

# An estimation of global volume of surgically treatable epilepsy based on a systematic review and meta-analysis of epilepsy

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**OBJECTIVE** Epilepsy is one of the most common neurological disorders, yet its global surgical burden has yet to be characterized. The authors sought to compile the most current epidemiological data to quantify global prevalence and incidence, and estimate global surgically treatable epilepsy. Understanding regional and global epilepsy trends and potential surgical volume is crucial for future policy efforts and resource allocation.

**METHODS** The authors performed a systematic literature review and meta-analysis to determine the global incidence, lifetime prevalence, and active prevalence of epilepsy; to estimate surgically treatable epilepsy volume; and to evaluate regional trends by WHO regions and World Bank income levels. Data were extracted from all population-based studies with prespecified methodological quality across all countries and demographics, performed between 1990 and 2016 and indexed on PubMed, EMBASE, and Cochrane. The current and annual new case volumes for surgically treatable epilepsy were derived from global epilepsy prevalence and incidence.

**RESULTS** This systematic review yielded 167 articles, across all WHO regions and income levels. Meta-analysis showed a raw global prevalence of lifetime epilepsy of 1099 per 100,000 people, whereas active epilepsy prevalence is slightly lower at 690 per 100,000 people. Global incidence was found to be 62 cases per 100,000 person-years. The meta-analysis predicted 4.6 million new cases of epilepsy annually worldwide, a prevalence of 51.7 million active epilepsy cases, and 82.3 million people with any lifetime epilepsy diagnosis. Differences across WHO regions and country incomes were significant. The authors estimate that currently 10.1 million patients with epilepsy may be surgical treatment candidates, and 1.4 million new surgically treatable epilepsy cases arise annually. The highest prevalences are found in Africa and Latin America, although the highest incidences are reported in the Middle East and Latin America. These regions are primarily low- and middle-income countries; as expected, the highest disease burden falls disproportionately on regions with the fewest healthcare resources.

**CONCLUSIONS** Understanding of the global epilepsy burden has evolved as more regions have been studied. This up-to-date worldwide analysis provides the first estimate of surgical epilepsy volume and an updated comprehensive overview of current epidemiological trends. The disproportionate burden of epilepsy on low- and middle-income countries

**ABBREVIATIONS** AEDs = antiepileptic drugs; AFR = African Region; AMR-L = Region of the Americas (Latin America); AMR-US/Can = Region of the Americas (United States/Canada); DALYs = disability-adjusted life years; DRE = drug-resistant epilepsy; EMR = Eastern Mediterranean Region; EUR = European Region; HICs = high-income countries; ICD = International Classification of Diseases; ILAE = International League Against Epilepsy; LMICs = low- and middle-income countries; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SEAR = South-East Asian Region; STE = surgically treatable epilepsy; WPR = Western Pacific Region.

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will require targeted diagnostic and treatment efforts to reduce the global disparities in care and cost. Quantifying global epilepsy provides the first step toward restructuring the allocation of healthcare resources as part of global healthcare system strengthening.

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**KEYWORDS** epidemiology; global; incidence; prevalence; burden; surgically treatable; systematic review; meta-analysis; drug-resistant epilepsy

**E**PILEPSY is a major global health problem, significantly contributing to premature death, lost work productivity, social stigma, and high healthcare costs ([http://www.who.int/healthinfo/global\\_burden\\_disease/estimates/en/index2.html](http://www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html)).<sup>59,168</sup> Furthermore, disparities in access to diagnosis, medications, and surgery compound poor patient outcomes. Historical estimates of epilepsy suggest that 50 million people suffer from the disease worldwide, and between 20% and 40% of cases may be drug-resistant epilepsy (DRE).<sup>15,54,100,188</sup> Patients with seizures refractory to medications also account for 80% of healthcare costs directly associated with epilepsy.<sup>12</sup> However, one-third of those with DRE may be appropriate candidates for surgical treatment.<sup>139</sup> Surgical treatment of DRE is an effective therapy that is undervalued in high-income countries (HICs), and with even more potential benefits for people with epilepsy in low- and middle-income countries (LMICs).<sup>53,54,184</sup>

Epilepsy disproportionately impacts LMICs, where access to surgical care is also disproportionately limited.<sup>188</sup> Prior studies have reported the incidence in LMICs to be nearly twice the rate of HICs—82/100,000 versus 45/100,000, respectively.<sup>122,125</sup> Because these LMICs are home to 80% of all persons living with epilepsy, the disease burden falls predominantly on countries with fewer healthcare resources. In 2012, epilepsy was responsible for 20.6 million disability-adjusted life years (DALYs) lost, accounting for 0.8% of the total global DALYs lost ([http://www.who.int/healthinfo/global\\_burden\\_disease/estimates/en/index2.html](http://www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html)).<sup>188</sup> Its burden is compounded by a global shortage of access to surgical care; 5 billion people lack access to timely and safe surgical care.<sup>6</sup>

To our knowledge, no studies have estimated the global burden of surgically treatable epilepsy (STE). There have also been no studies on the global epidemiology of epilepsy since the development of the revised epilepsy classifications in the 2010 International League Against Epilepsy (ILAE) Commission report.<sup>16</sup> Since the last consensus studies on the global epidemiology of epilepsy, there has been a remarkable increase in research published from LMICs in English that provides important new data that have been underreported historically.<sup>122,125</sup> Comprehensive data regarding the current global estimate of STE, and epilepsy as a whole, is critical for the ongoing support of multinational efforts to address access to surgical care and strengthening healthcare systems. As one of the most common neurological diseases, the burden of epilepsy must be carefully understood to improve diagnostic, pharmacological, and surgical efforts in both resource-rich and resource-poor healthcare settings. This report offers the first estimate of the global burden of STE, as well as the most current and comprehensive assessment of the

literature to estimate the global prevalence and incidence of epilepsy.

## Methods

### Systematic Review

We implemented the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to perform this systematic review.<sup>117</sup> A comprehensive literature search was conducted using PubMed, EMBASE, and the Cochrane Database of Systematic Reviews in October 2016. We captured epidemiological data on epilepsy in all age groups, including prevalence, incidence, demographics, and, if available, surgical treatment, classification, etiology, DALYs, years of life lost, years of life lost due to disease, and mortality by using a full list of MeSH and title/abstract terms (see *Appendix*). The search was limited to studies primarily reporting incidence, prevalence, or both, and that were published between 1990 and 2016 in countries recognized by the World Bank. Two reviewers (K.V., C.L.) screened for titles, abstracts, and full text of the resulting articles. All ages were included in our search. Practice guidelines, randomized controlled trials, case studies, commentaries, comparison studies, and historical articles were excluded. Articles that did not have the full text available in English were also excluded to ensure optimized coding for methodological quality by the authors. Other exclusion criteria included studies without reported standard definitions of epilepsy, lacking epidemiological data, articles pertaining solely to one specific type of seizure, undocumented or unreported methodology, or biased or nonrandom sampling technique.

