VALUE IN HEALTH ▮ (2018) ▮▮▮–▮▮▮

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# The Problem of Rarity: Estimation of Prevalence in Rare Disease

*Stéphane Auvin, MD, PhD*[1,*], *John Irwin, MSc*[2], *Paul Abi-Aad, MSc*[3], *Alysia Battersby, PhD*[3]

[1]*Service de Neurologie Pédiatrique, Université Paris Diderot, Paris, France;* [2]*Zogenix International Ltd., Maidenhead, Berkshire, UK;* [3]*Wickenstones, Oxfordshire, UK*

ABSTRACT

**Background:** From a disease's first description to its wider recognition, factors such as changes over time in diagnostic criteria, available therapies, and subsequent mortality rates may influence diagnosed prevalence of rare diseases. **Objectives:** To propose a novel methodology for estimating the true prevalence of rare diseases using current incidence adjusted to changing diagnostic practice over time. This article focuses on rare diseases whose diagnosis may have changed over time, and raises the hypothesis that prevalence calculated from current incidence may be higher than diagnosed prevalence, which may lag behind the current disease definition and diagnostic methods. A rare epileptic encephalopathy, Dravet syndrome (DS), is explored as an illustrative example. **Methods:** A targeted literature review was performed for DS to identify all reported incidence, prevalence, and mortality and depict how diagnostic practice has evolved over time. A conceptual model was developed to calculate prevalence derived from current incidence figures alone (incidence-derived prevalence) or incidence adjusted with factors that cause a diagnostic drag (diagnostic awareness–adjusted prevalence). **Results:** We identified sufficient publications of incidence and prevalence to test the conceptual model. For pediatric patients with DS, diagnosed prevalence in the field (as reported in current literature) matches incidence-derived prevalence, whereas for adult patients, it is overestimated by incidence-derived prevalence, but not by diagnostic awareness–adjusted prevalence. **Conclusions:** Care should be taken with current incidence-derived prevalence figures to not overstate the prevalence in rare diseases, as methodological challenges in counting small populations, coupled with advances in rare disease discovery, may cause discrepancies.

*Keywords:* Dravet syndrome, epidemiology, incidence, prevalence, rare disease.



## Introduction

Individual rare diseases affect less than 5 to 7 individuals in 10,000, but collectively affect approximately 6% to 8% of the global population. Historically, research in rare diseases has been hampered by a number of issues, ranging from the lack of an adequate understanding of the pathophysiology and natural history to the lack of incentives to fund the development of orphan drugs for small populations [1].

Regulatory frameworks, such as the US Orphan Drug Act (1983) and the European Union (EU) Regulation 141/2000 on orphan medicinal products (2000), have successfully raised awareness of rare diseases and encouraged research and development [2,3]. Regulators, such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), are responsible for the determination of orphan drug status and this, together with national-level reimbursement pathways based on rarity, is contingent on accurate estimates of disease prevalence. Drugs qualify for orphan status if they are intended to treat diseases affecting 5 per 10,000 people (EMA) or populations smaller than 200,000 in the United States (FDA) [4,5].

In addition to establishing the regulatory framework for marketing authorization, understanding the true number of individuals with a rare disease is critical to many steps of an orphan drug's life cycle, from clinical development (by, e.g., establishing ability to power clinical trials appropriately and the need for multicountry, multicenter involvement) to reimbursement negotiations (which often focus on the budget impact of the orphan drug).

Establishing the *true prevalence* (proportion of diseased individuals [whether diagnosed or not] in a population at a given time) of a rare disease is particularly challenging because epidemiological reports are often scarce, may not be standardized or are difficult to combine [6], may lack firmly established and specific diagnostic criteria [7–9], and may be biased depending on the geographical area studied [10,11]. There are also methodological challenges specific to measuring small populations [12]. In the absence of contemporary, large-scale population-based

Summary findings from parts of this work were presented in a poster (presentation code PHP310) at the International Society for Pharmacoeconomics and Outcomes Research 20th Annual European Congress, November 4–8, 2017.

* *Address correspondence to:* Stéphane Auvin, Service de Neurologie Pédiatrique, Université Paris Diderot, CHU Robert Debré, 48 Boulevard Serurier, Paris 75019, France.

E-mail: stephane.auvin@aphp.fr.

1098-3015$36.00 – see front matter 

https://doi.org/10.1016/j.jval.2018.03.002

prevalence studies, one method of estimating true prevalence is to extrapolate from current incidence data (the incidence of a disease is an epidemiological measure of the rate of new occurrence). Nevertheless, because diagnostic practice takes time to catch up with up-to-date diagnoses and therapies, current incidence-derived prevalence may overestimate the *diagnosed prevalence* in the field (the estimate of the prevalence that can be obtained at one specific point in time with the available diagnostic methods). Thus, particularly for a rare disease, the chronology of epidemiological data should also be taken into account because it often takes longer to transition from an initial characterization to a generally accepted condition with familiarity in the field.

