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Future directions for Epidemiology in Epilepsy

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Epidemiology is, among other things, the research branch of public health. Over 50 years ago, epidemiological studies began to provide us with a better understanding of the frequency, causes and natural history of epilepsy in the population [1, 2]. Epidemiology encompasses a powerful set of techniques for studying human health and illness. Over time, though, and across the world, different populations have had different arrays of health challenges and needs. This is an area where epidemiology can make a huge difference by identifying those needs and providing that information to political bodies charged with determining public health priorities and health care financing decisions. Further, the research of the last 10 to 15 years has brought to our attention the multitude of consequences that accompany epilepsy, even epilepsy of the relatively uncomplicated variety. We now understand that there is an essential relationship between epilepsy and a host of developmental, cognitive, behavioral, and psychiatric disorders. These consequences reflect that fact that epilepsy is a disorder of brain function, not just a disorder that produces seizures. People with epilepsy also have greatly increased mortality, some of it perhaps linked to the mechanisms of epilepsy itself. SUDEP (sudden unexplained death in epilepsy) is receiving increased attention and is the focus of several initiatives in the US and internationally. In addition to its public health applications in the population, epidemiology also provides the methodological framework for much clinical research and is relevant even in randomized trials. Today, epidemiological studies are being conducted in a new environment in which high quality neuroimaging and fast through-put genomic technologies have become routine tools in clinical diagnosis and therapeutics, and epilepsy is understood, not as a single, homogeneous disorder, but a multitude of different clinical syndromes and disease, each with its own cause(s), natural history, and treatment implications.

There are many exciting possibilities for epidemiology and many challenges for continuing to be a valuable part of the research armamentarium for epilepsy. In what follows, we will explore some of these themes.

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Causes of epilepsy

Much like cancer, epilepsy is many different disorders with many different causes [3]. To a certain extent, the epidemiology of epilepsy is a reflection of the epidemiology of different forms of neurological morbidity in the population. These sources of morbidity can themselves be the target of preventive efforts which, if successful, have the by product of primary prevention both for the initial morbidity and for the subsequent epilepsy. Even if prevention of the source of morbidity is not fully feasible, preventing the development of epilepsy or improved treatment of epilepsy secondary to that cause is a possibility. Two areas that may be models are neurocysticercosis and head trauma.

Neurocysticercosis (NCC)

NCC is seen in developing countries and regions where access to clean drinking water is often problematic. The actual risk of epilepsy associated with NCC is not entirely clear. Even though large proportions of people with epilepsy have NCC in certain countries, the prevalence of infection overall is quite high raising important questions about mechanisms involved in NCC and epilepsy and implications those may have for prevention and treatment. Several mechanisms have been implicated in NCC's propensity to cause seizures. These mechanistic explanations focus mostly on the site in the nervous system in which the parasitic larvae are located; on whether or not the larvae are alive, degenerating, or dead/calciified; and on the inflammatory and scarring processes associated with parasite death and degeneration. NCC is unique since it is the only known process where large numbers of otherwise asymptomatic persons are commonly infected with a seizure-causing agent. Properly designed studies of affected populations can be used to answer fundamental questions about the genesis and treatment of epilepsy secondary to a specific insult. Other reasons that support NCC as a suitable model to learn about human epilepsy secondary to an acquired insult include: (1) the high prevalence of NCC in endemic areas, potentially allowing investigators to evaluate large series of patients; (2) the defined localization of the NCC lesions; (3) the existence of symptomatic and asymptomatic NCC cases; (4) the overall good prognosis of patients with single degenerating lesions or a few intraparenchymal cysts; (5) the feasibility of intervening with specific antiparasitic drugs; (6) the chronic nature of residual brain calcifications; and (7) the presence of NCC in the United States and other industrialized countries, owing to increased travel and immigration. A sample of research topics that would be amenable to multicenter studies has been published elsewhere [4].

Head trauma

Post-traumatic epilepsy reflects a myriad environmental factors and social responses to them. Unlike NCC, it is not predominantly limited to the developing world but can be seen in affluent settings as well. Automobile and motorcycle accidents, equestrian accidents, sports injuries, and in the US over this past decade in particular, combat injuries are some of the more common causes of head trauma. This is one of those disorders in which primary prevention of head trauma should play a significant role, but unfortunately this is not always the case.