We extracted data for full-text articles that met inclusion criteria and cross-referenced for any potential further studies (K.V., C.L., J.A., M.S.). To ensure selection accuracy at all stages, reviewers jointly reviewed a random subset of articles to ensure consistent screening, and one reviewer cross-reviewed the extracted data for all studies (K.V.). All full-text articles were cross-referenced for relevant references, and these referenced studies were included if they fulfilled the selection criteria. Additionally, the references of previously conducted systematic reviews on the epidemiology of epilepsy were reviewed for pertinent articles not captured by our initial search. These referenced studies were also included if they fulfilled the selection criteria.

The methodological quality of each study was assessed on a 6-point scale from lowest (0: not population based, small sample size) to highest (5: large, ideal population based).<sup>161</sup> A lower score (minimum of 2) was accepted as an inclusion threshold for articles published in LMICs to account for publication bias from HICs (minimum of 3).

Even with a lower threshold of 2, the quality of the data in LMIC studies was found to be adequate for analysis given the rigorous exclusion criteria applied during initial study selection. Studies that did not report sufficient raw data for sorting into the meta-analysis were also excluded, even if methodological quality was sufficient.

### Meta-Analysis

We stratified data based on whether the studies reported true incidence, lifetime prevalence, or active prevalence, as well as by World Bank income level, age included (adult, children, or both), and WHO region for our subanalyses. All data analysis was performed by a dedicated statistician (R.A.M.) using Stata 14 (StataCorp) and Comprehensive Meta-Analysis Version 3 (Biostat, Inc.). Meta-analysis models were fitted to observed incidences and prevalences. Incidence estimates and 95% confidence intervals were obtained with a random-effects model as defined by DerSimonian and Laird, which accounted for variation between studies in addition to within-study variance.<sup>44</sup> To stabilize the variances, the pooled estimate was calculated after the Freeman-Tukey double arcsine transformation.<sup>63</sup> Forest plots were used to visualize the individual and summary estimates.<sup>104</sup> Heterogeneity was evaluated among studies by using Cochran's Q test ( $p < 0.10$ ) and the  $I^2$  to measure the proportion of total variation due to the heterogeneity. An  $I^2$  value  $> 40\%$  was considered to be high. Eleven potential sources of heterogeneity were explored using subgroup analyses by categorical covariates (WHO region and income level). To further evaluate potential sources of heterogeneity for each of the 3 outcomes (incidence, active prevalence, and lifetime prevalence), a univariate meta-regression was performed on continuous variables including study quality, study duration, publication year, and male/female ratio, in addition to age group (pediatric, adults, both) as continuous variables. Funnel plots, Egger's linear regression test, and Begg's correlation test were used to evaluate potential publication bias. If publication bias was found, the number of missing studies was evaluated by the trim and fill methods. A  $p$  value  $< 0.05$  was considered significant unless otherwise indicated.

### Surgical Burden Estimation

Using our results from the meta-analysis, we derived global and regional estimates for the total volume of epilepsy cases. Literature reports of the proportion of patients with DRE varied widely, from 20% to 40%, and stated that one-third of these patients may be surgical candidates.<sup>15,54,100,139</sup> However, these numbers exclusively represent the patient population with epilepsy in HICs and would be insufficient to adequately capture global trends in epilepsy and its neurosurgical management. Poor access to antiepileptic drugs (AEDs) in LMICs would strongly bias any attempt to estimate surgical burden by using the epidemiology of intractable or DRE, so we elected to use all epilepsy cases for our estimation. Given the lack of robust data available on global prevalence and incidence of STE, surgeon-based estimates of operative disease volume were used.<sup>45</sup> Among a global sample of 85 neurosurgeons

representing all WHO regions and country income levels, it was calculated that 40% of all epilepsy cases worldwide may warrant a neurosurgical consultation, and 24% may be amenable to surgical treatment.<sup>45</sup> WHO regions were classified as follows: African Region (AFR), Region of the Americas (divided into United States/Canada [AMR-US/Can] and Latin America [AMR-L]), South-East Asian Region (SEAR), European Region (EUR), Eastern Mediterranean Region (EMR), and Western Pacific Region (WPR) ([http://www.who.int/healthinfo/global\\_burden\\_disease/definition\\_regions/en/](http://www.who.int/healthinfo/global_burden_disease/definition_regions/en/)). Of the respondents, 31% were from AFR ( $n = 26$ ), 13% from AMR-L ( $n = 11$ ), 17% from AMR-US/Can ( $n = 14$ ), 18% from WPR ( $n = 15$ ), and 6%–7% each from EMR, EUR, and SEAR. By income level, 69% of respondents were from LMICs. The volume of STE was then estimated from the active prevalence and incidence rates derived from the meta-analysis and the expert-based neurosurgical consultation and evaluation rate. Regional survey data were available for each WHO region, which were used to calculate regional volumes of consultation and surgical cases.

### Data Reporting

Results were organized and presented by the WHO regions in which each study was conducted. Data were also categorized by country-based income level as defined by the World Bank, with multi-income-level studies listed by the most prevalent income level (<https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>). Descriptive statistics were reported as proportions of a population and median or mean, with population derived from 2015 projections by the United Nations Department of Economic and Social Affairs (<https://esa.un.org/unpd/wpp/>).

Acknowledging the large variation in the definition and diagnostic criteria of epilepsy across the numerous reports in this model, when possible we applied the operational clinical definition of epilepsy from the ILAE. The 2014 ILAE definition of epilepsy is at least 2 unprovoked seizures more than 24 hours apart, 1 unprovoked seizure with at least a 60% risk of further seizures, or diagnosis of an epilepsy syndrome.<sup>60</sup> A number of studies gathering data from medical records also used diagnostic codes for epilepsy from the International Classification of Diseases (ICD), either the 8th, 9th, or 10th edition. Active epilepsy was defined as a diagnosis of epilepsy in a person with at least 1 unprovoked seizure within the past 10 years or who was actively being treated with AEDs. Lifetime epilepsy was defined as any diagnosis of epilepsy during a person's life, whether the disease was active or resolved. Some studies reported data both for patients with single seizures and for patients diagnosed with epilepsy, in which case we excluded the data for patients with single seizures only.

