

## Epilepsy Mortality Trends in Cuba compared to England and Wales: 1987-2010

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Word count: 1827

References: 17

Tables: 1, 1 eTables

Figures: 1, 2 eFigures

Abstract: 187

Short Abstract: 97

There are limited epilepsy mortality data from developing countries and in particular Latin America. We examined national epilepsy mortality data from Cuba and contrasted them with comparable data from England and Wales. National epilepsy mortality data for Cuba between the years 1987 to 2010 was obtained from the Medical Records and Health Statistics Bureau of the Cuban Public Health Ministry ([www.sld.cu/sitios/dne/](http://www.sld.cu/sitios/dne/)) with the corresponding mortality data from England and Wales obtained from the UK Office of National Statistics ([www.ons.gov.uk](http://www.ons.gov.uk)). Indirect standardisation with calculation of a standardised mortality ratio (SMR) were used to compare trends.

The overall trend was of a slight decrease in mortality rates over the 23 years in Cuba, with higher mortality rates primarily occurring in young people. Annual age-adjusted rates were consistently lower in Cuba than those seen in England & Wales with the SMR ranging from 0.35 (95% CI: 0.30 to 0.48) in 2007 to 1.00 (95% CI: 0.85 to 1.15) in 1994.

Cuban epilepsy mortality rates are consistently lower than those of England and Wales. Reasons for this disparity in mortality rates are not immediately apparent but are likely to be multi-factorial.

## Introduction

Epilepsy is the most common serious neurological disorder affecting over 50 million people worldwide [1] and is associated with significant morbidity and mortality. The incidence of epilepsy is estimated to be 50 per 100000 per person years but is considered to be significantly higher in Latin America, in part due to different aetiological factors, particularly the high prevalence of toxoplasmosis and other infective aetiologies [2,3]. People with epilepsy have a 2-3-fold increased risk of premature mortality compared to the general population, a finding which has replicated in multiple population studies in Europe and the US [4]. However, there is little mortality data from the developing countries and in particular Latin America. There has been no published epilepsy mortality data from Cuba apart from one recent small cohort study in people with drug resistant temporal lobe epilepsy<sup>5</sup>. We have analysed national epilepsy mortality data, comparing it with mortality data from England & Wales during the same time period.

## Methods

National mortality data by all types of epilepsy reported as the primary cause of death (first line) on the death certificate, as coded 345 (ICD9) or G40-G41 (ICD10) between 1987 to 2010 were used with a total of 2,518 and 21,655 deaths from Cuba and England and Wales respectively. Both countries used the ICD -9 classification until the year 2000 and the ICD-10 classification thereafter.

Mortality data for Cuba between the years 1987 to 2010 was obtained from the Medical Records and Health Statistics Bureau of the Cuban Public Health Ministry ([www.sld.cu/sitios/dne/](http://www.sld.cu/sitios/dne/)) with the corresponding mortality data from England and Wales obtained from the UK Office of National Statistics ([www.ons.gov.uk](http://www.ons.gov.uk)). The Cuban database is an automated public health statistical information system established in 1987, which are subject to periodic evaluations, both internally (by the National Bureau of Statistics and Information) and internationally (by the WHO). In Cuba,

(as in England & Wales), death certificates for each patient are completed by medical doctors who have received specific training in order to do so. In addition, in Cuba, completed death certificates are routinely checked by technicians with specific qualifications in health statistics and management of ICD coding. The ONS database is similarly subject to regular internal validation. Given the relatively small numbers of epilepsy deaths in Cuba per year, examination of mortality trends for specific epilepsy sub-types such as focal onset epilepsy, generalised epilepsy or status epilepticus was not deemed feasible. During the 23-year observation period, the population of Cuba increased from 10,356,301 to 11,242,161 while the population in England & Wales increased from 50,123,000 to 55,692,300, representing increases of 9% and 11% respectively. Crude mortality rates were calculated per 100,000-person year. Standardised mortality ratios (SMRs) with 95% confidence intervals were calculated using the population of England and Wales in 2010 as the standard population with calculation of mortality rates for 5-year age groups up to 85+ years. SAS 9.3 was used for data analysis and Microsoft Excel was used to produce the tables and figures.

