Temporal trends in the epilepsy treatment gap in low- and low-middle-income countries: a meta-analysis

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Contributions

GS and JWS conceptualized and designed the study. BS, NM and GS developed and refined the protocol, performed the literature search, extracted and organized data, and jointly drafted the manuscript; GS undertook the statistical analysis; JWS and GS reviewed the manuscript and provided critical intellectual inputs to it. GS is the guarantor. All authors approved the final version of the manuscript.

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ABSTRACT

Introduction: Earlier systematic reviews estimated the epilepsy treatment gap in low- and low-middle-income countries above 75%. Reducing the gap due to healthcare improvements and socio-economic changes is plausible but unproven.

Aim: To review the epilepsy treatment gap evidence and determine if it has decreased over time.

Methods: We identified articles in English reporting estimates of the treatment gap in community samples from low- and middle-income countries from 1980 onwards. We used meta-proportion analyses to determine the treatment gap's pooled estimates using the Freeman-Tukey type arcsine square root transformation. Meta-regression analyses were undertaken separately for African and Asian countries to assess time trends.

Results: The analysis included 62 full studies and 14 abstracts covering 31 countries. We retrieved a single report for 19 countries. The pooled estimate for treatment gap for all countries was 71% (95% Confidence Intervals, 67% to 76%) and for Africa, 72% (95% CI, 65% to 79%) and for Asia, 70% (95% CI, 64% to 76%). We found wide between studies variance and observed a trend towards reducing the combined data from all countries. The reduction was significant for African countries (Regression Coefficient: -0.024; 95% CI, -0.048 to -0.0005; P=0.046) but not for Asia (Regression Coefficient: -0.0007; 95% CI, -0.022 to 0.007; P=0.32).

Conclusions: Despite limitations of significant variances, small sizes of individual studies, limited or no data from many countries, there is progress in decreasing the epilepsy treatment gap in low- and middle-income countries. This progress is considerable in Africa compared to Asia.

Introduction

Epilepsy is the enduring propensity to unprovoked seizures coupled with psychological, socio-cultural and economic consequences[1]. It affects over 50 million people worldwide, with an estimated disease burden of 13 million disability-adjusted life years (DALYs)[2]. Nearly 80% of the people with epilepsy live in low- and low-middle-income countries (LMICs). They often remain hidden due to a lack of diagnosis and system failures to provide treatment when diagnosed. Failure to treat epilepsy increases the disease burden as these people cannot lead an active life and are at an increased risk of premature mortality[3]. Treating epilepsy is straightforward and mainly involves using simple and "easy to use" antiseizure medications (ASMs) and can considerably reduce its burden. The gap between the number of people who have active epilepsy requiring treatment and the number actually on treatment is termed the treatment gap[4].

Treatment gap reporting goes back almost 40 years[5]. Two independent groups performed systematic reviews of this gap in 2007[6,7]. One review was limited to low- and middle-income countries and used conventional meta-analysis to estimate the gap from reports published in English up to mid-2007[6]. The other was more inclusive as it covered reports in all languages and estimated the gap globally using regression analyses to overcome some limitations of conventional meta-analysis[7]. Both found marked variations in gap estimates between and within countries. The global review also found a clear disparity between treatment gaps in low- (over 75%) and high-income countries (<10%). Neither

review could identify temporal trends in the gap at that time, i.e., till 2007. The quality and capacity of health care delivery may have changed in some countries since then, and socio-economic developments and political changes in some countries might have further impacted the gap. Re-examination of the treatment gap would be timely and could help drive global, regional and national efforts to reduce it. A search of the Prospective Register of Systematic Reviews (PROSPERO) identified a registered systematic review proposal to examine global variations in the gap and associated factors. (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=180209). We contemporaneously undertook a systematic review to determine whether the epilepsy treatment gap had diminished over the years across all LMICs combined and among countries divided along continental or World Health Organization region boundaries.

Methods

Sources, search methods and eligibility criteria

We developed the study protocol following PRISMA-P recommendations (Table s1)[8]. We sought to identify all peer-reviewed studies in English, published from 01.01.1982 onwards, reporting the treatment gap's magnitude with or without epilepsy prevalence in population-based samples from LMICs. The opening year was set to 1982 because our preliminary search suggested that the first report was published in 1982[9]. Databases searched were PubMed, Excerpta Medica database, Cumulative Index to Nursing and Allied Health Literature, Latin-

American and Caribbean System on Health Sciences Information Virtual Health Library, and Web of Science. Table s2 provides the search dates and terms and their adaptations to each database. We checked reports from before September 2007 against the reference lists from the previous systematic reviews[6,7]. We manually searched the reference lists of included articles for reports missed by the primary search. Published abstracts in peer-reviewed journals with extractable information were also included. Cochrane and PROSPERO (search term: epilepsy treatment gap, date of the first search: 27/7/2020) were searched for publications or study registrations in the past five years.