## Results

### Literature Yield

A total of 26,682 articles (PubMed: 16,902; EMBASE: 9613; Cochrane: 167) were captured by our literature search. A review of titles yielded 2243 abstracts, which in turn yielded 454 full-text articles. A total of 162 articles

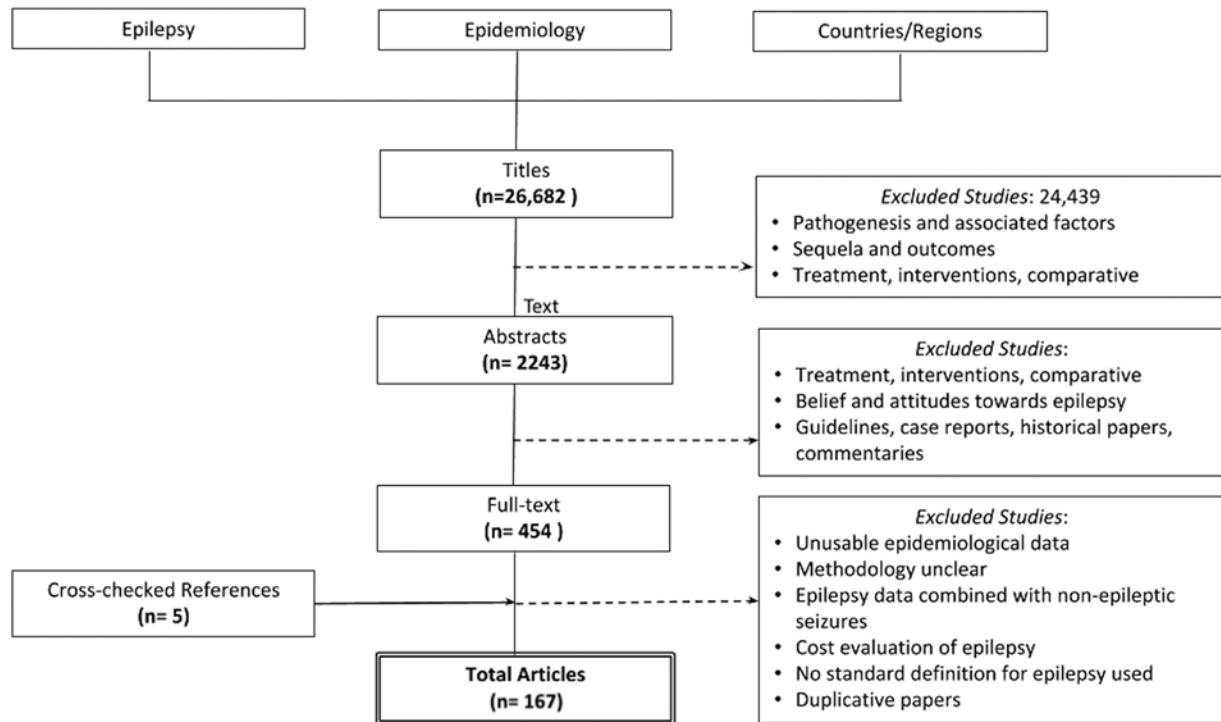


FIG. 1. PRISMA flowchart. Article selection for systematic review of the literature.

met all criteria for final inclusion in our study, with 5 additional studies garnered from cross-referencing, generating a total of 167 papers included in this systematic review (Fig. 1). The final studies included in this report represent 58 countries and all WHO regions (Supplementary Material, Table A).<sup>1–5,7–11,13,14,17–19,21,22,24–31,33–43,46–52,55–58,61,62,64,66–91,93–99,101–103,105–113,116,118–121,123,124,126–160,162–167,169–183,185–187,189–192</sup> Of the 167 articles, 111 used an ILAE definition of epilepsy to determine their cases, and 14 used an ICD code from medical records to identify patients. The combined ILAE and ICD definitions of epilepsy represent 74.1% of all study populations across all papers, and 53.9% of all patients with epilepsy across all reports were identified using one of these two classification systems.

Europe was the most well-represented region (56 studies from 22 countries), and EMR and SEAR were the least well-represented regions, with 9 and 10 studies, respectively. The regional distribution of studies was as follows: AFR (32 studies, 15 countries); AMR-US/Can (19 studies); AMR-L (20 studies, 9 countries); EMR (9 studies, 3 countries); EUR (56 studies, 22 countries); SEAR (10 studies, 1 country); and WPR (22 studies, 6 countries). One hundred sixty studies provided population-based data, compared to 7 hospital- or facility-based studies. Our meta-analysis for the incidence rate of epilepsy included 49 studies, whereas the active and lifetime prevalence of epilepsy were derived from 93 and 82 studies, respectively.

The average study quality from AMR-US/Can, EUR, and SEAR was 3.6/5, 3.7/5, and 3.6/5, respectively. In contrast, the quality was lower for studies conducted in AFR (2.9/5), AMR-L (3.0/5), and EMR (2.4/5). Thus, considering the methodological quality of all 167 studies, a higher quality was observed in HICs compared to LMICs (mean study quality 3.7 vs 3.0, respectively). The largest source

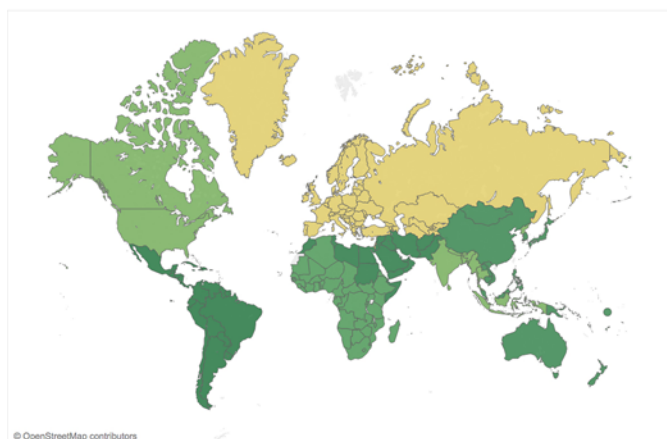
of articles originated from HICs (83), followed by MICs (69) and LICs (15). This confirmed the publication bias we expected based on regional research infrastructure disparities.

## Incidence

We projected the global incidence of epilepsy to be 62 per 100,000 person-years, yielding an estimated 4.6 million new epilepsy cases annually worldwide (Fig. 2). The 2 WHO regions with the highest pooled incidence of epilepsy were AMR-L and EMR, with 107 and 104 cases per 100,000 person-years, respectively. Europe had the lowest regional incidence for epilepsy, at 44 cases per 100,000 person-years (p-interaction < 0.01 comparing the WHO regions) (Table 1, Supplementary Material, Fig. B). The incidence of epilepsy was relatively higher in LMICs, with 104 per 100,000 person-years in low-income and 78/100,000 in middle-income countries, compared to that of HICs, at 51/100,000 person-years (p-interaction = 0.07 comparing the 3 categories) (Supplementary Material, Fig. C).

