Epilepsy care challenges in developing countries

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Purpose of review
This review discusses recent literature relevant to the diagnosis and treatment of epilepsy in developing countries with particular attention to underlying causes, natural history, and advances made toward optimizing systems of care and bridging the treatment gap.

Recent findings
Prospective data suggest that cerebral malaria-induced brain injury may explain the high prevalence of epilepsy in malaria-endemic regions. Population-based mortality studies support the long proposed hypothesis that seizure-related deaths contribute to excessive premature mortality. WHO guidelines have the potential to improve care, but macrolevel barriers related to pharmaceutical regulation and distribution continue to contribute to the treatment gap. Evidence-based guidelines endorsed by the WHO and American Academy of Neurology regarding the optimal management of comorbid epilepsy and HIV may raise awareness regarding critical drug interactions between antiepileptic drugs and antiretrovirals, but are also problematic as the treatment regimen and diagnostic facilities routinely available in developing countries will prevent most healthcare providers from following the recommendations.

Summary
New insights into the causes, natural history and best care practices for epilepsy in developing countries are available but without prioritization and action from policy makers, the present treatment gap will likely to persist.

Keywords
cost, developing country, drug interactions, epilepsy, HIV, mortality, pharmaceutical regulations, pharmacokinetics, public policy, treatment gap

INTRODUCTION

Epilepsy is the most common chronic neurologic disorder in the developing world, wherein 80% of people with epilepsy (PWE) reside. Where available, epilepsy care in low-income countries remains extremely basic and usually consists of first-generation antiepileptic drugs (AEDs) delivered by nonphysician healthcare workers who have no recourse to electroencephalography (EEG), neuroimaging, serum–drug level monitoring or specialist referral. Recent malaria research from Malawi may at least partially explain the extremely high rates of epilepsy reported from some regions of Africa [1▪]. Findings from the China Demonstration Project [2▪▪] confirmed the sad reality that epilepsy is a frequently fatal condition in low-income countries, perhaps even when treatment is made available [3]. Such advances in knowledge have provided clinicians with new information regarding risk factors for epilepsy and emphasize the critical need for counseling on physical safety and the prevention of seizure-related injuries, particularly where exposure to potential drowning or burns is probable. WHO clinical care guidelines for epilepsy in developing countries have drawn international attention to the 'treatment gap'.

The epilepsy treatment gap is typically defined as the proportion of people who require but are not receiving treatment. It has been proposed as an important parameter for access to care and quality of care across health systems and populations. With an average gap of approximately 75% for low-income countries and the poorest in Africa having a gap of more than 90%, perhaps 'chasm' would be a better term. Whether sufficient global political will can be harnessed to prioritize access to epilepsy care

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KEY POINTS

- Population-based mortality data from the China Demonstration project confirm that epilepsy is a frequently fatal condition in developing country settings.
- In malaria-endemic regions, cerebral malaria may be among the most common causes of epilepsy, causing up to 135 000 new cases annually in Africa.
- If broadly implemented, newly released WHO epilepsy care guidelines could decrease the treatment gap and improve care in low-income countries.
- Where enzyme-inducing antiepileptic drugs (AEDs) are the only treatment options, and HIV prevalence is high, the co-usage of these AEDs and antiretroviral agents presents a public health crisis that has yet to be addressed.

remains unclear, but we now know that lives clearly hang in the balance.

HEALTH SYSTEMS FOR EPILEPSY CARE IN DEVELOPING COUNTRIES

Understanding the challenges of the diagnosis and treatment of epilepsy in the developing world requires reflection on how developing countries are defined and how, even within these countries, parallel private and public healthcare systems exist that are distinctly disparate. For those with the financial capacity to access the private sector, epilepsy care is comparable to care provided by many centers of excellence in developing countries. However, most PWE who seek care at all must do so through the usually underfunded public health sector. Public health systems in many low-income countries, particularly those in tropical climes, continue to focus resources and training on the provision of care for acute, infectious diseases. Limited attention is given to the need for services appropriate for the management of chronic, noncommunicable disorders. Furthermore, within many lower middle-income countries (LMICs), neurologic disorders fall into the realm of mental health, one of the most notoriously underfunded health sectors. The median percentage of health expenditures dedicated to mental health was recently estimated at 0.5% in low-income countries compared to 5.1% in high-income countries [4].