Randomized trials have failed to demonstrate a protective effect of immediate treatment in preventing the later development of epilepsy [5]. Consequently, a better understanding of the risk factors for developing epilepsy after head trauma and what they contribute to identifying underlying mechanisms is still essential. Not surprisingly, the risk of epilepsy is greater after more severe trauma [6, 7]. Factors that are in general associated with an increased risk of epilepsy in the population are associated with an increased risk for epilepsy following head trauma. These include a history of depression [7] and a family history of epilepsy [6]. Whether this represents the additive effects of two independent risk factors or

whether there is an underlying mechanism that amplifies the effects of one in the presence of the other is unknown. Such statistical associations provide fertile areas for more mechanistic-based research.

The nature of head trauma is changing as well. At this time in the US, we have thousands of individuals who have suffered concussive, non-penetrating brain injuries in recent wars. Careful monitoring of these individuals may lead to helpful information about the development of epilepsy following such injuries as well as lead to preventive therapies in the future.

Co-morbid conditions in epilepsy

Epidemiological studies have been enormously valuable in identifying the unexpectedly high frequency of a variety of behavioral, cognitive, and psychiatric disorders and also the increased risk of sudden death seen in people with epilepsy [8, 9]. Some have pointed to the increased risk preceding the onset of epilepsy, therefore suggesting shared mechanisms may unite the different sets of disorders rather than epilepsy necessarily causing or somehow leading to the others [10-13]. This has been termed the “bi-directional” association by Kanner [14]. This awareness has led to significant discoveries in the laboratory and in clinical research that have improved the understanding of the role of serotonin and how epilepsy, SUDEP and depression may be mechanistically linked to each other [15, 16]. Studies of individuals with newly diagnosed epilepsy are demonstrating subtle but important relative deficits in various cognitive domains that can be measured at onset and before treatment is initiated [17, 18]. Increasingly, terms such as “epilepsy spectrum disorders” are being used in recognition of the fact that there is likely no such thing as “just epilepsy” and that all epilepsy, no matter whether previously characterized as “benign,” may be accompanied by other cognitive, behavioral, and psychiatric disorders. Many speculate that these disorders may ultimately have a greater impact on quality of life and life success than the epilepsy itself which often is well controlled and frequently resolves in time.

Two studies of unselected populations exploring somatic comorbidity of epilepsy allow estimation of prevalence ratios (PR). These are the UK General Practice Research Database (GPRD) study [19] and a Canadian study using data from two large national health surveys, the NPHS and the CHS [20]. The UK study used general practitioner recorded diagnoses on computerized medical records collected prospectively over a 5 year period in two age groups (16-64 and >64 years). The Canadian study relied on field interviews to ascertain up to 20 pre-specified medical conditions in the community. Both, the UK and the Canadian studies showed a higher prevalence of somatic conditions in people with epilepsy than in the general population, with a 2-5-fold increase of common chronic medical conditions. Conditions with particularly high prevalence in the Canadian study were allergies, back problems, arthritis, migraine, high blood pressure and asthma. In the UK study the most common identified comorbid conditions with epilepsy were fractures, asthma, stroke, heart disease, arthritis, diabetes and migraine. A methodological caution is that these types of studies are based on data collected for clinical purposes. It is entirely possible that patients under medical surveillance for one condition are more likely to have other conditions detected. Thus some or even much of these findings may simply be due to detection bias.

Recognizing that these associations with co-morbidities exist is essential for a number of reasons. From a treatment perspective, recognizing co-morbidities whose manifestations may be mistaken for seizures (migraine, behavioral automatisms, and movement disorders) can improve treatment of both the seizures as well as the co-morbid condition. At the same time, certain co-morbidities such as migraine may be effectively treated with the same drugs often used to control seizures. The reverse may happen and lead to a limitation on

acceptable drugs for a given patients. From a patient counselling perspective, the information can be extremely useful in determining the need for additional care and services and preparing patients to be aware of the potential challenges they may face.