After the searches, articles identified were eligible if the magnitude of the gap in a population-based sample in an LMIC was stated in the abstract. We used the World Bank country rankings during the year of publication of the articles to define and classify LMICs (https://openknowledge.worldbank.org/discover).

Study selection

We piloted the inclusion criteria on 20 records identified through the database search, which guided further refinement. After excluding duplicates, two co-authors (BS and NM) screened the abstracts to determine if they met inclusion criteria (Fig. 1). Disagreements were resolved by consensus mediated by a third co-author (GS). We excluded reports not providing a gap estimate, such as review articles, healthcare provider and hospital-based studies. We also excluded reports from high-income countries and qualitative studies. We then sourced full texts of the selected abstracts.

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145 Quality assessment

146 We adapted the Newcastle Ottawa scale[10] to assess bias-risk in cross-sectional
147 studies to a nine-item scale for quality assessment of component studies. This
148 comprised sample representativeness, sample size justification, reporting of
149 non-responders, case ascertainment and active epilepsy according to ILAE
150 criteria[11], and definition, criteria for the estimation of, and reporting methods for
151 the gap (Table s3). We scored each item on a scale of 0 to 5. We deemed study
152 quality as good if it scored >/=5 in at least seven items, satisfactory if having a
153 score of >/=5 in at least five items and insufficient if scores were less than five
154 on more than five items. We used funnel plots to explore publication bias (Fig.
155 s1).

156 Data extraction, items and definitions

157 We iteratively developed a data extraction form and piloted it on the first 20
158 studies. It captured the population's numerical size for treatment gap estimation
159 in each component study and the number of people not on ASM treatment. It
160 also recorded several study-level variables, e.g., year of publication, country of
161 origin, habitat (rural *Vs* urban), and population characteristics. The year of
162 publication was taken as a proxy for the calendar period for data collection as in
163 all but one (16) study; data collection immediately preceded publication.
164 Epilepsy characteristics included epidemiological categorization according to
165 ILAE criteria (active *Vs* lifetime epilepsy or all seizures), and if documented as

active, the time duration and number of seizures required. We recorded the definition for the gap and the time criteria (e.g., absence of treatment for a defined period; absence of treatment currently or never-treated from the outset) used in each study's definition of treatment gap. Lastly, we noted the operational criteria used to estimate the gap, e.g., whether the estimation was a primary aim, methods used, e.g., door-to-door survey or otherwise, and neurological confirmation after the screening. Two authors (BS & NM) independently undertook data extraction, followed by the conciliation of findings.

Statistical analysis

The primary outcome we used was the proportion of the treatment gap defined as the percentage of people in the sample who were not on treatment with ASMs, appropriately or otherwise. The primary explanatory variable was the year of publication. We included others, e.g., country and its income status, habitat, coverage of slum populations, characteristics of population assessed, epidemiological characteristics of epilepsy and definition and time criteria for the treatment gap as covariates.

We used the *metaprop* command of Stata IC (ver. 15) (Stata Corp. LP, College Station, TX) for analyses. We determined the pooled prevalence of the variances of raw proportions (r/n) after stabilization using a Freeman-Tukey type arcsine square root transformation[12].

y=arcsine[!(r/(n+1)] + arcsine[!(r+1)/(n+1)]

with a variance of 1/(n+1), where n=denominator, *i.e.*, subject population size.

Gap estimates in some studies were close to 100%, and this precluded the estimation of an upper 95% confidence limit by conventional meta-analytic methods as these would go beyond 100%. By using the Freeman Tukey transformation, all studies with 100% or near-100% gap were retained[12]

We measured overall variation in the gap proportion attributable to between-study heterogeneity by the I^2 statistic. We assumed high heterogeneity levels due to variable subject populations spanning different geographic locations and periods in addition to diverse economic settings and survey methods. We used the Der-Simonian Lard random effects method to pool the transformed proportions[13]

There was no missing data among the explanatory variable or covariates. We generated forest plots of the pooled proportion for various subgroups divided according to study-level covariates. These plots depicted the overall DerSimonian Lard pooled estimate and Clopper Pearson confidence intervals of the gap proportion for each study's gap proportion. We reported results as pooled gap proportion in each subgroup with 95% CIs and the difference in pooled proportions between various subgroups were noted. After that, we regressed the treatment gap proportion on the year of publication separately for Asia and Africa in the random-effects metaregression model using the metareg command in Stata ver 15.0., while specifying a variable representing the within-

study standard errors. The slopes of the graphs obtained and P values for both analyses were examined. P values were considered significant if <0.05.

