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Review article

A first-ever dedicated comprehensive review of incidence of epilepsy in South America and Caribbean

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ABSTRACT

In order to understand true incident burden of epilepsy in South America and Caribbean, several sources were searched in multiple languages using keywords and combinations. The results were presented as counts, proportions, means, and/or medians along with their 95% confidence intervals (CI). No information was found from Caribbean and no information was available from six South American countries. Based on 14 estimates, annual median incidence (N = 185319, 1984–2010, 7 in rural area) of epilepsy for South America was 115.2/100,000 (95% CI 61.0–133.4, range 0.0–410.0). Random-effect pooled annual epilepsy incidence was 84.8/100,000 (95% CI 65.2–104.5). The 25th and 75th percentile of annual epilepsy incidence were 62.2/100,000 and 130.9/100,000 respectively with an interquartile range (IQR) of 68.7. Between-study variance attributable to each explanatory factor was estimated to be: 38.8% from study year, 18.1% from urban-rural milieu, 15.4% from case size, and 0.6% from study size. Descriptively, on average, 445824 (between 236070 and 516258) new cases of epilepsy are possibly occurring every year in South America. In conclusion, Caribbean needs to come forward for its own epilepsy incidence data especially when risk from numerous factors such as substance abuse, mental health, etc. deems high. Epilepsy incidence in South America is likely to be slightly lower than previously reported although this varies considerably for each country. Inter-population differences are in-part (more than 50%) related to urban-rural differences and variations over time. Our work is especially important to monitor secular trends of epilepsy incidence especially when new data would emerge and countries continue to undergo transitions.

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1. Introduction

Epilepsy is a major neurological disorder with considerable but differing burden worldover[1,2]; which is yet to be fully understood and estimated.[3,4] For this reason, among others, agencies recommend the need for promotion of research and education on epilepsy, publication of detailed public health assessments, and development of national plans.[5] One of the ways by which we aimed to address these recommendations and determine true burden of epilepsy is through incidence, a parameter which is independent of disease-specific mortality, is particularly enriching and may provide better assessment of disease burden. A previous review conducted 10 years ago reported an annual incidence of epilepsy between 77.7–190/100,000 for Latin America.[6] Thus, with a view to bring its own reliable regional estimates, conclusions, and interpretations, we conducted a first-ever comprehensive review of epilepsy for South America and Caribbean (reported seperately) in order to help understand the true incident burden of epilepsy in these two supposedly unique regions.

2. Methods

We seperately searched for estimates of epilepsy incidence from South America and Caribbean, published in French, English, and Spanish at PubMed and LILACS. For this, we used specific keywords and their combinations: *epilepsy, epilepsia*, alongwith the name of individual countries to obtain maximum possible titles during result. For reducing extraneous titles from Brazil and Argentina which otherwise yielded 2016 and 407 titles respectively, an additional keyword *epidemiology* was used. The search was conducted principally on PubMed (English); followed by a similar search on other database in English and Spanish. All searches were independent of each other. No restrictions were made pertaining to the year of publication and definition of active epilepsy. All individual results were aimed to be filtered from the title itself. If title seemed appropriate then only abstract and/or full-text were read to identify studies that were population-based and had other basic methodological details. Those titles that had no abstract; were not population-based; didn't provide required estimate; addressed status epilepticus; particular syndromes; sudden unexpected death or single unprovoked seizure; specific populations; out-of-topic; clinical trials; case report were simply excluded. Our target was to identify all possible population-based estimates of the incidence of epilepsy from these two regions; Fig. 1.

In addition, a free search on Google was carried-out by using similar keywords and combinations in English, Spanish, and French, i.e. epilepsy, epilepsie, epilepsia, incidence, incidencia, Ministerio, frecuencia, along with the name of individual countries. Each time ten pages were looked-at for relevant studies or estimates.

Bibliography of articles was looked as well to search for additional studies or estimates. Each search was independent of each other.

2.1. Definitions

For this work, **South America** was defined as "twelve sovereign member states including Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Guyana, Paraguay, Peru, Suriname, Uruguay, Venezuela". For this work, **Caribbean** was defined as "six sovereign member states including Bahamas, Cuba, Dominica, Dominican Republic, Haiti, and Trinidad and Tobago". According to International League against Epilepsy (ILAE), **active epilepsy** is defined as "at least one epileptic seizure in last five years, irrespective of anti-epileptic drug treatment".[7]

2.2. Statistical analyses

Both regions were considered separate entities. We performed statistical analysis by using Stata, 2009. All results are described separately for each country. We initially tabulated crude incidence estimates alongwith their 95% confidence intervals (CIs). To estimate pooled incidence and test for heterogeneity, we fitted random-effects model to log-transformed crude incidence. We obtained median incidence and 25th and 75th percentile of the distribution of true incidence by back-transforming the log estimates to the original incidence scale. We used the Cochrane χ^2 test to calculate the degree of heterogeneity. To determine the influence of study-level factors i.e. study year, case numbers, urban-rural milieu, and sample size, we used random-effects meta regression. By estimating the coefficient of determination (r^2) we