A part from co-morbidities as discussed above, seizures themselves can have significant impact on people. This is perhaps best appreciated in terms of the risk of injury and sudden death. One of the most informative studies assessing the risk of accidents in PWE was published by Beghi and colleagues [21]. The study involved 951 referral patients with idiopathic, cryptogenic, or remote symptomatic epilepsy, followed for 17,484 person-months along with matched controls (relatives or friends). The cumulative probability of accidents in cases with epilepsy was 17% and 27% by 12 and 24 months, compared to 12% and 17% in controls ($P < 0.0001$). The authors concluded that most epileptic patients suffer from trivial injuries with a higher incidence than controls. A population based study in Canada explored the prevalence of injuries obtained through data from the CHS ($n = 130,882$) [22]. Twelve-month weighted prevalence of injuries serious enough to limit normal activities was calculated for people with epilepsy and for the general population. The prevalence of injuries was not different in PWE (14.9%) than in the general population (13.3%) (RR: 1.1, 95% CI: 0.90–1.3). Among individuals reporting injuries, the only significant differences were a lower frequency of sports-related injuries in PWE (RR: 0.7, 95% CI: 0.4–0.9), and a three times higher frequency of hospitalization following injuries in PWE (RR: 3.0, 95% CI: 1.3–4.7). The higher rate of injuries in PWE could reflect that hospitalizations are related to seizures and potentially comorbidities, and not injuries alone, or a more cautious attitude of clinicians towards injuries in PWE. Recently a population based study reported that the incidence of injuries was higher in patients with epilepsy than the general population [23]. The one-year incidence of one or more injuries was 20.6% among person with epilepsy and 16.1% among those without epilepsy ($p < 0.001$).

Both the US and Canada and other countries as well have indigenous populations that live in relative isolation and with relatively limited healthcare resources. Canada has large and growing First Nations, Inuit, and Métis communities. In some Canadian provinces such as Manitoba and Saskatchewan, these comprise as much as 17% and 12%, respectively. A large percentage of these populations live on reservations and usually are not targeted in large surveys or other epidemiological studies in Canada. Based on the clinical experience of one of the authors (Tellez) in Saskatoon, Saskatchewan, there is a perception that First Nations, Inuit, and Métis communities may have a higher frequency of epilepsy than the rest of the population in Canada. There is also concern that some types of epilepsy could be more frequent and severe such as posttraumatic epilepsy and some genetic syndromes of generalised epilepsy. Further there appears to be an underutilization of surgery with a lack of referral of candidates for epilepsy surgery. Finally, there are issues concerning compliance with Western medications. These findings have never been formally demonstrated and published, as yet, remain as impressions. In the US, however, Parko and Thurman found a prevalence of epilepsy among the Navajo Nation that clearly exceeded any estimates for the US overall suggesting a higher burden of epilepsy in this population [24]. Given the growth in these populations and given the concern of a potentially higher prevalence of epilepsy and less access to adequate care, there is a particular need for reliable epidemiological data concerning the frequency and causes in these indigenous populations.

Epidemiological estimates are crucial in health care planning and in setting national health care priorities and policies. This is particularly appreciated in settings with national health care services such as Ireland and Canada. With the increasing recognition of the array of other disorders that accompany epilepsy, this can bring together different fields such as epilepsy and disability to tackle a common problem. The situation in Ireland offers a model for the role of and problems with epidemiological data for these purposes.

The burgeoning field of disability epidemiology presents exciting opportunities for epilepsy research. Disability epidemiology aims to ‘promote improved health status among people with disabilities by: quantifying the prevalence of disability in given populations; recognizing factors that decrease quality of life among those with disabilities and; designing interventions to address these factors’ [26]. Disability is a multifaceted construct with varying causes and outcomes, and from an epidemiological perspective may be examined both as a dependent variable (e.g. examining risk factors for disability) and as an independent variable (e.g. assessing the likely development of secondary conditions). These complex relationships are ideally suited to epidemiological exploration, of which surveillance methodologies are key investigative tools.

