medicine) study highlights this finding in the United States of America, where referral systems were found to be peculiar to the treatment setting, not well-structured or standardized *(152)*.

Many experts completing the assessment reported ongoing treatment for epilepsy was delivered by the same providers who made the initial diagnosis, either in the hospital, clinic or specialized centres (Annex 4, Table A4.5). When seizure control is stabilized in the South Africa and the United Kingdom of Great Britain and Northern Ireland, people with epilepsy are typically referred back to primary care facilities, though the case is often different for children in many regions, where there can be great hesitancy to accept referral back to community providers for the ongoing care of epilepsy.

All countries had general outpatient facilities, such as clinics, to follow-up people with epilepsy. Some countries, including the United Kingdom of Great Britain and Northern Ireland and United States of America, report having specialized outpatient facilities for the follow up of people with epilepsy. In cases of severe epilepsy, or people with psychiatric comorbidities, India, Kazakhstan, Russian Federation, South Africa and the United Kingdom of Great Britain and Northern Ireland report utilizing specialized long-term facilities. Some private long-term facilities also exist in Chile. There is only one psychiatric hospital in Kenya which serves as a setting for treatment of epilepsy.

Advocacy and social support

All countries have national ILAE and IBE chapters (Annex 4, Table A4.6). Many countries, including Chile, China, Kazakhstan, Kenya, Russian Federation, South Africa, United Kingdom of Great Britain and Northern Ireland and United States of America, have one or more IBE chapters. Professional neurology bodies exist in a number of countries (Chile, China, India, Kazakhstan, Kenya, Russian Federation, South Africa, Uganda, United Kingdom of Great Britain and Northern Ireland and United States of America). Individual and family support and consumer organizations are also present in several of the countries included. In China, the Provincial

Association against Epilepsy and China Bureau for Epilepsy also play a role in training rural physicians. Epilepsy South Africa does this by advocating for the rights of people with epilepsy and focusing on skills development, community development, social development services and residential care for people with epilepsy. In Chile, the Refractory Group provides financial support to members having refractory epilepsy.

The results of this consultation with experts from 11 countries reveal major challenges and variation in the availability of epilepsy care. Challenges include: a paucity and heterogeneity of information for epidemiological surveillance, health care and social service monitoring; bottlenecks in health care delivery caused by lack of trained specialists, standardized treatment guidelines and ineffective referral pathways; disparities in stepped care resulting from the lack of, or delays in, the initial diagnosis, inaccessibility and/or delays in basic and/or specialized optimal care, inattention to comorbidities; and a lack of integrated social and educational services available to support people with epilepsy and their family members.

Potential solutions to improve epilepsy care

Many potential solutions to improve epilepsy care exist. These are noted below corresponding to the major challenges:

Challenge 1: Access to primary care diagnosis and treatment

In many LMIC where health resources are limited, there is an urgent need to improve training and quality of epilepsy care at the primary level. Training primary health care providers to identify cases of epilepsy, their management (including prescribing first-line antiseizure medication) and referral (in complex cases) is likely to be one effective way to bridge the existing treatment gap. Specialized services, inpatient and outpatient (neurology, neurosurgery, among others), located at the second level of care, are indispensable to support primary health care and for the care of complex or complicated cases that require specialized interventions.

Potential solutions

- Epilepsy primary care needs the following:
  - **Primary care providers:** to improve primary care for epilepsy, provide basic training in epilepsy diagnosis, treatment and management to physicians, nurses, and other primary care providers. Resources such as the *mhGAP intervention guide (137)* and associated training materials *(138)* should be considered and adapted to the local context.
  - **Epilepsy educators:** to assist individuals in self-management, all epilepsy clinics should have an "epilepsy educator" trained to educate people about behaviours they can adopt and maintain to better control their epilepsy and improve their quality of life.
  - **Non-medically trained providers:** greater integration of community-based services recognizing the role of, and training of, non-medically trained providers, for example community health workers. These cadres of the workforce are especially important in the identification of epilepsy, referral to health facilities where trained providers are available, to reduce stigma and promote psychosocial support for people with epilepsy and their families.
  - **Training of specialists:** there is a need to train more epilepsy specialists in many regions to whom other nonspecialists can refer to.

- A minimum acceptable standard of care should be agreed upon and implemented through the development of care guidelines.

- Countries without national guidelines should start with the mhGAP guidelines *(136)* for training primary care providers.

- An international working group should be formed on epilepsy primary care to assess the problem in more detail and develop an action plan and timeline for implementation.

Challenge 2: Access to antiseizure medicines and financial protection

Lack of access to medications has been identified as one of the greatest barriers to people with epilepsy receiving adequate treatment, especially in LMIC. Rising health care costs threaten access to appropriate care and strain public and private funding of direct services, health insurance coverage, and the ability of people with epilepsy to purchase needed medications out of pocket at the point of service. The costs of antiseizure medicines for basic epilepsy care often exceed the total amount of funding available for health care in LMIC *(153)*. New antiseizure medicines and therapy for drug-resistant epilepsy are expensive and often not funded by government programmes or covered by public or private insurance plans (see Chapter 4). In addition, lack of consistent and appropriate medicines available in many regions is a major challenge.

Potential solutions

- Provision of subsidized or free first-line antiseizure medicines, especially phenobarbital, carbamazepine and valproate, in countries with treatment gaps and ensure there are primary care providers who treat epilepsy so antiseizure medicines are prescribed.

- Examine implementable policies to control the costs of antiseizure medicines at a country level.

- Improve distribution to ensure delivery of the medicines to the point of contact with people in need.

- Identify and address access barriers that prevent initiation and maintenance of antiseizure medicines.

- Increase availability and awareness of disability grants for people with epilepsy.

Challenge 3: Limited implementation of epilepsy guidelines and standards of care

As highlighted in this chapter, epilepsy care is delivered along steps, with each level involving potentially different care providers. In all of the countries assessed, delays in initial diagnosis, lack of specialists, and substantial waiting time to see specialists or attend epilepsy centres were observed. The lack of guidelines (or lack of implementation of existing guidelines) and ambiguity in referral pathways ultimately resulted in the delivery of suboptimal care. Currently, challenges to understanding and monitoring quality care and referral pathways persist.

Potential solutions

- Greater international dialogue amongst clinicians on treatment and care for people with epilepsy with assistance from WHO and ILAE.

- Wider recognition of the comorbidities of epilepsy and the need for them to be addressed, with the involvement of psychiatrists and psychologists.

- Each country should clearly highlight in their epilepsy plan the referral cascade for the delivery of epilepsy care, including possible reasons for referral and the resources and care available at each level within the care cascade. Training for specialists and nonspecialists based on the national referral system should be provided.

- National health departments should ensure that each region, province or state has clear guidelines and referral pathways. This should be updated regularly. Local governments should be charged with identifying and ensuring quality care.

- Existing guidelines should be adapted to the local context and efforts to ensure their dissemination are needed.

- Ensure that primary health providers are aware that seizure recurrence is an indication for treatment even if diagnostic measures are not available or are delayed.

Challenge 4: Lack of epilepsy and health care data

A well-developed health information system is essential in providing evidence-based data for health planners. In the case of epilepsy, it is necessary to define a minimum data set (Tables 3.2 and 3.3) that provides the information needed to allow countries to set priorities, study trends and evaluate the impact of interventions. In most countries around the world such data systems do not exist to adequately inform resource allocation and care monitoring (including accessibility and cost). Lack of standardized definitions for assessing health care and different measures of the epilepsy treatment gap make comparisons across countries and within regions of countries difficult. In countries that do have data systems in place, often the type of data available vary by geographical context or provider setting, making it difficult to interpret findings.

Potential solutions

- There is a need for standardized data collection through national health information systems.

- National departments of health should recognize epilepsy as a priority condition to be recorded in vital statistics, either through government facility patient registries or insurance provider registries.

- The information recorded in these vital statistics must form part of a minimum harmonized dataset, with standardized definitions, developed by the ILAE with support from WHO.

- Research (see Chapter 7) on the accessibility of basic epilepsy care, especially in rural, resource-limited contexts, including the cost of care to the individuals and the health care system, should be prioritized.

Conclusion and way forward

This chapter has highlighted the multifaceted care needs of people living with epilepsy and the considerable gaps in care available for epilepsy. While each country is unique, many of the challenges faced in terms of their health care response to epilepsy are similar, which suggests opportunities for collaboration and learning from one another. To improve the delivery of quality health care for all people with epilepsy, regardless of where they live, requires recognizing common challenges to care and directing the necessary health care efforts.

CHAPTER 3

Comprehensive health care response to epilepsy

KEY MESSAGES

- **Providing quality epilepsy care is challenging because of its complexity, chronicity and considerable comorbidity.**
- **Epilepsy can negatively impact the psychosocial and economic well-being of people, their families and the community in which they live. A lack of access to and affordability of medications are two of the greatest barriers to people with epilepsy receiving adequate treatment.**
- **Although there are an increasing number of antiseizure medicines on the market, the percentage of people who respond to a single medicine continues to be approximately 70%. Therefore, improving access to medicines could have large impact globally.**
- **Access to care for people with epilepsy varies considerably across and within countries, resulting in a gap in universal health coverage and, thus, unmet needs exist in all countries, but particularly in low- and middle-income countries.**
- **Policy-makers need to ensure that there are sufficient population and health care system data for monitoring epilepsy care, appropriate training for providers, informing guidelines for quality care and directing adequate resources to ensure universal health coverage.**

CHAPTER 4

Access to antiseizure medicines

Access to antiseizure medicines

Introduction

Access to effective antiseizure treatment remains out of reach for the vast majority of people with epilepsy, particularly in LMIC. As reported in Chapter 1, estimates of the treatment gap in low-income countries is over 75%, and tend to be higher in rural versus urban areas *(10, 154)*. Numerous drivers of the global treatment gap have been identified, including inadequate access to trained professionals, diagnostics, transportation and health care facilities; sociocultural factors including stigmatization, awareness and acceptability of treatment; as well as poor availability and non-affordability of medicines *(155–157)*. Sustained access to antiseizure medicines is a major barrier to treatment in LMIC *(131)*.

People with epilepsy require regular treatment for many years, sometimes for a lifetime. An abrupt withdrawal of antiseizure medicines can have life-threatening consequences, including status epilepticus. Therefore, it is essential to ensure that access to these medicines is sustained over time to permit uninterrupted treatment.

In this chapter, we discuss factors affecting access to antiseizure medicines and suggest actions for improving access at the international, national, district and community levels.

WHO framework for understanding determinants of and barriers to access to medicines

The WHO 2004 Access Framework provides a paradigm for understanding and evaluating access to medicines involving consideration of the following components: rational selection and use of essential medicines, affordable prices, sustainable financing, and reliable health and supply systems *(158)*. A 2015 WHO discussion paper utilized this framework to examine barriers to access for essential medicines and health technologies for NCDs *(159)*. Numerous bottlenecks were identified along the four access components, including:

- Inconsistencies between essential medicines lists, procurement and reimbursement lists; insufficient implementation of treatment guidelines; and problems with adherence owing to the need for long-term use of medicines.

- Hurdles in terms of affordability of medicines, such as high, unregulated mark-ups, taxes, and insufficient use of generics.

- Barriers to sustainable financing included insufficient prioritization of NCDs and mental health at the national level, inadequate public sector financing for NCDs and mental

health, lack of UHC, and insufficient or non-existent risk sharing mechanisms (i.e. health insurance) resulting in out-of-pocket costs to the consumer.

- Lastly, key barriers within health and supply systems included problems with health systems and supply chain management, problems with forecasting and anticipating pharmaceutical needs, problems with ensuring quality of medicines, and reduced capacity to produce medicines locally in-country.

The 2016 WHO/Calouste Gulbenkian Foundation report *Improving access to and appropriate use of medicines for mental disorders* adapted the 2004 WHO Access Framework *(158, 160)* to consider rational selection and affordability, as well as availability and appropriate use of medicines *(160)*.

It focused on the following components of access: rational selection, availability, affordability and appropriate use of essential medicines (Fig. 4.1). This framework is applied below to understand barriers in access to medicines for epilepsy. Many of the barriers identified are applicable to medicines for all conditions. Some, however, are specific to epilepsy, resulting from the stigma associated with this condition. A lack of knowledge of health care providers and poor acceptability of medical treatments, duration and cost of medication due to the chronic nature of epilepsy, and limitations of available research and funding, also play a role. A lack of health care provider knowledge of epilepsy is a barrier to prescribing and appropriate use of antiseizure medicine (Box 4.1) and limited cultural acceptability of epilepsy can lead to poor adherence to treatment (Boxes 4.2 and 4.3).

Box 4.1 Health providers' lack of knowledge as a barrier to appropriate use of antiseizure medicines in the Lao People's Democratic Republic

To understand factors associated with the large epilepsy treatment gap in the Lao People's Democratic Republic, estimated to be over 90%, Harimanana and colleagues conducted a survey of 284 physicians and nurses in 50 different health facilities (province hospitals, district hospitals or health centres). Overall, knowledge of epilepsy diagnosis and treatment amongst physicians and nurses was found to be poor. Only about half of physicians and about a third of nurses identified any antiseizure medicines, and only 28% of physicians and 16% of nurses knew the appropriate dosages of phenobarbital. One-fifth of physicians and a third of nurses also believed that epilepsy could be transmitted by saliva. Only half of physicians and less than 40% of nurses identified differential diagnoses for epilepsy. Of note, knowledge and practices regarding epilepsy diagnosis and management were better amongst physicians from province hospitals versus district hospitals or health centres.

Source: Harimanana et al., 2013 *(161)*.

Box 4.2 Poor adherence to antiseizure medicines and use of complementary/alternative treatments in Honduras

In Honduras, a survey of 274 persons with epilepsy was conducted assessing rates of non-adherence to antiseizure medicines, as well as rates of complementary and alternative medicine usage. Some 44% of the people surveyed were non-adherent to antiseizure medicines, with lack of access to these medicines being responsible for non-adherence in nearly half of cases. Reasons for lack of access were the unavailability of medicines at the hospital or health centre, or the person being unable to afford the medicines. About half of people surveyed had utilized complementary and alternative treatments at some point in time and about one-third were using them currently. The top five most commonly utilized complementary and alternative treatments included prayer (to God, 57%; saints, 11%; or spirits, 8%), herbs (41%) and potions (29%). Additionally, 49 persons without epilepsy within the Miskito tribe were surveyed to understand local beliefs and practices surrounding epilepsy: nearly 35% of respondents used words for epilepsy that suggested supernatural causes of the disease. Further, about a quarter of respondents considered bad spirits and 6% considered witchcraft as etiologies of the disease.

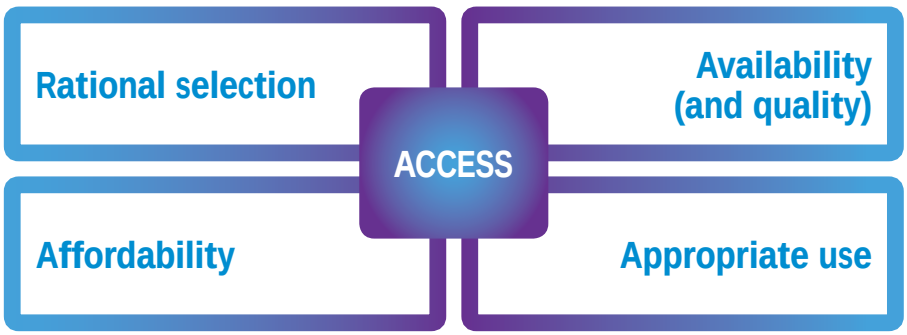
Source: Duron et al., 2009 *(162)*.

Box 4.3 Cultural acceptability of treatments in the United Republic of Tanzania

A survey in the Hai district of the United Republic of Tanzania identified 291 people with active epilepsy *(163)*. Of those, 253 had at one point attended health facilities, though only 118 were taking antiseizure medicines, which defined the treatment gap as 40%. Factors associated with not attending the health system included consuming alcohol and utilizing traditional healers. Conversely, having attended primary school was found to be protective and correlated with having been seen in the health system. The top four risk factors associated with dropping out of treatment included belief in a supernatural cause of the illness, "no ideas/knowledge" of the cause, consuming alcohol, and male gender. Having had the illness for a decade or more and having received a diagnosis of epilepsy (or Kiswahili diagnoses of *kifafa* or *degedege*) were found to be protective against dropping out of treatment.

Source: Hunter et al., 2016 *(163)*.

Fig. 4.1 Framework for understanding access to medicines



Source: WHO, 2017 *(160)*.

Rational selection of medicines

As defined by WHO, rational selection "focuses therapeutic decisions, professional training, public information, financing, supply and quality assurance efforts on those medicines which will have the greatest impact in a given health care setting" *(164)*. Rational selection encompasses the process of interpreting best practice evidence in the creation of medicines lists and adoption of guidelines. This includes the *WHO Model list of essential medicines*, national essential medicines lists, and district and facility-specific medicines lists *(165)*. Medicines lists streamline the supply chain process (including purchase, storage and distribution), and facilitate the scale up of harmonized, efficient and regularly updated trainings for clinical providers. Antiseizure medicines currently included in the *WHO Model list of essential medicines* are reported in Table 4.1.

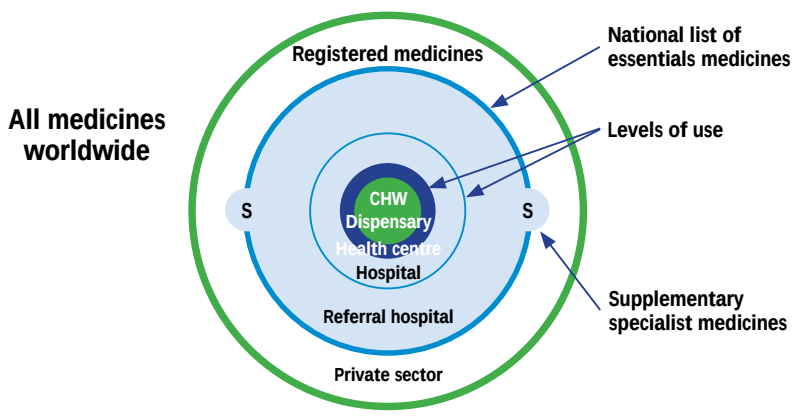
The *WHO Model list of essential medicines* provides a core set of medicines, which can be adapted to local needs. Some complex epilepsy syndromes may require treatments with antiseizure medicines which are not included in the *WHO Model list of essential medicines*. Thus, countries should consider availability of medicines in all settings, compliance of the person, and ensuring the availability of additional medicines for use at specialist level. Fig 4.2 provides a schematic representation of different categories of medicines and a model to ensure their availability at different levels of the health care system. For HIC, a case can be made for health care providers to have access to the full range of registered antiseizure medicines.

Table 4.1 Antiseizure medicines included in the *WHO Model list of essential medicines*

Medicine	Formulations
Carbamazepine	Oral liquid: 100 mg/5 mL. Tablet (chewable): 100 mg; 200 mg. Tablet (scored): 100 mg; 200 mg.
Diazepam	Gel or rectal solution: 5 mg/ mL in 0.5 mL; 2- mL; 4- mL tubes.
Lamotrigine*	Tablet: 25 mg; 50 mg; 100 mg; 200 mg. Tablet (chewable, dispersible): 2 mg; 5 mg; 25 mg; 50 mg; 100 mg; 200 mg. *As adjunctive therapy for treatment-resistant partial or generalized seizures.
Lorazepam*	Parenteral formulation: 2 mg/ mL in 1- mL ampoule; 4 mg/ mL in 1- mL ampoule. *Similar clinical performance within its pharmacological class.
Magnesium sulfate*	Injection: 0.5g/ mL in 2- mL ampoule (equivalent to 1 g in 2 mL; 50% weight/ volume); 0.5g/ mL in 10- mL ampoule (equivalent to 5 g in 10 mL; 50% weight/volume). *For use in eclampsia and severe pre-eclampsia and not for other convulsant disorders.
Midazolam	Solution for oromucosal administration: 5 mg/ mL; 10 mg/ mL. Ampoule*: 1 mg/mL; 10 mg/mL. *For buccal administration when solution for oromucosal administration is not available.
Phenobarbital	Injection: 200 mg/mL (sodium). Oral liquid: 15 mg/5 mL. Tablet: 15 mg to 100 mg.
Phenytoin	Injection: 50 mg/ mL in 5- mL vial (sodium salt). Oral liquid: 25 mg to 30 mg/5 mL.* Solid oral dosage form: 25 mg; 50 mg; 100 mg (sodium salt). Tablet (chewable): 50 mg. *The presence of 25 mg/5 mL and 30 mg/5 mL strengths on the same market would cause confusion in prescribing and dispensing and should be avoided.
Valproic acid (sodium valproate)	Oral liquid: 200 mg/5 mL. Tablet (crushable): 100 mg. Tablet (enteric-coated): 200 mg; 500 mg (sodium valproate).
Complementary list	
Ethosuximide	Capsule: 250 mg. Oral liquid: 250 mg/5 mL
Valproic acid (sodium valproate)	Injection: 100 mg/ mL in 4- mL ampoule; 100 mg/ mL in 10- mL ampoule.

Source: WHO, 2017 *(165)*.

Fig. 4.2 Essential medicines target for selection



Source: WHO, 2002 *(166)*.

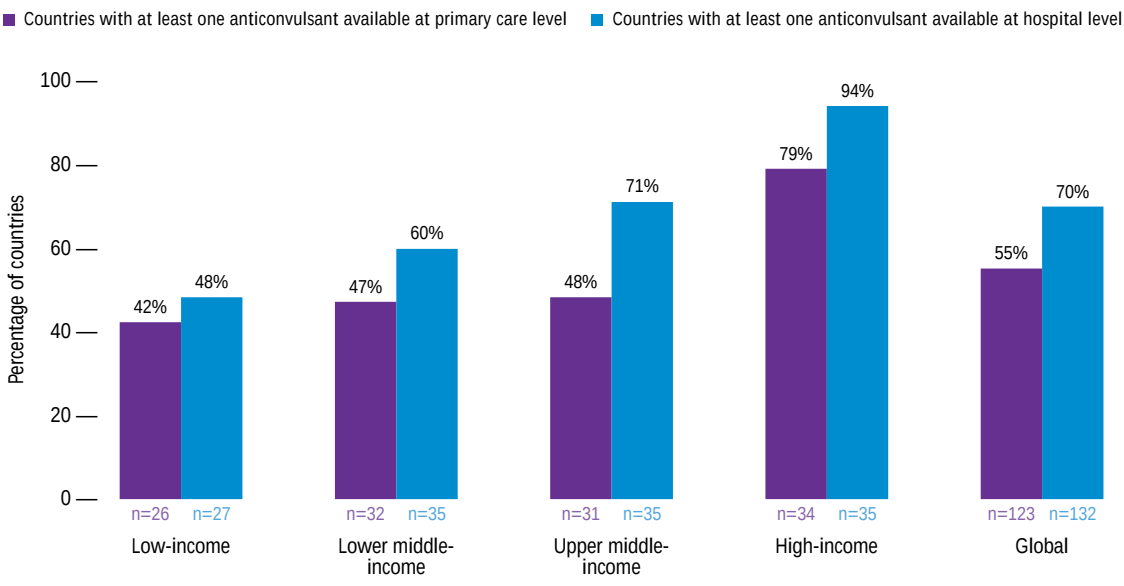
Availability (and quality) of medicines

Availability refers to the extent to which quality medicines can be found in the health system. Upstream variables affecting the availability of antiseizure medicines include efficient regulatory and approval processes and adequate management systems for purchasing, procurement, storage and distribution. Downstream factors include the accessibility and distribution for prescribing and dispensing within the health system including hospitals, clinics and pharmacies/dispensaries *(164)*.

Inadequate availability of antiseizure medicines is a major public health concern. A study conducted by WHO and Health Action International in 46 LMIC assessed the availability, price and affordability of five antiseizure medicines – diazepam, phenytoin, phenobarbital, carbamazepine and valproic acid – in the public and private sectors *(131)*. With the exception of diazepam injections, antiseizure medicines were available less than 50% of the time in the public sector. Private sector availability of generic oral antiseizure medicines ranged from 42% for phenytoin to 70% for phenobarbital. In the WHO *Atlas: country resources for neurological disorders* (second edition), less than one half of low-income countries were found to ensure sustained availability of at least one major antiseizure medicine (carbamazepine, phenobarbital, phenytoin or valproic acid) at either hospital or primary care level *(142)*. Sustained availability was also grossly inadequate in a large proportion other countries pointing to the need for improved distribution channels (Fig 4.3).