## **Results**

The annual number of deaths in Cuba attributable to epilepsy ranged from 74 to 164 with a crude mortality rate of 0.71 to 1.50 per 100,000 persons-years, while the number of epilepsy deaths in England and Wales ranged from 743 to 1075 with a crude mortality rate of 1.45 to 2.03 per 100,000 persons-years (Table 1). In Cuba, age-adjusted mortality rates ranged from a low of 0.39 per 100,000 person years (95% confidence intervals CI: 0.30 to 0.48) to a peak of 1.00 per 100,000 person years (95% CI: 0.85 to 1.15) in 1994. In general, the risk of epilepsy mortality was lower in Cuba compared with England & Wales. The overall trend was of a slight decrease in mortality rates over the 23 years. In Cuba epilepsy mortality predominantly occurred in the young with the mean age of death steadily increasing during the 23 years of observation from 36 years (95% CI: 32.2 to 39.1) to 48 years (95% CI: 44.3 to 52.6) (eFigure 1). Mortality was significantly consistently higher in males across three broad age groups (0-18 years, chi-squared  $p < 0.05$ ; 19-

59 years, chi-squared  $p < 0.001$ ; 60+ years, chi-squared  $p < 0.001$ ) (eTable 1) and higher than that seen in England & Wales where figures were close to parity.

Comparing epilepsy mortality in Cuba with England & Wales, annual age-adjusted rates were consistently lower in Cuba than those seen in England & Wales with the SMR ranging from 0.39 (95% CI: 0.30 to 0.48) (60% lower mortality rate) in 2007 to 1.00 (95% CI: 0.85 to 1.15) in 1994 (Figure 1). Indirect SMRs by gender are shown in eFigure 2 (males) and eFigure 3 (females).

## **Discussion**

This is the first report examining national epilepsy mortality trends over 23 years in Cuba with a comparison with the corresponding epilepsy mortality data from England and Wales during the same period of observation. The main observation is that mortality rates from epilepsy are consistently lower in Cuba compared to England and Wales.

The only previous study which examined epilepsy mortality in Cuba was in a cohort of 117 patients identified with refractory temporal lobe epilepsy attending a tertiary referral centre in Havana (National Institute of Neurology), and who were followed up over an 8-year period. During that time, six people died (5.1%), three of who committed suicide, one of which was a result of sudden unexplained death in epilepsy (SUDEP) following intentional anti-epileptic drug (AED) non-adherence. The other three people died following status epilepticus (1), pulmonary thromboembolism (1) and a traffic accident (1). The only factor found to be predictive of mortality on multivariate analysis was the presence of a prodromal depressive disorder ( $p < 0.0001$ ) [5].

Any analysis of mortality trends needs to be coupled with incidence and prevalence data. It is generally assumed that the incidence (and prevalence) of epilepsy is higher in Latin America, in large part to endemic infections such as toxoplasmosis, which predispose to the development of epilepsy [3,6]. One single study of AED prescriptions in children however suggests that the

prevalence of epilepsy (at least in children) may be lower in Cuba than that of other Latin American countries. In this observational study, all prescriptions for AEDs to children in the central province of Camagüey were identified. 923 children receiving 977 AEDs giving an estimated prevalence of 5.18 per 1000 children [7], which is comparable to prevalence figures seen in Europe and the US [4], unlike other Latin American countries where the prevalence of epilepsy is estimated to be higher at 8.7 to 12.4 per 1000 [8]. One reason for this may be that toxoplasmosis may not be a significant contributor to the aetiology of epilepsy in Cuba. In a retrospective study of all hospital admissions to the National Institute of Neurology in Havana with epilepsy over a 25-year period (1974-1989), only five patients having neurocysticercosis were identified, constituting 0.01% of all epilepsy admissions. Moreover, of these five patients with neurocysticercosis, three were foreigners, with evidence that the two Cubans had acquired neurocysticercosis elsewhere [9].