Surveillance is defined as the ongoing, systematic collection, analysis and interpretation of outcome data for use in planning, implementing and evaluating public health practice [27]. Population-based omnibus surveys are a common method of surveillance and may be considered to be theoretically more reflective of epilepsy in the general population and less representative of those in receipt of specialist epilepsy services, a population who comprise the participants of many epidemiological studies [28]. Internationally, the use of population-based omnibus surveys as a methodology to track the burden of epilepsy is somewhat sporadic, albeit gaining momentum. A review of 195 health interview surveys filed with the European Commission's Health Interview & Health Examination database (available at <http://www.euhsid.org/database.html>) identified 131 surveys that included an item on long-standing or chronic conditions, of which 30 surveys requested information on epilepsy [29]. Data were obtained on epilepsy prevalence for 15 of these surveys, with estimates ranging 2 per 1,000 to 17 per 1,000. The lower estimate was generated from an Irish sample responding to a disability module of the 2002 European Commission's Labour Force Survey which gathers comparable data across European countries. The prevalence estimate is acknowledged as a likely underestimate given the specific wording of the epilepsy item (personal communication, B. Denorre, European Commission, 17 January 2007). A more robust item, asking if ‘your doctor has ever diagnosed you with epilepsy’ reported a considerably higher prevalence estimate, 10 per 1,000, for Irish respondents when utilised in the 2007 Labour Force Survey [30]. The disparity between these findings highlights the need to interpret surveillance survey findings in context. In the absence of interpretation, a fivefold increase in self-reported prevalence from Irish respondents on the Labour Force Survey between 2002 and 2007 would give rise for concern.

While the major function of public health surveillance systems was traditionally to monitor the incidence and prevalence of disease, overtime surveillance has evolved beyond mere disease reporting to include an exploration of health phenomena such as behavioural risks, co-morbid conditions and health disparities [31]. In the USA, the Centre for Disease Control and Prevention (CDC) has supported the inclusion of epilepsy in large population-based health surveillance surveys by recommending that state health departments assess and monitor the burden of epilepsy using surveillance systems to determine prevalence, and most specifically ‘to add questions to the state BRFSS’ [32]. BRFSS, the Behavioral Risk Factor Surveillance System, is a state-based system of health surveys and is identified as the world's largest, ongoing telephone health survey system. Case ascertainment of epilepsy is typically assessed using the item ‘Have you ever been told by a doctor that you have a seizure disorder or epilepsy?’ To date, 19 states have utilized this methodology to determine prevalence estimates of epilepsy [33]. The true potential of these surveillance systems, however, is revealed where states have included additional items concerning seizure frequency, use of health related services and the impact of epilepsy on quality of life [34]. Work continues on the refinement and expansion of these items (personal communication, David Grant, UCLA Center for Health Policy Research, 8 September 2010). In addition to

the BRFSS, the National Health Interview Survey, the Health Styles Survey and California Health Interview Survey have been similarly employed in the US.

Undoubtedly there are limitations to the use of population-based omnibus surveys for epidemiological purposes. Certain groups may be automatically excluded from sampling frames, such as those who live in communal settings [35] or those who live in private households but are not contactable by phone. There may be a systematic memory bias for those who had epilepsy as a child but who are inactive cases throughout adulthood. For those who are included, case ascertainment of true cases of epilepsy is difficult to determine. Misdiagnosis rates among non-specialists are high and neurological validation is not undertaken [36]. In fact, details of epilepsy type are rarely included [28]. Despite these challenges, data from population-based surveillance surveys provide opportunities to focus beyond traditional measures of incidence and prevalence towards greater understanding of the impact of disability.

Population based surveillance studies targeting specific disability groups avoid a bias of many disability studies whereby small clinically-sourced samples are likely to over represent those with more severe levels of disability. The Metropolitan Atlanta Developmental Disabilities Study (MADDS), for example, sought to develop population-based surveillance of ten year old children for each of five developmental disabilities; epilepsy, intellectual disability, cerebral palsy, hearing impairment and vision impairment. Over one third of those with epilepsy reported two or more developmental disabilities. In addition to determining prevalence estimates of epilepsy [37] the study provided opportunities, through data linkage, to examine mortality trends among those with epilepsy at ten year follow up [38]. Data linkage to routinely collected mortality records addresses some of the inherent weaknesses of relying on death certificate information alone, where chronic conditions are known to be underreported as an immediate or antecedent cause of death [39]. The MADDS findings revealed that the mortality ratio for those with epilepsy and additional developmental disabilities (13.2 [7.6, 21.5]) was considerably higher than for those with isolated epilepsy (1.5 [0.3, 4.3]). The study illustrates the cumulative impact of co-morbid disability and the limitations of studies that fail to consider co-morbidities among participants with developmental disabilities.

