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The Problem of Rarity: Estimation of Prevalence in Rare Disease

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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

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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

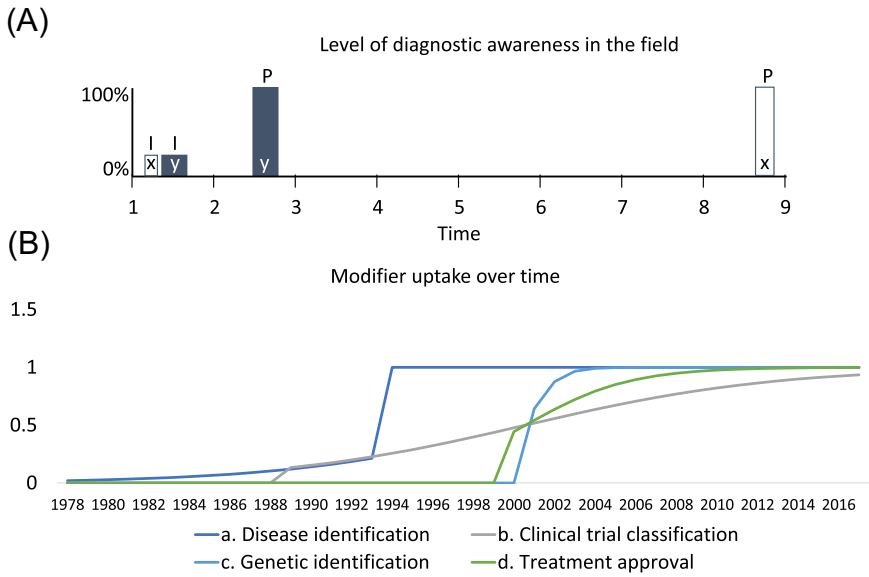

Fig. 1 – Drag factor (modifier) uptake over time. (A) Cartoon illustration of the level of DA in the field for hypothetical drag factors *x* and *y* plotted against time. The defining timepoints for drag factors are their inception (*I*, when the factor [such as disease description, diagnostic method, 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.

Table 1 – Drag factors (termed "modifiers" in the DA-adjusted prevalence model) for DS and inception and peak timepoints that determine the value of each drag factor.

Modifier	Inception timepoint	Peak time point	Definition of time to peak	Time to peak (Time 1)	α
a) Disease identification	1978	1994	Time between DS first being identified as SMEI in 1978 [16] and the first clinical trial of bromide with the specific intent of treating SMEI conducted in 1994 [50]	16 y	2.29605
b) Clinical trial classification	1989	2006	Time taken between the publication of the currently recognized description of DS in 1989 [20] and the first clinical study of topiramate with the specific intent of treating DS published in 2006 [51]	17 y	2.16099
c) Genetic identification	2001	2003	The time between the first identification of the *SCN1A* mutation in patients with DS [21] and its recognition as a major cause of DS in 2003 [31]	2 y	18.3684
d) Treatment approval	2000	2007	Time between publication of the only randomized control trial of stiripentol for the treatment of DS as published in the year 2000 [52] and stiripentol being given marketing authorization by the EMA in 2007 [30].	7 y	5.24811

Note. For all drag factors in this study (modifiers a–d), the "type of curve" is sigmoidal, Time 0 = 2, and peak = 100%.
DA, diagnostic awareness; DS, Dravet syndrome; EMA, European Medicines Agency; SMEI, severe myoclonic epilepsy of infancy.

expertise to translate into clinical awareness and widespread change in diagnostic practice.

Model population

Population growth rates and population figures were obtained from the Central Intelligence Agency's world factbook database 2016 [17]. Age groups were defined as 0 to 14 years, 15 to 24 years, 25 to 54 years, 55 to 64 years, and older than 65 years. Population growth rates were divided by 12 to calculate the growth rate by month and then applied to the raw population figures. The population used in this model is that of the EU in 2017 [17]. All calculations generate an absolute estimate of prevalence on the basis of the EU population.

Data inputs

Incidence and mortality proportions were extracted from the literature; the time horizon of this model is 360 months (30 years).

Incidence proportions are expressed as the percentage of newly diagnosed individuals per number of live births in the total population, for example, incidence proportion of 1 in 15,700 births = 6.37 births in 100,000 (6.37/1000 = incidence proportion of 0.0064%). Unless otherwise indicated, mortality is defined here as mortality of the disease population and not the mortality of the whole population. For all calculations of DS incidence-derived and DA-adjusted prevalence, the average mortality rate was 10% [18].

Incidence-derived prevalence

An incidence-derived prevalence calculator was built into the model to calculate the prevalence in the current year as the number of new cases expected each year plus the number of prevalent cases the previous year of those who were still alive. Incidence proportion is defined as the number of cases per 100,000 and mortality is the percentage of deaths in the affected population in the same time period.

Incidence-derived prevalence was then calculated by age group, according to Equation 1:

$$P1 = (N \times I) - ([N \times I] \times M), \quad (1)$$

where P1 is the incidence-derived prevalence, N is the size of the general population, I is the incidence proportion in the general population, and M is the percentage mortality in prevalent population.