Why are mental and neurological services so disproportionately underfunded? The dearth of human resources with neurologic or psychiatric clinical skills may be one key reason. A survey of key personnel in 109 countries conducted by the WHO in conjunction with the World Federation of Neurology found only 0.03–0.07 neurologists per 100 000 people in Africa and South-East Asia. Numbers were even direr for neurological nurses and subspecialists such as pediatric neurologists and neurosurgeons [5]. A recent survey of 58 LMICs estimated deficits in psychiatrists, psychiatric nurses, and psychosocial support workers in 67, 95, and 79% of countries, respectively. In terms of crude numbers, deficits of 11 000 psychiatrists, 128 000 nurses, and 100 000 psychosocial support providers were estimated [6▪]. These figures likely underestimate the true staffing shortfalls, given that survey respondents represented a convenience sample of countries willing and able to answer the survey questions and the calculations were based on care of eight specific conditions (including epilepsy), and thus do not account for the total burden of mental health disorders.

In 2012, findings from the Global Burden of Diseases, Injuries and Risk Factors Study should become available. This update of the seminal 1995 study includes a more objective weighting system for assigning disabilities to the Disability-Adjusted Life Years [DALY] [7]. Tens of thousands of people worldwide ranked lay descriptions that described a person's existence living in a particular health state and rank accordingly. See Table 1 for the lay descriptions of epilepsy used. The new DALY metric may propel the global attributable burden of epilepsy even higher.

Given the highly stigmatized nature of epilepsy and mental health disorders, structural bias may also exist. The Non-Communicable Disease (NCD) Alliance, which aims to garner commitments from wealthy donor countries, nongovernment organizations and Ministries of Health in LIMCs to address the burden of NCDs, excludes epilepsy as well as most other mental and neurologic disorders [8]. Consequently, the September 2011 landmark United Nations General Assembly on NCDs did not address the epilepsy treatment gap [9].

UNIQUE CAUSES FOR EPILEPSY

Environmental and genetic factors likely play a role in the relatively high prevalence and incidence estimates identified in low-income, tropical countries. Frequency estimates of specific causes of epilepsy are largely unknown in most LMICs, but the idiopathic (genetic), neurodevelopmental, and posttraumatic [10] causes of epilepsy recognized in the West undoubtedly also result in epilepsy in developing regions [11].

Recent reviews have better characterized the geographic distributions of infectious pathogens

Table 1. Lay description of the epilepsy health states proposed for disability weighting in the 2010 Global Burden of Diseases Study

Severe epilepsy	This person has very frequent, recurrent, unpredictable and sometimes long episodes of loss of consciousness with shaking of the limbs and sometimes with bowel or bladder incontinence. Medications cause significant drowsiness and impaired concentration. Gradually, the person is having problems thinking, remembering things and concentrating on a task. Between episodes, they worry about the injuries and embarrassment associated with future episodes. The risk of injuries and death is much higher in this person because the episodes are not responding to any treatment which might be taken.
Treated, seizure free	This person, in the past, has had recurrent, unpredictable episodes of loss of consciousness with shaking of the limbs and sometimes with bowel or bladder incontinence. The person is currently taking medications, which cause some drowsiness and impaired concentration but are successfully preventing these episodes. The person still worries about injuries and embarrassment associated with future episodes.
Treated, with recent seizures	This person has recurrent, unpredictable episodes of loss of consciousness with shaking of the limbs and sometimes with bowel or bladder incontinence. Medications are making these episodes less frequent and less severe, but cause some drowsiness and impaired concentration. Between episodes, the person worries about the injuries and embarrassment associated with future episodes.
Untreated, with recent seizures	This person has frequent recurrent, unpredictable episodes of loss of consciousness with shaking of the limbs and sometimes with bowel or bladder incontinence. Between episodes, the person worries about the injuries and embarrassment associated with future episodes. The risk of injuries and death is much higher in this person because they are not taking any treatment for these episodes.