The consistently lower mortality epilepsy rate in Cuba compared to those in England & Wales requires consideration. Even in the period of highest mortality (1992-4), mortality figures were still lower than those seen in England & Wales and significantly lower thereafter (Figure 1). Reasons for this disparity are not immediately apparent.

One of the major limitations of this study, and indeed any study of its type, is the validity in comparing mortality rates from different countries (using different datasets) and indeed with the method of indirect standardisation. Whilst it can be reasonably assumed that national mortality rates are internally consistent, thereby allowing for valid examination of national mortality trends, the methods of deriving these data may vary across countries, hence potentially introducing some bias into the comparative analysis [10].

This may be particularly the case comparing mortality rates from countries of different economic resources. However, the fact that both countries employed the same coding system (ICD-9 pre 2000, ICD-10 post 2000) facilitates comparisons between the two databases and provides confidence that there are no large differences in the source data for our analysis.

Whilst it is well recognised that the use of death certificates to estimate epilepsy mortality rates typically leads to a significant under-estimation of the true mortality rate attributable to epilepsy

causes [11], there is no reason to assume that death certificate classifications in Cuba would be less (or more) accurate than those in the UK. Moreover, another limitation, which affects all mortality studies in epilepsy (unless under direct supervision), is that the recorded mortality rate due to epilepsy is likely to represent only a proportion of all deaths attributable to epilepsy. This is due to the fact that epilepsy is typically only recorded on the death certificate when epilepsy is judged to be the primary cause of death (such as in SUDEP or status epilepticus) when in fact the majority of deaths in people with epilepsy occur not as a direct result of epilepsy but rather as a result of epilepsy-related co-morbidities [12] [17]. Nevertheless, such deficiencies should not bias interpretation of secular mortality trends attributable to epilepsy unless there is reason to suspect that the degree of inaccuracy of recording epilepsy as the primary cause of death on death certificates (in either country) has changed over time [12]. In addition, the quality of data documented on death certificates in both Cuba and the United Kingdom (England and Wales) is considered high as per WHO criteria [13].

One potential explanation is the confounding effect of Sudden Unexpected Death in Epilepsy (SUDEP). Prior to the publication of the SENTINEL audit in 2002 in the UK, which highlighted the prevalence of SUDEP, many cases of SUDEP were recorded on the death certificate as being attributable to non-epilepsy causes [14]. In the scenario where cases of SUDEP in Cuba were consistently recorded as attributable to non-epilepsy causes of death, this would lead to a lower estimation than the true epilepsy mortality rate and therefore contribute to the difference in mortality rates between the two countries. This however is unlikely to be the complete explanation, particularly as it would not explain the disparity prior to the publication of the SENTINEL audit and the increased national awareness of SUDEP.

Another potential hypothesis to explain the disparity between the mortality rates between Cuba and the UK may relate to differences between the two health care services. Whilst it is undoubtedly true that there is a significantly greater availability and numbers of anti-epileptic drugs in the UK, this does not forcibly translate into better care. Moreover, according to World Health Organisation (WHO) figures, Cuba has the highest ratio of doctors to patients in the world (7.579



doctors per 1000 population 2014 figures) compared to only 2.806 doctors per 1000 population in the UK (2015 figures) [15] which may be a more protective factor. Another possibility may lie in differences in patients' attitudes between the two countries, in that people with epilepsy in Cuba may have better AED-adherence than people in England & Wales, particularly as AED non-adherence has been shown to result in a 3-fold increased mortality rate [16]. A final possibility is that people with epilepsy in England & Wales may have more co-morbidities than people with epilepsy in Cuba leading to a higher mortality rate [17].

In conclusion this study demonstrates, despite a transient rise in epilepsy mortality rates in Cuba in the early 1990s, that Cuban epilepsy mortality rate is consistently lower than that of England and Wales. Reasons for this disparity in mortality rates is not immediately apparent but are likely to be multi-factorial. This merits further study.

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.

AN has received a speaking honorarium from Eisai Ltd. None of the other authors have any conflicts of interest to declare.

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