For one specific medicine, phenobarbital, regulations due to its classification as a controlled substance (a drug whose manufacture, possession or use is regulated by a government) represent a major hurdle to its availability in many LMIC. This is regrettable as phenobarbital is not only in the *WHO Model list of essential medicines* but also the first treatment for epilepsy in many of these countries *(167)*. Regulatory hurdles restricting availability of phenobarbital can be international or national. For example, import quota for phenobarbital assigned by international agencies to some LMIC represent only a small fraction of the needed medication *(168)*. Other countries introduced additional regulations that go beyond international conventions, by

Fig. 4.3 Countries with at least one antiseizure medicine always available at primary care and hospital level



Source: WHO, 2017 *(142)*.

imposing undue restrictions on importation or by introducing controls that limit its availability *(167)*. In Zambia, for example, introduction of additional controls resulted in nearly 50% of pharmacies not having a stock of phenobarbital, and in paediatric syrups being completely unavailable *(169)*.

Access to therapies is dependent not only on the availability of medicines, but also on the availability of health care personnel who act as prescribers. Inadequate numbers and sparse distribution of providers with neurological training and pharmacists further compound barriers to access for antiseizure medicines, especially in LMIC. The dramatic disparity between available neurologists in low-income countries is (0.03 per 100 000 population) compared with HIC at 4.8 highlights the inadequate preparedness in these countries *(142)* across regions. Specific regions are at highest risk, with the average number of neurologists in Africa < 0.1 and South-East Asia 0.1 per 100 000 people, versus 6.6 in Europe. For a more detailed discussion of available resources for epilepsy, see Chapter 3. Box 4.4 illustrates how difficulties in accessing medicines can be overcome.

In addition to the availability of medicines (and health personnel) the quality of medicines should be considered as well. WHO estimates that just over 1 out of 10 products available in LMIC are substandard or falsified. WHO defines substandard, unregistered/unlicensed and falsified medical products as the following *(171, 172)*:

- Substandard medical products are those that are authorized but "out of specification," meaning they fail to meet quality standards, specifications, or both.

- Unregistered or unlicensed medical products have not been evaluated and/or approved by the national or regional regulatory authority for their intended market.

- Falsified medical products are those that purposely misrepresent their identity, composition or source.

Box 4.4 Improving access to antiseizure medicines in the Philippines

In an archipelago of 7100 islands, access to medicines is a major hindrance in improving epilepsy treatment. With fewer than 400 trained neurologists attending to an estimated over 950 000 Filipinos with epilepsy *(142, 170)*, the Philippine League Against Epilepsy set out to address this problem in 2003. The Epilepsy Manager Program started as an initiative to train primary care physicians in basic epilepsy diagnosis and management to allow them to become rational prescribers of antiseizure medicines. The 10-month hands-on method has produced dozens of Epilepsy Managers over 15 years in key provinces in the country. Through the graduates of the training programme, the Philippine League Against Epilepsy sourced free supplies of the basic antiseizure medicines for distribution in the epilepsy clinics they established locally. Having trained rural physicians to make proper epilepsy diagnoses and prescribe appropriate medicines, the programme has made accessibility, availability and rational use of medicines a reality in the rural areas of the Philippines.

Source: Soto, 2013 *(170)*.

Surveys in the United States of America, the EU and some HIC, have shown that the quality of antiseizure medicines in these countries is generally of high quality *(173)*. The risk of substandard or counterfeit products distribution is higher in regions where quality is not strictly regulated or adequately controlled. Studies from some LMIC show that certain antiseizure medicines on the market contain amounts of active ingredients that differ from descriptions on the label *(174)*. And, studies have demonstrated that substandard quality is mostly due to poor storing conditions which leads to poor seizure control *(175)*. The use of substandard or falsified medical products can have serious, and sometimes fatal, consequences. This is because they may contain toxic chemicals or other impurities, wrong proportions of active ingredients, wrong active ingredients, or no active ingredient (Box 4.5). WHO established the Global Surveillance and Monitoring System in 2013 as a mechanism for countries to be able to report instances of substandard and falsified medical products. Through this system, WHO is able to collect evidence to be in a position to assess the global scale of substandard and falsified medical

Box 4.5 Counterfeit and falsified products in Central and West Africa

When a falsified phenobarbital product was used between May and July 2013 in a community-based service in south Guinea-Bissau *(176)*, seizures recurred in several individuals within 1 month. Within 2 months, almost two-thirds (74 out of 117 people) had a recurrence or increased frequency of seizures. Two people died during this time, which may have been seizure-related. A falsified phenobarbital product was also used in a community-based service in Izzi, Nigeria, between June and August 2014. As a result, most of the people surveyed (105 out of 120) had a recurrence or worsening of seizures. Independent laboratory testing of products used in Guinea-Bissau and Nigeria showed that neither had appreciable amounts of the active ingredient phenobarbital, with the levels either exceedingly low (0.8–1.5%) or undetectable *(176)*.

WHO also issued a medical product alert in February of 2016 regarding falsified tablets of phenobarbital in West Africa. WHO was notified by the Liberia Medicines and Health Products Regulatory Authority in December of 2015 of two products that claimed to contain 100 mg phenobarbitone (phenobarbital), but were discovered to be ineffective because people with epilepsy taking these tablets had a recurrence of seizures. There were spelling errors on the labels. On cross-checking with the WHO Substandard Spurious Falsely Labelled Falsified and Counterfeit Medical Products database, it was found that a similar product was circulating in Guinea-Bissau in 2013 (as detailed above). Both falsified products contained the same batch number, as well as nearly identical labelling and packaging *(177)*.

Falsified phenobarbital products found in Liberia, 2015 (left) and in Guinea-Bissau, 2013 (right):

WHO issued a medical product alert in July 2015 regarding two falsified diazepam products in the Democratic Republic of Congo. One falsified diazepam product was linked to acute dystonic reactions of the muscles of the face, neck or tongue in over 400 people. It was revealed through laboratory testing that the product actually contained haloperidol, an antipsychotic medicine, rather than diazepam as labelled. A second falsified diazepam product found in the Democratic Republic of Congo contained a false labelling, citing a manufacturer that did not produce diazepam *(178)*.

products, respond to emergencies, provide technical support to countries, link incidents in different areas, and issue medical product alerts. Towards these ends, WHO has trained over 550 regulatory staff globally and works with 18 large international procurement agencies. Up until November 2017, WHO had provided technical support in over 100 cases and issued 20 medical product alerts, two of which were related to antiseizure medicines *(171)*.

Affordability of medicines

Affordability is evaluated by the cost burden imposed by medicines on various levels of the

health system, on individuals and their families. Availability of medicines does not equate to access to medicines, because high prices may place medicines out of the reach of consumers.

In the survey conducted by WHO and Health Action International in 46 LMIC, prices of generic products of antiseizure medicines were found to be inordinately expensive in both the public and private sector *(131)*. In one example, compared with international reference prices, the price of carbamazepine was nearly five times higher in the public sector, and 11 times higher in the private sector. Originator brand prices were higher still by a factor of 30. When translated into daily wages, the lowest paid worker would need to spend between 2.7–16.2 days' worth of wages for a 1-month supply of carbamazepine *(131)*. The WHO *Atlas: epilepsy care in the world 2005* demonstrated that the median cost of essential antiseizure medicines is several times higher in LMIC than in HIC *(105)*.

Numerous barriers to affordability for medicines have been enumerated, including assertion of intellectual property rights, unregulated prices leading to high mark-ups (Box 4.6), insufficient use of generics, lack of public sector funds, as well as insufficient or lack of health insurance schemes *(160, 166, 179)*.

Box 4.6 Unregulated costs of antiseizure medicines in North America

In 2001, Questcor acquired HP Acthar gel, a drug used to treat epileptic infantile spasms, from Aventis Pharmaceuticals, Inc. for US$ 100 000 plus modest royalties *(180, 181)*. At that time, the price of the medicine in the United States of America was US$ 40 per vial. Questcor, which was acquired by Mallinckrodt in 2014, then raised the list price, to US$ 34 000 a vial, an 850-fold price increase *(173)*. Sales of the medicine brought in more than US$ 1 billion in revenue in 2015 for Mallinckrodt, according to a legal complaint filed by the US Federal Trade Commission and attorneys general from five states *(180)*. The lawsuit alleged that Mallinckrodt engaged in anti-competitive behaviour to preserve its monopoly on the medicine. On 18 January 2017 Mallinckrodt agreed to pay US$ 100 million to settle the lawsuit *(181)*.

For a large number of antiseizure medicines, patent protection has now expired, leading to the introduction of cheaper generic products into the market. This has obvious benefits in terms of improving affordability. However, as some antiseizure medicines have a narrow therapeutic index, concerns have been expressed that variability in active ingredient levels could entail a risk of seizure recurrence or toxicity if switching across products *(182)*. Evaluation of the available evidence from HIC on safety of generic antiseizure medicines, however, has indicated that in most cases, the variation in levels of the active ingredients was negligible. Such variation is comparable with that across different lots (e.g. serial numbers) of the same brand *(173)*. Results of studies comparing changes in levels of antiseizure medications when switching from one generic to another have also been reassuring with respect to the safety of these products *(183)*. Likewise, high-quality clinical studies did not identify changes in seizure frequency and adverse effects attributable to generics *(173, 184, 185)*. Occasional reports of adverse experiences from the use of generics could be ascribed to confounding factors, such as poor adherence resulting from people becoming confused by differences in shape and colour of generics *(173)*. Therefore, it is essential that individuals are adequately reassured about the safety of generics, and, as with all medicines, receive proper instructions on how these medicines should be taken.

In some countries, prescribing of generic antiseizure medicines can be complicated by the presence in the market of different categories of generics or "similar" products, which may differ in the amount of active drug that reaches the circulation and, therefore, may not be used interchangeably *(186)*. Particularly in LMIC, health care personnel need to be aware that some products may be substandard in quality given improper storage, as discussed above *(174, 175)*. The example from Malta (Box 4.7) reflects the decision of governments to following international guidelines for use of generic antiseizure medicines to ensure that medicines for epilepsy remain free of charge.

Box 4.7 Use of generic antiseizure medicines in Malta

The Government of Malta ensures that antiseizure medicines are free for all people with epilepsy. This also applies to many other chronic conditions, based on the principle of social solidarity safeguarded by the Social Security Act Cap 318 Article 23 and its amendment (Act No. I of 2012 and the Fifth Schedule of the same Act) *(187, 188)*. For many years, the national Drugs and Therapeutics Committee stated that only originator products of antiseizure medicines should be available in the national health care system. This was due to concerns over potential differences in quality of generic products and the possibility of breakthrough seizures when switching between products. As a result, the supply of antiseizure medicines was sometimes disrupted due to stock-outs and dependence on few suppliers. In recent years, however, the availability of these medicines has significantly improved, as Malta now follows the United Kingdom Medicines and Healthcare Products Regulatory Agency guidelines. The guidelines address concerns and organize antiseizure medicines into three categories based on therapeutic index, solubility and absorption *(189)*. Switching between manufacturers is generally not recommended for antiseizure medicines listed in Category 1, while it may be considered for medicines in Category 2 based on clinical judgment and/or other individual-specific factors. It is generally regarded as unnecessary to maintain one supplier for medicines in Category 3.

Appropriate use of medicines

Appropriate use is defined as "the expectation that people receive medicines appropriate to their needs, in doses that meet their individual requirements, for an adequate period of time, and at the lowest cost to them and the health system" *(160)*. Medicines work when taken regularly, and many factors contribute to problems with adherence, including cognitive difficulties, complex instructions, side-effects, misconceptions about epilepsy, lack of education, language barriers and cultural factors. Educating people with epilepsy and their carers about the risks associated with poor adherence, certain behavioural interventions and simplifying their drug regimens have been shown to improve adherence *(190, 191)*. Adherence and appropriate use must also take into account the age of the person with epilepsy as factors affecting adherence and appropriate use differ *(192)*. Inappropriate use can lead to treatment failure, poor adherence or treatment discontinuation, or increased adverse effects. Health system and provider level barriers to appropriate use of antiseizure medicines include inadequate training and supervision of prescribers, as well as inadequate clinical and laboratory monitoring of users of these medications. Treatment guidelines for clinical practice, which may be produced at the international, national or local levels are crucial for ensuring appropriate use *(193)*. Providing education to the community, caregivers and the users to address barriers to appropriate use, including interventions to address lack of awareness of epilepsy as a treatable condition, lack of awareness and acceptability of the benefits of pharmacological treatments, fear of adverse effects, and failure to understand the importance of regular use is needed.

Global initiatives to facilitate increasing access to medicines for epilepsy

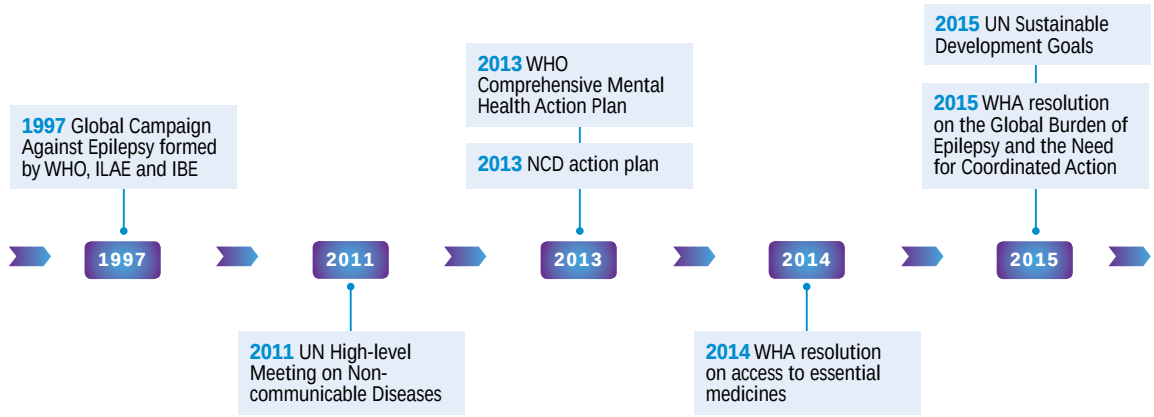
Nationally and internationally, there has been growing attention to NCDs, including mental and neurological disorders (Fig. 4.4) *(91, 92, 155, 194)*. Sustainable access to affordable treatments, including medicines, has been recognized as a key component of public health action plans.

The imperative to increase access to essential medicines was highlighted in the UN SDGs *(92)* via goals 3.4 and 3.8:

- Goal 3.4: "By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being."

- Goal 3.b: "Support the research and development of vaccines and medicines for communicable and non-communicable diseases that primarily affect developing

Fig. 4.4 Landmark international mandates to increase access to medicines for epilepsy



countries, provide access to affordable essential medicines and vaccines … regarding flexibilities to protect public health, and, in particular, provide access to medicines for all."

- Goal 3.8: "Achieve universal health coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all."

World leaders adopted a political declaration that outlined the actions to be taken to tackle NCDs at international and national levels *(91)*. The *WHO Global action plan for the prevention and control of noncommunicable diseases 2013–2020*, sets a target of 80% availability of affordable essential medicines required to treat major NCDs in public and private facilities *(195)*. At the Third United Nations High-level Meeting on NCDs in 2018, Member States committed to promoting mental health and well-being in synergy with WHO's efforts to accelerate the work being done to prevent and control NCDs. This included actions toward affordable, safe, effective and quality medicines to treat and manage NCDs and neurological conditions such as epilepsy.

In 2014, the Sixty-seventh World Health Assembly adopted a resolution on access to essential medicines "based on the principles of evidence-based selection of a limited range of medicines, efficient procurement, affordable prices, effective distribution systems, and the rational use of medicines" *(196)*. This was followed by *Towards access 2030: WHO medicines and health products programme strategic framework 2016–2030 (197)*, which underlines the need to increase access to essential, high-quality, safe, effective and affordable medical products for all. According to the strategic framework, medicines and health products "often make up the largest portion" of countries' and households' health spending, and the majority of people in LMIC pay for their medicines out of pocket, often leading to financial hardship and reducing opportunities for countries to achieve UHC.

The Sixty-eighth World Health Assembly adopted a landmark resolution on the global burden of epilepsy and the need for coordinated action at the country level to address its health, social and public knowledge implications *(12)*. This resolution urges Member States to undertake several actions to raise epilepsy awareness and to improve the prevention, diagnosis and treatment of epilepsy, making specific reference to the need to improve the accessibility to and affordability of "safe, effective and quality-assured antiseizure medicines, and include essential antiseizure medicines into national lists of essential medicines" *(12)*.

While leadership support and direction is increasing at the international level, there is much work to be done at the national, district and community levels to actually improve access to these medicines and close the epilepsy treatment gap globally.

Box 4.8 Personal recollection of a family experience with epilepsy in a Zimbabwean rural village

I am sharing my family's experience to inspire more actions against epilepsy in Africa. We live in a rural village in Buhera District, Zimbabwe. In 1998, my older sister Mambeva, a mother of two children, started "behaving strangely, hearing voices, speaking meaningless words and being too excited", in her husband's words. Christian faith leaders prayed for her and gave her holy water to drink or shower, but the attacks continued. Family members travelled on foot for 15 km to the Betera clinic and were advised to try phenobarbital, which was not always available. The medicine did not stop the attacks as quickly as expected, reinforcing the myths that the condition was generated by God, ancestors or witches, and only treatable with *chivanhu* (African methods) and *chipositori* (Christian methods). Non-medical treatment was expensive as livestock and cash were needed, but it was culturally acceptable. Mambeva would be in a state of confusion (*mamhepo*) for 3 days followed by energetic fitting (*kugwinha*) several times for 2 days. She would then faint (*kurara kunge akafa*) for 2 days followed by another state of confusion with very aggressive behaviour for 4 days. This experience lasted 11 days almost each month for 8 years. Her marriage broke down because of her condition.

In 2003, while at university I learnt about epilepsy and approached the Epilepsy Support Foundation of Zimbabwe for help. The nurse asked to see my sister, but it took us a year to raise the bus fare. The Epilepsy Support Foundation referred Mambeva to the then only neurologist in the country, the late Professor Jens Mielke. An EEG was done free of charge, and carbamazepine was prescribed. Since that day, 15 August 2005, she has been seizure free. A few years later she remarried and she had her third child. She remains on a low dose and our hope is for her to stop the medicine, but the physician advised otherwise. She has become more prayerful too, attending church every Friday.

Jacob Mugumbate, PhD
University of Wollongong, New South Wales, Australia; Vice-President (Africa), IBE and former Director, Epilepsy Support Foundation, Zimbabwe *(198)*.

Box 4.8 provides a personal recollection of the suffering that people in some parts of the world have to endure in receive an inexpensive and effective therapy. This case shows the importance of health education, epilepsy awareness and accessibility to cheap or free medical treatment. It also shows the value attached to non-Western treatments in many parts of Africa. The Zimbabwe Government showed its commitment by making a statement in support of the epilepsy resolution at the Seventy-first World Health Assembly in Geneva in May 2018.

Health policies to improve access to medicines at the country level

Ensuring appropriate access to medicines is one of the highest priorities to be addressed by any country when establishing health policies. WHO's *Good governance for medicines* programme provides guidance on how to implement a transparent approach in improving efficiency in procurement and supply of medicines *(199)*.

For people with epilepsy, abrupt interruption of antiseizure medicines could have serious consequences, including life-threatening status epilepticus. Consequently, policies should be in place to ensure sustained supply and delivery of quality and affordable medicines, and address possible disruptions.

Transparent policies to ensure the availability of medicines at no cost to the individual or at the lowest possible prices in the public sector would be a key step in reducing the epilepsy treatment gap and require policies to address rational selection, availability and quality, affordability and appropriate use. Policies are also needed to promote cost-effective use of antiseizure medicines by adoption of treatment guidelines, supporting cost–effectiveness studies, and ensuring the training of health care personnel in diagnosis and management of seizures and epilepsy *(196)*. Ultimately, ensuring access to antiseizure medicines should be regarded as a component of supporting UHC. This may be

Table 4.2 Key actions for policy-makers to improve access to medicines

Rational selection

- Develop a national list of essential medicines based on national treatment guidelines, concentrating on those which are most available and most effective.
- Use a national list of essential medicines for procurement, reimbursement, training, donations and supervision.
- Include World Trade Organization/Trade-Related Aspects of Intellectual Property Rights and compatible safeguards into national legislation.
- Improve monitoring of medicine quality, particularly in LMIC.
- Develop national treatment guidelines based on the best available evidence concerning efficacy, safety, quality and cost–effectiveness.

Availability (and quality)

- Assure quality of medicines through appropriate regulatory control.
- Encourage local production of essential medicines of assured quality when appropriate and feasible.
- Promote bulk procurement, quantification, tracking and ensure consistency of supply.

Affordability

- Use available and impartial price information.
- Allow price competition in the local market.
- Implement generics policies where quality and effectiveness can be assured.
- Negotiate equitable pricing for newer essential medicines for priority diseases.
- Undertake price negotiation for newly registered essential medicines.
- Eliminate duties, tariffs and taxes on essential medicines.
- Reduce mark-ups through more efficient distribution and dispensing systems.
- Increase public funding for health, including for essential medicines.
- Expand health insurance through national, local and employer schemes.
- Reduce out-of-pocket spending, especially by the poor.
- Target external funding (grants, loans, donations) at specific diseases with high public health impact.
- Explore other financing mechanisms, such as debt-relief and solidarity funds. In managing and monitoring medicine costs, governments and health authorities can refer to the *WHO Guideline on country pharmaceutical pricing policies (200)*.

Appropriate use

- Integrate medicines in health sector development.
- Create efficient public-private-NGO mix approaches in supply delivery.
- Explore various purchasing schemes: procurement cooperatives.
- Include traditional medicines, when appropriate, in health care provision.

Sources: WHO, 2017 *(160, 196)*.

supported through development of medicine reimbursement lists (aligned with national essential medicines lists) and promotion or financing schemes. For examples of policy approaches (see Table 4.2). These actions are not specific for antiseizure medicines, but they are fully applicable to the objective of reducing the epilepsy treatment gap.

Mechanisms for enhancing access

The 2016 WHO/Calouste Gulbenkian report on *Improving access to and appropriate use of medicines for mental disorders* outlined key priority actions to improve access to medicines at four levels of the health care system (international, national or subnational, district, and at the community, household or individual levels) *(160, 201)*. These priority actions can facilitate access to antiseizure medicines by enhancing the following four components: rational selection, availability, affordability and appropriate use.

- **International level:** International resolutions and commitments concerning UHC, access to medicines generally, or access to epilepsy treatment specifically (e.g. *WHO Guidelines on neonatal seizures (202)*, are critical to enhance medicine access. Prioritizing research to understand the determinants of and barriers to access to medicines is needed. Policy development by international agencies to address supply and delivery of medicines for vulnerable populations, e.g. those displaced by national disasters or conflicts, is necessary.

- **National level:** Risk-sharing mechanisms, such as subsidized insurance coverage, and public sector financing of antiseizure medicines at national levels is important. The *WHO Model list of essential medicines (165)*, should serve as a guideline for national essential medicine list development, enhancing the rational selection of antiseizure medicines. National guidelines for clinical diagnosis and treatment, and increased neurology training and supervision of providers at all levels can improve availability and appropriate use of antiseizure medicines. Efficient regulatory and approval processes, as well as streamlined and regulated supply chain management systems with adequate quality control measures can improve availability of quality antiseizure medicines. Undue regulatory hurdles to accessing phenobarbital, a controlled substance, should be addressed. Developing transparent pricing and tendering policies for antiseizure medicines and fostering a sustainable financing system for the procurement and distribution of these medicines can help ensure affordability. Further, policies should be developed to ensure equitable individual affordability of antiseizure medicines. Lastly, effective monitoring of the availability and use of these medicines should be implemented.

- **District level:** District-level and facility-level essential medicines lists that are harmonized with the national essential medicines list can enhance rational selection. Availability can be facilitated by identifying local regulatory or statutory restrictions and possible hindrances to the procurement and deployment of effective antiseizure medicines. Increased training and supervision of providers in neurological care at the district or facility level can improve availability and appropriate use, with adaptations in care delivery guidelines accounting for differences between urban and rural areas.

- **Community level:** Implementing epilepsy care delivery models embedded in community-based primary care can improve availability and appropriate use. Awareness-raising initiatives and community-based advocacy concerning the treatable nature of epilepsy and the benefits and importance of regular use of antiseizure medicines may improve cultural acceptability and thus, appropriate use of these medicines. Training programmes for service users on adherence can also improve appropriate use.