in developing countries along with their neurological manifestations and sequelae [12,13]. Central nervous system infectious pathogens with epilepsy-related sequelae are more common in developing countries and include bacterial meningitis and viral encephalitides, such as Japanese encephalitis [14], dengue [15], and chikungunya [16]. Common tropical pathogens with associated postinfectious seizure disorders include tuberculosis, HIV, toxocariasis [17], paragonimiasis [17] and schistosomiasis [18,19]. Neurocysticercosis continues to contribute substantially to the global burden of epilepsy [20–22]. Public health endeavors aimed at improving public sanitation and animal husbandry may ultimately decrease neurocysticercosis infections and subsequently epilepsy rates [18], but no successful interventions have been documented to date.

An understanding of the neurological sequelae of cerebral malaria is also beginning to emerge [23–28]. Malaria has long been thought to contribute to the global burden of epilepsy, particularly in sub-Saharan Africa. However, diagnostic uncertainty and the lack of prospective studies previously limited our ability to estimate its contribution. The WHO definition of cerebral malaria includes any patient with unexplained coma and *Plasmodium falciparum* parasitemia [29]. This pragmatic definition results in the over-diagnosis of cerebral malaria and the misattribution of postinfectious coma to the malaria parasite [30,31]. A recently described malaria-specific retinopathy has emerged as a way to differentiate patients with coma and asymptomatic parasitemia from those with pathological changes indicative of cerebral malaria at autopsy as confirmed by sequestration of parasitized erythrocytes in the cerebral microvasculature [32▪▪]. The presence of retinopathy in comatose children identifies the pathological changes of cerebral malaria seen at autopsy with 95% sensitivity and 90% specificity [24,32▪▪,33▪]. In 2010, the first prospective cohort study of neurological outcomes in well characterized cerebral malaria survivors was published. Utilizing age-matched noncomatose children as controls, 12 of 132 (9%) cerebral malaria survivors developed epilepsy within 3 years compared to zero of 264 controls [odds ratio (OR) 4.8–15.3] [1▪]. Risk factors for epilepsy following cerebral malaria included a higher maximum temperature and seizures during the acute infection. Careful follow-up and a low threshold for suspicion of epilepsy in pediatric cerebral malaria survivors are warranted. Neuroprotective interventions during cerebral malaria to decrease long-term sequelae including epilepsy also deserve consideration.

TECHNICAL CAPACITY FOR DIAGNOSIS

Clinical history and physical examination are generally the only routinely available diagnostic modalities available to clinicians in developing regions.

Neuroimaging is limited. Even at the tertiary care level, computerized tomography (CT) scanners are available in only 70.5% of low-income countries and MRI capacity is even more limited at 29.6% [4]. In Africa, resources were even more significantly constrained at 61.8% for CT and 20.6% for MRI. EEG capacity is similarly limited and guidelines for care in developing countries explicitly recommend that EEG is not to be used for routine diagnosis and treatment [34,35▪▪]. Therapeutic drug monitoring availability is also low among many low-income regions, including Africa (45.1%) and western Pacific (54.6%).

TREATMENT DELIVERY

The challenges of providing AEDs in developing countries can be divided into three broad and intersecting categories: patient-level, provider-level, and health system-based factors.