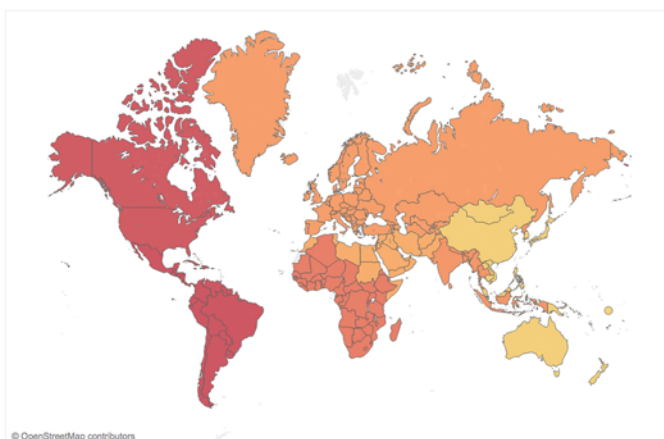
Regarding country population-based incidence estimates in LMICs for all age groups, Placencia et al. (Ecuador) and Kaiser et al. (Uganda) reported the highest incidence of epilepsy, at 190/100,000 and 156/100,000 person-years, respectively.<sup>87,140,141</sup> Wagner et al. (South Africa) reported the lowest incidence, at 17/100,000, but only studied patients with active convulsive epilepsy.<sup>179</sup> The highest incidence described in HICs was from the US: Kaiboriboon et al. reported an incidence of 320/100,000 person-years and Faught et al. reported an incidence of 240/100,000.<sup>56,86</sup> However, these studies only included Medicaid and Medicare beneficiaries, respectively.

Global incidence of active epilepsy by WHO region



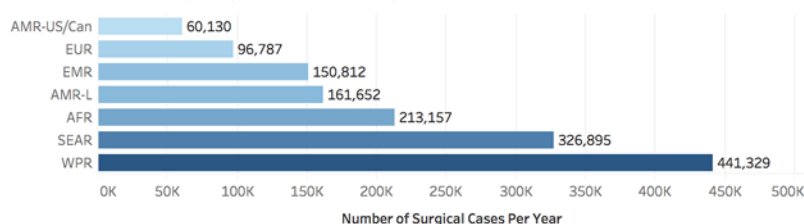
Annual incidence (per 100,000 person-years)  
40 110

Global prevalence of active epilepsy by WHO region



Active prevalence (per 100,000 persons)  
350 1,000

Global burden of surgically treatable epilepsy



World map of region-specific model-derived prevalence and incidence of epilepsy. Incidence of epilepsy is reported per 100,000 person-years. Prevalence is reported as prevalence of active epilepsy (AE) per 100,000 persons. The World Health Organization (WHO) regions are AMR-US/Can – United States/Canada, AMR-L – Latin America, AFR – African Region, EMR – Eastern Mediterranean Region, EUR – European Region, SEAR – South-East Asia Region, and WPR – Western Pacific Region.

**FIG. 2.** World map of the prevalence and incidence of active epilepsy by WHO region and the annual volume of new STE cases by WHO region. © OpenStreetMap contributors (<http://www.openstreetmap.org/copyright>). Published with permission. Figure is available in color online only.

Meta-regression analysis revealed that higher-quality studies tended to have a lower reported global incidence of epilepsy than lower-quality studies (slope =  $-0.33$ ;  $p = 0.01$ ), yet this association became nonsignificant when adding either WHO regions or income level in the meta-regression models, suggesting the presence of confounding by these last 2 variables. Study duration, publication year, and male/female ratio did not appear to be a significant source of heterogeneity in the meta-regression analysis.

A significant publication bias was detected both visually as an asymmetrical funnel plot and statistically (Begg and Egger's  $p$  values  $< 0.01$ ), suggesting potentially missing studies showing a larger incidence. In an attempt to correct for these missing studies, the trim-and-fill methods imputed 22 studies to the right of the weighted average of the global incidence. The final imputed pooled global incidence increased only slightly in comparison to the original results (Supplementary Material, Fig. D).

## Prevalence

Our model estimated 690 cases of active epilepsy per 100,000 persons globally, compared to 1099 cases of lifetime epilepsy. This global model translates to 51.7 million people with active epilepsy and 82.3 million people diagnosed with epilepsy during their lifetime. Using the modeled regional active and lifetime prevalence and the 2015 population estimates from each WHO region, this

yields slightly lower global sum estimates of 51.0 million people with active epilepsy and 81.1 million people with any lifetime diagnosis of epilepsy due to population rounding (Table 1). Active epilepsy cases were more prevalent in AMR-L and AMR-US/Can (925 and 903 respectively) than in other regions (Supplementary Material, Fig. E). The WPR had the lowest prevalence of active epilepsy, at 384 per 100,000 people. Trends for active epilepsy and lifetime epilepsy were similar to incidence trends relative to income level. LMICs were disproportionately affected, exhibiting a prevalence of 1210 and 670 in low- and middle-income brackets (Supplementary Material, Fig. F).

We found that disease patterns for the prevalence of lifetime epilepsy differed somewhat from those of active epilepsy. Lifetime epilepsy cases were more prevalent in AFR (1726 per 100,000 people) and AMR-US/Can (1702), and they were least common in the SEAR (523) and WPR regions (543) (Supplementary Material, Fig. G). Low-income countries were disproportionately affected, with 2069 cases of lifetime epilepsy per 100,000 persons, compared to 1117 and 941 cases in middle-income countries and HICs, respectively (Supplementary Material, Fig. H).

There was a significant publication bias suggesting that studies reporting a higher lifetime prevalence were missing, which was confirmed by the asymmetrical funnel plot and Begg's test ( $p < 0.01$ ) but not Egger's ( $p = 0.16$ ). The trim-and-fill method resulted in imputing 36 studies to the right of the weighted average of the lifetime prevalence, and this resulted in a higher estimate by 0.6% (Supple-