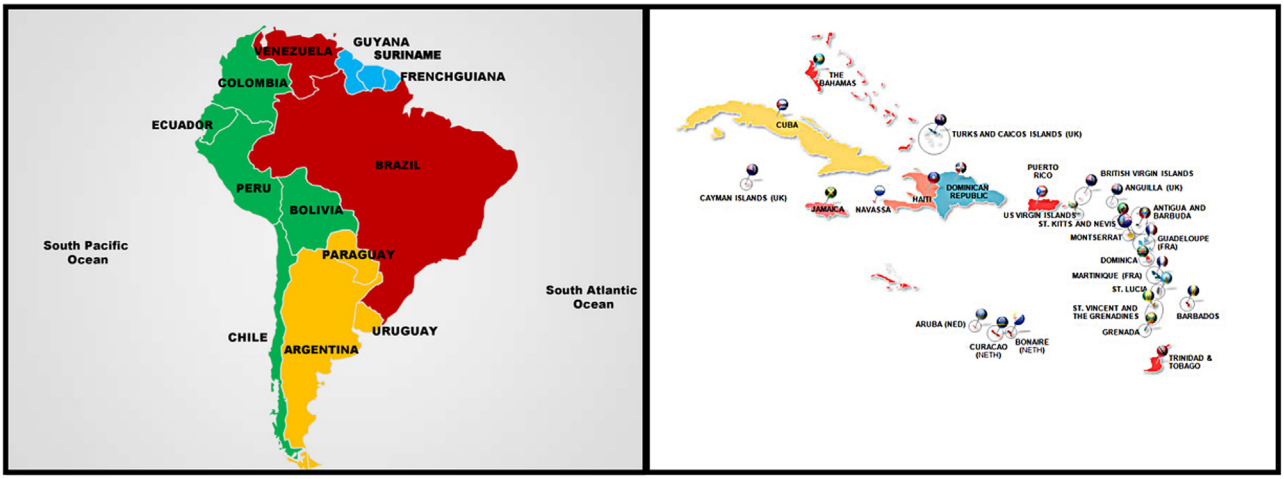

Fig. 1. Geographic location of Caribbean and South America.

also calculated proportion of variance in epilepsy incidence that is predictable from the explanatory variables (study year, case numbers, urban-rural milieu, and sample size). To subsequently determine the influence of the study-level factors on the observed variability, we used random-effects meta-regression and proportion of heterogeneity attributable to each factor by looking at the between-studies component. Metabias (Egger's test) was also performed to determine bias through various study-level variables. We also provide region's map. The results are presented as counts, proportions, means, and medians along with respective 95% CIs. For deriving number of incident cases, individual country's population data was used.

3. Results

3.1. Epilepsy incidence results (Caribbean)

From PubMed, 121 titles were looked-at and no epilepsy incidence data was found. From LILACS, 10 and 13 titles in English and Spanish, respectively, were looked-at and no incidence data was found. From Google, no estimate of epilepsy incidence was found for any of the Caribbean country.

3.2. Epilepsy incidence results (South America)

The source for each title is listed in Table 1. From PubMed, 852 titles were looked-at, while from LILACS (English) and LILCAS (Spanish) 278 and 296 titles in English and Spanish, respectively, were looked-at by using keywords explained on page 4. These searches provided 13 incidence estimates from five titles from five countries. Remaining (n = 847 from PubMed, and 277 English and 295 Spanish from LILACS) titles had unrelated/no required data and were removed from the title alone. From Google, only one additional estimate of epilepsy incidence from Venezuela was found, Table 1.

Overall, based on 14 incidence estimates, annual median incidence (N = 185319, 1984–2010, 7 in rural area) of epilepsy for South America was estimated to be 115.2/100,000 (95% CI 61.0–133.4, range 0.0–410.0). Annual mean epilepsy incidence was higher (121.3/100,000; 95% CI 64.6–177.9). Random-effect pooled annual epilepsy incidence was estimated to be 84.8/100,000 (95% CI 65.2–104.5). The 25th and 75th percentile of annual epilepsy incidence were estimated to be 62.2/100,000 and 130.9/100,000 respectively with an interquartile range (IQR) of 68.7.