Patient-level factors

Individual-level patient characteristics common in developing countries that limit access to care include lack of financial resources for evaluation or transport to a local healthcare facility, the direct cost of drug [36], sociocultural beliefs about epilepsy [37] and epilepsy-associated stigma [37]. The latter have not only been well documented, but persist in knowledge–attitude–practice studies [38]. In some cultures, epilepsy is understood as a disease of the supernatural, a spiritual possession, evil spirits, or retribution for sin [39]. Perhaps naturally then, many patients in these cultures seek help first from traditional indigenous healers who offer psychological and spiritual support in a sociocultural context that likely exceeds their experience in medical clinics [40]. Traditional healers also often exist within local communities, negating the need for travel to a distant healthcare posts, and cost significantly less. For example, a study in a rural Nigerian community noted that although the nearest community health post was 13 km away, seven traditional healers existed within the community [41]. Some innovative approaches have tried to incorporate traditional healers into the referral system. A survey of 102 (51% response rate) traditional healers serving a population of over 90 000 people in northwest Cameroon found that 95% would refer a patient with epilepsy to hospital [40]. Traditional healers in this survey may have been biased toward this answer given that surveys were conducted in person and in the presence of medical staff, but the interest of these healers must have been high, as participating in the study required trekking several kilometers without any provided incentives. Given the local preference toward traditional medicine for epilepsy care in many such communities, the finding that 52% would place an object in the mouth of a person actively convulsing and 40.2% would hold or tie the person, and other possible dangerous actions being identified, also speaks to the need to incorporate traditional healers into educational programs on epilepsy care. In Lao People's Democratic Republic (PDR), traditional concepts of health and illness complicate treatment of chronic illnesses like epilepsy, and medications are discontinued after 3 days [42].

Healthcare worker factors

Given that most epilepsy care in developing countries is delivered by nonphysician healthcare workers who may have little formal neurologic training, the lack of appropriate knowledge among available clinicians is a major problem. Data from Kerala, India indicate that among 500 physician-level primary care providers, only 2.6% acknowledged having treated patients with focal seizures, suggesting many go undiagnosed. Subtherapeutic dosing was also noted to be an issue, with 28–66% recommending doses below defined daily doses [43]. Few training manuals exist that are aimed at preparing nonphysician healthcare workers to provide relatively independent care for people with neurologic disorders, although wherein such educational tools exist, translations into languages other than English are becoming available [44].

Macro-level barriers to care

Among patients who overcome personal barriers to accessing epilepsy treatment and who are also fortunate enough to encounter a healthcare provider with sufficient training to diagnose and prescribe an appropriate treatment, many will encounter health system limitations that further complicate treatment and AED adherence. Phenobarbital has long been recognized as the most affordable and broadly available AED in the poorest countries, but between 2006–2009 reduced phenobarbital availability was reported in several countries including Vietnam, Lao PDR and Zambia [36,45,46]. In Zambia, interviews with pharmacy staff directly linked this change to increased regulatory enforcement of phenobarbital as a controlled substance [36]. Increased enforcement came largely as a result of pharmaceutical regulatory capacity building activities led by the WHO. An unintended consequence of the capacity-building activities is that many pharmacies in developing countries have stopped