Results

We identified 80 reports, including 14 abstracts and excluded four, as these were duplicate reports on the same samples albeit published at different periods. Of the countries included, China became an upper middle-income country in 2012 and Ecuador in 2008. Hence, we excluded five studies from China published after 2012[14-18.] There were no published studies from Ecuador after 2008. Three studies reported treatment gap in geographically distinct population samples within or across different countries. One study undertook estimation of treatment gap in four different countries[19]. Three countries were included but South Africa was excluded as it did not qualify as a LMIC. Therefore, there were 78 population units from 58 studies and 13 abstracts, representing 30 LMICs (eight low- and 22 low middle-income countries) from Africa (n=15); Asia (n=9), South America (n=5) and North America (n=1). The analysis included 30 (38%) population units from the WHO African region, eight (10%) from Americas, two (3%) from Europe, nine (12%) from East Mediterranean Region, 18 (23%) from Southeast Asia and 11 (14%) from the Western Pacific Region. There were 17 studies from India[20-36] and seven from China[37-43]. The number of studies grew over time from the 1980s: 31 (44%) were from the 2011-20 period[11,19,22,27,30,31,37,38,44-62] (Fig. s2). The study settings were exclusively rural in 32 (41%)[20,25-29,32,35,36,39,41,42,46,48,54,60,63-78], exclusively urban in 4

(5%)[23,58,79,80], combined in 29 (37%)[19,21,22,24,30,31,33,38,43,46,47,52,55,57,59,62,67,79,81-87] and unspecified in 13 (17%)[34,37,40,44,45,49-51,53,56,61,88,89]. Two (2%) studies solely covered slum populations[22,58]. Ten (13%) studies[24,29,31,46,51,62,67] covered children and two (2%)[48,58] excluded them, while the remainder included all age-groups. Estimation of the gap was the primary objective in 19 (24%) population units.[19,28,30,31,39,40,42,43,49,53,59,60,65,73,78,80].

We retrieved a single report for 19 countries (Box s1). The availability of more than one study at different time points allowed for examining time trends in two countries. A large demonstration project for epilepsy care provision was implemented across four Northeastern and eastern China locations between 2000 and 2004[18,43]. Using similar methods, the treatment gap was examined in representative samples across the four provinces. The gap was estimated to be 63% at the start of the intervention and dropped to 49% after the intervention. In Kilifi District, Kenya, the treatment gap was first estimated in a representative sample in 2003 and then again in 2008[44,45].

Studies with sample size < 100 (n=35)[23,24,31,41,42,45-47,49-51,53,55,57,58,62-67,69,70,72,77,79-81,83,84,87,89] contributed 39% of the weights in the meta-analysis. The pooled gap estimate in these studies was 66%, similar to pooled estimates of 75% in larger (n>=100)[19,20-22,25-30,32-36,37,38,39,40,43,44,46,48,52,54,59-61,71,73-76,78,82,85,86,88] and 71% in all studies.

Treatment gap criteria

After excluding abstracts (n=13), 64 population units from 58 studies remained. Of these, 51 studies (88%) explicitly described and used active epilepsy as the denominator in estimating the gap. The duration of time and numbers of seizures required to define active epilepsy, however, varied: one seizure in one year – 9 (15%)[19,25,39,52,63,73,86-88], one seizure in two years – 1 (1.7%)[74], one seizure in five years – 22 (38%)[21-23,26,30,31,33,36,41,55,58,59,61,64-66,70,71,77,79,82,84], one seizure in ten years – 1 (1.7%)[62], two seizures in one year – 11 (19%)[29,38,40,42,43,49,53,54,60,68,80], two seizures in two years – 2 (3.4%)[83,89], two seizures in five years – 6 (10%)[24,48,75,78,81,85], and unclarified in 6 (10%)[28,46,47,67,72,76]. Similarly, the definition used for gap estimation varied considerably as well as the time frame used (not taking treatment currently or at the time of survey [n=47; 81%]; absence of treatment in the preceding six month [n=1; 1.7%], or four years [n=1; 1.7%]; or never taken treatment [n=7; 12%] and unspecified [n =2; 3.4%].