We also looked at the coefficients of determination to determine the percentage variance in epilepsy incidence that could possibly be explained by explanatory variables within our work. These variances in epilepsy incidence were estimated to be as follows: 13.6% for urban-rural milieu, 8.9% from study size, 8.6% from case size, and 0.5% from study year. Heterogeneity (between-study variance) attributable to each explanatory factor was estimated to be: 38.8% from study year, 18.1% from urban-rural milieu, 15.4% from case size, and 0.6% from study size. Metabias was found to be statistically significant only for the rural-urban milieu ($p = 0.01$).

Based on individual country's population data and based on our median epilepsy incidence, it was estimated that on average 445824 (between 236070 and 516258) new cases of epilepsy are possibly occurring every year in South America. These incidence differences between countries (Venezuela and Brazil excluded, Table 1) were statistically significant ($p = 0.00008$) although not significant amongst Chile-only (all-urban) studies ($p = 0.23$) and amongst Peru-only (all-rural) studies ($p = 0.40$). These results with respect to Chile match with the observations of the original authors.

4. Discussion

We conducted a comprehensive review of incidence of epilepsy in South America and Caribbean, albeit seperately. Our search was comprehensive and had several databases and a non-database

Table 1
Incidence of epilepsy (per 100,000) in Central America.

Country	R-U	Year	Age	N	Annual I/100,000	Extra	Database
Brazil [37]	U	2003	C	1687	7.0 (3.0–12.0)	Birth cohort with children born in 2003	P, L
Number of new cases possibly occurring: specific children population							
Chile [38]	U	1984	All	17694	128.0; F = 118.4; M = 137.4	Four desertous, mountainous localities of one province	P
Chile [38]	U	1985	All	17694	109.7; F = 110.3; M = 109.1	Four desertous, mountainous localities of one province	P
Chile [38]	U	1986	All	17694	117.8; F = 101.7; M = 133.8	Four desertous, mountainous localities of one province	P
Chile [38]	U	1987	All	17694	146.4; F = 115.4; M = 175.9	Four desertous, mountainous localities of one province	P
Chile [38]	U	1988	All	17694	62.2; F = 68.1; M = 56.3	Four desertous, mountainous localities of one province	P
Number of new cases possibly occurring: 19210 (46.5% females)							
Ecuador [39]	R	1987	All	72121	190.0	A range (122.0–190.0) of incidence provided instead of one point estimate	P
Number of new cases possibly occurring: Upto 28500							
Peru [40]	R	2000	All	817	112.7	Cysticercosis endemic area	P
Peru [40]	R	2001	All	817	128.5	Cysticercosis endemic area	P
Peru [40]	R	2002	All	817	130.9	Cysticercosis endemic area	P
Peru [40]	R	2003	All	817	410.0	Cysticercosis endemic area	P
Peru [40]	R	2004	All	817	0.0	Cysticercosis endemic area	P
Number of new cases possibly occurring: 48690 in cysticercosis-endemic areas of Peru							
Venezuela [41]	–	–	All	–	90–100	None	None
Number of new cases possibly occurring: 30,000							
Bolivia [42]	R	2010	All	18956	55.4 (49.5 age-adjusted) F = 58.9; M = 51.9	Three-stage door-to-door survey of convulsive epilepsies over ten year period	P
Number of new cases possibly occurring: 5540 (53.5% females)							

notes: C: Children; F: Females; I: Annual incidence/100,000; M: Males; N: Population size; R: Rural; U: Urban.

source (Google). Earlier, this non-database source has been formally demonstrated as a useful and less cumbersome way to identify epilepsy data.[8] Our work also meet the recommendations made for Latin America region with regards to the "*need for promotion of research and education on epilepsy as well as publication of detailed public health assessments and development of national plans*".[5]

Caribbean is a small, ethnically diverse and a unique region mix of English, Spanish, African, and French influences. No incidence data of any kind was found for this region; that shows a major *research gap* in this region; although on the positive side an open opportunity for conducting initiatives. Unlike prevalence, incidence is independent of mortality, public/patient attitudes, etc. and depends mainly on the exposure of population to many possible epilepsy risk factors. In the absence of direct incidence data on epilepsy, some information on the nature of population risk exposure could be deduced from our experience. For instance, existing data from Dominica shows a pre-eminent burden from infectious diseases (but mostly Trichuris) but with epilepsy as the second most frequent (although far lower frequency) occurring disease among chronic conditions.[9] Exposure to mental health conditions is likely to be prominently present.[9] Haiti exhibit important burden from cysticercosis instead which,[10] on the other hand, differ for Cuba.[11] Predominantly, non-neurocysticercosis (and non-infection) relevance for epilepsy was noted in Cuba[12] which resembles with what has been demonstrated before by the first author that the odds of developing epilepsy from non-infection factors is far higher than neurocysticercosis (and most other infections) even though it is indeed the *most popular* epilepsy risk factor.[13] All Caribbean countries are island Nations, implying a possible role of natural disasters in incidence of epilepsy,[14] particularly for Cuba and Haiti.[15] Other risk factors such as substance abuse, trauma, etc. are also dramatically present (80.0% alcohol use, 35.0% tobacco, 8.0% marijuana among as young as 14 years) in several countries, such as Trinidad.[16] A report by United Nations concluded that the most violent region in the World is Latin America (instead of Middle-East as popular beliefs might indicate).[17] There can be number of risk (ex. lifestyle, urban-rurality) and other (ex. misdiagnosis, tools' sensitivity) factors[18] that may define incidence of epilepsy for the Caribbean that require a series of formal evaluations.