Conclusion and way forward

Access to antiseizure medicines offers the potential for 70% of people with epilepsy to live seizure free *(24)*, with an opportunity to impact their quality of life and participation in society. Understanding the myriad financial, educational and sociocultural barriers to access antiseizure medicines is crucial for the adequate planning of financial, health system and clinical interventions to help improve access to treatment for people with epilepsy. Numerous actions undertaken at the international, national, district and community levels can effectively improve access to antiseizure medicines.

CHAPTER 4

Access to antiseizure medicines

KEY MESSAGES

- **An imperative to increase access to essential medicines was highlighted in the United Nations Sustainable Development Goals.**
- **People with epilepsy require regular treatment for many years, sometimes for a lifetime. It is essential to ensure access to medicines in a sustained manner to avoid interrupted treatment which can have life-threatening consequences, including status epilepticus.**
- **The *WHO Model list of essential medicines* provides a core set of medicines, which can be adapted to local needs.**
- **Governments should have a deliberate policy to prioritize the procurement of antiseizure medicines and ensure appropriate use by giving adequate training to health care providers. It is important therefore that in all settings, awareness of newer generation medicines and up-to-date guidelines exists.**
- **Improving access to antiseizure medicines requires consideration of rational selection, affordability, availability and appropriate use at all levels of the health care system (international, national, district and community). Improving access to antiseizure medicines is an essential component of policy development to improve the lives of people with epilepsy.**

CHAPTER 5

The social response: misconceptions and stigma in epilepsy

The social response: misconceptions and stigma in epilepsy

Introduction

The history of epilepsy is relevant to understanding the origins of many of the misconceptions and myths that continue in many cultures today. These misconceptions can perpetuate stigma and can lead to social isolation, delays in seeking treatment and care, unemployment, poverty and poor mental health in people with epilepsy. Identifying and dispelling the misconceptions that cause stigma is a first step to reducing stigma.

This chapter focuses on the dimensions of felt and enacted stigma (see definitions). It draws on recent systematic reviews of stigma and attitudes towards people with epilepsy. The prevalence and consequences of stigma reinforce the need for a public health system response that recognizes the burden of epilepsy stigma on the individual, their family, their health care providers, their community and the economy.

Stigma is a significant contributor to poor physical and social health in people with epilepsy and will not be improved with a single approach. A multipronged strategy that is culturally appropriate, multisectoral and collaborative is needed. This chapter concludes with examples of interventions that have been successful in reducing epilepsy stigma with a caveat that further qualitative and quantitative studies are needed to inform relevant and targeted intervention studies.

DEFINITIONS

Stigma: An attribute, behaviour or reputation which is socially discrediting in a particular way: it causes an individual to be mentally classified by others in an undesirable, rejected, stereotyped way *(203)*.

Health-related stigma: Health-related stigma is typically a social process characterized by exclusion, rejection, blame or devaluation that results from experience, perception or reasonable anticipation of an adverse social judgement about a person or group. The judgement is based on an enduring feature conferred by a health problem or health-related condition, and the judgement is in some essential way medically unwarranted *(204)*.

Felt stigma: The shame, embarrassment or disgrace of having epilepsy or the fear of being discriminated against.

Internalized stigma: Felt within the person with epilepsy and reflects their feelings, thoughts, beliefs and fears about being different.

Enacted stigma: The actual instances of discrimination because of the diagnosis of epilepsy (e.g. being fired after having a seizure at work).

Institutionalized stigma: The societal position taken, as embodied in its law and statutes.

Interpersonal stigma: The negative actions and reactions of significant others (within and external to the family system) towards the person with epilepsy.

Reflected stigma: Stigma by association, and affects family members, care and health providers.

History of epilepsy

The entomology of "epilepsy" is from the Greek word *epilambanein*, meaning "to seize" or "to attack". It is described, by many cultures, in ways that suggest mystical or supernatural origins. In ancient times, epilepsy was believed to be a sacred disease resulting from invasion of the body by a god; it was thought that only a god could deprive a healthy person of their senses, throw them to the ground, convulse them, and then rapidly restore them to consciousness *(205)*.

In many societies, long-held, often traditional, misconceptions about epilepsy exist, leading to varying degrees of stigmatization and sometimes overt discrimination. The idea that epilepsy is a brain disorder started appearing in the 18th century. In 1873, John Hughlings Jackson (a British neurologist) proposed the following definition: "Epilepsy is the name for occasional, sudden, excessive, rapid and local discharges of grey matter" *(206)*.

Types of stigma

The multiple ways in which stigma can be experienced contribute to the burden of epilepsy. There are two main types of stigma. Felt or internalized stigma refers to the shame of having seizures and the fear of encountering epilepsy-linked enacted stigma. Enacted, or institutionalized stigma reflects actions of discrimination that people with epilepsy face in their communities.

Felt (internalized) stigma

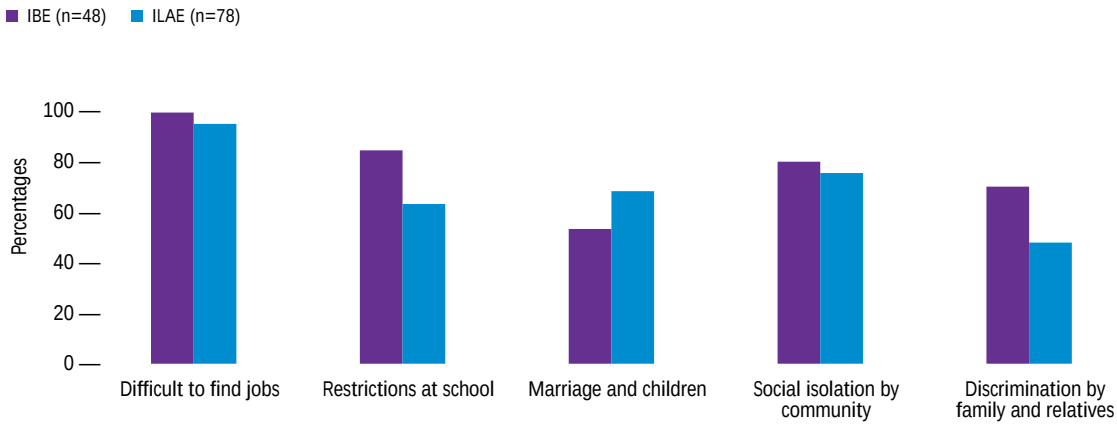
Misconceived notions about epilepsy, once internalized, may cause more personal anguish and unhappiness than enacted *(207)*. It is also experienced far more often than enacted stigma. In one study, only 33% of the respondents could recall having encountered enacted stigma while 90% admitted to experiencing felt stigma *(208)*.

From the time of diagnosis, people with epilepsy often make a decision about whether they will conceal their illness or not *(204)*. Keeping one's status of epilepsy a secret reduces the opportunities for enacted stigma but can cause substantial internal conflict and increased levels of social anxiety and felt stigma *(209–211)*. In a demonstration project in Georgia, a substantial level of stigma, erroneous beliefs and low public awareness caused people with epilepsy to hide the condition, posing a significant barrier to help-seeking behaviour *(212)*. In a Turkish study, those who hide their epilepsy condition from others were more likely to seek non-medical treatments and were more likely to report higher levels of stigma *(209)*. People with epilepsy in a Bulgarian study were most concerned about the lack of knowledge of other people about their condition, and a fear of having a seizure in public *(213)*. The ability to hide an epilepsy diagnosis is a burden in itself. People with epilepsy look no different from others when they are not having a seizure. As such, given proper diagnosis and treatment, up to 70% get seizure control, allowing for the person to decide whether they want to conceal their diagnosis or not. The remaining 30% who have recurrent seizures become the public face of epilepsy. The media and entertainment industry often depict the sudden onset of a seizure in an exaggerated, violent, frightening and dangerous way, creating stereotypes that are erroneous and harmful. Negative stereotypes promote concealment of the condition and concealment in turn heightens felt stigma *(209, 214)*.

Enacted (institutionalized) stigma

Institutionalized discrimination in epilepsy goes back centuries with legislation restricting employment, schooling, marriage and childbearing, as well as driving regulations. Even though some of these discriminatory laws were repealed decades ago, the legacy of these laws can still lead to misconceptions and discrimination. Respondents in the ILAE/IBE survey (Annex 1) reported barriers for people with epilepsy at the country level of difficulty in finding jobs, restriction at school, for marriage and children, social isolation by community, as well as discrimination by family and relatives (Fig. 5.1).

Fig. 5.1 Barriers for people with epilepsy



Source: see Annex 1.

Violations of human rights are often more subtle and include social ostracism, being overlooked for promotion at work, denial of the right to participate in school and social activities taken for granted by others in the community. There is evidence that people with epilepsy may also be discriminated against by health care providers *(215, 216)*. In Saudi Arabia, 67.2% of health care providers would not want their child to marry a person with epilepsy *(217)*.

Factors linked to stigma in epilepsy

A systematic review of 25 quantitative studies in stigma identified culture, demographic, illness-related and psychosocial factors can all predict stigma to varying degrees *(218)*. Higher levels of felt stigma are associated with a reduced sense of self-efficacy, poor epilepsy outcomes and seizure severity *(218)*. Frequently identified predictors of enacted stigma include low level of knowledge about epilepsy, and lower educational level, social class and socioeconomic status, living in a rural area, and religious grouping *(218)*.

Variation in stigma across geographical regions and within regions and countries is also significant in epilepsy. Regions with a strong cultural perception of disease that relies on non-scientific explanations, such as spiritual, contagious and a form of insanity (e.g. Asia and Africa), tend to have poorer attitudes towards epilepsy *(219)*.

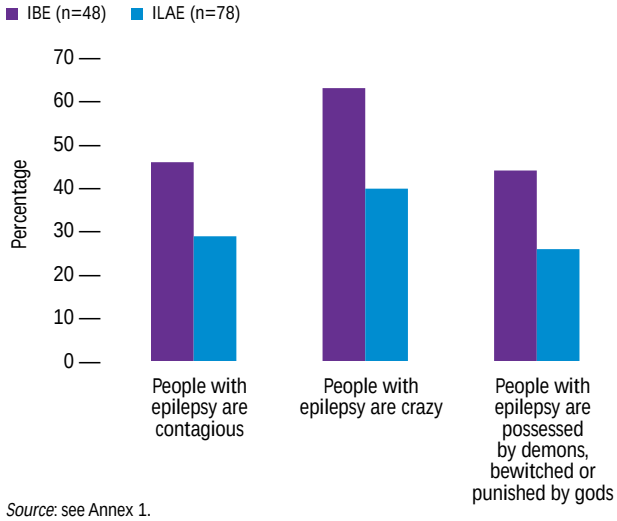
Knowledge about epilepsy also plays an important role in reducing the degree of discrimination and negative attitudes toward epilepsy. Studies show that people with less knowledge about epilepsy, or without personal contact with someone with epilepsy, have poorer attitudes *(220)*. The magnitude of the negative attitudes seems to be aggravated by the presence of misconceptions about epilepsy, which include the perception of epilepsy as a form of insanity, being untreatable, contagious, hereditary, or a form of learning disability.

Misconceptions that perpetuate stigma in epilepsy

People with epilepsy and their families may be confronted with social ostracism and outright discrimination in part due to misconceptions that have existed for centuries. The ILAE/IBE survey (Annex 1) identified three prevalent misconceptions that can fuel stigma in epilepsy: people with epilepsy are contagious, crazy and possessed by demons, bewitched or punished by gods (Fig. 5.2).

People with epilepsy are not contagious, possessed, demons, crazy or insane. Many of these misconceptions originated in times where there was a poor understanding of brain diseases. Misconceptions are prevalent in cultural communities where there is poor knowledge of epilepsy or a lack of access to evidence-based treatment.

Fig. 5.2 Common misconceptions of epilepsy



Source: see Annex 1.

In a systematic review, Kaddumukasa and colleagues *(221)* categorized the misconceptions identified in 23 stigma studies in sub-Saharan Africa (Table 5.1). The studies included assessments and misconceptions among health care providers, medical students, teachers, the general public and people with epilepsy from Nigeria, Cameroon, Uganda, Zambia, Ethiopia, the United Republic of Tanzania, Kenya, Ghana, Zimbabwe, Benin and Mali. The authors concluded that epilepsy misconceptions and stigmatizing cultural beliefs are pervasive and that there is a need for scalable stigma reduction interventions in sub-Saharan Africa.

Misconceptions contribute to the burden of illness in epilepsy and lead to stigma. They cause people with epilepsy to feel shame, embarrassment and disgrace. The emotional impact of feeling socially excluded contributes to the physical, psychological and social burden of epilepsy. Stigma can delay appropriate health seeking, access to care, health financing and availability of treatment *(222)*.

The largest gaps in epilepsy care are in communities where seizures are considered contagious through saliva or blood or seen as a demonic curse or the result of witchcraft *(205)*. Studies from Zambia *(223)*, Ghana *(224)*, Cameroon *(215)* and Burkina Faso *(225)* identified that fear of contagion puts the person

Table 5.1 Misconceptions identified from studies of stigma in sub-Saharan Africa

Categories	Examples
Employment	• People with epilepsy have insanity • Objection to employment of people with epilepsy
Restrictions and limitations	• Prefer people with epilepsy be in separate classes/schools • People with epilepsy cannot participate in sports
Cause and nature of epilepsy	• Epilepsy is due to demonic possession/evil spirit • Epilepsy is a psychiatric disorder • Epilepsy is transmitted by saliva • Epilepsy is a blood disease (people with epilepsy have weak blood)
Treatment	• Should be treated by traditional healers • Wearing an amulet • Epilepsy is not curable
First aid for seizures	• Sacrifice to gods • Compliance with cultural taboos • Smell the smoke of a struck match • Pour water on face of the subject • Sprinkled with olive oil • Place a spoon between the teeth • Give sweets during a seizure
Integration into communities	• Objecting to marriage to people with epilepsy • People with epilepsy should not play with normal people • People with epilepsy can transmit disease (i.e. epilepsy is contagious)

Source: Kaddumukasa et al., 2018 *(221)*.

with epilepsy at risk during a seizure as others are unwilling to intervene to prevent injury or to provide seizure first aid. Interviews of traditional healers in Cameroon indicated that half of respondents associated epilepsy with insanity and many would object to their children associating or marrying a person with epilepsy *(215)*.

Researchers interviewed 36 traditional and faith healers in Ghana to document how one's cultural perception alters their treatment and care pathway. A person with epilepsy that seeks help from a Christian healer may be offered prayer, exorcism, fasting, holy water and anointed oils *(226)*. A Muslim healer may use verses of the Qur'an and herbs, while a shrine priest may offer chants, incantations, confession and other rituals to banish or repel the spiritual forces that are identified as responsible for the illness *(226)*. In areas where the perceived cause of epilepsy is widely associated with witchcraft or demonic possession, care seeking is directed toward traditional healers rather than hospital or clinic based healing *(223, 224, 227–229)*.

Many studies show that traditional treatments can lead to dangerous actions such as placing a spoon or cloth in the mouth, tying a person down or putting their head in a toilet hole *(215, 224)*.

Misconceptions, negative attitudes and stigma surrounding epilepsy are not limited to sub-Saharan Africa or low-resource settings. A systematic review of studies in high-income and developed countries found that misconceptions of epilepsy persist and there is a relative paucity of recent information from the Americas, Europe and Australia, and a very limited literature on stigma-reduction strategies in these settings. Key misconceptions about epilepsy over the past decade include limitations on social roles (e.g. marriage and employment), personal characteristics (dangerous or unreliable), restrictions placed on activities (e.g. driving or sports), and inaccurate beliefs regarding the causes, treatment and prognosis of epilepsy *(230)*.

Consequences of stigma in epilepsy

Globally, stigmatized people with epilepsy are more likely to have lower self-esteem and quality of life, greater social isolation, poorer psychological health and worse epilepsy control *(95)*. The burden of stigma, however, is greatest for people who live in low-income, less developed settings, and for this reason, stigma contributes to social and economic morbidity *(7)*. Further stresses and stigmatization can occur to those who are elderly *(231)*. In fearing contamination or alienation from others, families may banish the person with epilepsy from the community to live as outcasts or force them to live in separate sleeping quarters away from the rest of the household *(215, 223)*. In many Asian and African cultures, females with epilepsy are viewed as poor wives: unable to properly take care of children, cook on a fire or contribute to household chores. Unmarried adult females are vulnerable to sexual exploitation, physical abuse and extreme poverty. In a study from Zambia, sexual assault rates for women with epilepsy were 20% versus 3% among women with other chronic conditions *(232)*. Women with epilepsy in Nigeria face multiple social and economic challenges with one-third victimized with physical abuse from members of their household and 10% reporting sexual assault *(233)*. In the United Republic of Tanzania, youth with epilepsy were more likely to experience adverse employment, educational and relationship outcomes in the transition to adult life, with the greatest disadvantage experienced by females *(234)*.

Marriage

People with epilepsy frequently experience problems in marriage, including reduced marital prospects, poor marital outcomes and diminished quality of married life *(235)*.

In arranged marriages, families of women with epilepsy often hide the fact that they have epilepsy during marital negotiations due to fear that disclosure will lead to rejection of the proposed marriage; hiding epilepsy is associated with increased rates of separation and divorce *(235, 236)*.

The belief that epilepsy is inherited contributes to the reduced marriage prospects and is believed to contribute to high levels of stigma in Ethiopia (81%) and Benin (69%); in the United Republic of Tanzania, families do not want their sons to marry women with epilepsy based on a belief that they would have difficulty with childbirth *(236)*.

Population studies have looked at attitudes towards marriage in people with epilepsy. In sub-Saharan Africa, refusing to let your child marry a person with epilepsy ranges from 33% in Badissa, Cameroon, 82.5% in Ethiopia *(221)* to 88% in Nigeria *(237)*. In Ecuador 22% would object to their child marrying someone with epilepsy *(238)*, in Kuwait 55% *(239)*, in the Russian Federation 57% *(220)*, in Greece 66% *(240)*, in Hungary 41% *(241)*, in the Republic of Korea 94% *(242)* and in Thailand 44% *(243)*. A community or culture that emphasizes a family's honour may be more likely to object to marriage with a person with epilepsy as compared with a community that emphasizes freedom of choice in marriage *(219)*.

Legislation restricting marriage among people with epilepsy existed in both HIC and LMIC. People with epilepsy were forbidden to marry in 17 states in the United States of America until 1956 and in the United Kingdom of Great Britain and Northern Ireland until 1971. In 1956, 18 states in the United States of America called for the sterilization, on eugenic grounds, of people with epilepsy; the last state to repeal this law did so only in 1980 *(244)*. In some parts of the world, epilepsy is still commonly viewed as a reason for annulling marriages or simply prohibiting them. In India, the Hindu Marriage Act of 1955 was amended in 1976 to enable people with epilepsy to legally marry *(245)*. In India, 25% of women with epilepsy had problems getting married, and 70% concealed their epilepsy from their husbands *(246)*.

Driving legislation

Ineligibility for a driving licence frequently imposes restrictions on social participation and choice of employment. To avoid contributing to stigma, social policy should be guided by scientific evidence *(222)*. This is particularly relevant to punitive driving legislation where there is a lifelong ban on driving after a diagnosis of epilepsy in many parts of the world including the English-speaking Caribbean, China, Georgia, India and Malaysia *(247)*. Chapter 2 provides information on what governments can do to address restrictive driving legislation.

Insurance

Civil rights violations, such as unequal access to health and life insurance, or prejudicial weighting of health insurance provisions are common in epilepsy *(121)*. Health insurance premiums are very high for people with epilepsy irrespective of seizure status or, as a pre-existing condition, may not be covered at all. Even if covered, visits to specialists and certain procedures are not likely to be covered.

School

A systemic review of knowledge and attitudes towards epilepsy among teachers in 27 countries found pervasive negative attitudes and deficits in knowledge *(248)*. Many teachers do not receive formal training in epilepsy and lack confidence to work with a child with epilepsy *(249, 250)*. In Nigeria, 25% of school teachers would object to having a child with epilepsy in their class *(251)*, and teachers in Ethiopia wrongly believe epilepsy is caused by insanity *(252)*.

Removal from school or denial of access to school for a child due to epilepsy, because of their epilepsy, has lifelong impacts on the development of social, emotional and vocational skills. WHA68.20 urges Member States "to ensure public awareness of and education about epilepsy, in particular in primary and secondary schools, to help to reduce the misconceptions, stigmatization and discrimination regarding people with epilepsy and their families that are widespread in many countries and regions".

To reduce stigma in the classroom, a group in Canada evaluated a programme called Thinking about epilepsy to teach children aged 9 to 11 years how to support a classmate who has epilepsy. Evidence from a randomized controlled trial shows the programme significantly improved a student's

epilepsy knowledge and attitudes *(253)*. Australia's Epilepsy Smart Schools is a national evidence-based programme by the Epilepsy Foundation, developed to support schools to provide a safe and inclusive educational environment for students living with epilepsy *(254)*. In Austria, a three-lesson teaching unit significantly increased high school students' knowledge about epilepsy and positively influenced their attitude towards the disease *(255)*. An educational video and an educational drama were effective in improving the knowledge of epilepsy in school-aged children in the Czechia *(256)*. A comic book used in Ethiopia positively changed misconceptions and provided correct information about epilepsy *(257)*.

In the Myanmar Epilepsy Initiative, led by WHO and the Ministry of Health and Sports, a diverse range of information, education and communication materials were developed to raise awareness about epilepsy in the general public and services available in the community. Service announcements on TV and radio featured local celebrities, a comic book was distributed in schools, and posters were shared with family members, teachers and other community members to reduce stigma (see Chapter 2).

Income and employment

Over 60% of the world's employed population are in informal employment *(258)*. In many LMIC the majority of people are informally employed as farmers and entrepreneurs. Many enter the informal economy not by choice, but as a consequence of a lack of opportunities in the formal economy and in the absence of other means of livelihood. People with epilepsy tend to not be adequately trained for informal sector work because of fears that they will not perform or they will be injured. In the same countries, social welfare systems are poorly resourced so unemployed people are not adequately supported.

Asia and Africa were shown to have unfavourable attitudes towards employment in epilepsy, where 50% of the published papers in Asia and 80% of the published papers in Africa reported more than 40% of participants with negative attitudes, as compared with none in North and South America *(219)*. A systematic review showed people with epilepsy had lower employment rates as compared with the general population in all continents *(259)*. Lower employment status may be related to felt stigma *(7)*. Many individuals with epilepsy report that stigma poses a barrier to employment and leads to fear, embarrassment, rejection and hostility by others at the workplace. Unemployment may be linked to the threat of enacted stigma for those who chose to conceal their disease fearing they will be terminated or treated poorly by co-workers *(260)*. In an Australian study, 47% of people with epilepsy who were currently employed reported unfair treatment while at the workplace *(261)*.

In Brazil, having epilepsy was strongly associated with higher unemployment rates, job layoffs and being unfit to work *(262)*. Possible reasons why employers fear hiring people with epilepsy, even when they are capable of doing the job, is that seizures are unpredictable and do not remain hidden in all social situations. Witnessed seizures can interfere with the public image of the employer. In the United States of America, the Epilepsy Foundation also cited public "fear" of witnessing a seizure as a reason for high rates of unemployment for people with epilepsy.

It is clear is that stigma is a major burden that people with epilepsy have to live with to varying degrees, depending on where they are in the world. In most LMIC, stigma can have enormous social, economic and safety consequences, greatly impacting those with epilepsy and their capacity to work, develop relationships and to be productive citizens *(232, 263)*.

Poorer quality of life

The combination of poverty, social role expectations, limited health care and traditional beliefs can severely limit the lives of people with epilepsy. Besides social consequences, stigmatization is shown to be related to negative psychological and psychiatric comorbidities, leading to poor quality of life. Stigmatization and discrimination lead to worsening of psychological well-being, resulting in greater stigmatization than experienced before *(264)*.

Stigma is associated with higher levels of depression and anxiety *(265, 266)*. The psychological distress, failure of adjustment and coping, and self-perceived stigma contribute to poor quality of life.

In addition to personal impact, the family and care partners of people with epilepsy also experience increased burden and stress, and poorer family functioning. This may result in either poorer family support or family overprotection, and consequently may reinforce stigma in epilepsy. And stigma is an important predictor of depression among those with epilepsy following employment status and social support *(267)*.

Cultural approaches to reducing stigma

In many parts of Asia and Africa, treatments linked to indigenous beliefs are widely used by people with epilepsy and their families. Promoting integration of religious, traditional and indigenous treatments into health systems has the potential to reduce stigma and improve psychosocial outcomes. The experience of epilepsy is culturally mediated and the meanings attributed to the condition can have a great impact on its social course. Developing partnerships with traditional health practitioners may help to reach more people with epilepsy and is a strategy to improve access to effective treatment and alter misconceptions and stigmatizing practices *(215, 268)*.