Treatment gap estimates

The overall pooled gap proportion across all studies was 71% (95% Confidence Intervals: 65%, 77%; I^2: 98.4%) (Fig. 2a). The pooled proportion in Asian countries (n=33) was 69% (95% CIs: 59%, 79%; I^2: 98.8%) (Fig. 2b). The 35 studies from Africa yielded a pooled proportion of 73% (95% CIs: 66%, 80%; I^2: 97.9%). Gap estimates did not differ much according to WHO regions: African region - 75% (95% CIs: 67%, 82%); Eastern Mediterranean Region – 67% (95% CIs, 49%, 83%); European region – 69% (95% CIs: 60%, 78%); Southeast Asia – 60% (95%CIs: 45%, 74%); Western Pacific Region – 82% (95% CIs: 66%,

92%) and Americas – 72% (95% CIs: 58%, 85%) (P=0.34). The wide variance between study estimates were not explained by origin in a random-effects meta-regression model (Regression Coefficient, 0.033; 95%CI, -0.082 to 0.147; P=0.57). Gap estimates did not vary according to the defined criteria for epilepsy (active Vs. all epilepsies) and the definitions used for the gap (see above). When studies were divided according to the decade of publication, the treatment gap was found to remain high till the last decade, during which it dropped to 62% (Table 2; Fig. s3) (P=0.12). There remained, however, considerable heterogeneity between studies performed within decades (P=0.001). When gap estimates were modelled over the year of publication in a random-effects meta-regression model, a significant reduction was obtained for African countries (Regression Coefficient: -0.024; 95%CI, -0.048 to -0.0005; P=0.045) (Fig. 3a) but not for Asian countries (Regression Coefficient: -0.0036; 95%CI, -0.023 to 0.0067; P=0.27) (Fig. 3b). The pooled gap from 10 studies published in the last five years from all LMICs was 43% (95% CI, 24% to 63%; %; $I^{\wedge 2}$ – 98.7%,), which included seven from Africa yielding a pooled proportion of 52% (95% CI, 32% to 72%; $I^{\wedge 2}$ – 97.3%, P=0.001) and only two from Asia.

Discussion

Our findings suggest a reduction in the epilepsy treatment gap in LMICs over the four decades but particularly in the last five years. The decrease in the gap was not significant when the LMICs were grouped according to WHO subregions. However, when the countries were bracketed together according to traditional

continental divisions, Africa demonstrated a substantial and statistically significant reduction in the gap compared to Asia (Figs 3a & b). Apart from the reduction, there was marked heterogeneity in gap estimates with differences between studies and countries. Understanding factors underlining the treatment gap and associated temporal trends is crucial. We were unable to extract explicit information on these factors from a large number of studies as our focus was on study-level factors.

Intercontinental differences

Several African countries endure the world's highest DALY rates for epilepsy per 100,000 people[2]. Conversely, these countries perform poorly in terms of universal health coverage indices. Despite this, Sub-Saharan Africa recorded the highest growth in the annualized rate of Universal Health Care effective coverage indices during 2010-2019[90]. By contrast, many other global sub-regions, including South Asia, demonstrated the slackened progress in effective coverage by Universal Health Care in 2010-2019 compared to 1990-2010. Expectedly, the most gains in treatment coverage are likely in countries with the broadest gaps. Different Universal Health Care evolution trajectories may partly explain the distinct temporal trends in the epilepsy treatment gap estimates from Africa and Asia. Recent stand-alone initiatives designed to improve knowledge and attitudes to epilepsy, mitigating stigma and facilitating clinic attendance by the WHO and non-governmental agencies may also have partly stimulated gains[91]. Lastly, most of the Asian studies were from India and China. Studies

mostly limited to these two countries could be responsible for the narrow slope of Asia's time trends.

Within-country time trends and variations

Two sets of studies allowed the examination of temporal trends within countries. One pair was from Kenya[44,54]. Assessment of the gap was a primary aim of the earlier survey, and hence, estimation used several methods, including serum ASM levels, to determine the gap. The subsequent study derived estimates from recorded field data, and thus, the two assessments were not strictly comparable. The surveys from China, however, were identical and demonstrated a reduction in the gap after an effective intervention[39,40]. While multiple studies over time were available from some countries, these were often dissimilar in terms of methods used or were markedly disparate in their sampling bases or geographic locations.

Considerable variations can be expected in the socio-demographic structure, economic attributes, health systems and risk factors between different locations in large countries such as India and China. Subnational variations in health status and neurological disease burden across India have been recently demonstrated[92]. Likewise, variations might exist in China as its eastern part is urbanized and industrialized, while the West is predominantly agrarian[93,94]. Studies from eastern and northeastern China, mostly on ethnic Han groups, found modest variations in the epilepsy treatment gap estimates. In contrast, those from other ethnic groups reported higher estimates with wide variations

(44% to 100%) between groups [17,41-43]. These variations were noted despite similar methodologies used in the studies. Two small studies from Tibet stand apart on account of including Western as well as traditional medicines to estimate the gap and very high gap estimates (97-100%)[42,43].