Disability-specific administrative records have been similarly employed to examine mortality trends among those with developmental disabilities and epilepsy. Researchers in California linked annual evaluation reviews of persons receiving services from the Californian Department of Developmental Services (DDS) with mortality records from the Department of Health Services [40]. The challenge of defining a population as heterogeneous as those with developmental disabilities is illustrated by the authors' observation that over two thirds of the full sample (n=106,193) were classified under the category 'other' and were deemed by the authors to have either mild or moderate intellectual disabilities. Those with more severe or profound levels of disability were excluded by the sampling criteria on the basis that they would introduce a confounding effect due to their impaired mobility and severe cognitive deficits. Notwithstanding these definitional issues, those participants who had epilepsy in addition to a developmental disability, defined as 'traumatic brain injury, cerebral palsy, autism, chromosomal anomalies or other', reported elevated mortality rates due to seizures (SMR 53.1, 95% CI 28.0-101.0) and convulsions (SMR 25.2, 95% CI 11.7-54.2). The authors acknowledge that it is not surprising that people with epilepsy are at increased risk of death due to seizures or convulsions but note that the finding had not been widely reported previously. The authors also acknowledge the likelihood that a proportion of these deaths were unobserved and are potentially attributable to SUDEP.

These mortality studies reveal some key challenges for epidemiology research within the disability field, most especially regarding definitions. Such definitional issues abound in disability research and are of particular concern regarding the population of people with intellectual disabilities. Recent proposals for the development of population-based surveillance systems specifically for this population [31] aim to increase the representation of those with intellectual disabilities who either by choice or circumstances do not avail themselves of services and are deemed a ‘hidden population’ [41, 42]. This population is of particular relevance for epidemiologists in the field of epilepsy given that they report considerably higher prevalence estimates of epilepsy than the general population and yet are typically excluded from traditional surveillance systems [35, 43].

The growing use of population-based surveillance is apparent not only in the field of epilepsy but also in the broader disability field. In situations where clinically-sourced data are problematic for epidemiological purposes, population-based surveillance systems may provide robust evidence on which to develop health care and public policy initiatives. Notably, health services research (HSR), hailed as the ‘new frontier in disability epidemiology’ [26] encourages the use of under utilised secondary data sources to explore the relationship among a myriad of variables including service costs, health service utilization and population health [31, 44]. The challenge for epidemiologists is to determine how best to utilize these non-clinical sourced data opportunities to best effect while retaining scientific rigor.

Future Challenges for Epidemiology

Clearly the information needs filled by epidemiological studies vary from population to population depending on the issues and questions surrounding epilepsy and its care in each setting. Over the last several years, there have been technological explosions in electrophysiological techniques, neuroimaging, and molecular genetics and genetic testing. At the same time, the range of available pharmacological and nonpharmacological treatments including use of surgery has greatly expanded. Thus as epileptology has become much more sophisticated, it would behove epidemiological studies to follow suit in order to provide information relevant to current concepts in diagnosis, treatment and management. For example, a recent ILAE report recommended abandoning the antiquated concepts and old approach to grouping causes of epilepsy (idiopathic, symptomatic, and cryptogenic) and ultimately replacing them with terms and concepts based on causes and mechanisms [45]. This recommendation acknowledges the extraordinary developments in diagnostic capabilities of the last several years. Learning how to incorporate information from these technologies remains a challenge for large-scale population-based epidemiological studies. A particular challenge is to find a way to do this such that there can still be meaningful translation and comparability across settings with varying levels of scientific and medical sophistication (e.g. Europe and sub-Saharan Africa). Certainly more clinic-based studies are doing this already.

Neuroimaging

In the earlier epidemiological studies, very little if any neuroimaging was done; it was not yet available. With the expanded use of neuroimaging in the diagnostic evaluation of most patients with seizures and the improvement in imaging technology, we are getting a clearer understanding of the role of structural lesions in epilepsy. For example, one community-based study with 85% MRI coverage was able to estimate the frequency of brain lesions in childhood-onset epilepsy, the rate of surgically resectable epilepsy that might be expected in the population, and also an estimate of the frequency of epilepsy center referrals in a population with good tertiary epilepsy center access [46]. A national estimate for the UK was also provided in one study [47]. Reliable information about the frequency of potential

surgical patients in populations or of medically refractory patients regardless of surgical eligibility [48] is necessary in order to justify the allocation of resources for tertiary epilepsy care centers.