**TABLE 1. Global incidence and prevalence of epilepsy according to a systematic review of 167 articles**

WHO Region	Incidence	Active Prevalence	Lifetime Prevalence	Total Pop w/ Lifetime Epilepsy	Current Epilepsy Case Vol for Neuro Consult	Current STE Case Vol	Annual Vol of New Epilepsy Cases for Neuro Consult	Annual Vol of New STE Cases
AFR	84.8 (44.3, 137.6)	729.5 (601.3, 869.7)	1726.3 (1217.9, 2320.3)	18,080,444	3,351,970	1,819,067	389,646	211,456
AMR-L	106.5 (50.9, 178.8)	924.7 (758.0, 1107.6)	1488.0 (121.4, 1790.9)	9,410,749	2,534,286	1,095,640	291,880	126,188
AMR-US/Can	70.4 (16.4, 161.4)	902.8 (668.5, 1171.9)	1701.6 (391.4, 3906.5)	6,055,742	1,061,506	1,247,661	82,776	97,292
EMR	103.9 (39.7, 196.4)	517.9 (376.9, 680.6)	982.1 (639.4, 1396.5)	5,939,711	776,901	844,178	155,860	169,357
EUR	44.2 (37.2, 51.9)	579.5 (393.7, 800.5)	912.7 (339.9, 1766.6)	8,327,450	2,653,487	1,028,452	202,389	78,443
SEAR	70.7 (3.0, 221.0)	615.4 (483.5, 762.9)	523.1 (384.7, 682.4)	10,077,727	3,794,988	2,334,554	435,986	268,204
WPR	96.6 (95.3, 97.9)	384.2 (242.0, 558.7)	542.6 (445.1, 649.5)	10,328,906	2,993,035	1,744,535	752,543	438,631
Global	61.6 (45.5, 80.0)	690.1 (603.9, 782.0)	1098.5 (824.9, 1410.3)	81,102,352	17,166,172	10,114,087	2,311,080	1,389,571

Neuro consult = neurosurgical consultation; pop= population.

All values are presented as number (95% CI) based on our meta-analysis. Incidence is reported as cases per 100,000 person-years. Active prevalence is defined as prevalence of active epilepsy per 100,000 persons. Lifetime prevalence is defined as prevalence of lifetime epilepsy per 100,000 persons.

mentary Material, Fig. I). Similarly, a publication bias was found in studies reporting a higher active prevalence of epilepsy, as evident by the funnel plot and both Begg's ( $p < 0.01$ ) and Egger's ( $p = 0.02$ ) tests. Imputing 30 potentially missing studies in active prevalence resulted in a larger prevalence by 0.01% (Supplementary Material, Fig. J). Study quality remained a significant source of heterogeneity, even after adjusting for either WHO regions or income level, but only for active prevalence, and not for lifetime prevalence. Study duration, publication year, and age categories were not significant sources of heterogeneity in both outcomes.

**STE Estimates**

Worldwide, we estimated that currently 10.1 million people are candidates for surgical treatment of their epilepsy, and in 17.2 million neurosurgical consultations for epilepsy may be considered appropriate (Table 1). The estimates of active prevalence of STE are highest in SEAR, AFR, and WPR, and lowest in EMR. Extrapolating from the incidence in our meta-analysis, we predicted a global annual volume of 1.4 million new STE cases, and 2.3 million new potential neurosurgical epilepsy consultations (Fig. 2). The WPR, SEAR, and AFR showed the highest estimates for both new annual volume of STE and neurosurgical epilepsy consultations. We found that the lowest estimates for incidence of STE was in AMR-US/Can and EUR, both overwhelmingly composed of HICs.

Within the studies included in our systematic review, only 2 studies quantified neurosurgical management of epilepsy. Based on their study, Picot et al. noted that there were approximately 34,000 cases of DRE in France, yielding a prevalence of 70/100,000 persons, of which one-third were eligible for surgery.<sup>139</sup> In a Hong Kong pediatric population, Wong reported that neurosurgical intervention was indicated for only 3% (33 cases) of the patients.<sup>187</sup> Other studies commented on surgical treatment in passing, such as noting a qualitative lack of progress in neurosurgical care for epilepsy in Mongolia.<sup>174</sup>

**Epilepsy Demographics and Medical Management**

We estimated a mean global sex ratio of 1.1:1 (M/F). A predominance of male cases was observed in AFR, EMR, EUR, SEAR, and WPR, whereas females composed the majority of cases in the AMR-US/Can, and in AMR-L countries. The largest sex disparity was documented in Nigeria, with a ratio of 2.35:1 (M/F), followed by 2.1:1 (M/F) in Estonia.<sup>134,173</sup> Five countries (Brazil, Ecuador, Iceland, Netherlands, and Tanzania) demonstrated no sex differences in their studies. Meta-regression analysis revealed that higher-quality studies tended to have a lower reported lifetime prevalence of epilepsy than did lower-quality studies (slope =  $-0.26$ ;  $p = 0.04$ ) and that men tended to have a lower lifetime prevalence than women (slope for M/F ratio =  $-0.53$ ;  $p < 0.01$ ). Similar results were found in the active prevalence for both study quality (slope =  $-0.21$ ;  $p < 0.01$ ) and M/F ratio (slope =  $-0.60$ ;  $p = 0.01$ ).

Twenty-nine studies analyzed epilepsy in pediatric-only patient populations, and age-based definitions of a child varied, with an upper limit from 15 years to 20 years of age. Our model from these studies predicted a global pe-

diatric incidence of 78 cases per 100,000 person-years, or nearly 2 million new cases of pediatric epilepsy per year based on the United Nations pediatric population estimates from 2015 (<https://esa.un.org/unpd/wpp/>). Meta-regression analysis indicated that pediatric patients seemed to have a higher global incidence of epilepsy (78.3/100,000 person-years) as compared to adults (50/100,000 person-years) or even the group with mixed categories (52.3/100,000 person-years) ( $p$ -interaction = 0.01). This association remained significant in the meta-regression even after controlling for either WHO regions or income level ( $p < 0.01$  for both). Moreover, we found a prevalence of 517 cases of active pediatric epilepsy per 100,000 people, lower than the adult prevalence of 874 cases. The European pediatric population represented more than half of the pediatric studies encountered in the literature review. Active epilepsy was only reported in 8 studies. The highest lifetime and active prevalence was reported in Rwanda, at 4100/100,000 and 1100/100,000, respectively.<sup>151</sup> The largest incidence of epilepsy was also reported in the same cohort at 187/100,000. The lowest lifetime and active prevalences reported were observed in children living in Greenland (340/100,000) and Sweden (340/100,000).<sup>18,101</sup>

A total of 67 studies noted the number of patients with epilepsy in their cohort who were actively being treated with AEDs. Seven of these studies identified epilepsy cases based on AED usage, resulting in 100% use of AEDs.<sup>32,74,97,102,103,147,157</sup> Removing these studies, the lowest mean percentage of AED usage occurred in AFR (24.5%) and WPR (26.8%), and the highest mean percentage was observed in AMR-US/Can (77.1%) and EUR (73.9%).

## Discussion

This systematic review and meta-analysis provides the first global estimate of STE, and is the most comprehensive global perspective on epilepsy disease burden to date. In light of ever-evolving regional healthcare disparities and an important increase in research publications in English from LMICs, an updated analysis is crucial for healthcare providers, policymakers, and outreach personnel to maintain a current understanding of epilepsy trends and burden. Since the few prior global reports were published, we have been able to significantly expand upon the strength and quality of data to estimate large-scale incidence and prevalence and include initial estimates for possible surgical candidates among patients with epilepsy.

