An increased risk of premature death associated with epilepsy is well known. Recent reports have documented an even higher risk of premature mortality among people with epilepsy living in low- and middle-income countries (LAMICs). The epidemiology of epilepsy-associated mortality in LAMICs is of great relevance, as more than 85% of those with epilepsy live in resource-limited countries. Not only is the risk of premature mortality higher in LAMICs, but a greater proportion of deaths in these regions are epilepsy-related (e.g., falls, burns, drowning, and status epilepticus).

The burden of epilepsy in LAMICs is extensive and partly driven by stigma that contributes to the treatment gap in these regions. Regrettably, the treatment gap is more than 75% in low-income countries and more than 50% in most lower-middle- and upper-middle-income countries, compared to gaps of less than 10% in most high-income countries. The evidence is sufficiently compelling to suggest that reducing the treatment gap should reduce premature mortality in those with epilepsy in LAMICs.

In the current issue of Neurology®, Ngugi et al. report on premature death among a large cohort of people with active convulsive epilepsy (ACE) in rural Kenya followed up for 3 years with regular visits. This population-based cohort study included 754 persons with ACE and 231,410 without ACE, although there was some degree of attrition (18% for those with and 32% for those without ACE). Causes of mortality were assessed using the World Health Organization (WHO) verbal autopsy tool within 1–4 months of death. The WHO verbal autopsy tool is a standardized questionnaire that is administered to next of kin or caregivers to assess cause of death.

The authors reported a staggering mortality rate of 33.3/1,000 person-years for those with ACE compared to a rate of 6.1/1,000 person-years for those without ACE, with a standardized mortality ratio of 6.5, slightly higher than that previously reported in a similar study in rural China. Factors associated with premature mortality included nonadherence to antiepileptic drugs, cognitive impairment, and age older than 50 years. As the authors suggested, the association between cognitive impairment and premature mortality among those with ACE is probably due to confounding and not a true causal relationship because cognitive impairment may be a marker for severe epileptic encephalopathies (e.g., Lennox-Gastaut syndrome) that are associated with high mortality rate.

Perhaps the most important finding is that more than half of all deaths were directly related to epilepsy, with status epilepticus representing the most frequent “presumed” cause of death (38% of cases). Many of these deaths probably could have been prevented with basic medical management of seizures and status epilepticus. This finding is in contrast to another carefully designed prospective cohort study of the long-term risk of premature mortality in people with epilepsy in the UK, where fewer people died from epilepsy-related causes. In the UK study, death certificates, which are known to be fraught with their own limitations, were used to determine cause of death. In the Kenya study, verbal autopsy reports were used, which could in part explain some of the discordant findings between these 2 studies.

Despite the many strengths of this carefully designed study by Ngugi et al., there are some limitations that must be considered, all of which were carefully discussed by the study authors. First, only patients with ACE were examined. This selection bias is important because convulsive seizures, particularly if frequent, are associated with higher mortality. Second, the inclusion of only patients who had a seizure in the past year probably resulted in a cohort with more severe epilepsy. In general, a person is classified as having active epilepsy when he or she has experienced a seizure in the past 2 or 5 years, although a 1-year period may be acceptable in some settings. Another issue that must be acknowledged is that the authors used an ACE prevalence cohort rather than also including those with incident epilepsy. This study limitation likely underestimated premature mortality in those with ACE, as mortality is higher during the first year after diagnosis. Other limiting factors included the lack of information regarding epilepsy syndromes, epilepsy seizure types (beyond convulsive), and cause of death in the general population. Finally and
most importantly was the lack of postmortem examinations, which is not unique to this otherwise carefully designed study but rather is a limiting factor in most resource-poor settings. Despite these limitations, the authors should be applauded for their careful methodologic approach to this important study.

What can we now say with certainty? Inadequate treatment of epilepsy kills large numbers of people in developing countries, and many of these deaths are preventable. A recent study found that the treatment gap in Kilifi, Kenya was 62.4%. If we appropriately diagnose and treat most people with epilepsy in LAMICs, epilepsy-related premature death can be prevented. We know enough now to take action and save lives. Our primary objective should be to make preventing death due to inadequate epilepsy treatment a public health priority—framing epilepsy-associated death as a problem that can be solved by appropriate access to diagnosis and treatment and seriously pursuing implementation research in this important area. In 2011 the WHO’s Mental Health Gap Action Programme published evidence-based guidelines for use in LAMICs. Implementation of these guidelines requires local adaptation but represents the first step in guiding care in resource-limited settings. There is no doubt that "the challenges to these important processes are substantial," but if neurologists around the world grasp the opportunity to save lives by the many thousands through simple diagnosis and treatment of epilepsy, we can end these senseless deaths.

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REFERENCES