DA-adjusted prevalence

To incorporate features from evolving diagnostic practice, a DA-adjusted prevalence calculator was built into the model. This was done by adding four drag factors (termed "modifiers" in the model) to the incidence-derived prevalence calculator. Each modifier represents a different element of diagnostic drag and is defined numerically by the following independent variables: Type of curve, α, Time 0, Peak, and Time to peak (Table 1).

A sigmoidal function (as opposed to a linear or exponential function, both of which are not further described in this study) was selected as the Type of curve to represent the uptake of each modifier (from 0% at Time 0 [when the value of the modifier = 0] to 100% at the Peak [when the value of the modifier = 1]) because for most distributive technologies or changes that rely on adoption by a large cohort (in this case physician uptake and acceptance as well as awareness), sigmoidal forms have been shown to most accurately reflect behaviors [15].

When the sigmoidal function is selected in the model, Equation 2 is used:

$$\mathrm{MOD} = \mathrm{Peak}/(1+\exp[-\alpha \times \{\mathrm{Time}\ i - \mathrm{Time}\ 0\}]), \quad (2)$$

where Peak is the peak uptake, Time i is the time of measurement of I, Time 0 is the function starting point (defined by the date on which the disease was first described), and α is the constant defined by two timepoints in the curve as per Equation 3:

$$\alpha = (\ln[1/\mathrm{Value}\ 1 - 1] - \ln[1/\mathrm{Value}\ 2 - 1])/\mathrm{Time}\ 1, \quad (3)$$

where Value 1 is the sigmoidal gradient reflecting the rate of uptake, Value 2 is the percentage uptake at peak, and Time 1 is

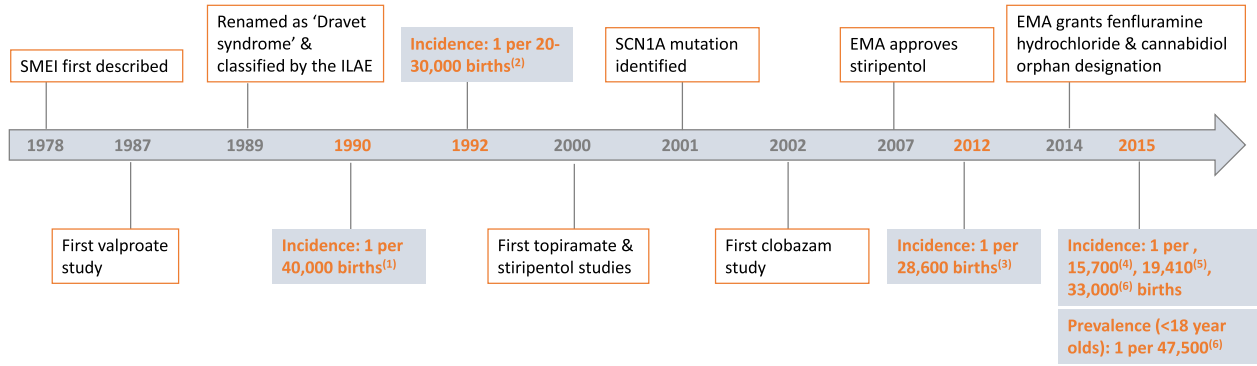

Fig. 2 – Chronology of diagnostic practice and publications of incidence and prevalence in DS. Reports of incidence and prevalence are indicated in the timeline by numbers in parentheses as follows: (1) Hurst et al. [33]; (2) Yakoub et al. [34], incidence figure calculated by extrapolation from percentage of all cases of epilepsy in the first year of life; (3) Brunklaus et al. [29], incidence figure extrapolated from incidence of *SCN1A* mutation positive cases and assuming 30% *SCN1A* mutation negative cases; (4) Wu et al. [27]; (5) Bayat et al. [32]; (6) Rosander and Hallböök [28]. DS, Dravet syndrome; EMA, European Medicines Agency; ILAE, International League against Epilepsy; SMEI, severe myoclonic epilepsy in infancy.

the time to peak (time between a modifier's inception and peak). DA-adjusted incidence proportion is then calculated by factoring in the modifiers in Equation 4:

$$I' = I \times (\text{MOD } a \times \text{MOD b} \times \text{MOD c} \times \text{MOD d}), \quad (4)$$

where I' is the DA-adjusted incidence proportion, I is the incidence proportion in general population, and MOD a to e represent the percentage suppression of incidence proportion in the current year due to modifiers a to d (Table 1).

Finally, the DA-adjusted incidence proportion (I') is used to calculate the DA-adjusted prevalence using Equation 5:

$$P1' = (N \times I') - ([N \times I'] \times M), \quad (5)$$

where $P1'$ is the DA-adjusted prevalence in absolute figures for the current year.

Results

A review of the literature on the epidemiology and diagnostic practices revealed that since their first descriptions in the 1960s and 1970s, the definition of DS has undergone several changes (Fig.2; see also Supplemental Materials). We identified sufficient current reports of incidence and prevalence for DS to test the conceptual model.