To explore this discord, the chronology of epidemiological data and diagnostic practices for an illustrative rare disease, Dravet syndrome (DS), is reviewed. DS was identified and defined within the last 40 to 50 years. Although its diagnosis has evolved with advances in research and diagnostic practice, the disease remains difficult to treat.

DS is a rare developmental and epileptic encephalopathy caused almost invariably by de novo genetic mutations [13]. DS typically presents in the first year of life with febrile and afebrile, generalized clonic or hemiclonic epileptic seizures [14]. Subsequently, multiple seizure types develop, including myoclonic, focal, and atypical absences, frequently prolonged and refractory to antiepileptic drug treatment. Developmental and cognitive slowing, behavioral disorders, mobility problems, and other comorbidities appear during childhood [15,16].

In our review of diagnostic events for DS, we identify "drag factors" that capture the time it takes a newly discovered practice to become widely used in the field. We incorporate the drag factors into a model to estimate prevalence on the basis of incidence alone (incidence-derived prevalence) or incidence adjusted to diagnostic drag (diagnostic awareness [DA]-adjusted prevalence) to test our hypothesis that for rare diseases that undergo improvements in diagnostic practice and treatment over time, current incidence-derived prevalence is likely to exceed diagnosed prevalence at any given time. We discuss factors that may contribute to this diagnostic drag.

## Methods

### Literature Review

The PubMed database was searched between November 8 and 15, 2016, for studies reporting incidence, prevalence, or mortality in DS using search strings defined in Appendix Table S1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.03.002 without restriction on publication date. Identified articles were screened at title and abstract levels. Articles meeting eligibility criteria were read in full and data were extracted (see Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.03.002). Additional articles identified from full articles during the extraction process were added to the review.

A second targeted PubMed literature search was conducted between November 25 and 30, 2016, into the history of diagnosis in DS using the search strings defined in Appendix Table S2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.03.002. Themes explored included time from syndrome being first identified, confirmation of disease definition, diagnostic tools development, awareness and availability of effective and specific treatments (making differential diagnosis important), improvements in disease coding/medical records, and inclusion (or lack thereof) in relevant guidelines.

### DA-Adjusted Prevalence Model

#### Overview

A conceptual model was built in Excel to compare the prevalence of a noncommunicable rare disease calculated from incidence-derived prevalence or from DA-adjusted prevalence (Fig.1 and Table 1; see also Supplemental Materials), representing the time it takes for new diagnostic definitions, technologies, and

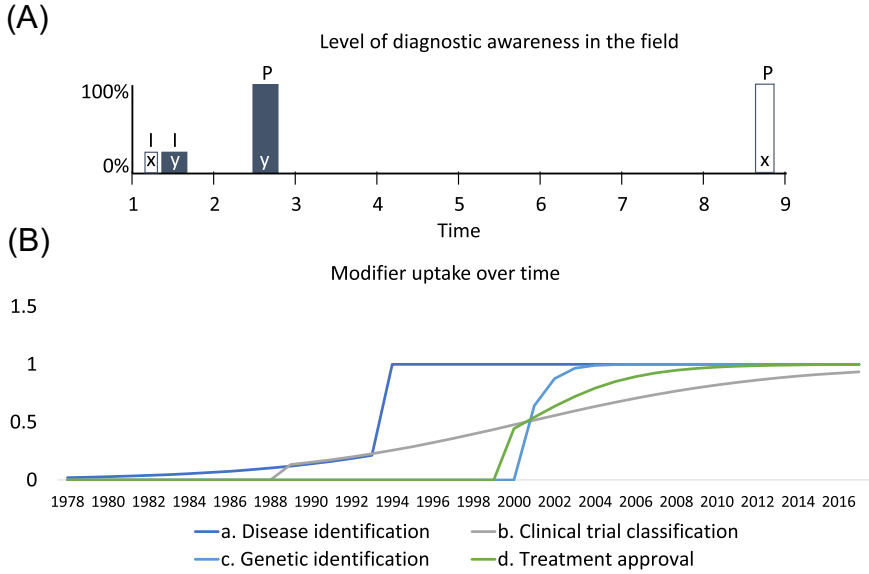


**Fig. 1 – Drag factor (modifier) uptake over time. (A) Cartoon illustration of the level of DA in the field for hypothetical drag factors *x* and *y* plotted against time. The defining timepoints for drag factors are their inception (*I*, when the factor [such as disease description, diagnostic method, and medical treatment] first appeared) and peak (*S*, when the factor reached broad clinical awareness). (B) Sigmoidal curves depicting the uptake of drag factors (modifiers a–d) for DS over time in the DA-adjusted prevalence model (see Table 1 for a description of the modifiers a–d). DA, diagnostic awareness; DS, Dravet syndrome.**