The Global Burden of Epilepsy Report: Implications for Low and Middle Income Countries.

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Word count: 996

Number of tables: 1

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ABSTRACT

The Global Burden of Epilepsy Report estimates that there are 13 million disability adjusted life years due to epilepsy each year. Estimates of years lived with disability attributed to uncontrolled and untreated epilepsies are particularly raised in comparison to controlled epilepsies in countries with low socio-demographic indices. There are 50 million people with epilepsy in the world and of these, 125,000 die each year and over 80% of these deaths occur in low- and middle-income countries. Overall, a global decline in the number of epilepsy-related deaths has been seen between 1990 and 2016. The least improvements have been, however, recorded in countries with low socio-demographic indices. These countries include 13 African countries, which have recorded an increase in number of epilepsy deaths over the 26 years. The huge burden of untreated and uncontrolled epilepsy, and of epilepsy-related deaths in low and middle income countries calls for urgent efforts to improve access to epilepsy management.

The Global Burden of Epilepsy Report: Implications for Low and Middle Income Countries.

The recently published Global Burden of Epilepsy Report is a major accomplishment.[1] For the first time, it has been possible to derive national, and by using the source data, sub-national estimates of the prevalence and burden of epilepsy for almost all countries in the world. This has largely been accomplished by inputs from a combination of data sources and unique statistical modelling methods, which enable estimates for even those regions for which no real data exist. Briefly, the report described the burden of epilepsy in terms of prevalence, incidence and mortality. Systematic review of published sources of incidence and prevalence data to which three years of claims data from the United States was used to derivate rates. Mortality data was inferred from vital registrations. The extracted data were then modelled using a Bayesian meta-regression tool.[1] The Global Burden of Disease Study computes years of life lost (YLL) from mortality data and for this reason as an incident function (see below). The other major component of disability adjusted life years is years lived with disability (YLD) was earlier a product of disability weight attached to epilepsy, incidence and the duration of illness (hence, determined by remission rates). Currently, however, prevalence is used as there are very few data on remission from different parts of the world.

Disability adjusted life years (DALYs) = Years of life lost (YLL) + Years lived with disability (YLD)

YLL = Number of deaths X Standard life expectancy at age at death (in years)

YLD = Incidence X Disease duration X Disability weight

Or

YLD = Prevalence X Disability weight

Approximately 4/5ths of the world's people with epilepsy live in low and middle income countries (LMICs).[2] Paradoxically, between 50 and 75% of the people with epilepsy in these countries are deprived of the treatment that they should be receiving.[3,4,5] The huge burden of epilepsy and the magnitude of the epilepsy treatment gap call for an appraisal of the findings of the Global Burden of Epilepsy Report that specifically apply to LMICs. Here, we reexamine certain key findings in the report to reflect upon the burden of epilepsy in LMICs.

The report has somewhat refined previous estimates of the global burden of epilepsy[2]. It confirms that there are now almost 50 million people with epilepsy in the world. Disability-adjusted life years (DALYs) attributable to epilepsy are estimated at 13 million/year. The report draws attention to an overall decline in deaths associated with epilepsy for all countries combined between 1990 and 2016. This decline should be interpreted in the face of stable global prevalence rates of epilepsy between 1990 and 2016. This means that gains have been made in at least preventing deaths in people with epilepsy. Most certainly, this has been possible because of better care for people with epilepsy including improved access to treatment.

The split up in prevalence and years lived with disability (YLD) estimates for severe/untreated epilepsies and controlled (seizure-free) epilepsies across different socio-demographic index (SDI)-quintiles in the global burden of epilepsy report provides actionable targets for national and global policy-makers (Table 1).[1] The ratio of prevalence of severe/untreated epilepsies to controlled epilepsies seems to increase with reducing SDI of countries.[1] Likewise, the ratio of median estimates of YLD associated with

severe/untreated epilepsies to controlled epilepsies seem to rise as SDI drops. The quantum of increase in ratios with falling SDIs is, however, considerably more for YLDs in comparison to prevalence. These point towards the high burden of the untreated and severe epilepsies combined in LMICs.

The Global Burden of Epilepsy Report estimated that there were over 125,000 deaths associated with epilepsy in 2016. Remarkably, however, 81% of the deaths occurred in countries with low and middle SDI (Table 1).[1] These data emphasize the huge fraction of mortality burden contributed by countries with low and low-middle SDI. These deaths could be partly accounted for by a larger number of people with epilepsy in LMICs. However, the elevated fraction of epilepsy deaths from LMICs might also be the result of higher case fatality rates associated with epilepsy in these countries.

A decline in mortality associated with epilepsy between 1990 and 2016 was noted across all SDI quintiles. Leaving apart high SDI countries, the least improvements were, however, from countries with low SDI. The largest gains were recorded for countries with middle and high-middle SDIs. This might imply that improvements in epilepsy care during this period were substantial in the middle and high-middle economies. Perhaps, the high SDI countries already had evolved levels of epilepsy care leaving little scope for further improvement. To support this contention, treatment gaps for epilepsy in high SDI countries are less than 10% and surgical treatment gaps are likewise low.[3] The clear message, then is that the epicenter of efforts to reduce premature mortality should shift to low income countries and this should be possible by improving care and access to care.

Most countries followed the global trend in decline in epilepsy mortality but 27 countries recorded a perceptible increase in mortality during 2016 in comparison to 1990.[1] These included some HICs, e.g., Germany, Iceland and Belgium but also 13 African countries and some Central Asian and Western Pacific countries. These African nations are amongst the poorest in the world and hence, should be the focus of attention of their respective governments as well as global bodies such as the World Health Organization for future demonstration projects.