Genetics

Earlier studies demonstrating familial patterns of occurrence consistent with dominant or recessive transmission used to be the main evidence for the roles of genetics in epilepsy. The development of the electro-clinical syndrome, a specific epilepsy diagnosis, provided homogenous phenotypes as targets for genetic investigation [3]. In recent years, major advances in identification of genetic factors such as *SLC2A1* [49], *STXBP1* [50], *SCN1A* [51], and so many others are explaining bit by bit some of the most devastating forms of epilepsy, often of very early onset which were previously called “symptomatic generalized” epilepsies. In some cases, there are substantial treatment implications. Individually, these are rare disorders; however, as a group, they account for an important minority of typically devastating conditions often associated with life-long disabilities. How will epidemiology come to grip with these advances and the ones that continue to arrive daily?

Finally and largely related to the growing presence and value of genetic technologies, the recognition that there are specific forms of epilepsy with specific presentations, causes, implications for treatment and genetic counselling, and prognosis, is gaining greater recognition and understanding, often bolstered by the genetic findings. While this approach is particularly relevant in pediatric settings, it is not irrelevant to adult-onset patients. Perhaps most importantly, some of the most intractable forms of epilepsy begin in childhood. Those children later become prevalent cases of epilepsy in adults. There are currently no estimates of the proportion of adult patients with childhood-onset epilepsy whose epilepsy might now be better treated if it were properly diagnosed or of how adult epilepsy may change as a result of improvement in pediatric epilepsy care.

Epidemiology has been a major tool in the public health efforts to identify the frequency, causes, and overall prognosis of epilepsy as well as the consequences associated with it. It has made contributions to societal policies regarding driving and has been central in developing practice guidelines for selected clinical situations. There are still many areas and new ones developing each year to which epidemiology can provide an important resource in the research for tackling the problem of epilepsy and its associated conditions.

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Biography

Tellez-Zentano:

The first time that I became interested in epidemiology of epilepsy was with the project developed by me and Dr. S. Wiebe to explore the prevalence of epilepsy in Canada in 2004. This article described for the first time the overall prevalence of epilepsy in Canada and its provinces. The estimates were similar to other developed countries, but the article provides an original description in Canada and very useful piece of information to identify needs and provide information to political bodies in order to perform health care financing decisions. I feel that the main contributions that I have performed in the field are some landmark studies describing the prevalence of epilepsy in Canada and some relevant epidemiological descriptions describing important aspects of somatic and psychiatric comorbidity in people with epilepsy. These studies have produced significant interest in the potential

multimorbidity pattern of epilepsy and its implications for the diagnosis and treatment. In the future I would like to continue exploring epidemiological aspects of epilepsy in Canadian population, such as incidence and prevalence of epilepsy in protected groups, between provinces of Canada and epidemiological trends over the years. The multimorbidity pattern of epilepsy also interests me. The observed multimorbidity pattern reported in epidemiological studies based on large databases could be only a potential detection bias. Therefore subsequent studies are needed to demonstrate common etiological pathophysiological pathways between epilepsy and some of the potential reported comorbidities, as has been demonstrated for some well recognized comorbidities of epilepsy like stroke and migraine.

C. Lineham:

My interest in the field of epilepsy stemmed from an approach by Brainwave, the Irish Epilepsy Association, for advice from the Centre for Disability Studies, University College Dublin where I was employed as a Senior Researcher, for a suitable methodology to determine the prevalence of epilepsy in Ireland. I had previously worked on some epidemiological studies in the field of autism spectrum disorders and was acutely aware how important basic prevalence figures, while not an empirical breakthrough, were for those charged with determining policy and service delivery in Ireland. I read with interest a study by Öun et al. [25] which aimed to determine the prevalence of epilepsy in Estonia. The paper reported a 5.3 per 1,000 prevalence of active epilepsy, an estimate within predicted ranges. It was not, however, the derived prevalence estimate that was of specific interest, but more the challenges noted by the researchers when attempting to gather valid empirical data for prevalence purposes. I then looked further afield, to other European countries, then onward to Africa, Australasia, South America and North America. A total of 139 studies were reviewed, each illustrating the impact of local challenges on the final determination of prevalence. Throughout Europe alone numerous studies have been conducted, embracing a variety of methodologies including case ascertainment via clinical registers, analysis of anti-epilepsy prescription databases, and most recently, self-report surveys. The opportunity existed in Ireland to conduct a nationwide study, the first such nationwide study in Europe, using a variety of these methods.

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