Our meta-analysis of 167 articles represents a total sample population of more than 241 million people across 58 countries, and nearly 5 million patients with epilepsy. The global burden calculation confirms prior estimates in the literature of 50 million patients with epilepsy.<sup>188</sup> Our model predicted 51.7 million people currently diagnosed with epilepsy, and 82.3 million with any lifetime diagnosis of epilepsy. Each year, 4.6 million people will be newly diagnosed with epilepsy. Globally, 10.1 million people with active epilepsy might benefit from surgical intervention, and we predict 1.4 million new patients with epilepsy each year who could be additional surgical candidates.

Reports on the proportion of neurosurgical consultation and surgical treatment of epilepsy are predominantly

based on HIC patient populations. Only 2 reports included in our systematic review reported data for neurosurgical evaluation and treatment; 1 report was in a pediatric population and both were based in HICs.<sup>62,139</sup> Beyond our systematic review, there are very sparse LMIC studies on the frequency of STE, including a neurosurgeon survey by Menon and Radhakrishnan in India.<sup>114</sup> Small case series have shown the feasibility of neurosurgical evaluation and treatment for epilepsy in LMICs such as Uganda and Tunisia.<sup>20,92</sup> We elected to use a global survey of neurosurgical volume as our basis for global STE estimates, which yields a more accurate representation of the disproportionate disease burden found in LMICs. This survey includes neurosurgeons from all WHO regions, allowing us to estimate regional and global potential neurosurgical involvement in epilepsy management. Although our estimates remain simplistic, they are a crucial first step in understanding disparities in surgical and epilepsy care.

There are multiple factors that contribute to disparate levels of neurosurgical care, particularly observed in LMICs, including the limited availability of diagnostic studies to localize epileptogenic foci, intraoperative monitoring, surgical tools, and qualified neurosurgeons. The high costs of diagnostic workup and surgical care are also prohibitive. In addition, given the large treatment gap observed in these countries, it is difficult to ascertain which patients would benefit from surgery without the access to or proper use of pharmacological therapies. We therefore strongly recommend future studies, especially those from LMICs, to include data regarding potential neurosurgical intervention as well as challenges to surgical care. These data are necessary for further policy efforts and stakeholder analyses in the process of strengthening healthcare and surgical systems worldwide.

Prior global analyses have provided an important framework for addressing epilepsy. Ngugi et al. concluded in their meta-analysis that the median active and lifetime prevalence in developing countries was approximately twice the prevalence in developed countries, with peaks in rural areas of developing countries.<sup>122,125</sup> Their estimated burden of lifetime and active epilepsy in developed countries alone was 6.8 million and 5.7 million, respectively. Our current meta-analysis is a significant update—of the 167 studies included, 102 (61%) were published in the past decade. The bias toward more recent publications speaks strongly to an underlying increase in healthcare and research resources being dedicated to epilepsy epidemiology. There remains a significant gap in surgical treatment, a result of disproportionately limited access to surgical care and limited resources to evaluate epilepsy in LMICs.

Ngugi et al. also estimated the total median incidence of epilepsy at 50/100,000 person-years, and this was lower in HICs (45/100,000) compared to LMICs (82/100,000), compared to 62 new cases per 100,000 person-years in our analysis.<sup>125</sup> This may reflect an increase in awareness and diagnosis of epilepsy across the world, rather than purely an increase in the number of patients with epilepsy since this study. Our data for AMR-US/Can shows an unexpectedly high active prevalence relative to other HICs, which may be partly the result of demographic and sampling methods. Ultimately, we confirm previous findings that

LMICs have a higher incidence and a trend toward a higher prevalence of epilepsy.<sup>23,122,123,125</sup> The known publication bias may indicate that our analysis slightly underestimates incidence and active and lifetime prevalence, as demonstrated by the trim-and-fill method. Based on our analysis, the largest annual volume of new epilepsy cases arises in AFR and AMR-L, whereas the surgically treatable cases may be most numerous in SEAR, AFR, and WPR. These trends are probably in part related to limited healthcare that increases possible risk factors for epilepsy such as perinatal injuries and infectious etiologies.

Demographic patterns in disease distribution showed that men had a lower prevalence of epilepsy than women, and that adults had a lower incidence than children. Although the mean global sex ratio shows a slight male predilection at 1.1:1 (M/F), analysis revealed that active and lifetime prevalence for men were lower than for women. This may reflect underlying predisposing factors for epilepsy that may affect men and women at different rates in certain regions, leading to a disease gap between the sexes. Pediatric populations showed a higher incidence than adult populations. Differences in diagnosis and definitions of seizure and epilepsy, etiologies such as neonatal infections, and reporting could partly contribute to this variation in incidence. We do not yet have enough data to provide adequate global pediatric estimates of STE; more studies of global pediatric neurosurgical management of epilepsy will further inform the discussion of epilepsy resource allocation. Active treatment with AEDs was observed to be lower in LMICs compared to HICs, consistent with previous studies describing the larger treatment gap observed in countries with poor access to healthcare resources.<sup>43,49,82,106,115</sup>

### Limitations and Future Directions

Our analysis has several limitations. An important—and inevitable—limitation is publication bias from HICs relative to LMICs. The current global imbalance in access to healthcare and research resources can be seen in part through this bias. This imbalance is also determined by the predominantly English article databases we queried for our literature search to which LMICs may not have access, as well as our exclusion of non-English full texts. Although there is a strong historic publication bias emphasizing HICs' population data, this bias should slowly decrease as LMICs develop more healthcare and research infrastructure. We see this manifested in our meta-analysis in a decreasing publication bias over time: there were nearly twice as many LMIC-based publications included from 2007 onward (55 reports, or 54% of publications) as were included from 1990 to 2006 (28 reports, or 43% of publications). Our statistical analysis also assessed publication bias, and imputing missing studies demonstrated that there were minor differences in results (< 1%) for incidence and prevalence.

There remains an expected overrepresentation of high-income countries, especially in regard to the neurosurgical treatment of epilepsy. No LMIC studies included in our meta-analysis reported quantitative information on STE volume. Our estimate of STE volume is limited by the overall lack of data for the proportion of DRE and of

candidates for surgical treatment of epilepsy. Although the STE volume is based on surgeons' practice patterns from a global survey, regional volume data would strengthen global STE volume estimations. The survey respondents represented all WHO regions, and nearly 70% were from LMICs. Although we had representation from every region and were able to calculate region-specific estimates based on regional survey data, the limited respondent sample size could lead to bias in our estimates. The accuracy and applicability of our estimates will be greatly enhanced by further study of regional epilepsy surgical treatment trends and availability of newer technology such as laser ablation and responsive neurostimulation. Regional variations in epilepsy etiology and access to care would also significantly inform our initial volume estimates, such as patterns in temporal lobe epilepsy and medically intractable cases that may be more amenable to surgery.