Derogatory language and negative media depictions hurt people with epilepsy and perpetuate stigma. In addition, vocabulary, e.g. "epileptic" versus "person with epilepsy" was shown to negatively influence perceptions and have consequences in terms of stigma *(269)*. In various Asian countries, advocates have played a key role in changing the word "epilepsy" in their region as it was associated with stigmatization and misconception. For example, epilepsy in Chinese and many other Asian countries is associated with insanity and animals such as goats and pigs, contributing to misconceptions and stigma. The word "epilepsy" has been replaced by a neutral term in several countries, including in Malaysia and the Republic of Korea. The name change was approved by the Government in the Republic of Korea in 2011 *(270)*. The general principles of the new terminology applied included: a neutral position; implying a scientific basis; easily differentiated from words of resemblance (e.g. convulsion, fits, spasm, etc.); easy to use as a noun and an adjective; and more likely to be acceptable in global epilepsy communities.

Reducing felt or internalized stigma

General investments in health care do not necessarily lead to improvements in epilepsy-related stigma. To reduce stigma, funds need to be directed toward epilepsy awareness and stigma-reduction programmes for the wider public *(218, 222)*. In the Americas, Australia and Europe only a dozen interventional studies have been reported over the past decade targeting stigma reduction in the general population and were limited to health care and educational settings *(230)*.

Perceptions of internalized stigma in children with epilepsy are associated with fear and worry about having epilepsy and the need for information and support *(271)*. Social support has been found to lower stigma *(272)*. Peer support groups in Zambia reduced felt stigma in youth with epilepsy *(273)*. Counselling, individual and group interventions that develop resiliency in people with epilepsy have been shown to reduce stigma *(274)*.

Reducing institutionalized stigma

Knowledge about epilepsy is an important factor in reducing the degree of discrimination and negative attitudes towards people with epilepsy *(219)*. Studies show that people with less knowledge about epilepsy, or without personal contact with someone with epilepsy, have poorer attitudes *(219)*.

Policy-makers can reduce stigma by changing legislation beginning with discriminatory driving, education, employment and marriage laws. Workshops and curricula can be developed for

Box 5.1 Getting started

Individuals and families: Provide information to improve health literacy and support to cope with the fear of living with the unpredictability of seizures. Health care providers and community epilepsy agencies can support individuals and families to learn more about their diagnosis and ways to disclose their epilepsy to others.

Epilepsy support/self-help groups: People with epilepsy develop resourcefulness and resilience in putting the stigma of their condition aside by participating in support group meetings, virtual chat rooms and private forums where they can exchange ideas and learn coping strategies through peer support. Sharing stories of resilience can also be empowering for persons with epilepsy *(274, 275)*.

School education programmes: Teacher and student education is generally advocated as the best approach to reduce misconceptions and improve knowledge in the school setting and to keep children with epilepsy in the classroom where they can become educated and develop friendships and social skills.

Stigma training for health and social care providers: Appropriate epilepsy education and training can help nurses, primary care providers, midwives, mental health workers, social workers, pharmacists and community health workers to understand the psychosocial impact that epilepsy has on the individual and their family.

Partnerships with traditional healers: Task-sharing models where community members and traditional medicine healers are trained to decrease stigma and improve referral to appropriate health care.

Awareness-raising campaigns: A main barrier to reducing the epilepsy treatment gap in LMIC has been the misconceptions that surround the condition. Raising awareness and educating the public about epilepsy remains a key priority. This includes learning more about people's current attitudes and knowledge about epilepsy, developing key messages which address the knowledge gaps, and creating communication materials that are pointed, relevant and practical for use by their intended audiences. Engagement with stakeholders at the local, national and international levels is also critical to ensuring sustainability of any awareness-raising campaign.

Legislation: Formal recognition of the rights of people living with epilepsy and their caregivers through legislation, funding and regulatory processes will help reduce discriminatory practices.

Source: WHO, 2015 *(276)*.

teachers, employers, and health and social service providers to create inclusive, safe environments. Providing people with epilepsy and their family with information about their disease at the time of diagnosis is a strategy for increasing disclosure rates.

A multipronged public health response is necessary to address stigma and misconceptions in epilepsy (Box 5.1). The approach needs to include interventions for the person with epilepsy and their family, teachers, employers, health and social care providers, traditional healers, media, community and policy-makers.

Conclusion and way forward

There is a need for further qualitative and quantitative studies to inform relevant and targeted intervention studies related to stigma in epilepsy. There are gaps in our understanding of the mechanisms of stigma and a shortage of data about the long-term outcomes of and costs of stigma to individuals, families and society. There is an identified need for culturally responsive, person-oriented approaches to exploring the subject and its amelioration and a need for robust interdisciplinary trials of stigma reduction interventions.

CHAPTER 5

The social response: misconceptions and stigma in epilepsy

KEY MESSAGES

- **Stigma is a significant contributor to poor physical, mental and social health, lower educational and employment opportunities in persons with epilepsy and requires a multipronged strategy that is culturally appropriate, multisectoral and collaborative.**
- **Identifying and dispelling the misconceptions that cause stigma might be the first step to reducing stigma.**
- **Funding needs to be directed toward epilepsy awareness and stigma reduction programmes as knowledge is an important factor in reducing the degree of discrimination and negative attitudes towards people with epilepsy. This includes education of traditional and faith healers, and the wider community.**
- **The burden of stigma is greatest in persons who live in low-income, less developed settings contributing to social and economic morbidity.**
- **Supporting people with epilepsy with treatment, schooling, vocational education, formal and informal employment might support their individual resilience against stigma.**

CHAPTER 6

Prevention of epilepsy

Prevention of epilepsy

Introduction

The global burden of epilepsy, affecting an estimated 50 million people *(277)*, points to the need for its prevention where such possibilities exist. In this chapter we address opportunities for primary prevention, which is, preventing the occurrence of brain insults which may trigger the development of epilepsy. We also note the need to develop and employ secondary prevention treatments, that is, early therapies following an initial insult to limit the extent of brain injury or otherwise interrupt the process of epileptogenesis. The definitions of primary and secondary prevention are listed opposite and concepts illustrated in Fig. 6.1.

The ILAE Prevention Task Force identified: pre- or perinatal brain insults; CNS infections; TBI; and stroke as major preventable causes *(278)*. Together, these account for a large proportion of all epilepsies – nearly one-fourth – a finding common to LMIC, as well as HIC. These proportions do not fully convey the absolute public health burdens attributable to preventable causes.

In this chapter, we consider each of the four etiologic categories, taking into account ILAE Prevention Task Force estimates of their occurrence, as well as evidence for effectiveness of prevention strategies.

DEFINITIONS

Primary prevention: Preventing the initial event (insult, injury or disease) that affects the brain to begin the development of epilepsy.

Secondary prevention: Early therapies following an initial event to limit the extent of brain injury or otherwise interrupt the process of epileptogenesis.

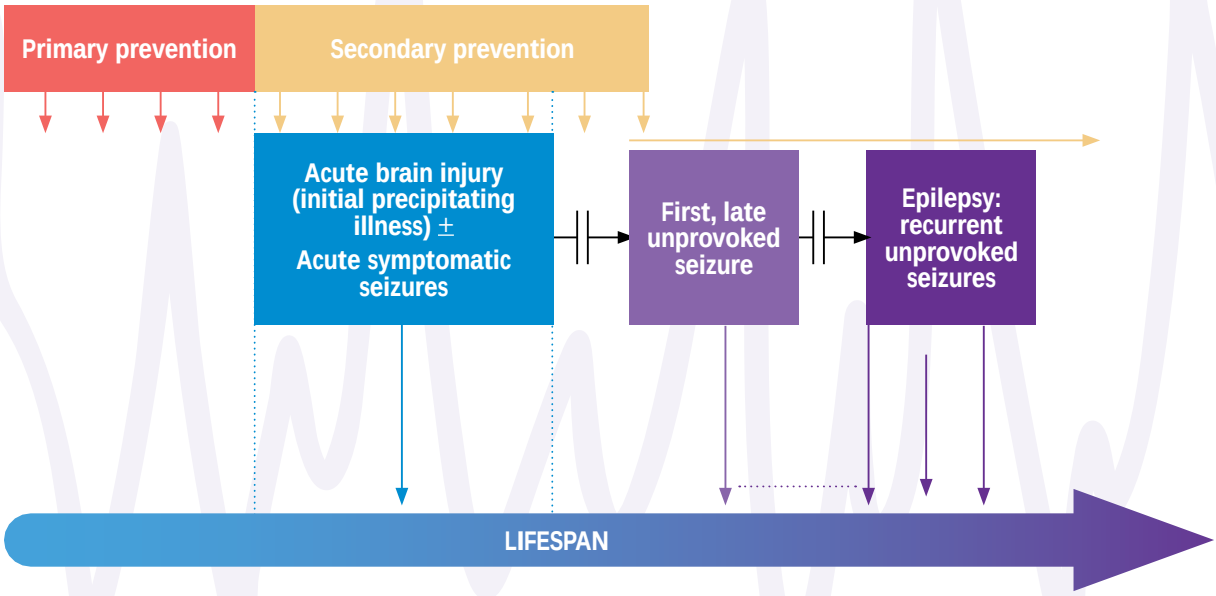
Epileptogenesis: An evolving process following brain insults by which the brain develops recurrent spontaneous seizures.

Comparative risk: A ratio of incidence comparing two populations or groups of people, often used to compare groups with and without a suspected "risk factor." Comparative risks are described by measures of association such as rate ratio, odds ratio and hazard ratio.

Cause of disease: An event or characteristic that initiates or accelerates the development of a disease. Disease may arise from the interaction of more than one cause. Proof that an event or characteristic causes disease requires consistent, reproducible evidence of association, a plausible time relationship, and other supportive evidence. The process of drawing conclusions from such evidence may be termed "causal inference."

Attributable etiologic fraction: The proportion or percentage of cases of epilepsy cases that can be attributed to a specific cause.

Fig. 6.1 Hypothetical timeline for primary and secondary epilepsy prevention



Preventing the burden of epilepsy

Potentially preventable causes of epilepsy (pre- or perinatal brain insults, CNS infections, TBI and stroke) account for a large proportion of all epilepsies. In HIC, stroke is the leading potentially preventable cause and perinatal insults are leading causes in LMIC. However, estimating the global burden of epilepsy attributable to preventable etiologies is complicated, given wide regional variations in epilepsy incidence and the scarcity of sound epidemiological data from many world regions. Studies from LMIC may tend to underestimate proportions of cases attributed to specific etiologies due to missing data; insufficient diagnostic tools (e.g. MRI and EEG) to establish causality of epilepsy. Uncertainty over causality often precludes confident determinations of attributable etiology. With that caveat, we describe the burden and associations of the following reported risk factors.

Perinatal risk factors

Perinatal risk factors related to epilepsy include gestational age at delivery, birth weight, maternal conditions such as pre-eclampsia, presence and skill of birth attendants, method of delivery, hypoxic-ischemic encephalopathy (a type of brain damage in infants where there is a lack of blood flow and oxygen), neonatal hypoglycaemia (low blood sugar), perinatal infection, and other adverse events and conditions. Among children with epilepsy, the ILAE Prevention Task Force reports median estimates of about 15% and 17% of cases attributed to such perinatal causes in HIC and LMIC, respectively *(278)*. These factors appear to be particularly important in Africa *(74)* and Asia *(279)*, reflecting inequities in access to health services and poor perinatal care *(280)*. In one multicentre study in sub-Saharan Africa, perinatal problems were estimated to account for about a third of the epilepsies *(281)*.

Prenatal risk factors for development of epilepsy include poor intrauterine growth and fetal exposure to infections (such as cytomegalovirus and toxoplasmosis), toxins (maternal smoking) and vascular events *(282–284)*. There is a lack of examination of the role of heavy metals and other compounds, gene-environment interactions, or multiple risk factor interactions that involve brain damage with comorbid conditions such as intellectual or motor disabilities.

Most studies have reported an association between prematurity (gestational age less than 37 weeks) and epilepsy *(285–288)*. As gestational age decreases, the risk of developing epilepsy increases *(282, 289)*. Neonatal seizures often reflect underlying brain damage consequent to prematurity *(290)*, hypoxic-ischemic encephalopathy, brain haemorrhage or stroke *(291)*. These may also be early manifestations of cerebral palsy *(292)*. Neonatal hypoglycaemia, more frequent in preterm infants and infants of diabetic mothers, is another risk factor for the development of epilepsy *(293, 294)*, as is neonatal jaundice *(295)*. Hypoxic-ischemic encephalopathy is an important cause of brain damage during the perinatal period, in term and preterm babies. It is associated with the development of epilepsy in children and adolescents, often following neonatal seizures *(296–298)*.

Pre-eclampsia or eclampsia is associated with the development of epilepsy in exposed infants *(284, 287, 299–301)*. Prolonged labour and instrument delivery also appear to be associated with the development of epilepsy in the infant *(286, 299)*. Delivery by caesarean section was protective in one study *(302)*.

Central nervous system infections

Central nervous system infections addressed by population-based studies mainly comprise the following categories: bacterial meningitis, viral encephalitis, cerebral malaria and neurocysticercosis. These studies suggest a perceptible difference in the attributable fraction according to country income status. The incidence of CNS infections is perhaps much higher in LMIC, but precise estimates are lacking.

The ILAE Prevention Task Force review indicates that bacterial meningitis and viral encephalitides combined account for approximately 2–3% of all epilepsies in HIC, with annual incidence around 14 per 100 000 population *(278, 303, 304)*. On the other hand, bacterial meningitis and viral encephalitides combined account for about 5% of epilepsies in LMIC *(278)*. WHO estimates that 448 000 cases of bacterial meningitis (due to *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*) occur every year *(305)*.

WHO estimates 216 million cases of malaria occur every year *(306)*. Of the estimated number of malaria cases, some 600 000 children in sub-Saharan Africa under 5 years of age are afflicted by its most serious form, cerebral malaria *(307)*. Neurological sequelae, including seizures, occur in 10–17% children affected by cerebral malaria *(308)*.

In some LMIC regions where *Taenia solium* – the parasite causing cysticercosis – is highly endemic, roughly one-third of all epilepsies, 2.6–8.3 million cases, are attributed to brain involvement, termed neurocysticercosis *(278, 309)*. This high proportion should be interpreted with some caution, as most of the studies examined prevalent cases of epilepsy where temporal relationships between neurocysticercosis infection and seizure onset could not be determined *(310)*.

An association between epilepsy and a number of infections has been suggested on the basis of ecological, epidemiological, clinical and pathological studies. A number of these infections are preventable, particularly with rapid treatment, which could potentially reduce the high rates of epilepsy, especially in countries where these infections are most prevalent and access to health care is limited. A list of such infections is provided in Table 6.1.

For reasons already noted, causal relationships have not been fully established for all the associations noted in Table 6.1 *(311)*. For some infections (e.g. *Herpes simplex* encephalitis and bacterial meningitis), epilepsy causality is long accepted. For others (e.g. toxocariasis and onchocerciasis), notwithstanding demonstrated associations in representative populations, causality is not well established for want of evidence of clear epileptogenic substrates. Evidence of more indirect mechanisms (e.g. immunological or genetic) that might underlie causal connections between infection and epilepsy may be useful. Preliminary evidence for the existence of immunological mechanisms has been evidenced in the case of onchocerciasis-associated epilepsy *(312)*.

Table 6.1 Infections as putative risk factors for epilepsy

Infectious disorder	Agents
Bacterial meningitis	*Haemophilus influenzae* type b, *Streptococcus pneumoniae*, *Neisseria meningitidis*
Sporadic encephalitis	Herpes simplex virus type 1 and 2, varicella zoster, Epstein-Barr and cytomegalovirus viruses and human herpes viruses type 6 and 7; Coxsackie, echo, enterovirus 70 and 71, parecho and polio viruses; Measles and mumps viruses
Geographically restricted encephalitis	Americas: West Nile, La Crosse, St Louis, Rocio, Powassan encephalitis, Venezuelan encephalitis, eastern and western equine encephalitis, Colorado tick fever, dengue and rabies viruses Europe/Middle East: Tick-borne, West Nile, Tosana, rabies, dengue and louping ill viruses Africa: West Nile, rabies, Rift valley fever, Crimean-Congo haemorrhagic fever, dengue and Chikungunya viruses Asia: Japanese B encephalitis, West Nile, Murray valley encephalitis, dengue, Nipah, Chikungunya and rabies viruses Australia: Murray valley encephalitis, Japanese encephalitis, dengue and Kunjin viruses
Cerebral malaria	Plasmodium falciparum
Cestode infestations	*Taenia solium, T. multiceps, Spirometra* spp., *Echinococcus (E. granulosus/E. multilocularis)*
Nematode infestations	*Trichinella spiralis, Angiostrongylus cantonensis, Strongyloides stercoralis, Toxocara canis, Onchocerca volvulus*
Trematode infestations	*Schistosoma (S. mansoni/S. haematobium/S. japonicum) Paragonimus (P. westermani/P. mexicanus)*

Source: Adapted from Misra et al, 2008 *(311)*.

Traumatic brain injury

Traumatic brain injury yields similar attributed fractions of epilepsy cases in LMIC and HIC, with respective median estimates of 4.2% and 5.3% *(278)*. These estimated proportions diverge among children, where they are higher in LMIC (6.6%) compared with HIC (2.6%). Road traffic injuries, falls and violence are the cause of most TBI *(313, 314)*. Road traffic injuries include those involving pedestrians, bicyclists, motorcyclists, as well as motorized and other vehicle occupants. Rates vary considerably among localities and countries, as do the proportions attributed to each category *(315)*. In general, pedestrian injuries are more common in LMIC and among children in all countries. Falls may be categorized as those occurring at the same or ground level and those occurring from elevations such as ladders, balconies, trees or rooftops. Same- or nearly same-level falls are most frequent among very young children and older adults, sometimes resulting in serious TBI. Falls from elevations or heights occur across all age groups, often resulting in more severe injury. Many falls from elevations are occupational, ranging from construction injuries in all countries *(316)* to picking fruit from high trees, especially in tropical countries. Lastly, TBI resulting from violence occurs across all ages and under many circumstances. TBI can result from abusive trauma in very young children, violence against women, elder abuse, youth violence and armed conflicts *(317)*. In recent years an increasing number of people has been seen with military and military-type injuries *(318)*. The full public health burden of violence – and particularly of TBI resulting from violence – is poorly documented, especially in LMIC. In general, it appears that rates of injury arising from violence are higher in LMIC.

Most studies show elevated rates of TBI in small children, youths and young adults, and seniors. Males are at higher risk than females. Estimates

of medically attended TBI incidence vary widely among numerous studies, most of which represent localities in Europe or North America *(319)*. A recent meta-analysis yielded a pooled annual incidence rate of 228 per 100 000 in European studies and 331 per 100 000 in North American studies. There are few published studies representing Asia, Africa or South America; these do not provide a sufficient basis for confident continental estimates.

Risks of epilepsy appear greatest with penetrating brain injury with a reported adjusted odds ratio of 18.8 *(320)*. A population-based cohort study of people hospitalized with severe, compared with mild TBI, yielded a risk ratio of 2.5 *(321)*.

Stroke

Stroke – including ischemic and haemorrhagic forms – is one of the most common preventable causes of epilepsy, with median estimated fractions of 11.9% in HIC and 2.7% in LMIC *(278)*. Globally, stroke is the second most common cause of deaths and the third most common cause of disability; estimates indicate there are nearly 26 million stroke survivors *(322)*. Seizures after stroke are associated with significantly increased premature mortality, disability and higher resource allocation and costs *(323–325)*. In population-based studies, stroke was identified as a common etiology of status epilepticus (12–40% in HIC, 5–15% in LMIC) – a condition associated with premature mortality and morbidity *(326)*.

Stroke is the leading cause of epilepsy in older adults, the attributed etiology in 19–24% of prevalent cases and half or more of all new-onset cases *(278)*. There could be several reasons for projecting an increase in the public health burden of post-stroke epilepsy across the world in the coming decades. First, advances in acute stroke treatment, including early thrombolysis and endovascular treatment, reduce stroke mortality *(327, 328)*, thus increasing numbers of stroke survivors. The long-term cumulative risk of post-stroke epilepsy is also high (8.2% after 2 years and 12.4% after 10 years) *(329, 330)*. Lastly, demographic projections indicate that the number and proportions of older adults – the population at greatest risk of stroke – will increase several-fold in the future. By 2050 the global population of adults aged over 60 years is projected to more than double its size in 2015, reaching nearly 2.1 billion. This proportionate increase is expected to be greater in Latin America, Asia and Africa (64–74%), compared with North America and Europe (23–41%) *(331)*.

Epilepsy after stroke is also not uncommon in children. Stroke is the second most common cause of seizures in term neonates and is associated with adverse long-term neurodevelopmental outcomes. In several recent studies of children and adolescents with stroke, the rate of post-stroke epilepsy ranged from 19% to 27% within 2–4 years after the stroke onset *(332, 333)*.

Haemorrhage, as well as early seizures in the acute interval following stroke, are associated with increased risk of epilepsy. Risks of epilepsy also vary according to stroke subtype, stroke severity, lesion location and the occurrence of post-stroke bacterial infections *(323, 334, 335)*.

There is also a bidirectional association between epilepsy and stroke demonstrated by studies showing higher risk of stroke in people with epilepsy. The risk of stroke in people with epilepsy appears similar to that in controls aged 10 years or older. An increased risk of stroke has been reported in people with seizure onset after age 60, with a relative hazard risk of 2.9 *(336, 337)*.

Other factors

Other factors, such as alcohol and substance abuse use, may increase the development of epilepsy through increasing the risk of TBI or stroke. In addition, withdrawal from alcohol is associated with seizures *(338)*.

Comorbidities

An increasing amount of evidence suggests an association between epilepsy and multiple somatic and psychiatric conditions (see Chapter 1). There is an established bidirectional relationship between epilepsy and a number of comorbidities,

e.g. depression and anxiety, which is best explained by common underlying mechanisms and risk factors *(53, 339, 340)*. Presence of these psychiatric comorbidities increases risk of epilepsy after brain insults (TBI and others) *(320, 321)* and should be taken into account when preventive strategies are considered.

Strategies for the prevention of epilepsy

The prevention of epilepsy is an appealing concept, but regrettably has not attracted much attention until recent times. Identifying preventable causes of epilepsy is a critical step to the development of primary preventive strategies. Secondary preventive strategies require an understanding of epileptogenesis after a brain injury (whether due to an infection, trauma or brain degeneration). Unfortunately, how the brain produces seizures after such insults is highly complex and poorly understood.

Epileptogenesis is fortunately a slow process, involving a series of complex structural, network, cellular, molecular and electrophysiological changes. Epileptogenesis is also driven by multiple genetic and environmental risk factors (apart from rare monogenetically inherited conditions), further complicating the development of preventive approaches. Some of these risk factors are modifiable, while others are not.

There is yet no good clinical marker for the process of epileptogenesis. Nor has the prophylactic use of available antiseizure medicine been shown to influence epileptogenesis *(341)*. While several studies have clearly shown that antiseizure medicines effectively reduce the occurrence of early (acute, provoked or symptomatic) seizures particularly after TBI, stroke and CNS infections, currently used antiseizure medicines do not appear to have a clinically significant effect on the development of late (or unprovoked) seizures.

Hence, the four important preventable risk factors discussed – perinatal insults, CNS infections, TBI and stroke – present opportunities and challenges in developing preventive approaches to epilepsies. Below, we discuss primary and secondary prevention opportunities.

Primary prevention

Several experimental and observational studies have documented impressive impacts of primary prevention in reducing the incidence of perinatal insults, CNS infections, TBI and stroke as described below. The impact of preventive approaches on the burden of epilepsy per se has not been studied. We discuss below primary preventive approaches for each of the four conditions. A summary of preventable causes of epilepsy and interventions can be found in Table 6.2.

Perinatal insults: A large proportion of the pre- and perinatal risk factors described above may be preventable where sufficient maternal health services are available. Barriers to access to such services – involving economics, distance and scarcity of facilities and personnel – are widespread in many LMIC *(342)*, but are also seen in some HIC *(343, 344)*. WHO recommends components of such care that should be universally available *(345)*. At a minimum, the essential components of pre- and perinatal care include access to screening mechanisms for pregnancy complications for all women, the availability of trained birth attendants and hygienic birthing environments, appropriate referrals to specialist obstetrical and neonatal care where needed, and the adoption of standardized protocols for care during the pre-, peri- and postnatal periods *(345)*.