A supporting finding in the report was the large gap in disability adjusted life years (DALYs) attributed to epilepsy between high and low SDI countries. Two-thirds of the gap consists of years of life lost (YLL). This implies that premature mortality associated with epilepsy accounts for a considerable proportion of the gap in DALYs between high and low SDI countries.

In population-based studies from high-income countries (HIC), the standardized mortality in epilepsy is elevated 2-7 times in comparison to the general population.[6] Similar estimates for LMICs are not available but could be higher. The full causes of premature deaths associated with epilepsy in LMICs are unknown however, these are plausibly different from HICs.[7] Status epilepticus, drowning, road traffic accidents and probably sudden unexpected death in epilepsy (SUDEP) are the leading causes of early death in people with epilepsy in LMICs.[7,8] These deaths are largely preventable by improving access to care including diagnosis and treatment and promoting adherence to treatment. In summary, the Global Burden of Epilepsy data underline the need for improving care for untreated epilepsies by promoting health care provider education to recognise and diagnose seizures/epilepsy,

developing management guidelines which are easy to follow at a primary health care level, ensuring uninterrupted access to antiseizure medications, reducing stigma, effectively managing co-morbidities associated with epilepsy, improving and setting up where none exist, high-level (i.e., pre-surgical and surgical centers) care of drug-resistant epilepsies and lastly, by preventing perinatal accidents and neuroinfections. The agenda is clearly set. How soon will it be realized remains to be seen.

Author Statement and Disclosures:

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Both authors conceived and discussed the idea behind the manuscript. GS drafted and JWS critically reviewed the mansucript for content.

GS contributed to the Global Burden of Epilepsy Report as one of the co-authors. JWS has no disclosures to report in relation to this work.

Acknowledgements:

This work was carried out at the NHIR University College London Hospitals Biomedical Research Centre, which receive a proportion of funding from the UK Department of Health's Research Centres funding scheme. JWS receives research support from the Marvin Weil Epilepsy Research Fund, the UK Epilepsy Society, and the Christelijke Vereniging voor de Verpleging van Lijders aan Epilepsie, The Netherlands.

References

1. Collaborators GBDE. Global, regional, and national burden of epilepsy, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology* 2019; **18**(4): 357-75.

2. World Health Organization. Atlas: Epilepsy care in the world 20052005. http://www.who.int/mental_health/neurology/Epilepsy_atlas_r1.pdf (accessed 15.10.2017).

3. Meyer AC, Dua T, Ma J, Saxena S, Birbeck G. Global disparities in the epilepsy treatment gap: a systematic review. *Bulletin of the World Health Organization* 2010; **88**(4): 260-6.

4. Mbuba CK, Ngugi AK, Newton CR, Carter JA. The epilepsy treatment gap in developing countries: a systematic review of the magnitude, causes, and intervention strategies. *Epilepsia* 2008; **49**(9): 1491-503.

5. Neligan A, Sander JW. The treatment gap in epilepsy. A global perspective. Epileptology 2013; 1:28-30.

6. Thurman DJ, Logroscino G, Beghi E, et al. The burden of premature mortality of epilepsy in high-income countries: A systematic review from the Mortality Task Force of the International League Against Epilepsy. *Epilepsia* 2017; **58**(1): 17-26.

7. Levira F, Thurman DJ, Sander JW, et al. Premature mortality of epilepsy in low- and middle-income countries: A systematic review from the Mortality Task Force of the International League Against Epilepsy. *Epilepsia* 2017; **58**(1): 6-16.

8. Ding D, Wang W, Wu J, et al. Premature mortality in people with epilepsy in rural China: a prospective study. *The Lancet Neurology* 2006; **5**(10): 823-7.

Table 1. Ratios (with uncertainty limits) of age-standardized prevalence/100,000 population and years lived with disability of untreated/severe epilepsy and controlled epilepsy in different SDI quintiles.

S. No.	SDI Quintile	Prevalence ratio (Uncontrolled epilepsies/Controlled epilepsies)	Years lived with disability (YLD) ratio (Uncontrolled epilepsies/Controlled epilepsies)	Proportion of global epilepsy deaths in 2016	Combined proportions
1	High SDI countries	0.78 (0.41, 1.53)	8.40 (3.17, 23.44)	10.10% (9.00%-11.43%)	19.04%
2	High-Middle SDI countries	1.40 (0.69, 2.92)	15.21 (5.44, 41.41)	8.67% (7.52%-10.12%)	
3	Middle SDI countries	2.13 (1.18, 3.92)	22.97 (8.84, 60.29)	28.48% (25.40%-30.92%)	80.96%
4	Low-Middle SDI countries	4.01 (1.93, 8.44)	43.44 (14.79, 117.67)	38.70% (32.10%-47.09%)	
5	Low SDI countries	11.87 (4.79, 33.81)	128.57 (38.21, 461.00)	13.77% (11.58%-16.17%)	

*Uncertainty limits estimated by dividing the upper confidence limit for untreated/severe epilepsy by the lower confidence limit for controlled epilepsy and the lower confidence limit for untreated/severe epilepsy by the upper confidence limit for controlled epilepsy each SDI.

** Uncertainty limits (in parentheses) estimated by dividing the upper confidence limit for the SDI group by the lower confidence limit for the global count and *vice versa*.