Given the relatively long range selected for article inclusion (from 1990 to 2016), multiple definitions of seizure events and epilepsy were used across the included studies. Although many categorized their data according to widely accepted standard definitions (e.g., the ILAE), there was significant variation across studies. The diagnosis of epilepsy had numerous definitions in our literature review, from a purely historical diagnosis based on suspected seizure events, to an extensive workup with electroencephalography and imaging. When adapting disease data published from studies in which multiple definitions of epilepsy were used, there is some inherent data mismatch that decreases the accuracy of the meta-analysis. We elected not to limit our study to patients with intractable epilepsy because that would exclude numerous LMIC populations without adequate access to AEDs, and would worsen the effect of the publication bias.

Although our study included 167 articles, only 49 studies reported incidence numbers. Many incidence numbers in LMICs were also derived from cross-sectional surveys performed at different points in time rather than prospectively studying their population-based cohort. Every effort was made to balance rigorous inclusion and exclusion criteria to maximize data quality while also retaining studies from underrepresented regions and LMICs that may have limited healthcare and research resources. Sampling bias due to the 7 hospital-based studies that were included is probably negligible, because 96% of reports in this review were population-based.

Future research directions should continue to evaluate the global burden of epilepsy in terms of healthcare costs, access, diagnostic modalities, and treatment strategies. Regional studies have begun to quantify the impact of epilepsy, both in measures of healthcare and social impact. Existing reports on epilepsy mortality rates, and related quality of life and disability should be further explored to quantify healthcare disparities. Ongoing investigations into global trends in the social and medical impact of epilepsy may lead to more effective allocation of resources for patients with epilepsy and their communities.

### Conclusions

Epilepsy affects 4.6 million new individuals each year,

with 51.7 million currently diagnosed. We estimate that 10.1 million people with epilepsy may be candidates for surgical treatment, or 1.4 million new cases of STE every year. The highest estimated prevalence is found in Africa and Latin America, although the highest incidence is demonstrated in the Middle East and Latin America. Given that epilepsy remains one of the most common neurological disorders, comprehensive epidemiological and surgical data provide a strong foundation for improving medical and surgical epilepsy care. Healthcare providers and policymakers should consider allocating resources accordingly to those regions with the highest disease burden and the most limited healthcare delivery platforms.

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## Appendix

### PubMed Search Terms

((“epidemiology” [Subheading] OR “Epidemiology” [MESH] OR epidemiology[tiab] OR epidemiological[tiab] OR population[tiab] OR population-based[tiab] OR inciden\*[tiab] OR prevalen\*[tiab] OR burden[tiab] OR DALY[tiab] OR “disability adjusted life year\*[tiab] OR YLL[tiab] OR “years of life lost”[tiab] OR YLD[tiab] OR “years lost to disability”[tiab] OR “years lost due to disability”[tiab] OR ratio[tiab] OR QALY[tiab] OR “quality adjusted life year\*[tiab]))

AND

“epilepsy” [MESH] OR “generalized epilepsy” [tiab] OR “focal epilepsy” [tiab] OR “partial epilepsy” [tiab] OR “complex partial seizure\*[tiab] OR “simple partial seizure\*[tiab] OR “status epilepticus” [tiab] OR “epilepsy” [tiab] OR “epilepsies” [tiab] OR “epileptic seizure\*[tiab] OR “epileptic syndrome\*[tiab] OR “localization related epilepsy” [tiab] OR “seizure disorder\*[tiab]

AND

(“Africa” [MESH] OR “Asia” [MESH] OR “Central America” [MESH] OR “Developing Countries” [MESH] OR “Geographical Locations Category” [MESH] OR “Internationality” [MESH] OR “Latin America” [MESH] OR “South America” [MESH] OR “Dominican Republic” [tiab] OR “Principe” [tiab] OR “Puerto Rico” [tiab] OR “Sao Tome” [tiab] OR “Saudi Arabia” [tiab] OR “Sierra Leone” [tiab] OR “Virgin Islands” [tiab] OR Afghanistan\*[tiab] OR Africa\*[tiab] OR Albania\*[tiab] OR Algeria\*[tiab] OR America\*[tiab] OR Andorra\*[tiab] OR Angola\*[tiab] OR Antarct\*[tiab] OR Antigua\*[tiab] OR Arab Emirate\*[tiab] OR Argentina\*[tiab] OR Armenia\*[tiab] OR Aruba\*[tiab] OR Asia\*[tiab] OR Atlantic[tiab] OR Australia\*[tiab] OR Austria\*[tiab] OR Azerbaijan\*[tiab] OR Azores Islands[tiab] OR Baham\*[tiab] OR Baha\*[tiab] OR Bangladesh\*[tiab] OR Barbad\*[tiab] OR Barbuda\*[tiab] OR Barthélemy[tiab] OR Barthélemy[tiab] OR Belarus\*[tiab] OR Belg\*[tiab] OR Belize[tiab] OR Bengal[tiab] OR Benin\*[tiab] OR Bermuda\*[tiab] OR Bhutan\*[tiab] OR Bissau[tiab] OR Bolivia\*[tiab] OR Bosnia\*[tiab] OR Botswana\*[tiab] OR Brazil\*[tiab] OR Brunei[tiab] OR Bulgaria\*[tiab] OR Burkina Faso[tiab] OR Burma[tiab] OR Burmese\*[tiab] OR Burundi\*[tiab] OR Cabo Verd\*[tiab] OR Caicos[tiab] OR Cambodia\*[tiab] OR Cameroon\*[tiab] OR Canad\*[tiab] OR Cape Verd\*[tiab] OR Cayman[tiab] OR Central[tiab] OR Chad\*[tiab] OR Chile[tiab] OR