Central nervous system infections: Measurable decreases in frequency of occurrence of bacterial meningitis have been documented in several regions of the world. Widespread use of vaccines against *H. influenzae* b, *N. meningitidis* and – in selected populations – *S. pneumoniae*, the three main agents responsible for bacterial meningitis, have been largely responsible for this documented decline *(346–348)*. However, much needs to be achieved in this area of infectious disease control, given meningococcal meningitis remains highly

Table 6.2 Summary of preventable causes of epilepsy and interventions

Cause	Estimated attributable fraction	Primary preventive measures
Pre- and perinatal insults E.g. prematurity, fetal exposures to infections, toxins, cerebral haemorrhage or infarction, hypoxic-ischaemic encephalopathy	5% (HIC)	Maternal and child health care systems with universally available: screening for pregnancy complications; trained birth attendants and hygienic birthing environments; referral to obstetrical and neonatal care as needed; and standardized protocols for care during the pre-, peri- and postnatal periods
	11% (LMIC)	
Central nervous system infections E.g. bacterial meningitis, viral encephalitis, parasitosis	2% (HIC)	Communicable disease control programmes making universally available: immunizations for *H. influenzae* b, *N. meningitidis* and *S. pneumoniae*; malaria control programmes in endemic areas; and hygienic pig husbandry programmes and human sanitary waste management
	5% (LMIC)	
Traumatic brain injury E.g. attributable to road traffic collision, falls and violence	5% (HIC)	Multiple road traffic safety measures and programmes; fall prevention measures for children, older adults and high-risk occupations; violence prevention programmes
	4% (LMIC)	
Stroke Cerebral infarction and haemorrhage	12% (HIC)	Individual interventions and community programmes to reduce cardiovascular risk factors: e.g. hypertension, diabetes mellitus, hyperlipidaemia, obesity and tobacco use
	3% (LMIC)	
Total Combined pre- and perinatal insults, CNS infection, traumatic brain injury and stroke	25% (HIC)	See above
	24% (LMIC)	

Note: The estimated attributable fraction is the estimated proportion of all epilepsy cases in a general population that may be attributed to each cause category.
Source: Thurman et al., 2018 *(278)*.

endemic in much of sub-Saharan Africa *(349)*. Implementing vaccination programmes against these most common pathogens can reduce the burden of bacterial meningitis, and thereby epilepsy associated with meningitis. Similarly, effective vaccination measures have been demonstrated for the prevention of Japanese encephalitis, the leading cause of viral encephalitis in Asia *(350)*.

Falciparum malaria is another infectious disorder for which comprehensive multidimensional control programmes have been recommended and successfully tested *(351-354)*, but large-scale application is still pending owing to social, economic and political constraints. The programmes essentially employ simple means such as indoor residual spraying with insecticides and long-lasting insecticide-impregnated nets used as barriers during sleep to control mosquito-borne illnesses. The success of these methods has led to a resurgence of control efforts, with increased political commitment and financial investment from governments and nongovernmental agencies. Their intent is to implement these measures in at least 80% of the malaria-endemic regions of the world *(355)*.

Lastly, in the case of cysticercosis, some control strategies have been tested while still others are being developed *(356, 357)*. The two-host lifecycle of *T. solium* and the absence of a wild reservoir make the parasite particularly amenable to control. Interventions to eliminate cysticercosis include porcine vaccination and cysticidal chemotherapy, enforcement of pork hygiene, early detection and treatment of human adult tapeworm carriers, corralling pigs, and sanitary faecal disposal. National policies including public education are needed in cysticercosis-endemic countries to control and eliminate the infestation (see Chapter 2).

Traumatic brain injury: Approaches to primary prevention of TBI vary according to the injury category. HIC have had substantial success in lowering rates of road traffic injuries in the last half

century *(314)*, using strategies such as legislation and enforcement of speed limits and alcohol use while driving, engineering safer vehicles and roadways, helmet use and occupant safety restraints. Data show that LMIC bear the greatest burden of road traffic fatalities and injuries *(315)*. Further improvements, and especially the adaptation and implementation of such strategies in LMIC, are needed to prevent TBI *(315, 358)*.

Strategies have also been developed to reduce the incidence of falls in children *(359)* and older adults *(360)* and of occupational fall injuries *(316)*. These strategies have been successfully implemented in many HIC with documented reductions in the incidence of TBI. Likewise, many strategies to reduce violence have been proposed. These include education and support for parents and caregivers; education in life skills for children and adolescents; reducing the availability and harmful use of alcohol; reducing access to weapons; promoting gender equality; education to change cultural and social norms that support violence; programmes to provide early identification, care and support for victims of violence; and others *(317)*. To date, the implementation of such strategies has been partial at best, even in HIC, and much more effort involving public policy and programmes is needed.

Stroke: The primary prevention of stroke is focused on cardiovascular risk factor reduction, e.g. measures to prevent or control hypertension, hyperlipidaemia, diabetes and obesity, and to avoid tobacco and excessive alcohol use. Strategies include pharmacological and nonpharmacological (including lifestyle) interventions. In the case of hypertension, several trials have demonstrated that effectively treating elevated blood pressure leads to reduction in the risk of ischemic and haemorrhagic stroke by nearly 40% *(361)*. The beneficial effects of weight reduction, exercise and smoking cessation have not been studied in experimental conditions, but are evident from observational data. These strategies can be applied at individual, community and population levels *(362, 363)*.

Secondary prevention

The assumption that antiseizure medicines administered during and soon after preventable risk factors of epilepsy (perinatal insults, CNS infections, TBI or stroke) will actually prevent or halt epilepsy development lacks supportive evidence. Specifically, no trials of antiseizure medicines administered in the acute or early recovery phase of a brain injury have demonstrated a meaningful impact on the development of epilepsy long term. These and other existing strategies for secondary prevention are examined below.

Pre- and perinatal insults: A number of approaches to mitigate the effects and sequelae of perinatal brain injury have been studied. Examples of such approaches include the use of hypothermia, intravenous magnesium and of the calcium channel blocking agent, flunarazine. While theoretically appealing, a substantiated impact on the outcome of perinatal brain injury has not been adequately documented.

Central nervous system infections: Antibiotic (for bacterial meningitis), antiviral (for *H. simplex* encephalitis), and antiparasitic (for neurocysticercosis) agents constitute the principal treatments of CNS infections. While the benefits of these agents in reducing mortality and morbidity are unquestionable, evidence that anti-infective treatment reduces the subsequent development of epilepsy is tenuous. For instance, clinical trials have clearly demonstrated improved rates of cyst resolution in neurocysticercosis with the use of antiparasitic treatment, e.g. albendazole *(364, 365)*. Evidence of improved seizure control or the prevention of epilepsy is less certain. A randomized placebo-controlled clinical trial did not show that albendazole significantly reduced the risk of seizure recurrence in comparison with the placebo control group *(365)*.

Corticosteroids are used as adjunctive therapy in acute bacterial meningitis. A systematic review demonstrated that adjunctive corticosteroid treatment reduced neurological sequelae (cognitive, motor or sensory deficits). The proportion of

people with neurological sequelae was smaller in the corticosteroid group *(366)*. However, none of the several trials of adjunctive corticosteroids in bacterial meningitis were sufficiently powered or of sufficient duration to detect a beneficial effect on the development of epilepsy or late unprovoked seizures.

In falciparum malaria, the period of active infection is associated with an increased risk of acute symptomatic seizures, which in turn increases the risk of late unprovoked seizures. There is no evidence, however, that antiseizure medicine reduces the risk of late unprovoked seizures or epilepsy. Three trials of phenobarbital treatment in acute cerebral malaria (most severe form of falciparum malaria) clearly demonstrated its use was associated with significantly reduced seizures during the cerebral malaria episode *(367)*. However, only one of the trials evaluated the effect of phenobarbital on late neurological complications (at 3 months) *(368)*. Again, the trial was not sufficiently powered to detect an impact on the incidence of late unprovoked seizures.

Traumatic brain injury: Research has focused on secondary prevention of epilepsy following TBI through the prophylactic use of antiseizure medicines for a period during and following TBI recovery. Unfortunately, as noted above, studies to date have not demonstrated reductions in incidence of post-traumatic epilepsy *(369–373)*. The routine use of antiseizure medicines to prevent the development of late post-traumatic seizures or epilepsy is therefore not recommended.

Stroke: Despite recent advances in understanding post-stroke epileptogenesis *(374, 375)*, evidence-based preventive strategies have not yet been developed. It is unclear whether early thrombolytic or endovascular stroke therapies affect epilepsy risk. No clinical trial has ever demonstrated that temporary antiseizure medicine after stroke prevents or mitigates epilepsy *(376)*. It remains unclear whether antiseizure medicines or other compounds (e.g. non-steroidal anti-inflammatory drugs or statins) are useful in the primary prevention of post-stroke epilepsy. As with other forms of brain insult, basic and translational studies focused on mechanisms underlying epileptogenesis are needed to identify targets for anti-epileptogenic treatment approaches, including adequately powered randomized controlled trials.

Key roles in implementing epilepsy prevention

Preventing epilepsy – whether attributable to pre- or perinatal insults, CNS infection, TBI or stroke – involves collaboration between public policy-makers, public health officials, health researchers and health care providers. Policy-makers, including legislators, can identify programmes and funding strategies to increase the adequacy of resources for public health programmes and improve access to adequate health care. Especially for TBI prevention, policy-makers can also enact regulations, monitoring and enforcement measures to promote safety in road traffic, in workplaces, in housing and buildings, and to prevent violence. Given adequate resources, public health officials can ensure appropriate programmes are implemented to promote maternal and child health, immunization, infection prevention and control, injury prevention, and public education to reduce health risks, all of which can serve to reduce risks of epilepsy. These should be implemented using evidence-based strategies adapted to local health needs. Health care providers can provide individual education and help facilitate the self-management behaviour and skills needed to reduce the risks identified above. Health care providers are also important advocates for public policy and public health measures serving to prevent epilepsy. Lastly, health researchers have important roles to investigate new strategies in primary and secondary epilepsy prevention and to advocate for the implementation of those proven effective.

Conclusion and way forward

A substantial fraction – perhaps 25% – of the global burden of epilepsy is preventable. However, present estimates of the burden of epilepsy attributable to preventable causes are at best approximate and the true burdens undoubtedly vary among world regions and localities. Available data, especially for LMIC, may underestimate the true burden of epilepsy, and well-designed studies are needed.

The strategies for preventing epilepsy arising from pre- and perinatal brain insults, CNS infections, TBI and stroke should be further developed and implemented. The development and implementation of prevention programmes adapted to local resources and needs warrant a higher priority and commitment to action by policy-makers and other public and private health agencies. These strategies can also be integrated into a broader public health response to the needs in maternal health care and obstetrics services, communicable disease control, injury prevention and cardiovascular health.

The primary prevention of epilepsy deserves more sustained attention and advocacy from health care providers, researchers, people with epilepsy and their families. Secondary prevention interventions, i.e. those timed to the period of active brain insult and thereafter, might have a beneficial effect from novel and innovative interventions in the future.

CHAPTER 6

Prevention of epilepsy

KEY MESSAGES

- **The high global burden of epilepsy requires prevention where possible.**
- **Perinatal risk factors, central nervous system infections, traumatic brain injury and stroke are the major preventable causes of epilepsy.**
- **These preventable causes account for an estimated quarter of epilepsy cases.**
- **The primary prevention of these causes requires a multisectoral approach to improving perinatal health care, communicable disease control, injury prevention and cardiovascular health to reduce the major risk factors.**
- **Despite recent advances in understanding epileptogenesis after brain injuries, there is limited evidence for secondary preventive strategies; further translational studies are needed.**

CHAPTER 7

Research on epilepsy

Research on epilepsy

Introduction

Epilepsy research has achieved remarkable progress by providing insights into possible mechanisms of epilepsy, causes and risk factors, targets for treatments, treatments for various seizure or epilepsy types and their associated conditions and consequences. Epilepsy is one of the leading neuroscience research areas, not only in terms of the number of therapeutics that have entered clinical practice, but also because it has provided electrophysiological tools to probe brain function that are widely used in neurosciences. There has also been remarkable progress in public health and epidemiological research, health services research and implementation science aimed at creating more effective policies and programmes to improve care for those living with epilepsy. Substantial epilepsy research gaps remain, however, particularly in resource-limited countries. Even in higher resource countries, a third of individuals with epilepsy have drug-resistant epilepsy, which emphasizes the need to better understand the pathogenesis of epilepsies so as to develop better therapies to optimize epilepsy care *(377)*.

In this chapter, we review the types of epilepsy research across the globe, the barriers and facilitators to epilepsy research and research priorities around the world. We outline research successes and challenges, as they pertain to different regions of the world.

Epilepsy research across the globe

Epilepsy research can range from bench to bedside and beyond, at the population level. Numerous research frameworks exist describing the different areas of investigations. Common types of research are listed below (Fig. 7.1), keeping in mind that these often overlap with each other and with other research areas (e.g. population health, not listed below, often overlaps with epidemiology). Common research areas, defined in Table 7.1 include basic research, translational research, clinical research, health services research, epidemiology and implementation science.

Fig. 7.1 Examples of types of research

Table 7.1 Definitions of various epilepsy research types

Research type	Definition	Example
Translational research	Research aiming to translate basic and clinical research into clinical practice *(379)*	Testing and validating treatments to prevent epilepsy in animal models and/or humans; this can include research that aims to monitor brain activity, algorithms and artificial intelligence solutions to interpret EEG data, etc.
Basic science	Aims to understand the basic structure and function of the nervous system, whether or not it maintains a disease focus, and may utilize in vitro studies, animal models or human specimens *(378)*	Research on understanding the function of mechanisms through which various genes may influence neuronal excitability or epilepsy development
Clinical research	Research that studies people through direct interaction or the collection of sample(s) (e.g. blood, tissues, cerebrospinal fluid)	Studies aimed at understanding the impact of epilepsy interventions on outcomes (e.g. quality of life)
Epidemiology	The study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems. Various methods can be used to carry out epidemiological investigations: surveillance and descriptive studies can be used to study distribution; analytical studies are used to study determinants	Understanding risk factors associated with epilepsy outcomes, usually at the population-based level
Health services and social science research	Studies how social factors, financing systems, organizational structures and processes, health technologies and personal behaviours affect access to, the quality and cost of health care, and, ultimately, health and well-being *(380)*	Studies about disparities in epilepsy care
Implementation science	Research that aims to improve programmes and policies that impact the operation, utilization and efficacy of health services depending on the community needs and resources *(381)*	Implementation of various epilepsy care model to examine which model is best improves access to care

To obtain a measure of productivity in epilepsy research across the globe, a PubMed search was done with the keywords "epilepsy OR seizure". This resulted in 206 913 hits that were grouped by region (Fig. 7.2). These data show significant imbalance in the distribution of epilepsy or seizure-related research across countries that is not necessarily a result of the population growth in each country; and that even within regions with significant scientific productivity there is uneven scientific growth across the various countries.

This is a crude demonstration of the variability in resources, expertise, research training and practices, funding or other priorities across countries or regions. Many factors can account for such variation, such as access to information and expertise, research training and practices, research funding and infrastructure, socioeconomic and cultural environment, and language barriers. The varied expertise and resources required for the different types of research also require different levels of funding.

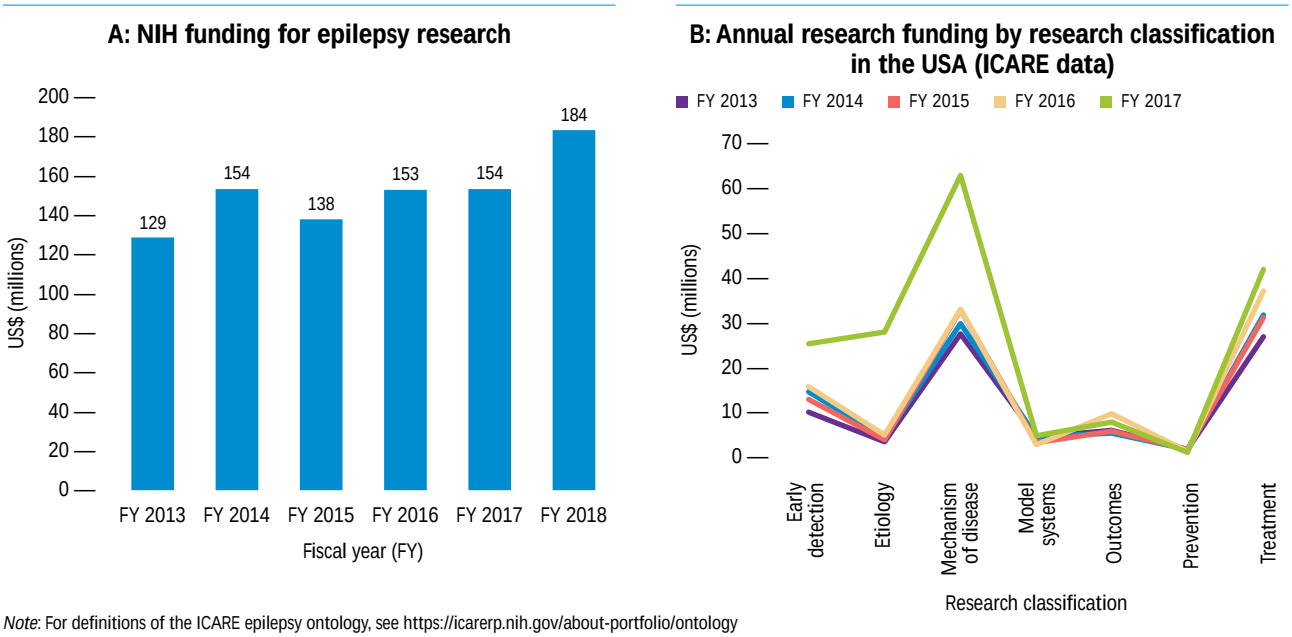
Fig. 7.2 Productivity according to PubMed publications on "epilepsy OR seizure"

Note: An article may be included in more than one region if there are multiple authors from different regions listed.

Investment in research for epilepsy is insufficient

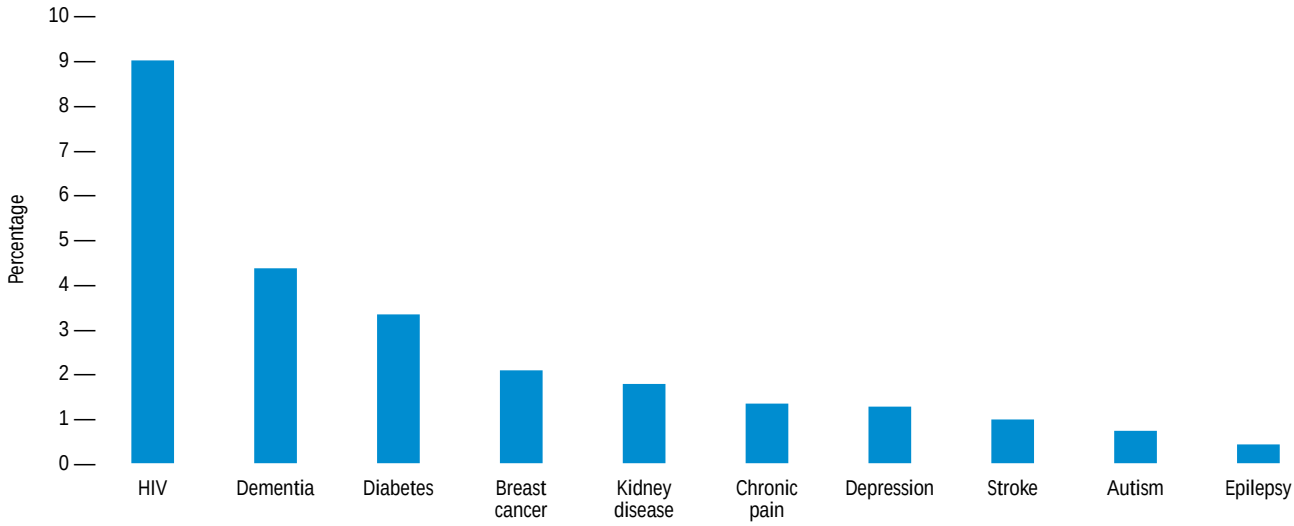
Globally, investment in epilepsy research is woefully under supported, particularly in LMIC. Even in HIC where significant investments in epilepsy research have been made, funding for epilepsy only represents a small proportion of overall funding. For example, in 2018 the NIH provided US$ 184 million to support epilepsy research (Fig. 7.3). This reflects less than 0.09% of the total NIH budget dedicated to research and lags significantly behind the research funds dedicated to other neurological research areas (Fig. 7.4). The proportion of the research budget dedicated to epilepsy has stagnated over the last 3 years, unlike other areas, which have attracted increasing research support, e.g. Alzheimer disease research, autism and rare diseases. This striking difference is largely due to increasing advocacy for these other neurological conditions to ensure appropriate federal commitment to research, e.g. through the Alzheimer's Breakthrough Act of 2011 (H.R. 1897) *(382)*. When accounting for the prevalence of epilepsy in the United States of America, the annual NIH awarded research budget means that for each person with epilepsy in the United States of America, the NIH awards US$ 47 per year *(383)*.

Fig. 7.3 NIH funding for epilepsy research (2013–2018)



Note: For definitions of the ICARE epilepsy ontology, see https://icarerp.nih.gov/about-portfolio/ontology

Fig. 7.4 Percentage of overall NIH funding in selected research areas



Source: NIH, 2018 (https://report.nih.gov/categorical_spending.aspx).

In the United States of America, federal agencies and non-profit organizations have joined forces to form ICARE (https://www.ninds.nih.gov/Current-Research/Focus-Research/Focus-Epilepsy/ICARE) (Box 7.1). Another important NIH investment in epilepsy research is to Centers Without Walls, a unique consortium of investigators from the United States of America and abroad. One of the main goals of Centers Without Walls is to focus on major hurdles to the advancement of epilepsy research and treatment that are likely to only be overcome through large, collaborative approaches.

A similar type of overall global funding landscape worldwide is being discussed by the European Commission and other country-specific funding agencies to understand the opportunities and gaps in funding epilepsy research that can be filled with new collaborations and funding strategies.

Box 7.1 Interagency Collaborative to Advance Research in Epilepsy (ICARE)

ICARE is a group of individuals representing health care providers, investigators, individuals with epilepsy and funders. The group's aim is to discuss epilepsy research issues that impact everyone, as well as the funding landscape across all funding agencies and organizations in the United States of America.

It is made up of representatives from the following institutes, centres and organizations: National Institutes of Health, Centers for Disease Control and Prevention, Federal Drug Administration, Centers for Medicare and Medicaid Services, Department of Defense, Department of Veterans Affairs, Health Resources and Services Administration, Agency for Healthcare Research and Quality, American Epilepsy Society (AES), AES/National Institute of Neurological Disorders and Stroke (NINDS) Epilepsy Research Benchmarks Stewards, Citizens United for Research in Epilepsy, Dravet Syndrome Foundation, Epilepsy Foundation, Epilepsy Study Consortium, Epilepsy Leadership Council (formerly Vision 20-20 – representing multiple epilepsy organizations), Patient-Centered Outcomes Research Institute and the Tuberous Sclerosis Alliance.

Thanks to the ICARE epilepsy research portfolio, it is possible to monitor funding allocation by category, source and thematic area. In 2016, for example, the majority of research funding for epilepsy went towards treatment development and mechanism investigation.

Sources: NIH ICARE Epilepsy Research Portfolio, 2019 *(384)*; NINDS, 2019 *(385)*.

In LMIC, funding for research comes from domestic organizations and substantial contributions from high-income research agencies and international organizations, such as the Wellcome Trust in the United Kingdom of Great Britain and Northern Ireland; NIH in the United States of America, the Medical Research Council, the Canadian Institutes of Health Research, the European Commission and developmental aid agencies (e.g. United Kingdom of Great Britain and Northern Ireland Department for International Development). However, most funding is directed towards communicable diseases and little towards epilepsy. Some epilepsy research is funded by NGOs, such as the World Federation of Neurology, the ILAE and the International Child Neurology Association, though these funds are more limited.

Barriers and facilitators to epilepsy research

To maintain vibrant epilepsy research, whether preclinical, clinical or at the population level, it is important to engage and sustain the best pool of researchers in the field, at all career stages, and enrich the available resources by maintaining collaborations within and beyond the epilepsy community. Barriers to achieving this are issues pertaining to job security or competitiveness, particularly for early career investigators (Table 7.2). In many resource-rich countries, there are sources to provide career development grants to support collaborations and novel directions. There is also an increasing trend to provide funding for consortia or collaborative multicentre studies. Efforts to provide mentoring and training of young investigators from resource-limited countries are increasing but more needs to be done to maintain trained investigators in LMIC so that research can continue to evolve in those countries.