Study sample size effect

Small studies are often susceptible to selective reporting and are conducted with less rigour. Hence, these tend to overestimate proportions. Gap estimates for small-size studies (n< 100) were not much different from overall estimates in this meta-analysis. The 95% Confidence Intervals of the pooled proportion of small-size studies were wider, indicating a relative lack of precision. It is impossible to rule out the effect of chance in estimates provided by smaller surveys, and the variance might not have been independent.

Limitations

Data on the epilepsy treatment gap was available from only a few countries. A single report was available for 19 countries. This precluded the examination of country-specific time trends. Considerable variations in study populations, methods and criteria used to estimate the gap were identified. For instance, criteria for active epilepsy varied from having one seizure in the preceding one year to one in 10 years. Definitions and ascertainment methods of the treatment gap also varied across studies (Table 1). The gap estimation was the primary objective in a few studies, but it was only a secondary analysis in most studies.

Few included studies were truly representative of the countries or region of origin. Lastly, the definition of epilepsy has evolved in recent times, which may have impacted estimates [96]. Studies in this review, however, used traditional, older, albeit varied epilepsy definitions[1,96]. It would be interesting to examine how epilepsy treatment gap estimates vary using the current epilepsy definition. Regardless, it is reassuring that epilepsy definitions and seizure types (Table 1) did not significantly influence gap estimates and are unlikely to account for the observed temporal trends.

In its resolution 68.20 in 2015, the WHO Assembly called for improved surveillance systems to obtain a clear picture of the global epilepsy burden[97]. Systematic assessments of the treatment gap in representative populations across different LMICs and in under-resourced populations similar to periodic vaccine coverage surveys[98] might be one step in follow-up to the WHO resolution. Countries need to align themselves to follow this approach. Identifying gap determinants, particularly local factors, will also aid efforts to improve treatment coverage. The last decade witnessed modest gains in closing the gap. Much of the gains are seemingly from the poorest countries. The scope for additional improvements is unquestionable as the epilepsy treatment gap still remains wide. "Flipping the gap" ", i.e., from the current estimates of 70% to 30%, over a defined period ought to brand the next round of care provision efforts for epilepsy.

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Table 1. Epilepsy treatment gap definitions, criteria for active epilepsy and seizure types used in the component studies of the meta-analysis.

Types of epilepsies from the epidemiological standpoint used as a denominator in the estimation of treatment gap.
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Type of Epilepsy	Studies
Active	58
All epilepsies	1
All seizures	1
Lifetime epilepsy	3
Not defined	15
Total	78

Definitions of active epilepsy in various studies

Active epilepsy definition	Studies
Seizure in past 1 year	23
Seizure in past 2 years	03
Seizure in past 5 years	27
Seizure in past 10 years	01
Not defined	24
Total	78

Seizure types included for the estimation of treatment gap

Type of seizure	Studies
All seizure	55
Convulsive	13
Not defined	10
Total	78

733 **Table 2**. Decade-wise pooled epilepsy treatment gap estimates for all LMICs
734 combined.

Decade	Pooled epilepsy treatment gap estimates (95%CI)[#]	I^2; Statistical significance (P)
1981-1990	79% (57% to 94%)	96.34%; P=0.001
1991-2000	79% (67% to 89%)	98.31%; P=0.001
2001-2010	73% (63% to 83%)	98.35%; P=0.001
2011 onwards	64% (58% to 70%)	98.15%; P=0.001

Commented [MOU1]: this table needs correction, pls guide

735 # Overall P=0.07.

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LEGENDS TO FIGURES

Fig. 1. Flow chart depicting the abstract and study selection process.

Fig. 2. Forest plots of epilepsy treatment gap proportions generated separately for African (a) and Asian (b) LMICs.

Fig. 3. Graphs depicting slope of regression of treatment gap proportions on the year of publication in African (a) and Asian (b) LMICs.

Fig. s1. Funnel plot to explore publication bias.

Fig. s2. Bar chart depicting number of studies decade-wise.

Fig. s3. Forest plot of treatment gap of studies arranged decade-wise.

Table s1: PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist.

Table s2: Summary of Search Results and search strategy.

Table s3: Risk of bias assessment.

Box s1: List of countries with single study.