China[tiab] OR Chinese[tiab] OR Colombia\*[tiab] OR Comoros[tiab] OR Congo\*[tiab] OR Costa Rica\*[tiab] OR Cote[tiab] OR Cote d'Ivoire[tiab] OR Croatia\*[tiab] OR Cuba[tiab] OR Cuban[tiab] OR Cyprus[tiab] OR Czech Republic[tiab] OR Denmark[tiab] OR developing countr\*[tiab] OR developing nation\*[tiab] OR Djibouti[tiab] OR Dominica\*[tiab] OR East[tiab] OR East Timor[tiab] OR Ecuador\*[tiab] OR Egypt\*[tiab] OR El Salvador\*[tiab] OR Eritrea\*[tiab] OR Estonia\*[tiab] OR Ethiopia\*[tiab] OR Europ\*[tiab] OR Fiji\*[tiab] OR Finland[tiab] OR France[tiab] OR French Guiana[tiab] OR Gabon\*[tiab] OR Gambia\*[tiab] OR Gaza\*[tiab] OR Georgia\*[tiab] OR German\*[tiab] OR Ghana\*[tiab] OR Greece[tiab] OR Grenada\*[tiab] OR Grenadines[tiab] OR Guadeloupe[tiab] OR Guatemala\*[tiab] OR Guinea\*[tiab] OR Guyan\*[tiab] OR Haiti\*[tiab] OR Herzegovina\*[tiab] OR Hondura\*[tiab] OR Hungary[tiab] OR Iceland\*[tiab] OR income[tiab] OR India[tiab] OR Indian\*[tiab] OR Indonesia\*[tiab] OR Iran\*[tiab] OR Iraq\*[tiab] OR Ireland[tiab] OR Israel\*[tiab] OR Italian[tiab] OR Italy[tiab] OR Ivory Coast[tiab] OR Jamaica\*[tiab] OR Japan\*[tiab] OR Jordan\*[tiab] OR Kazakh\*[tiab] OR Kenya\*[tiab] OR Kiribati[tiab] OR Kitts[tiab] OR Korea\*[tiab] OR Kosovar\*[tiab] OR Kosovo[tiab] OR Kuwait\*[tiab] OR Kyrgyz\*[tiab] OR Lao[tiab] OR Laos\*[tiab] OR Laotian\*[tiab] OR latin america[tiab] OR Latvia[tiab] OR Lebanon\*[tiab] OR Lebanon[tiab] OR lebanese[tiab] OR Lesotho[tiab] OR less developed countr\*[tiab] OR less developed nation\*[tiab] OR Liberia\*[tiab] OR Libya\*[tiab] OR Liechtenstein[tiab] OR Lithuania[tiab] OR Imic[tiab] OR Imics[tiab] OR low income countr\*[tiab] OR low income nation\*[tiab] OR Lucia[tiab] OR Luxembourg[tiab] OR Macedonia\*[tiab] OR Madagascar\*[tiab] OR Madeira Island[tiab] OR Malawi\*[tiab] OR Malaysia\*[tiab] OR Maldives[tiab] OR Mali[tiab] OR Malta[tiab] OR Marshall Island\*[tiab] OR Martinique[tiab] OR Mauritania\*[tiab] OR Mauriti\*[tiab] OR Mexican\*[tiab] OR Mexico[tiab] OR Micronesia\*[tiab] OR middle income countr\*[tiab] OR middle income nation\*[tiab] OR Moldova[tiab] OR Moldova\*[tiab] OR Monaco[tiab] OR Mongolia\*[tiab] OR Montenegro\*[tiab] OR Montserrat[tiab] OR Morocco\*[tiab] OR Mozambique[tiab] OR Myanmar[tiab] OR Namibia\*[tiab] OR Nauru[tiab] OR Nepal\*[tiab] OR Nevis[tiab] OR New Zealand[tiab] OR Nicaragua\*[tiab] OR Niger\*[tiab] OR Nigeria\*[tiab] OR North[tiab] OR Norway[tiab] OR Oman\*[tiab] OR Pacific[tiab] OR Pakistan\*[tiab] OR Palau[tiab] OR Palestin\*[tiab] OR Panama\*[tiab] OR Papua[tiab] OR Paraguay\*[tiab] OR Peru\*[tiab] OR Phillipin\*[tiab] OR Poland[tiab] OR poor countr\*[tiab] OR poor nation\*[tiab] OR Portug\*[tiab] OR Principe[tiab] OR Qatar\*[tiab] OR Romania\*[tiab] OR Russia\*[tiab] OR Rwanda\*[tiab] OR Saint Lucia[tiab] OR Saint Vincent[tiab] OR Samoa\*[tiab] OR San Marino[tiab] OR Sao Tome[tiab] OR Senegal\*[tiab] OR Serbia\*[tiab] OR Seychelles[tiab] OR Sierra Leone\*[tiab] OR Singapore[tiab] OR Slovakia\*[tiab] OR Slovenia\*[tiab] OR Solomon[tiab] OR Solomon Island\*[tiab] OR Somalia\*[tiab] OR South [tiab] OR Spain[tiab] OR Sri Lanka[tiab] OR Sudan\*[tiab] OR Suriname\*[tiab] OR Swaziland\*[tiab] OR Swed\*[tiab] OR Switzerland[tiab] OR Syria\*[tiab] OR Taiwan[tiab] OR Tajik\*[tiab] OR Tanzania\*[tiab] OR Thai\*[tiab] OR third world countr\*[tiab] OR third world nation\*[tiab] OR Timor Leste[tiab] OR Timor\*[tiab] OR Tobago[tiab] OR Togo\*[tiab] OR Tonga\*[tiab] OR Trinidad\*[tiab] OR Tunisia\*[tiab] OR Turkey[tiab] OR Turkish[tiab] OR Turkmen\*[tiab] OR Turks[tiab] OR Tuvalu\*[tiab] OR Uganda\*[tiab] OR Ukrain\*[tiab] OR under developed countr\*[tiab] OR under developed nation\*[tiab] OR underdeveloped nation\*[tiab] OR United Kingdom[tiab] OR United States[tiab] OR Uruguay[tiab] OR Uzbeki\*[tiab] OR Vanuatu\*[tiab] OR Vatican[tiab] OR Venezuela\*[tiab] OR Viet nam\*[tiab] OR Vietnam\*[tiab] OR Vincent[tiab] OR West[tiab] OR West Bank[tiab] OR Yemen\*[tiab] OR Zambia\*[tiab] OR Zimbaww\*[tiab])

NOT

(“Animals” [MESH] NOT “Humans” [MESH])

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### Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

### Author Contributions

Conception and design: Vaughan, Rattani, Dewan, Park. Acquisition of data: Vaughan, Lopez Ramos, Amundson. Analysis and

interpretation of data: Vaughan, Lopez Ramos, Mekary, Amundson, Shah. Drafting the article: Vaughan, Lopez Ramos, Buch. Critically revising the article: Vaughan, Lopez Ramos, Buch, Mekary, Shah, Rattani, Dewan, Park. Reviewed submitted version of manuscript: Vaughan, Lopez Ramos, Buch, Mekary, Amundson, Shah, Rattani, Dewan. Approved the final version of the manuscript on behalf of all authors: Vaughan. Statistical analysis: Mekary. Administrative/technical/material support: Rattani, Dewan. Study supervision: Vaughan, Dewan, Park.

### Supplemental Information

#### Online-Only Content

Supplemental material is available with the online version of the article.

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