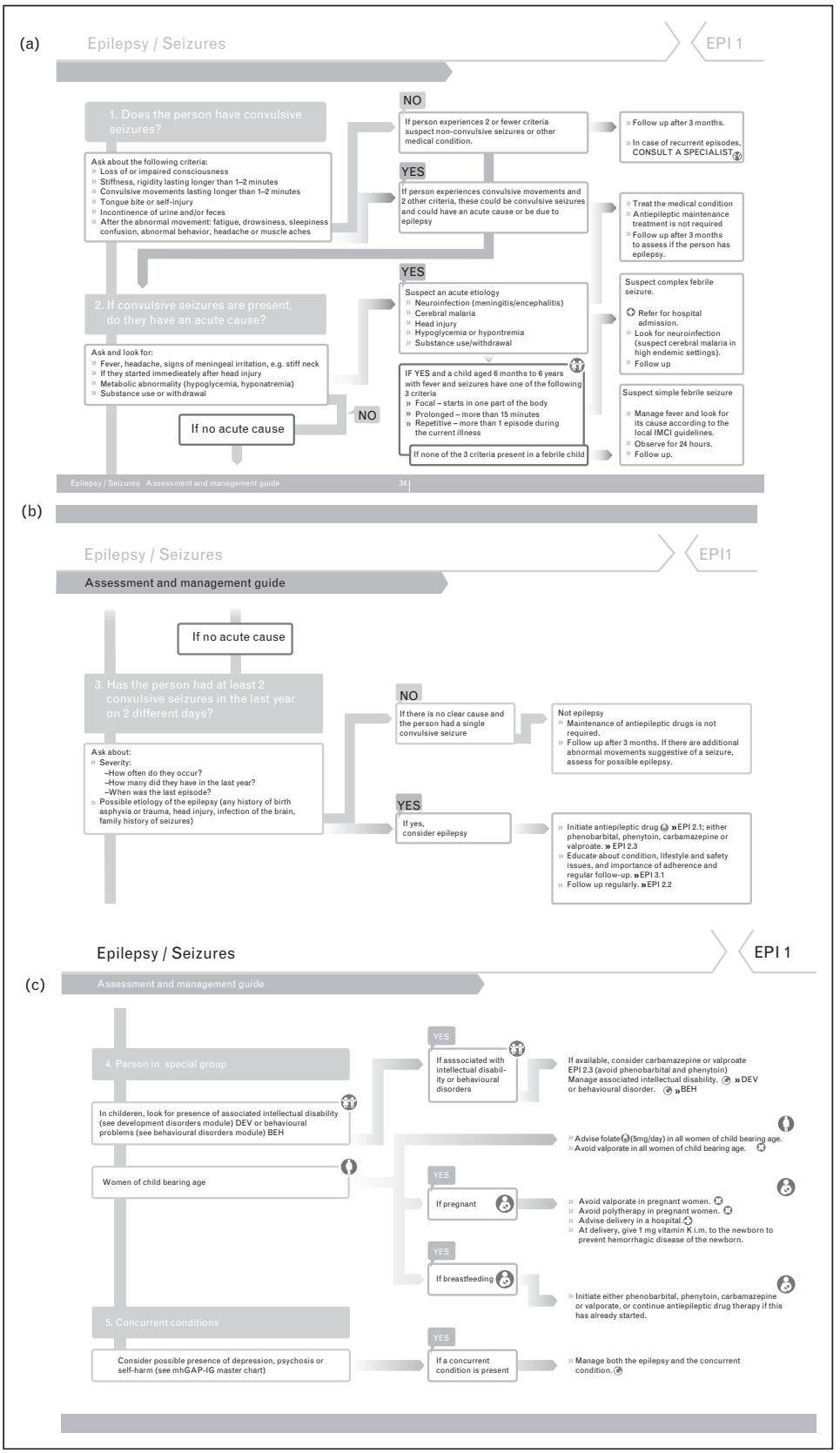

FIGURE 1. Epilepsy diagnosis and care algorithm from the WHO Mental Health Gap Action Program (mhGAP) guidelines. BEH, behavioral; DEV, developmental; EPI, epilepsy. Modified with permission from WHO, mhGAP Intervention Guide, World Health Organization, 2011.

stocking phenobarbital altogether or have increased costs to offset the additional burden of handling a controlled substance. Unfortunately, the remaining available AEDs are largely out of the economic reach of many people in low-income settings.

Efforts to identify macrolevel factors that explain international variation in the treatment gap have determined that coming from a poorer country [OR 1.55; 95% confidence interval (CI) 1.32–1.82] and residing in a rural region (OR 2.10; 95% CI 1.40–2.98) are independent risk factors for a higher treatment gap [33▪]. Unfortunately, temporal trends assessed from 1987–2007 suggest there has been no significant global improvement in the treatment gap over the past 20 or more years (OR 0.92; CI 0.79–1.07). Development of multitiered healthcare programs with a strong primary care base and referral systems, increased infrastructure and models of drug distribution, as well as media campaigns to increase awareness and combat prejudice and stigma surrounding epilepsy could offer hope for treatment gap reduction.