Table 7.2 Barriers and facilitators to epilepsy research

Examples	Possible solutions	Examples of initiatives to break down barriers
Barriers in attracting and sustaining research due to academic or other professional issues		
• Physician-scientists and other health care providers involved in research, face challenges in balancing a productive research career with clinical duties • Uncertainty about securing grant support may drive investigators away from academic careers	• Advocacy for epilepsy research • Improve academic environment to encourage entry and sustain productive scientists	• Early career awards and career development grants offering start-up resources or protected time for research (e.g. NINDS, AES, CURE) • Start-up funds for scientists upon obtaining a new academic position • Fellowship opportunities to train investigators from low-resource countries about research (e.g. IBRO fellowships, Fogarty grants, Wellcome Trust in United Kingdom of Great Britain and Northern Ireland
Barriers in systems and tools to investigate pathogenesis and probe brain functions and treatment effects in vivo		
• Across species differences in biology, brain structure and connectivity, and treatment response • Challenges in developing biomarkers to gain insight on target brain biology and function	• Promote initiatives to encourage progress in methods and tools to advance brain research • Promote training and transfer of expertise across labs and across country borders • Promote knowledge sharing and cross-fertilization of resources across disciplines of different but complementary expertise	• Translational initiatives to optimize preclinical research and its translation to the clinics (e.g. ILAE/AES Joint Translational Task Force, ARRIVE guidelines from NC3R) • BRAIN initiative (NINDS)
Barriers in research infrastructure		
• Lack or poor research opportunities in LMIC, including inadequate coverage of administrative costs by funding agencies • Low access to education and training in LMIC • Lack or poor availability of databases to share data and information on active research • Need for repository of common tools for research • Need for registries of research studies to avoid unnecessary duplications • Lack of time within clinical service, with no help for administrative processes • Multiple processes for ethics requirements, restricting centre participation	• Promote access to research resources in centres with insufficient resources • Promote transfer of expertise to sustain and encourage research growth • Create and train on broadly accepted sets of best and ethical practices to improve research conduct and reporting • Promote databases to share and mine data collected from various labs • Minimize cost associated with epilepsy research • Provide common infrastructure, to allow multicentre studies	• Fogarty grants (NIH, United States of America) to promote research in LMIC • Initiatives to educate about best practices in research in areas of need (e.g. Ghana initiative of ILAE/IBRO) • Big databases initiatives (e.g. NINDS/CURE EGI for genetics, Department of Defense FITBIR database for traumatic brain injury research, NINDS-funded Centers Without Walls, PANACHE database from ETSP, NINDS Data Commons) • Repositories of mouse strains (EuCOMM European conditional mouse mutagenesis programme; NorCOMM North American Conditional Mouse Mutagenesis Project, JAX database from Jackson Laboratories) • Pan European initiatives such as the European Research Infrastructure Network providing support and advice regarding ethics submission and contracts across countries

Table 7.2 Barriers and facilitators to epilepsy research (continued)

Examples	Possible solutions	Examples of initiatives to break down barriers
Barriers in translation from preclinical to clinical findings • Across species/studies comparisons and validation of data • Limitations of existing models of human seizures and epilepsies • Limitations of techniques and methodologies • Heterogeneity of approaches that hinders comparability and cross validation of preclinical data • Lack of widely accepted/agreed methods to interpret data (e.g. rodent EEGs and seizures) • Lack of biomarkers to guide translation of preclinical data • Limited interactions among key stakeholders due to competing interests, time commitments and funding		
• Concerns on reproducibility and translatability of preclinical data	• Recognize importance of ethical and justified use of animal experimentation for epilepsy research progress • Optimize ethical use of human-derived model systems or basic science research • Encourage translational initiatives to optimize reproducibility and translatability of preclinical epilepsy research • Encourage collaboration towards creating widely accepted standards for translational epilepsy research • Encourage research towards creating and validating biomarkers to guide translation and implementation of preclinical data into clinical research and practice	• Translational initiatives to optimize preclinical research and its translation to the clinics (e.g. ILAE/AES Joint Translational Task Force, ARRIVE guidelines from NC3R)
Barriers to clinical research/trials • Regulatory processes • Lack of appreciation of differences between trials and other research, e.g. epidemiology, prevention etc. • Need for clinician time • Limited time in health service provision • Lack of infrastructure		
• Increasing awareness of epilepsies to be a group of rare diseases for which limited numbers in each centre • Poor recruitment even across European studies e.g. RESCUE, EDIBLE	• Provision of common process and ethics to aid administrative process • Provision of support for advice, written submissions and negotiations • Early training in health professional programmes on benefits and structure of research • Increased sources of funding	• European Clinical Research Infrastructure Network (ECRIN, www.ecrin.eu) – EU funded network for review of studies and support • European reference networks to work towards common platforms and registries of rare diseases utilizing specialist centres • Collaborative Network for European Clinical Trials for Children (C4C) – as part of the Innovative Medicines Initiative 2 Joint Undertaking programme, a public-private partnership between the EU and the European pharmaceutical industry

Table 7.2 Barriers and facilitators to epilepsy research (continued)

Examples	Possible solutions	Examples of initiatives to break down barriers
Barriers in research reporting • Language barriers • Publication biases in favour of novel/positive data • Deficits in research transparency and rigour • Cost associated with open access publications		
• A minority (~15%) of data are published with a bias against data with negative or lack of novelty findings (e.g. confirmatory) • Unnecessary studies replicating unpublished studies that have not been published result in waste of resources • Sparsity of studies evaluating reproducibility of data • Open access publication fees may be prohibitive for investigators with low resources and funding • Standards promoting transparency and rigour are not always followed	• Encourage opportunities for non-English speaking researchers to effectively communicate their work • Minimize publication bias by encouraging high-quality research, including novel or confirmatory or negative • Disseminate and train researchers in research reporting standards that promote transparency and rigour • Encourage open access opportunities for publishing research	• Increasing number of journals encouraging publication of negative or confirmatory data • Registries for preclinical studies (https://preclinicaltrials.eu) • Registries of negative or preliminary data • Training for best reporting, publishing and research conduct practices • Waivers towards LMIC to publish in open access journals
Barriers in collaboration • Across epilepsy researchers, various areas of research and technological expertise, industry and academia, preclinical and clinical scientists and consumers • Due to inadequate infrastructure to promote collaboration and sharing data and expertise (e.g. multicentre studies, big interoperable database)		
• Individual labs follow diverse procedures, methodologies or study designs that hinder collaborations or utilization of common databases • Intellectual property issues or need to publish high-impact novel research data for academic advancement may hinder data sharing and collaborations	Promote: • Multicentre or collaborative basic/preclinical studies • Academic, industry or other professional incentives to encourage collaboration • Big interoperable databases to share data • Common data elements to improve comparability of data and use of big databases • Training and transfer of expertise across labs and across country	• NINDS-funded CWOW (Epi4K, EPGP, CSR, EpiBioS4Rx) • EU-funded collaborative research initiatives (e.g. EPITARGET) • NEURON-ERANET funded programmes • NIH-funded Fogarty grants • CURE infantile spasms and TBI initiatives • Utilization of participatory action research methodology in planning and execution of future clinical trials
Barriers in funding epilepsy research		
• Funding for epilepsy lags despite high incidence rates and health care costs relative to other conditions	• Identify gaps and priorities in epilepsy research funding (e.g. ICARE, benchmarks) • Improve funding for epilepsy research • Advocacy for epilepsy research	• ICARE database (NINDS) • Benchmarks for Epilepsy Research (AES/NINDS, ILAE) • Advocacy groups (ILAE, private organizations

Table 7.2 Barriers and facilitators to epilepsy research (continued)

Examples	Possible solutions	Examples of initiatives to break down barriers
Community, societal or cultural related barriers • Perception that animal research yields findings that do not translate into clinically relevant discoveries • Epilepsy research is not promoted to the same degree across various countries • Cultural stigma against epilepsy may hinder research into epilepsy		
• STOP Vivisection initiative to stop animal experimentation (2015)	• Advocacy for epilepsy research • Promote humane and ethical conduct of epilepsy research across the spectrum • Integrate and promote epilepsy research and training across countries considering richness of resources, potential and societal and cultural factors	• ILAE, EARA, Understanding Epilepsy Research advocacy for the benefits of ethical experimentation in animals • Public Engagement Core of EpiBioS4Rx CWOW

Abbreviations: AES: American Epilepsy Society; ARRIVE: Animal Research: Reporting of In Vivo Experiments; CSR: Center for SUDEP (sudden death in epilepsy) Research (http://csr.case.edu/index.php/Main_Page); CURE: Citizens United for Research in Epilepsy; CWOW: Centers Without Walls; ECRIN: European Clinical Research Infrastructure Network; EPGP: Epilepsy Phenome Genome Project; Epi4K: Collaborative for genotyping-phenotyping of patients with infantile spasms and Lennox-Gastaut syndrome (https://www.epi4k.org/about/); EpiBioS4Rx: Epilepsy bioinformatics study for anti-epileptogenic therapy; EPITARGET: Targets and biomarkers for anti-epileptogenesis; ETSP: Epilepsy Therapy Screening Program; IBRO: International Brain Research Organization; NC3R: National Centre for the Replacement Refinement and Reduction of Animals in Research; NINDS: National Institute of Neurological Disorders and Stroke; PANACHE: Public Access to Neuroactive and Anticonvulsant Chemical Evaluations (https://panache.ninds.nih.gov/).

Promoting epilepsy research

The research community has set checks and balances to monitor and optimize the directions epilepsy research is following. These measures include improving infrastructure and collaboration amongst stakeholder groups, monitoring progress and the challenges of promoting advocacy around the world, engagement of people with epilepsy, and setting priorities for future directions and promoting research in LMIC *(98, 386–400)*. More research support, in particular for health care providers who are non-medically trained in LMIC, is critical as they provide the majority of frontline care to those living with epilepsy.

Improving infrastructure to promote research

Efforts to promote epilepsy research require improving infrastructure (e.g. common language and standards for collecting, publishing and sharing data). One example of such efforts at a global level are the translational initiatives organized by the ILAE/AES Joint Translational Task Force *(401)*. The task force has organized working groups aimed at proposing best research practices and proposals to improve infrastructure and optimize preclinical epilepsy research. To address the concerns on reproducibility of preclinical studies *(378, 390)*, the task force has undertaken initiatives to promote collaboration, transparency, rigour and comparability of data derived from different labs. A first set of epilepsy-related common data elements for preclinical studies has been generated by the task force *(402–408)*. Adoption of common data elements promises to facilitate the use of a common language and standards for research, making it more comparable, facilitating collaborations and input in big databases.

Publishing and sharing data in a transparent manner while adhering to the FAIR guiding principles (findable, accessible, interoperable, reusable) *(409)* as well as the principles of rigorous and transparent reporting has become an increasing need. Only a small portion of research findings are published (estimated at 15%) *(410)*, leaving the majority of data unknown to investigators leading to fruitless experiments and limited ability to judge the value of a finding. Big databases for sharing data and open access publications will be critical for encouraging epilepsy research.

A structure to ensure that proper ethical guidelines and expectations on research conduct and reporting of research are followed is paramount. Efforts to generate registries for preclinical research studies are

starting to emerge, such as the international register of preclinical trial protocols (https://preclinicaltrials.eu) which aims to promote transparency. Careful planning of such initiatives to preserve academic rights and intellectual property expectations will, however, be necessary for them to be widely accepted and adopted.

Advocacy efforts to promote research and encourage funding

Collaboration through clinical care networks and research consortiums have shown some success in advocating for epilepsy research and funding at national, regional and global levels.

At the national level in Canada, Neurological Health Charities Canada was formed to raise awareness of the challenges faced by people living with brain conditions. Neurological Health Charities Canada combines academic and non-academic expertise as a model that has shown success in influencing research funding for epilepsy (Box 7.2).

Box 7.2 The influence of civil society and research collaborations on resource allocation in Canada

Following the establishment of the Neurological Health Charities Canada coalition and its advocacy efforts, in 2009, the federal government committed Can$ 15 million over 4 years for the National Population Health Study of Neurological Conditions. The study was funded by the Public Health Agency of Canada, Canadian Institutes of Health Research and Health Canada. The expansive programme of research successfully engaged 130 researchers from 30 academic and non-academic institutions across Canada. In addition, approximately 177 000 Canadians with neurological conditions and their caregivers offered insight and personal experience on key areas of the study. Findings from the 4-year study (2009–2013) were released in September 2014 in the report *Mapping connections: an understanding of neurological conditions in Canada*. As a direct result of this study, epilepsy was added to the Canadian Primary Care Sentinel Surveillance Network and to the Canadian Longitudinal Study of Aging. The study findings are used by governments and organizations to inform programmes and develop policies related to neurological conditions.

Source: Public Health Agency of Canada, 2014 *(411)*.

Box 7.3 Successful advocacy by people affected by epilepsy led to increased funding from the US Government

Tony Coelho, a man living with epilepsy, and Steny Hoyer, whose wife Judith lived with epilepsy, were elected representatives in the US Congress. They advocated and continue to advocate for increased funding and equality of people with epilepsy. Their knowledge of the political system and relationships with advocacy organizations like the Epilepsy Foundation of America has had a significant impact.

In 2018, their advocacy contributed to funding increases for epilepsy research at the NIH to US$ 184 million. As part of this funding, there has been a 5-year US$ 16 million cooperative partnership between the Epilepsy Foundation and the Department of Health and Human Services and its Centers for Disease Control and Prevention, focusing on educating the public, health care professionals and improving care and support. These agencies are implementing the recommendations of the 2012 report *Epilepsy across the spectrum: promoting health and understanding (412)*, as well as the recommendations from the periodic NIH conferences on the cures for epilepsy. The federal government's activities have been reviewed through the Interagency Coordinating Committee on Epilepsy, and each of the major epilepsy advocacy organizations has been closely involved with establishing the agenda, goals and evaluation towards outcomes for the federal agencies addressing epilepsy.

The 2012 report, *Epilepsy across the spectrum: promoting health and understanding*, from the US National Academy of Sciences (formerly the Institute of Medicine), was the result of a close collaboration among several federal agencies, NGOs and epilepsy advocates *(412)*. This report provides a blueprint of how to proceed in the future in improving the care of people with epilepsy by harnessing collective research efforts by groups across the globe and thus augmenting the power of epilepsy data. The 13 recommendations included in the report have directed advocacy and public health efforts to improve the care and quality of life of people with epilepsy. With the help of advocates, implementation of the recommendations has led to increased funding for epilepsy research and health education programmes both (Box 7.3).

A regional collaboration in Europe, the e-pilepsy project (http://www.ucl.ac.uk/www.e-pilepsy.eu), is a pan-European project that aims to improve awareness and access to epilepsy surgery across Europe and involves broad multistakeholder collaboration. The Directorate-General for Research of the European Commission contributed to epilepsy research in the Sixth, Seventh and Eight Framework Programmes (respectively FP6, FP7 and Horizon 2020), reaching a total of €197.6 million for 135 different projects over the last 12 years.

A joint task force of the ILAE and the IBE in Europe was set up in 2010 to organize and implement an advocacy strategy for epilepsy directed at the European Parliament and Commission. In parallel, a group of elected Members of the European Parliament from several Member States was created to support epilepsy. In 2015, the ILAE and IBE created a dedicated European legal entity, Epilepsy Alliance Europe (EAE), which oversees the activity of the ILAE/IBE joint task force and strengthens its influence (Box 7.4).

One major achievement of the joint task force and epilepsy advocacy group was the European Written Declaration on Epilepsy passed by the EU Parliament on 15 September 2011. This declaration paved the way for several important EU-funded initiatives, including a research call on the process by which a normal brain develops epilepsy (epileptogenesis) that funded four large projects with a total budget of €50 million, and the development of a European health care network on epilepsy surgery that later evolved into a European reference network covering all rare and complex epilepsies (ERN-EpiCARE – www.epi-care.eu). These EU-funded initiatives recently joined forces to delineate future epilepsy research priorities in etiology, mechanisms of disease, biomarker identification and innovative treatments. More recently, the joint task force has considered a more global approach to epilepsy research, with the view that some very challenging clinical research objectives can only be tackled at an international level. Examples are clinical studies tackling anti-epileptogenesis and SUDEP prevention that require large sample size of highly selected patients and very significant funding, two challenges that can only be tackled through global initiatives.

A comparable global initiative has been resourced by EU and North American research funding in the field of TBI. Representatives from the EAE, ILAE, IBE, AES, Epilepsy Foundation, NIH, Canadian Research Council and the Research and Health Directorates of the European Commission have been involved in initiatives aimed at creating a framework to fund future global brain research, including funding calls on epilepsy.

In 2012, a group of 50 international epilepsy experts from the American Epilepsy Society and the ILAE agreed that the priorities for new therapy development for epilepsy are to develop treatments: with anti-epileptogenic and disease modifying properties; for drug-resistant seizures; and for epilepsy-related comorbidities *(392)*. To develop novel therapeutics, research needs to focus on the basic neurobiology of various types of seizures and epilepsies, and their interactions with other biological systems, as well as environmental factors that influence seizures. In parallel, there

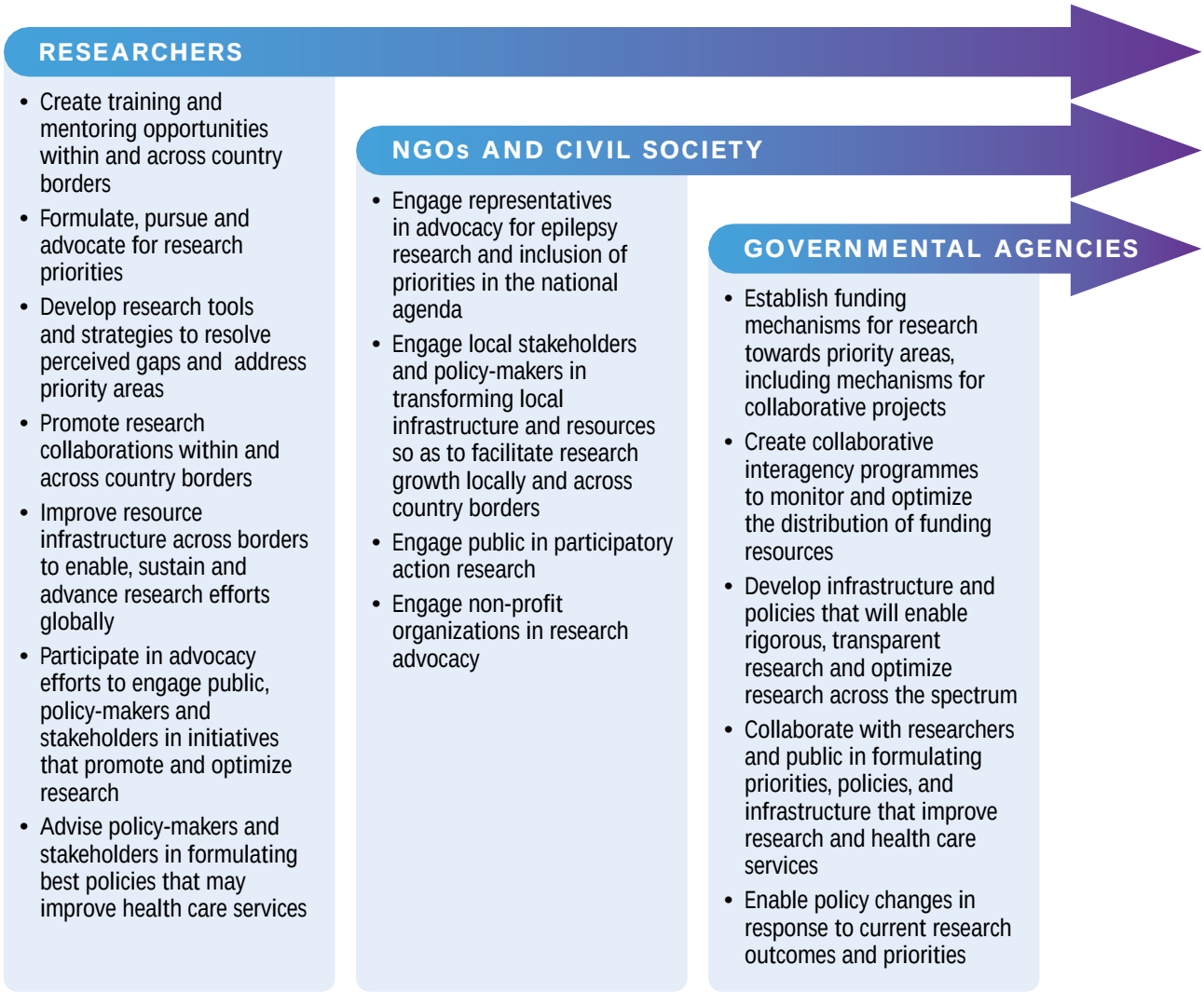
Box 7.4 Epilepsy Alliance Europe

Epilepsy Alliance Europe is a not-for-profit joint organization that brings together European professional and lay stakeholders associated with the ILAE and the IBE. Its main objectives are the protection of the rights of people with epilepsy, the improvement of epilepsy care, the dissemination of awareness and knowledge, and the promotion of research in epilepsy and its comorbidities, and to establish epilepsy as a health care priority in Europe.

Epilepsy Alliance Europe collaborates with medical centres, technology companies, universities, hospitals, epilepsy organizations, the pharmaceutical industry and other groups. It also develops information programmes to raise awareness and understanding of epilepsy in the general public, in people with epilepsy and in those who care for them, to develop interventions to dispel stigma and to protect the rights of people with epilepsy.

Source: www.epilepsyallianceeurope.org

Fig. 7.5 Roadmap for collaboration of researchers and advocates to promote research agenda



is the need to develop biomarkers that will help tailor candidate treatments, considering age, sex and other individualized factors that could affect efficacy and tolerability.

Finally, some areas of epilepsy research are expanding, but many areas still need major progress. For example, there are opportunities at the intersection between medicine and new digital technologies. New health digital technologies are revolutionizing medicine in other fields (i.e. heart diseases). Nevertheless, very little progress has been made so far in the field of epilepsy in terms of predictive or wearable monitoring devices, for example. This is an area of research and development where collaborations across different sectors might be promoted and strengthened. New digital technologies may have a huge impact on the way epilepsy is treated and on the quality of life of people with epilepsy and their families.

Research collaboration (multisectoral, international, etc.) should be fostered, particularly with consumers and consumer organizations, policy-makers and other relevant stakeholders (Fig. 7.5).

Engagement of people with epilepsy in research

An important approach to ensure research success and implementation is the inclusion of people with epilepsy, their families and civil society organizations. Participatory action research is an approach where the target audience of a study, often people with a health condition, are involved in all stages of a project, from conceptualization to implementation.

Such an approach aims to ensure that research questions are relevant to consumers and consumer organizations, and other key stakeholders, and can facilitate study acceptance and feasibility. The Australian Epilepsy Research Register is one example of this. It is a database of people with epilepsy and family members who have given permission to participate in social and psychological research. The surveys ("waves") are conducted every 3 years *(413)*. Some of the research funding invested in the Epilepsy Foundation by the Australian Government was on the outcome of efforts made by parents of children with rare genetic epilepsies *(414)*.

To address the barriers and facilitators listed in Table 7.2, there is a need to create an inclusive consortium of consumers and consumer organizations, scientific (professional) societies, health organizations and investigators to identify strategies to design large-scale clinical trials with effective recruitment and retention.

Setting epilepsy research priorities

The joint ILAE/IBE Task Force for Research Priorities and Advocacy aimed to identify epilepsy research priorities on a global scale. A survey was conducted with members of ILAE/IBE which received responses from 209 individuals representing 40 countries across all regions. The survey identified the top research priorities (Box 7.5).

Box 7.5 ILAE/IBE Task Force for Research Priorities and Advocacy

A. Priorities that would require questions to be addressed on a global scale

1. How can we establish affordable treatments and research resources for the epilepsies?
2. Determine the phenotype variability to the epilepsies, with the objective of personalizing therapies for seizures, epilepsies and related comorbidities.
3. What is the prevalence of comorbidities affecting people with epilepsy; what interventions are effective across cultures?
4. What is the benefit of existing interventions in the epilepsies?
5. Determine the epilepsy treatment gap in different regions of the world by the study of a large multi-regional cohort.

B. Priorities that would require questions to be addressed on a local scale but would have global applicability

1. The identification of novel strategies and effective treatments for those with drug-resistant epilepsy.
2. What is the basis to epileptogenesis, comorbidities and the role of disease-modifying treatments?
3. What is the role of nonpharmacological interventions?
4. What are the psychiatric outcomes of epilepsy treatment – pharmacological and surgical, especially inclusive of people with intellectual disability?
5. What is the interactive relationship between epileptic and psychiatric disorders, such as depression and psychosis, also in association with surgical intervention?