On the other hand, in South America, few incidence data from six countries was found. This shows that *research gap* is also a major issue in this region.[8] Generally speaking, our median incidence is higher than that projected for developed countries and similar to that projected for developing countries[2]; even though in South America, 8 of 12 countries are economically strong, excluding only Bolivia, Ecuador, Guyana, and Paraguay.[19] Based on another review that included all prospective and retrospective studies of epilepsy of all geographic regions reported lower (than ours) epilepsy incidence and interquartile range (81.7/100,000; 95% CI 28.0–239.5, IQR 45.0) for resource-poor countries.[20] In comparing our incidence with previous reports on Latin America,[6,21] we may deduce that our epilepsy incidence is lower by 18.1% (from Median), 13.0% (from Mean), and 47.8% (from pooled), page 5. There may not be direct comprehensive explanations for these putative differences but may likely be due to lesser number of estimates included, different inclusion criteria, and taking larger regional definition (Latin America instead of South America). Nevertheless, over-interpretation[2] of epilepsy incidence has been shown for Africa earlier by first author.

In finding out possible reasons for differences through coefficient of correlations and between-study variances, the most important factors were study year and urban-rural milieu, page 5. These are not unlikely since exposure of any given population to risk factors may vary over time and may also differ between urban and rural environments; that in turn may affect incidence of epilepsy.[22] In comparing South American epilepsy incidence with that for the Central America, differences were noted (currently unpublished, D Bhalla 2016), which may further support that even *similar-looking* populations (regions/countries) may differ[23–26] in terms of their nature and degree of exposure. The fact, page 5–6 that metabias was only significant for urban-rural milieu ($p = 0.01$) may further substantiate this.

Based on our incidence, it was estimated that on average 445824 (between 236070 and 516258) new cases of epilepsy are possibly occurring every year in South America. This number may not be hugely insurmountable for a region as large as South America. This is important for several reasons. *First*, there are reports that indicate burden of epilepsy is an unknown quantity.[4] *Second,* epilepsy is often marketed in negative connotations (huge burden, etc.) however, projecting epilepsy as a positive, favorable, better disorder may also seem an option especially when effective solutions for epilepsy are already available for most patients. For instance, in Bolivia, only 5540 patients are expected to develop epilepsy every year.

A slightly higher incidence among females was noted but in Bolivia alone, Table 1. It is generally assumed that epilepsy risk is higher among males because of several male-dominant factors but inverse results also exist.[27] One of the hypotheses may surround pregnancy and birth period.[13] While development of risk factors such as infection during pregnancy and birth might cause epilepsy among offsprings, a risk of developing epilepsy through such risk factors may also, at the same time, be for those women as well. This might be the reason that even in populations where structured neurocysticercosis (NCC) control program is taking place since several years,[28] epilepsy due to pregnancy-birth remains equally high. Similar is the case for other populations.[29–36]

Lastly, we are confident that we did diligent and exhaustive work towards bringing regional conclusions and interpretations for South America and Caribbean. Major limitations of our work include that because of its *post-hoc* nature, we were obliged to rely on those informations that were available. However, this is not a limitation for our work alone. Our work is based on few studies alone which may have affected results to some extent. Our study-level factors explain only a part of between-study variance and residual variance could be related to both unmeasured and unmeasurable factors.

5. Conclusions

We addressed two geographic regions seperately in an attempt to bring authentic interpretations and estimates of epilepsy incidence. Caribbean needs to come forward to have its own epilepsy incidence data especially when risk environment due to numerous risk factors such as substance abuse, mental health conditions, etc. seems compelling in this region. Incidence of epilepsy in South America is likely to be slightly lower than previously reported although this varies considerably for each country. Inter-population differences are *in-part* (more than 50%) related to urban-rural milieu and variations over time. It is expected that on average 445824 (between 236070 and 516258) new cases of epilepsy are occurring every year in South America. This work provides appropriate basis for better devising health policies and resource allocations in these regions. Our work is also pertinent to monitor time-trends of epilepsy incidence especially when new data would emerge in coming years and countries would continue their epidemiological transitions.

Conflict of interest

The authors have none to declare.

No conflicts of interest. 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.

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