CLINICAL CARE GUIDELINES

Given the relative lack of support for mental health sector funding and human resources, most of the burden of diagnosing epilepsy falls on the primary care providers in LMICs, making the optimal role of the few neurologists working in such environments one of advocate and educator of primary care workers [47]. The recently released WHO evidence-based guidelines for epilepsy and seizure care in low-income countries offer a multitiered framework for addressing the mental health gap [35▪▪] (see Fig. 1). The clinical care algorithms provided in these guidelines have to be adapted to local resources and needs. Facilitators' guides to accompany the guidelines will be released in 2012. The development and validation of quality indicators for epilepsy care appropriate for use in developing countries is needed to provide baseline estimates of care quality and facilitate evaluations to determine if implementation of the Mental Health Gap Action Program (mhGAP) program improves epilepsy care.

The mhGAP guidelines include recommendations regarding counseling and safety assessments to avoid seizure-related injuries, and the need for patient and family education on these matters is more critical than perhaps was previously appreciated. As part of the China Demonstration Project, population-based, proportional mortality ratios (PMRs) for PWE in rural West China were obtained. The findings which compared mortality rates over a 28-month period for PWE relative to age-matched individuals under age 35 from the same region found an overall standardized mortality ratio of 4.92 (95% CI 4.0–6.1). Deaths were due to accidents (59%), drowning (45%), sudden unexplained death in epilepsy (14%) and status epilepticus (6.9%), with the risk of drowning being 82 times higher in PWE than the general population [2▪▪].

Another critical yet only recently appreciated global issue in epilepsy care is the risk of drug interactions between AEDs and antiretrovirals (ARVs), an interaction with potentially devastating public health consequences if AED-induced subtherapeutic levels of ARVs cause ARV failure, increased HIV infectivity and the spread of ARV-resistant forms of the HIV virus. Up to 55% of people living with HIV may require an AED for seizures or another indication (e.g. neuropathic pain) at some time during the clinical course of their disease. In January 2012, an American Academy of Neurology (AAN)–WHO collaboration released the following clinical care guidelines for the treatment of comorbid epilepsy and HIV [48▪]:

(1) Patients receiving phenytoin may require a lopinavir/ritonavir dosage increase of about 50% to maintain unchanged serum concentrations.
(2) Patients receiving valproic acid may require a zidovudine dosage reduction to maintain unchanged serum zidovudine concentrations.
(3) Coadministration of valproic acid and efavirenz may not require efavirenz dosage adjustment.
(4) Patients receiving ritonavir/atazanavir may require a lamotrigine dosage increase of about 50% to maintain unchanged lamotrigine serum concentrations.
(5) Coadministration of raltegravir or atazanavir and lamotrigine may not require lamotrigine dosage adjustment.
(6) Coadministration of raltegravir and midazolam may not require midazolam dosage adjustment.
(7) Patients may be counseled that it is unclear whether dosage adjustment is necessary when other AEDs and ARVs are combined.
(8) It may be important to avoid enzyme-inducing AEDs in people on ARV regimens that include protease inhibitors or non-nucleotide reverse transcriptase inhibitors, as pharmacokinetic interactions may result in virologic failure, which has clinical implications for disease progression and development of ARV resistance. If such regimens are required for seizure control, patients may be monitored through pharmacokinetic assessments to ensure efficacy of the ARV regimen.

Unfortunately, unless/until epilepsy care becomes a priority for public policy makers and global donors, enzyme-inducing AEDs will remain

the only treatment option in developing countries where monitoring of AED and/or ARV drug levels is not an option, making these critical recommendations a mute point.

CONCLUSION

New insights into the causes and consequences of epilepsy in developing countries offer opportunities for prevention and/or improved treatment, which are complemented by recently released epilepsy care guidelines for use in such a setting, but without substantial investments from the international community and increased prioritization by Ministries of Health, epilepsy will continue to be characterized as an extremely cost-effective condition to treat, which, inexplicably, remains largely untreated.

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Conflicts of interest

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 212).

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