Table 7.3 Epilepsy research priorities – regional and country examples

National Institute of Neurological Disorders and Stroke (NINDS) epilepsy research benchmarks (USA) *(415)*	**European Forum on Epilepsy Research (ERF2013)** *(98)*	**Research priorities in epilepsy for the Asia-Oceania region** *(395)*
• Understand the causes of epilepsies and epilepsy-related neurological, psychiatric and somatic conditions • Prevent epilepsy and its progression • Improve treatment options for controlling seizures and epilepsy-related conditions without side-effects • Limit or prevent consequences of seizures and their treatment across the lifespan	• Understand and manage epilepsy in the developing brain • Novel targets for innovative diagnostics and treatment of epilepsy • Prevention and cure of epilepsy • Epilepsy and comorbidities, with a special focus on ageing and mental health	• Recognition of the health burden of epilepsy, particularly relating to the treatment gap • Better understanding of the preventable causes of epilepsy • Reduce the psychosocial consequences of epilepsy • Develop better therapies and improved therapeutic outcomes • Improve the research infrastructure

Appreciating the diversity seen in the availability of resources and health care provision across different regions and countries of the world, priorities may differ depending on resources as well as the etiological nature of epilepsy. Regional priorities have been identified in Europe and Asia; at a country level the United States of America has also set epilepsy research priorities (Table 7.3).

Promoting research in low-resource countries

Over the past 20 years the ILAE, IBE and WHO have promoted efforts emphasizing the effectiveness of advocacy for epilepsy research, public awareness and legislation. Focused on epilepsy care in low-resource settings, the WHO Programme on reducing the epilepsy treatment gap has demonstrated success at improving access to epilepsy treatment and care at the community level (see Chapter 2). This programme has been successful at enhancing monitoring and evaluation of services and advocating for government commitment.

The programme's projects examined incidence and prevalence of epilepsy, mostly through door-to-door surveys, and measured stigma, attitudes and knowledge amongst the general population, followed by intervention and education. These collaborations involved community leaders and traditional healers to maintain sensitivity to cultural practices. Funding for these projects was sought from local sources, specifically to have local commitment to funding and subsequent implementation.

To facilitate research in LMIC, it is important to work with local health care providers and researchers to improve access to information, training and mentoring, and also to create the necessary infrastructure and conditions to sustain and grow research in the LMIC. Some journals are slowly shifting towards open access, which can improve access to information. However, requested publication fees may still be a concern for authors with limited funding. A challenge for investigators from low-resource countries is to obtain the training needed, as well as access to enriching research facilities and resources. For basic and translational research, this will also require the creation of specialized research facilities and facilitating access to materials and resources that can be otherwise cost-prohibitive. Training and engaging clinicians in research may also be challenging due to heavy clinical loads, poor availability of mentors or specialist training programmes, or challenges in implementing clinical research due to challenging socioeconomic conditions. These include epilepsy-related stigma, gaps in diagnosing epilepsy, deficiencies in treatment options that make it difficult to diagnose "drug-resistant" epilepsies, or the complexity of health conditions that make it difficult to tease out etiologies from comorbid conditions. Epidemiological studies are also challenging when local study populations change due to influx of new populations or migration of local people.

Further, opportunities for training researchers, retaining and attracting talented investigators who may integrate into the local research environment are limited. To sustain such efforts, it will be imperative to build on and expand local resources. Conditions pertaining to the local environment (recruit, fund, sustain and support investigators, promote collaborations and further training) are essential and need to be implemented by local policy-makers and stakeholders so as to avoid efflux of talent.

An example of efforts to encourage research in epilepsy was the IBRO/ILAE Neuroscience School organized in Accra, Ghana (16–22 January 2010) on "Fundamentals on Epilepsy: Neurobiological, Clinical and Therapeutic Approaches" *(416)*. Participant trainees from LMIC and international experts came together in this week-long course that provided an update and introduction on the fundamentals of epilepsy research. Several of these LMIC trainees were able to identify mentors and opportunities for training in a more resource-equipped country with the plan to return and continue building research in their home country. A big challenge for such efforts is to ensure that at the end of the training the trainee will be able to return to their country and apply new skills and expertise to

build and grow local research capacity. For this to occur, local stakeholder collaboration is essential to formulate attractive local conditions to assist them in establishing a research system infrastructure in their country. Training in project and grant proposal development also needs to be supported.

Another example are summer schools that take place in Venice, Italy (San Servolo Epilepsy Course) and São Paulo, Brazil (Latin American Summer School on Epilepsy). In these schools, faculty members instruct researchers from LMIC countries in all aspects of epilepsy, including research opportunities and how to form effective collaborations, with the development of mock research projects. Ongoing mentorship is required once individuals return to their local environment, paying attention to the local facilities available. The ILAE has also initiated programmes, based at international congresses, for junior investigators to develop leadership qualities, as well as for more junior investigators to obtain mentorship from clinical or basic science investigators and to enhance their presentation skills. Some regions also operate visiting fellow schemes within the region, e.g. Commission for Asian Oceanic Affairs, South Africa (Red Cross Children's Hospital, Cape Town). Examples of local programmes that promote training of young physicians include the African Paediatric Fellowship Programme *(417)* and the World Federation of Neurology supported adult neurology training programmes in African centres, such as in Cairo (Egypt), Rabat (Morocco) and Cape Town (South Africa). It is imperative to retain trainees within regions to avoid the talent drain when they venture abroad for longer periods of study; some initial training abroad as highlighted above may sow the seed for research development but longer term programmes, e.g. PhDs, should be supported within the local environment. The recent report of the African Paediatric Fellowship Programme provided an example of how training young physicians in their native environment and enabling them to acquire skills that will be useful in meeting the demands of their countries may result in high retention rates *(417)*.

Conclusion and way forward

Epilepsy research has enabled remarkable progress in deepening our understanding of the risk factors and mechanisms leading to the epilepsies and comorbidities, and providing us with interventions and treatments to improve the management of seizures and their comorbid conditions or consequences. There are, however, significant strides to be made to deliver effective cures that may improve the quality of life, preventing epilepsy and its comorbidities. There is also a dramatic inequality in access to and utilization of research resources and expertise across the globe that limits our ability to engage in such efforts the global scientific community makes and to explore research priorities at a global range.

CHAPTER 7

Research on epilepsy

KEY MESSAGES

- **There is a need to increase capacity, funding and training for epilepsy research globally. This can only be done with enhanced funding and infrastructure. In countries with more limited resources in particular it is paramount to help reform the local infrastructure, expertise, academic and socioeconomic environment and culture so as to support and sustain the growth of epilepsy research and researchers within the country's borders.**
- **It is important to continue to optimize research process standardization and to adapt existing research frameworks and guidance where feasible.**
- **The ongoing establishment of global and, at times, more regional research priorities, are important as they can facilitate advocacy for research funding for high needs areas.**
- **There is a need to enhance efforts to optimize epilepsy research translation and implementation globally.**
- **Research collaboration (multisectoral, international, etc.) should be fostered, particularly with consumers and consumer organizations, policy-makers and other relevant stakeholders.**

CHAPTER 8

Way forward

Way forward

This report demonstrates the imperative to make epilepsy a public health priority and that further action is needed to address the global burden of epilepsy.

The burden of epilepsy is high

With around 50 million people affected worldwide and more than 5 million new cases every year, epilepsy is one of the most common chronic neurological conditions. It accounts for 0.5% of the global burden of disease and affects people of all ages living in countries of all income levels. The burden is greatest in LMIC, where nearly 80% of people with epilepsy live: in low-income countries three-quarters of people do not receive the treatment they need. People with epilepsy have an increased risk of premature death. Roughly half of adults with epilepsy experience physical and psychiatric comorbidities that worsen seizures and reduce quality of life. People with epilepsy also often face barriers in achieving their full potential due to unmet needs in the areas of civil rights, education, work, and residential and community services.

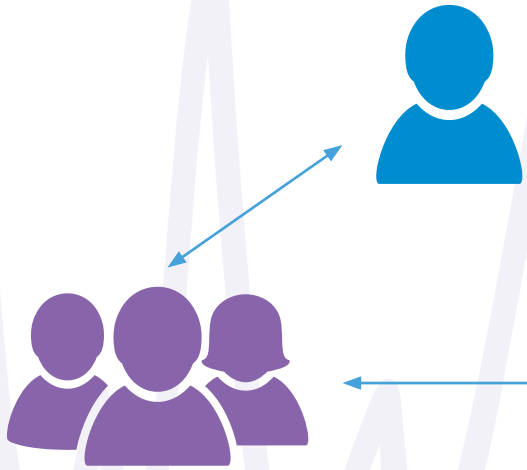
Cost-effective and scalable strategies exist

Epilepsy is a treatable condition – up to 70% of people with epilepsy could become seizure free with appropriate management and cost-effective antiseizure medications. There is strong evidence and good models for improving epilepsy care across the world. WHO has demonstrated that treatment for epilepsy can be provided using a primary health care approach, ensuring all people in need of services have access to good quality care without financial hardship. However, people with epilepsy still have difficulty accessing appropriate and affordable health care in many countries.

This report reveals the substantial progress made since the initiation of the Global Campaign Against Epilepsy in 1997, and clearly shows the power of collaboration between WHO and civil society organizations in advancing a public health agenda, but also the large amount of work remaining. The WHA resolution on the global burden of epilepsy was a milestone, giving strength to raising epilepsy on public health agendas and calling for coordinated action to defeat its burden.

Now, efforts are needed at the individual, health system and societal levels to reduce the high burden of epilepsy and improve the quality of life of people affected by this condition (Fig. 8.1). More action is needed globally, in every country, across these levels.

Fig. 8.1 Action needed to defeat epilepsy



INDIVIDUAL LEVEL

- Promote help seeking for appropriate and comprehensive health care of epilepsy and comorbid conditions
- Enhance adherence to antiseizure medicines
- Improve access to information on epilepsy and social support within the community

SOCIETAL LEVEL

- Improve community programmes and disability grants for people with epilepsy
- Promote legislation for people with epilepsy, including protection for education, employment and civil rights
- Improve epidemiologic data collection systems across governments
- Invest in research funding globally to improve epilepsy care, including promoting research in LMIC where the burden is the highest

HEALTH SYSTEM LEVEL

- Develop national guidelines for epilepsy care
- Train nonspecialist providers for epilepsy care and comorbid conditions, improve referral systems and access to diagnostic testing
- Improve access and sustainability of affordable antiseizure medicines
- Improve care for preventable causes of epilepsy, such as perinatal risk factors, CNS infections and stroke

INTERVENTIONS AT THE INDIVIDUAL LEVEL

People with epilepsy require long-term and comprehensive health care. Understanding the need and improved outcomes for good medication adherence is crucial to epilepsy treatment. Furthermore, epilepsy is associated with other conditions, including depression, anxiety, dementia and learning disabilities. Screening for these conditions is important.

People with epilepsy and families should be included within community programmes to help increase awareness and knowledge about epilepsy treatment and to reduce stigma and discrimination. Efforts from within communities for peer and community support are important parts of care.

INTERVENTIONS AT THE HEALTH SYSTEM LEVEL

System building needs to expand from government and nongovernmental partners, to health centres and communities.

Health systems across countries need to strengthen guidelines for integrated delivery of physical and mental health care, including epilepsy. Guidelines should incorporate screening for epilepsy and comorbid conditions, training primary care providers to deliver epilepsy treatment and improve referral systems. The WHO mhGAP guidelines are an example with epilepsy as a priority condition.

Increased access to sustainable and affordable medication supplies is imperative.

The WHO Programme for reducing the epilepsy treatment gap is an example of how to approach health systems strengthening for epilepsy (see Chapter 2).

Effective interventions for prevention are available and can be delivered as part of broader public health responses (e.g. perinatal health care and communicable disease control).

INTERVENTIONS AT THE SOCIETAL LEVEL

Social programmes and legislation for promotion and protection of the rights of people with epilepsy are essential as they often encounter barriers in employment, education, civil rights, residential and community services, and access to appropriate, affordable health care.

Programmes for stigma reduction and peer and community support programmes can improve attitudes and reduce discrimination.

Enhanced funding for research and public health programmes are necessary to improve epilepsy care.

Better data and information systems are needed to make the case for prioritizing epilepsy in global public health agendas.

The implementation of policies and plans for epilepsy is required to enhance universal coverage for services.

Everyone has a role to play

There are specific actions that different stakeholder groups can take to ensure that people with epilepsy live healthier, longer lives. Government policy-makers, public health managers, health care providers and NGOs need to work together in a coordinated way that includes people with epilepsy and their families in order for progress to be made *(276)*.

Policy-makers and public health managers

- Prioritize epilepsy as an important health care issue.
- Provide funding to decrease stigma and to conduct epilepsy research.
- Integrate epilepsy management into primary health care.
- Guarantee the reliable and affordable supply of antiseizure medicines.
- Formulate, strengthen and implement effective and inclusive national health policies and legislation that protect the human rights of people with epilepsy.
- Ensure that local and national stakeholders, including people with epilepsy and their families, become involved in policy-making plans.
- Strengthen health information and surveillance systems to capture better data on epilepsy.

Health care providers

- Learn more about epilepsy and the associated burden in the community.
- Identify and collaborate with other health care providers or community groups who can help advocate for and support people with epilepsy.
- Request and participate in training on epilepsy management to build skills in assessing and treating epilepsy.
- Advocate to administrators and policy-makers for the integration of epilepsy treatment and care into the primary health care system of your region or country.

Nongovernmental organizations

- Ensure governments provide better health care for people with epilepsy.
- Help reduce stigma and prevent discrimination by organizing education and awareness-raising activities for the community and health service providers.
- Implement support programmes to help people with epilepsy and their families to be fully integrated into the community, in professional and social capacities.
- Activate networks and lobby administrators, policy-makers and other stakeholders to learn more about epilepsy and establish national policies.

An opportunity for all stakeholders to join together and speak with one global voice

International Epilepsy Day, celebrated annually, is a day for people with epilepsy to share their experiences, to raise awareness about epilepsy and the need for improved treatment, counter misconceptions and to advocate for policy change and investment in research. The day is celebrated around the world with events led by IBE and ILAE in more than 120 countries.

International Epilepsy Day

International Epilepsy Day provides a platform to lend a global voice to people with epilepsy. These voices are the most powerful advocates and can demonstrate clearly that epilepsy is much more than seizures. Each year people with epilepsy share photos, videos and personal stories.

More information can be found at: https://internationalepilepsyday.org/

People with epilepsy and their families

- For people who have epilepsy, seek treatment.
- Learn more about epilepsy and talk to health care providers about available treatment.
- Find out if there are community support groups or NGOs that raise awareness about epilepsy and provide support.
- Work with advocacy groups or create a support group for people with epilepsy and their families.

The general public

- Support people with epilepsy to have the highest possible quality of life.
- Learn more about epilepsy. Help reduce stigma by talking openly about the facts of epilepsy with family, friends and community.
- Lobby administrators, policy-makers and other community members to learn more about epilepsy.
- Get involved with epilepsy-focused groups or NGOs to support their efforts.

EPILEPSY
A public health imperative

The time to act is NOW.

Urgent actions are needed, and these include:

- **Promote** epilepsy as a public health priority to reduce its burden.
- **Improve** public attitudes, reduce stigma and promote protection of the rights of people with epilepsy.
- **Invest** in health and social care systems to improve accessibility to epilepsy care.
- **Enhance** access to cost-effective antiseizure medicines globally.
- **Prevent** acquired epilepsies through improved care for common causes, such as perinatal injury, central nervous system infections, stroke and traumatic brain injuries.
- **Increase** priority given to epilepsy in research agendas.

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ANNEX 1

Survey methodology

Aim

An international survey was conducted among ILAE and IBE chapter representatives to gather information on current resources, gaps and initiatives for supporting people with epilepsy. Data were received from 112 countries, spanning all WHO regions and World Bank income groups, representing low-, middle- and high-income countries.

The methodological steps undertaken to develop the survey are briefly outlined below.

- **Stage 1: Questionnaire development**
  Domains included in the questionnaire (e.g. epidemiology, legislation, health care services, availability of medicines, misconceptions and stigma, funding and research) were based on the WHO *Atlas: country resources for neurological disorders* (second edition) (2017), consultations with WHO regional offices, the report's advisory committee and other international experts.

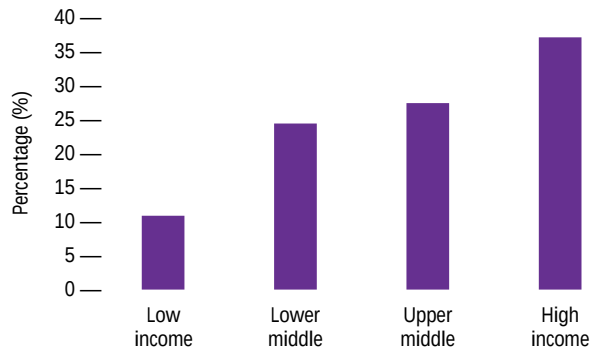
- **Stage 2: Questionnaire dissemination**
  ILAE and IBE requested chapter representatives to complete the survey. The focal point was encouraged to contact other experts in the field to obtain responses. The questionnaire was available online in English and Spanish.

- **Stage 3: Data analysis**
  Questionnaires were screened for consistencies between country representatives and, when necessary, respondents were contacted and asked to clarify their responses. Data were aggregated, analysed and reported both by WHO region and by World Bank income group. Data were then integrated into chapters of this report.

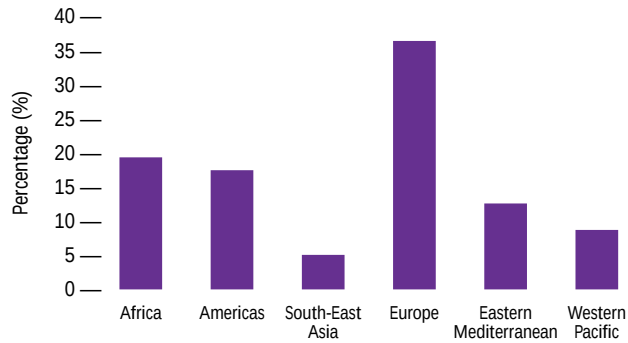
Survey respondents

Completed questionnaires were received from 107 countries across all six WHO regions (Africa, Americas, South-East Asia, Europe, Eastern Mediterranean and Western Pacific) with representation across income groups. About three-quarters of respondents were from ILAE chapters (n=82), and 25 were from IBE chapters.

Responses by World Bank income group



Responses by WHO regions



Limitations of the survey were that country representatives of ILAE and IBE, including individuals from ministries of health, NGOs, specialist and nonspecialist providers, were requested to provide information based on best estimates.

ANNEX 2

Incidence and prevalence of epilepsy

Table A2.1 Incidence (per 100 000 per year) of epilepsy in HIC

Author, year	Country	Age	Incidence rates	Notes
Christensen, 2007	Denmark	All ages	68.8	
Beilmann, 1999; Oun, 2003	Estonia	All ages	35.4–45.0	
Joensen, 1986	Faroe Islands	All ages	42.0	
Gaily, 2016; Saarinen, 2016; Keranen, 1989; Sillanpaa, 1998; Sillanpaa 2006	Finland	All ages	24.0–124.0	Higher rates in infants (data from nationwide children registers, improved diagnosis, wider acceptance of antiseizure medicine, ICD codes data in the first year of life).
Loiseau, 1990	France	All ages	44.0	
Freitag, 2001	Germany	Children	60.3	
Olaffson, 1996; Olaffson, 2005	Iceland	All ages	33.3–46.5	
Cesnik, 2013; Casetta, 2012; Giussani, 2014; Granieri, 1983	Italy	All ages	32.5–57.0	Higher rates in children.
Nakano, 2014	Japan	All ages	24–53	Higher rates in older ages.
De Graaf, 1974; Breivik, 2008	Norway	All ages	32.8–46.8	Higher rates in children.
Pavlovic, 1998	Serbia	Children	650.0	Cumulative incidence.
Forsgren, 1996; Brorson, 1987	Sweden	All ages	50.0–56.0	
Jallon, 1997	Switzerland	All ages	71.0 (69.4 age-adjusted)	Incidence of first epileptic seizures in Geneva canton.
Kotsopoulos, 2005	The Netherlands	> 13 years old	29.5	
MacDonald, 2000; Eltze, 2013	United Kingdom of Great Britain and Northern Ireland	All ages	46.0–70.1	Higher rates in infants.
Hauser, 1993; Holden, 2005; Zarrelli, 1999; Hauser, 1993	United States of America	All ages	35.0–71.0	Higher rates in administrative data.

Source: Fiest et al., 2017 *(1)*.

Table A2.2 Incidence (per 100 000 per year) of epilepsy in LMIC

Author, year	Country	Age	Incidence rates	Notes
Houinato, 2013	Benin	All ages	10.5	
Debouverie, 1993	Burkina Faso	All ages	83.0	
Lavados, 1992	Chile	All ages	113.0	Retrospective review of clinical charts of one hospital.
Li, 1985	China	All ages	35.0	
Placencia, 1992	Ecuador	All ages	122.0–190.0	Urban and rural area; reasons for this difference not identified. House-to-house survey, assessment for false negatives and false positives performed.
El Tallawy, 2010	Egypt	All ages	43.14	
Tekle-Heimanot, 1997	Ethiopia	All ages	64.0	
Medina, 2005	Honduras	All ages	92.7	
Mani, 1998	India	All ages	49.3	
Ibinda, 2014; Mung'ala-Odera, 2008	Kenya	All ages	39.16–187.0	Lower rates in women and higher rates in children. Surveys with children 6–12 years and people of all ages identified from community census. Active convulsive epilepsy.
Burneo, 2005	Latin America	All ages	77.7–190	Heterogeneous methodologies (cross-sectional studies, retrospective, prospective studies) (review).
Jallon, 1999	Martinique	All ages	64.1	Prospective identification of all cases of epilepsy in 1-year period.
Ba-Diop, 2014	Sub-Saharan Africa	All ages	81.7	
Dogui, 2003	Tunisia	Children	102.1	First unprovoked seizures in all children aged 1 month–15 years. Confirmed by neurologists. Use of validated questionnaires.
Kaiser, 1998	Uganda	All ages	215.0	High onchocerciasis endemicity.
Winkler, 2009	United Republic of Tanzania	All ages	81.1	

Source: Fiest et al., 2017 *(1)*.

Table A2.3 Prevalence (per 1000) of active epilepsy in HIC

Author, year	Country	Age	Prevalence ratios	Notes
Kruja, 2012	Albania	All ages	14.2	Door-to-door survey of neurological disorder in different areas for socioeconomic background.
D'Souza, 2012	Australia	All ages	4.4	
Tellez-Zenteno, 2004; Prasad, 2011; Schiariti, 2009	Canada	All ages	4.03–5.5	
Josipovich-Jelic, 2011	Croatia	All ages	10.9	Survey in a Croatian county. High prevalence due to living conditions and age distribution.
Christensen, 2007	Denmark	All ages	6.0	
Beilmann, 1999; Oun, 2003	Estonia	All ages	3.6–5.3	Lower ratios in children and higher in adults.
Joensen, 1986	Faroe Islands	All ages	7.6	
Sillanpaa 1973; Keranen, 1989; Eriksson, 1997	Finland	All ages	3.2–6.3	Lower ratios in children.
Picot, 2008	France	Adults	5.4	
Olaffson, 1999	Iceland	All ages	4.8	
Gallitto, 2005; Cossu, 2012; Giussani, 2015; Giussani, 2016; Granieri, 1983	Italy	All ages	3.0*–7.9	*Aeolian Islands
Nakano, 2014; Oka, 2006	Japan	All ages	2.7–40.0	Lower ratios in children and higher in older ages.
Endziniene, 1997	Lithuania	Children	4.2	
Waaler, 2000; Syvertsen, 2015	Norway	All ages	5.1–6.5	Lower ratios in children.
Bilikiewicz, 1988	Poland	>16 years	3.7	
Lee, 2012	Republic of Korea	All ages	2.41	Cases identified through antiseizure medicine prescription and diagnostic codes for epilepsy and seizures (ICD-10) in the national health insurance database.
Al Rajeh, 2001	Saudi Arabia	All ages	6.5	
Pavlovic, 1998	Serbia	Children	6.5	
Luengo, 2001, Benavente, 2009; Garcia-Martin, 2012	Spain	All ages	4.1–6.3	Higher ratios in adolescents.
Brorson, 1987; Forsgren, 1992; Sidenvall, 1996; Bolin, 2015	Sweden	All ages	4.2–8.8	Lower ratios in children.
Chen, 2006; Hsie, 2008	Taiwan, China	All ages	2.7*–4.2	Lower ratios in adults.
De La Court, 1996	The Netherlands	Adults and elderly	9.0	Door-to-door survey in a suburb of Rotterdam.

Table A2.3 Prevalence (per 1000) of active epilepsy in HIC (continued)

Author, year	Country	Age	Prevalence ratios	Notes
Goodridge, 1983; Wallace, 1998; MacDonald, 2000; Wright, 2000; Gaitatzis, 2004; Steer, 2014	United Kingdom of Great Britain and Northern Ireland	All ages	4.0–8.0	
Hauser, 1991; Kobau, 2004; Holden, 2005; Chong, 2013; Ablah, 2014	United States of America	All ages	7.2*–21.0	*Only adults in Georgia and in Tennessee.
Dogui, 2003	Tunisia	Children	102.1	First unprovoked seizures in all children aged 1 month–15 years. Confirmed by neurologists. Use of validated questionnaires.
Kaiser, 1998	Uganda	All ages	215.0	High onchocerciasis endemicity.
Winkler, 2009	United Republic of Tanzania	All ages	81.1	

Source: Fiest et al., 2017 *(1)*.

Table A2.4 Prevalence (per 1000) of active epilepsy in LMIC

Author, year	Country	Age	Prevalence ratios	Notes
Magalov, 2012	Azerbaijan	All ages	9.02	
Yemadje, 2012; Houinato, 2013	Benin	All ages	8.2–12.7*	* Capture-recapture method in rural community. Lower ratios in ≥ 15 years.
Nicoletti, 1999	Bolivia (Plurinational State of)	All ages	11.1	
Marino, 1987; Gomes, 2002; Borges, 2004	Brazil	All ages	5.1–8.2 active 13.0 lifetime	
Nitiema, 2012	Burkina Faso	All ages	45.0	Lifetime.
Preux, 2011	Cambodia	All ages	5.8	
Prischich, 2008	Cameroon	All ages	105	Door-to-door survey with electro-clinical evaluation. Age-specific prevalence peaked between 20 and 29 years with 42% of the cases. No people with epilepsy aged 0–9 years and over 50 years were found.
Lavados, 1992	Chile	All ages	17.7	
Li, 1985; Kwong, 2001; Wang, 2003; Fong, 2008; Zhao, 2010; Hu, 2014; Pi, 2014	China	All ages	1.52–4.4 active 23.5 lifetime	Lower ratios in adults with active convulsive epilepsy.
Gomez, 1978; Pradilla, 2003; Velez, 2006	Colombia	All ages	10.3 active 19.5 lifetime	Case ascertainment through questionnaire, neurological examinations, instrumental examinations.
Placencia, 1992; Cruz, 1999; Del Brutto 2005	Ecuador	All ages	6.7–22.62	Higher ratios in migrant populations. Included single seizures, acute symptomatic seizures, ILAE classification 1981, house-to-house surveys.
El Tallawy, 2010; Farghaly, 2013	Egypt	All ages	2.1–6.9	Lower ratios in adults.
Tekle-Heimanot, 1990	Ethiopia	All ages	5.2–29.46	Higher ratios in the Zay society after a door-to-door survey.
Coleman, 2002	Gambia	All ages	4.9	Lifetime.
Lomidze, 2012	Georgia	All ages	8.8	
Mendizabal, 1996; Garcia-Noval, 2001	Guatemala	All ages	5.8–18.0*	Higher ratios in two rural Guatemalan communities.
Medina, 2005	Honduras	All ages	15.4	Epilepsy survey administered to 88% of residents by census in a rural county.
Bharucha, 1988; Radhakrishnan, 2000; Banerjee, 2009; Pandey, 2014	India	All ages	3.6–7.0	Higher ratios in children.

Table A2.4 Prevalence (per 1000) of active epilepsy in LMIC (continued)

Author, year	Country	Age	Prevalence ratios	Notes
Ebrahimi, 2012	Iran (Islamic Republic of)	All ages	7.9	
Mung'ala-Odera, 2008; Ibinda, 2014	Kenya	All ages	2.59–11.0	Lower ratios in active convulsive epilepsy, higher ratios in children.
Burneo, 2005	Latin America	All ages	6.0–43.2	Lifetime prevalence. Validated questionnaires, door-to-door surveys, interviews, different definition of epilepsy, heterogeneous studies (review).
Sridharan, 1986	Libya	≥ 15 years old	2.3	Cases identified in policlinics, EEG laboratories and university hospital in a defined region. Lower prevalence in the ≥ 60 years old (1 per 1000).
Rajbhandari, 2004	Nepal	All ages	7.3	
Osakwe, 2014	Nigeria	All ages	4.7–20.8	Lower ratios in the rural community and higher ratios in the semi-rural community.
Aziz, 1997; Malik, 2011	Pakistan	All ages	7.0–9.98	
Gracia, 1990	Panama	All ages	22.0–57.0	Lower ratios in Panama City populations than in the Caribbean coast.
Gonzales, 2015	Peru	Adults	15.3–25.0–35.6	Lower ratios in the urban group, middle ratios in the rural group, higher ratios in migrant group.
Ndoye, 2005	Senegal	All ages	14.2	Door-to-door survey.
Wagner, 2014	South Africa	All ages	7.0	
Ngugi, 2013; Ba-Diop, 2014	Sub-Saharan Africa	All ages	6.8–14.8	Large population-based cross-sectional and case control studies. The prevalence varies along with the presence of different risk factors.
Balogou, 2007	Togo	All ages	15.7	Sensitization campaign and a door-to-door survey.
Attia-Romdhane, 1993	Tunisia	All ages	4.0	
Aziz, 1997; Karaagac, 1999; Onal, 2002; Aydin, 2002; Huseynoglu, 2012; Velioglu, 2010; Canpolat, 2014; Ozkan, 2015	Turkey	All ages	2.5–8.6	Lower ratios in adolescents and higher rates in children.
Dent, 2005; Winkler, 2009; Hunter, 2012	United Republic of Tanzania	All ages	2.91–8.7	Lower ratios in adults and higher ratios in a door-to door survey.
Birbeck, 2004	Zambia	All ages	12.5	

Source: Fiest et al., 2017 *(1)*.

Table A2.5 Community-based studies of mortality in epilepsy in HIC

Author, year	Country	Age	Mortality measures	Notes
Camfield, 2002	Canada	Children	SMR 7.5	
Holst, 2013	Denmark	< 35 years old	HR 11.9	
Rakitin, 2011	Estonia	Adults	SMR 2.6	
Sillanpaa 2013; Nevalainen, 2013	Finland	All ages	SMR 6.4 HR 3.21	SMR in childhood-onset epilepsy, < 16 years old.
Olafsson, 1998; Rafnsoon, 2001	Iceland	All ages	SMR 1.6 F 0.79 M 2.25	
Zielinsky, 1974	Poland	All ages	SMR 1.8	
Nilsson, 1997; Lindsten, 2000	Sweden	All ages	SMR 2.5–3.6	SMR in cohort ≥ 15 years old.
Cockerell, 1997; Lhatoo, 2001; Morgan, 2002; Neligan, 2011	United Kingdom of Great Britain and Northern Ireland	All ages	SMR 2.1–3.0	
Hauser, 1980; Berg, 2004; Benn, 2008; Nickels, 2012	United States of America	All ages	SMR 1.7–7.54	SMR in childhood-onset epilepsy < 16 years old. SMR in cohort < 18 years old.

F: female; HR: hazard ratio; M: male; SMR: standardized mortality ratio.
Source: Thurman et al., 2017 *(25)*.

Table A2.6 Community-based studies of mortality in epilepsy in LMIC

Author, year	Country	Population	Mortality measures	Notes
Kochen, 2007	Argentina	All ages	SMR 2.45	
Houinato, 2013	Benin	All ages	Mortality rate 22.2 per 1000	
Nicoletti, 2009	Bolivia (Plurinational State of)	All ages	SMR 1.34	
Kamgno, 2003	Cameroon	All ages	Mortality rate 28.9 per 1000	
Mu, 2011; Ding, 2013	China	All ages	SMR 2.9–4.9	Lower ratios in a follow-up survey and higher rates in a prospective study.
Carpio, 2005	Ecuador	All ages	SMR 6.3	
Carpio, 2005; Banerjee, 2010	India	All ages	SMR 0.76–2.58*	Lower ratio in a postal and telephone survey among the Parsi community and higher ratio in a two-stage door-to-door survey of a stratified random sample in Kolkata.
Ngugi, 2014	Kenya	All ages	SMR 6.5	
Carpio, 2005	Mali	All ages	Mortality rate 34.9 per 1000	
Carpio, 2005	Martinique	All ages	SMR 4.25	
Tsai, 2005	Taiwan, China	All ages	Mortality rate 0.8 per 100 000	
Kaiser, 2007	Uganda	All ages	SMR 7.2	

Source: Levira et al., 2017 *(26)*.

Table A2.7 Population-based longitudinal studies on the remission rates in epilepsy

Author, year	Country	Age	Follow-up time, years	% (duration) remission
Houinato, 2013	Benin	All ages	18 months	45% (total seizure remission)
Nicoletti, 2009	Bolivia (Plurinational State of)	All ages	10	43.7% (5-year)
Camfield, 2005	Canada	Children	8	71% (3-year)
Placencia, 1992	Ecuador	All ages	4	21% (terminal remission)
Sillanpaa, 2014	Finland	Children	45	61% (5-year)
Geerts, 2010	Holland	Children	15	71% (5-year terminal)
Okuma, 1981	Japan	All ages	3–10	56%, 59% and 62% (terminal remission)
Wakamoto, 2000	Japan	Children	19	62.8% (5-year)
Jonsson, 2011	Sweden	All ages	10	In children 75.6% In adults 68% (1-year), 64% (3-year), 58% (5-year)
MacDonald, 2000; Lhatoo, 2001; Cockerell, 1995; Cockerell, 1997	United Kingdom of Great Britain and Northern Ireland	All ages	Up to 12	95% (1-year) 86% (3-year) up to 71% (5-year) 54% (5-year terminal)
Annegers, 1979; Berg, 2015	United States of America	All ages	Up to 20	76% (5-year) In children 95% (1-year), 92% (2-year), 89% (3-year), 81% (5-year)

Source: Beghi et al., 2015 *(63)*.

ANNEX 3

SIXTY-EIGHTH WORLD HEALTH ASSEMBLY **WHA68.20**

Agenda item 13.5 **26 May 2015**

Global burden of epilepsy and the need for coordinated action at the country level to address its health, social and public knowledge implications

The Sixty-eighth World Health Assembly,

Having considered the report by the Secretariat on the global burden of epilepsy and the need for coordinated action at the country level to address its health, social and public knowledge implications;[1]

Considering resolution WHA66.8, in which the Health Assembly adopted the comprehensive mental health action plan 2013–2020, and resolution WHA67.22 on access to essential medicines;

Acknowledging United Nations General Assembly resolution 68/269 and resolution WHA57.10 on road safety and health, resolution WHA66.12 on neglected tropical diseases, resolution WHA67.10 on the newborn health action plan, resolution WHA67.15 on strengthening the role of the health system in addressing violence, in particular against women and girls, and against children, and the discussions on the control of neurocysticercosis and its association with epilepsy at the Fifty-sixth World Health Assembly;[2]

Noting the Political Declaration of the High-level Meeting of the United Nations General Assembly on the Prevention and Control of Non-communicable Diseases,[3] in which Heads of State and Government recognized that mental and neurological disorders are an important cause of morbidity and contribute to the global noncommunicable disease burden, necessitating provision of equitable access to effective programmes and health care interventions;

Considering the health-related Millennium Development Goals, the outcome document of the United Nations Conference on Sustainable Development entitled "The future we want",[4] and the report of the Open Working Group on Sustainable Development Goals, established pursuant to United Nations General Assembly resolution 66/288, which proposes Goal 3 (Ensure healthy lives and promote well-being for all at all ages) and target 3.4 (by 2030 reduce by one-third premature mortality

[1] Document A68/12.

[2] See document WHA56/2003/REC/3, summary record of the fourth meeting of Committee A.

[3] United Nations General Assembly resolution 66/2.

[4] United Nations General Assembly resolution 66/288.

from non-communicable diseases through prevention and treatment, and promote mental health and well-being);[1]

Recognizing that epilepsy is one of the most common serious chronic neurological diseases, affecting 50 million people of all ages globally, and that people with epilepsy are often subjected to stigmatization and discrimination because of ignorance, misconceptions and negative attitudes surrounding the disease, and that they face serious difficulties in, for example, education, employment, marriage and reproduction;

Noting with concern that the magnitude of epilepsy affects people of all ages, gender, race and income levels, and further that poor populations and those living in vulnerable situations, in particular in low- and middle-income countries, bear a disproportionate burden, posing a threat to public health and economic and social development;

Cognizant that large differences exist in the level of epilepsy management in different countries, with, for example, the median number of neurologists in low-income countries standing at only 0.03/100 000 population, that the essential antiepileptic medicines are often unavailable, that the treatment gap is estimated to be over 75% in low-income countries and to be substantially wider in rural areas than in urban areas;

Noting that the majority of people with epilepsy can be kept free from seizures if appropriately treated with cost-effective, affordable antiepileptic medicines;

Recognizing in addition that certain causes of epilepsy can be prevented and that such preventive action can be promoted in the health sector and in sectors outside health;

Aware that in 1997, WHO and two international nongovernmental organizations, the International League Against Epilepsy and the International Bureau for Epilepsy, launched the Global Campaign against Epilepsy – "Out of the Shadows", and that in 2008 WHO launched its mental health gap action programme, which provided a sound basis for WHO to further lead and coordinate global development work on epilepsy;

Aware also that practice in China and some other low-income countries has proved that country-level coordinated action may be very effective in controlling the disease and improving the quality of life of millions of people with epilepsy at little cost;

Recognizing the remarkable progress made recently in the technology of epilepsy management, from basic research to diagnosis and treatment;

Considering that international governmental organizations, nongovernmental organizations, academic societies and other bodies have recently enhanced their investment in epilepsy management and have undertaken a significant amount of work in collaboration with national governments, such as the International League Against Epilepsy and the International Bureau for Epilepsy, which are in official relations with WHO and have been collaborating with WHO in epilepsy management for several decades;

Recognizing the role of WHO to demonstrate further leadership and coordination and take effective action for epilepsy management, in view of the large public health impact,

[1] Document A/68/970.

1. URGES Member States:[1]

(1) to strengthen effective leadership and governance, for policies on general health, mental health and noncommunicable diseases that include consideration of the specific needs of people with epilepsy, and to make the financial, human and other resources available that have been identified, as necessary, to implement evidence-based plans and actions;

(2) to introduce and implement, where necessary and in accordance with international human rights norms and standards, national health care plans of action for epilepsy management, aiming to overcome inequalities and inequities in health, social and other related services, paying special attention to people with epilepsy living in conditions of vulnerability, such as those living in poor and remote areas, including by strengthening public health care services, and by training local human resources with proper techniques;

(3) to integrate epilepsy management, including health and social care, particularly community-based services, within the context of universal health coverage, including community-based rehabilitation, into primary health care, where appropriate, in order to help to reduce the epilepsy treatment gap, by training non-specialist health care providers in order to provide them with basic knowledge for the management of epilepsy so that epilepsy can be diagnosed, treated and followed up as much as possible in primary health care settings, as well as by empowering people with epilepsy and their carers to make greater use of specified self- and home-care programmes, by ensuring a strong and functional referral system and by strengthening health information and surveillance systems to routinely collect, report, analyse and evaluate trends on epilepsy management;

(4) to support the establishment and implementation of strategies for the management of epilepsy, particularly to improve accessibility to and promote affordability of safe, effective and quality-assured antiepileptic medicines and include essential antiepileptic medicines into national lists of essential medicines;

(5) to ensure public awareness of and education about epilepsy, in particular in primary and secondary schools, in order to help to reduce the misconceptions, stigmatization and discrimination regarding people with epilepsy and their families that are widespread in many countries and regions;

(6) to promote actions to prevent the causes of epilepsy, using evidence-based interventions, within the health sector and in other sectors outside health;

(7) to improve investment in epilepsy research and increase research capacity;

(8) to engage with civil society and other partners in the actions referred to in subparagraphs 1(1) to 1(7) above;

2. INVITES international, regional, national and local partners from within the health sector and beyond to engage in, and support, the implementation of the actions set out in subparagraphs 1(1) to 1(8) above;

[1] And, where applicable, regional economic integration organizations.

3. REQUESTS the Director-General:

(1) to review and evaluate the actions relevant to epilepsy that WHO has been leading, coordinating and supporting in order to identify, summarize and integrate the relevant best practices with a view to making this information widely available, especially in low- and middle-income countries;

(2) to develop, in consultation with relevant stakeholders, on the basis of work requested in operative paragraph (1), a set of technical recommendations guiding Member States in the development and implementation of epilepsy programmes and services, and to provide technical support to Member States in actions for epilepsy management, especially in low- and middle-income countries;

(3) to report to the Seventy-first World Health Assembly on progress in the implementation of this resolution.

Ninth plenary meeting, 26 May 2015
A68/VR/9

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ANNEX 4

Multi-country assessment of comprehensive health care

Table A4.1 Available diagnostic technology

	Chile	China	India	Kazakhstan	Kenya	Russian Federation	South Africa	Uganda	United Kingdom	United Republic of Tanzania	United States of America
Urban											
Basic	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Advanced	✔	✔	✔[a]			✔[a]	✔		✔		✔
Rural			None		None		None	None		None	
Basic	✔	✔		✔[b]		✔[b]			✔		✔
Advanced									✔		✔

Notes: Basic diagnostic technology included electroencephalography - sleep/awake, inpatient monitoring, magnetic resonance imaging and computed tomography scans. Advanced diagnostic technology included single-photon emission computed tomography, positron emission tomography and magnetoencephalography.

[a] Positron emission tomography only.

[b] Electroencephalography and computed tomography only.

Table A4.2 Availability of antiseizure medicines

	Chile	China	India	Kazakhstan	Kenya	Russian Federation	South Africa	Uganda	United Kingdom	United Republic of Tanzania	United States of America
Urban											
Essential	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Newer	✔	✔	✔	✔		✔	✔		✔		✔
Rural										None	
Essential	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔
Newer	(Waiting list)[a]			✔		✔			✔		✔

Notes: Essential medicines include: phenobarbital, phenytoin, sodium valproate and carbamazepine. Newer medicines include: lamotrigine, levetiracetam, oxcarbazepine and topiramate.

[a] Newer medications are available but in short supply.

Table A4.3 Nonpharmacological epilepsy treatment

	Chile	China	India	Kazakhstan	Kenya	Russian Federation	South Africa	Uganda	United Kingdom	United Republic of Tanzania	United States of America
Urban											
Behavioural	✔	✔	✔	✔		✔	✔	None	✔		✔
Dietary	✔	✔	✔	✔		✔	✔		✔		✔
Vagus nerve stimulation[a]	✔	✔	✔	✔		✔	✔		✔		✔
Surgery[b]	✔	✔	✔	✔	✔	✔	✔		✔	✔	✔
Deep brain stimulation, and/or responsive neurostimulation[c]	✔	✔	✔	✔		Delay	✔		✔		✔
Rural											
Behavioural	None	None	None	None	None	None	None	None	✔	None	✔
Dietary									✔		✔
Vagus nerve stimulation[a]									✔		✔
Surgery[b]						Delay			✔		✔
Deep brain stimulation, and/or responsive neurostimulation[c]									✔		✔

Notes:
[a] Vagus nerve stimulation: treatment involving the use of a device to stimulate the vagus nerve with electrical impulses.
[b] Type of surgery not specified.
[c] Deep brain stimulation and/or responsive neurostimulation: neurosurgical procedure involves implanting electrodes within certain areas of the brain that produce electrical impulses to regulate abnormal impulses or affect certain cells and chemicals within the brain. Only the United States of America has both deep brain stimulation and responsive neurostimulation.

Table A4.4 Epilepsy training for health care providers

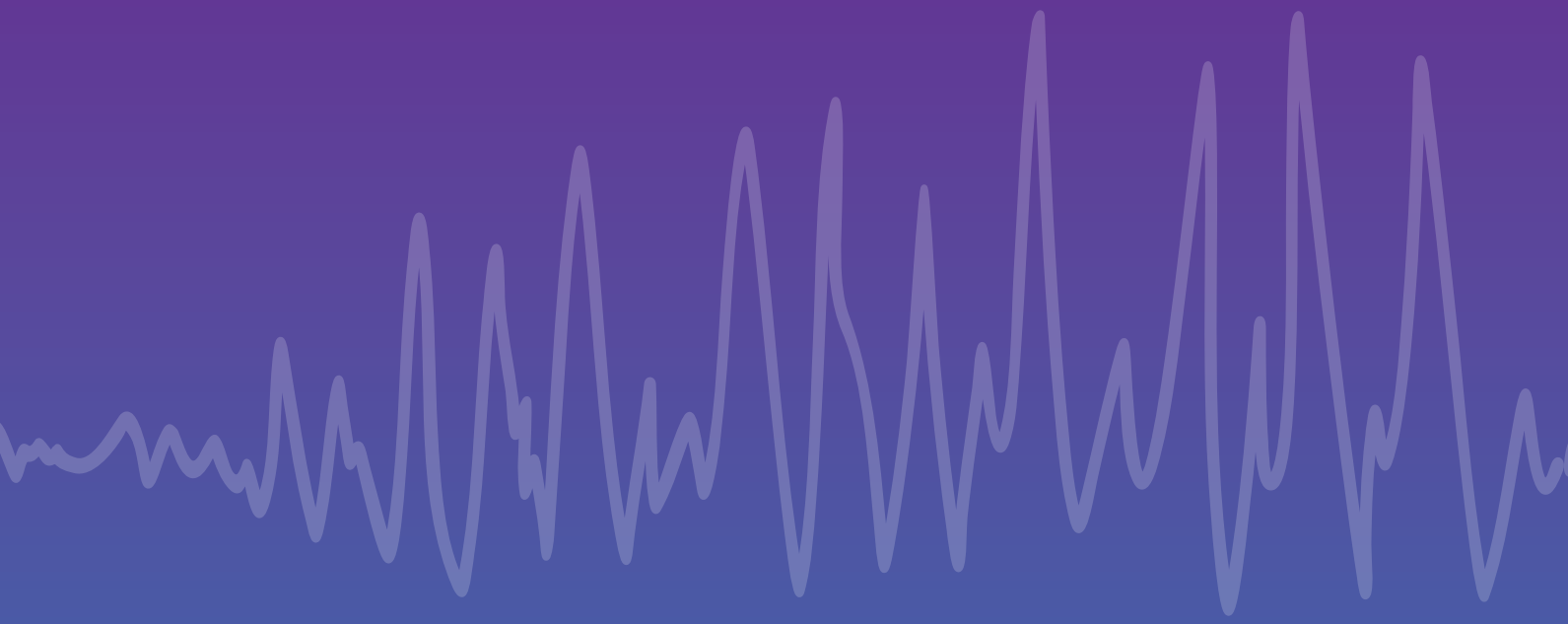
	Chile	China	India	Kazakhstan	Kenya	Russian Federation	South Africa	Uganda	United Kingdom	United Republic of Tanzania	United States of America
Advanced training for epilepsy specialist physicians	✔	✔	✔	✔		✔	✔		✔		✔
Formal training for primary health care providers (physicians, nurses, other)	✔	✔		✔	✔	✔	✔	✔	✔	✔	✔
Formal training for non-medically trained providers			✔		✔					✔	

Table A4.5 Treatment and care management of epilepsy

	Chile	China	India	Kazakhstan	Kenya	Russian Federation	South Africa	Uganda	United Kingdom	United Republic of Tanzania	United States of America
Initial treatment											
Specialist	✔	✔	✔	✔	✔	✔			✔	✔	✔
Generalist primary care provider, nurse	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Non-medically trained provider			✔		✔					✔	
Long-term treatment and care management											
Specialist	✔	✔	✔	✔	✔	✔	✔		✔		✔
Generalist primary care provider, nurse	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Non-medically trained provider			✔								

Table A4.6 Epilepsy advocacy and social support groups

Organizations	Chile	China	India	Kazakhstan	Kenya	Russian Federation	South Africa	Uganda	United Kingdom	United Republic of Tanzania	United States of America
ILAE	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
IBE	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔
Professional neurology associations	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔
Consumer organizations	✔						✔	✔	✔		✔



Epilepsy
Treat it. Defeat it.

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