The History of Diagnostic Practice in DS

The term DS was first used in 1989 by the International League against Epilepsy to describe severe myoclonic epilepsy of infancy (SMEI) and borderline SMEI (without myoclonic seizures) [19,20]. SMEI was first described in 1978. The diagnosis of DS remains predominantly clinical, but since the 2001 discovery that mutations in *SCN1A* [21] and other [22–25] genes are associated with DS (and with a small proportion of other epilepsy syndromes [26]), genetic analysis has aided diagnosis in most, but not all, cases [27–29]. Treatment options are limited, with stiripentol being the only drug currently licensed by the EMA (but not the FDA) for the treatment of DS (when combined with valproate and clobazam) since 2007 [30].

Diagnostic Drag Factors in DS

Drag factors, the events that contributed to changes in diagnostic practice (called "modifiers" in the DA-adjusted prevalence model), in DS were identified from the literature review (Fig. 1): the identification of the disease, the use of its current classification in clinical trials, the discovery of a genetic component, and improved treatments. Each drag factor was designated an inception timepoint (i.e., when the event started, e.g., for modifier c, the inception timepoint was the first report of *SCN1A* mutations in DS in 2001 [31]) and a peak timepoint (i.e., the first sign of the event reaching diagnostic practice in the field, e.g., for modifier c, the peak timepoint was the first publication indicating the adoption of *SCN1A* sequencing in diagnostic practice in 2001 [13]) to calculate its value (Table 1).

Literature-Reported Incidence, Prevalence, and Mortality in DS

The most recent (2015) population-based estimates of DS incidence lie between 1 in 15,000 and 1 in 33,000 live births and are based on three studies from Sweden, Norway, and the United States [27,28,32]. Before this, a 1990 study using the now outdated SMEI criteria (which excluded cases of borderline SMEI that are now diagnosed as DS) estimated the incidence at 1 in 40,000 live births [33]. Earlier studies estimated an incidence of 1 in 30,000 to 1 in 40,000 live births on the basis of extrapolations from the percentage of patients with DS identified in cohorts of pediatric epilepsy cases [34,35]. Mortality in DS was reported in four large studies, ranging from 3.7% in a parent-led database to 15.8% in a medical series [18,29,36,37]. Sudden unexpected death in epilepsy accounts for nearly half of all deaths (see Appendix Tables S3 and S4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.03.002) [38].

The prevalence of DS was reported in two studies published in 2015 as 1 in 45,700 for the pediatric population of Sweden [28] and 1 in 90,742 for the total population in Buskerud County in Norway (see Appendix Table S5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2018.03.002) [39].

Incidence-Derived Prevalence of DS

Because the Swedish study [28] reported both incidence and prevalence of DS in a pediatric population (younger than 18 years), we could compare incidence-derived prevalence with diagnosed prevalence from a single study [28]. Indeed, in the pediatric population, the incidence-derived prevalence (52 individuals) more or less matches the diagnosed prevalence reported in the study (42 individuals) (Table 2). The Swedish study did not report a prevalence for the adult population, and therefore we extrapolated from the prevalence reported by a contemporary study in Buskerud County in Norway[39] a diagnosed prevalence in Sweden of about 104 patients (64 adults, assuming 42 pediatric patients). This number is 3.2 times less than the adult incidence-derived prevalence (using the Swedish study's incidence of 1 in 33,000 live births) of 205 adults in Sweden (Fig.3).

Table 2 – Calculation of the number of pediatric cases of DS in Sweden using incidence-derived prevalence and DA-adjusted prevalence on the basis of incidence data from the Swedish study [28].

Equation	Formula	Calculations
1	$P1=(N\times I)-([N\times I]\times M)$	P1 = (1,919,206 × 0.0000303) – ([1,919,206 × 0.0000303]× 0.1) = 52
2	$MOD=Peak/(1+\exp[-\alpha\times\{Timei-Time0\}])$	MOD a = 1/(1 + exp[−2.29605 × {2.475 − 2}]) = 1 MOD b = 1/(1 + exp[−2.16099 × {2.475 − 2}]) = 0.84417 MOD c = 1/(1 + exp[−18.3684 × {2.475 − 2}]) = 0.99999 MOD d = 1/(1 + exp[−5.24811 × {2.475 − 2}]) = 0.98375
3	$\alpha=(\ln[1/Value\ 1-1]-\ln[1/Value\ 2-1])/Time\ 1$	$\alpha_{(MODa)}$ = (ln[1/0.333 − 1] − ln [1/1 − 1])/16 = 2.29605 $\alpha_{(MODb)}$ = (ln[1/0.333 − 1] − ln[1/1 − 1])/17 = 2.16099 $\alpha_{(MODc)}$ = (ln[1/0.333 − 1]− ln[1/1 − 1])/2 = 18.3684 $\alpha_{(MODd)}$ = (ln[1/0.333 − 1] − ln[1/1 − 1])/7 = 5.24811
4	$I'=I\times(MOD\ a\times\ MOD\ b\times\ MOD\ c\times\ MOD\ d)$	I′ = 0.0000303 × (1 × 0.84417 × 0.9999 × 0.98375) = 0.000024914
5	$P1'=(N\times I')-([N\times I']\times M)$	P1' = (1,919,206 × 0.000024914) – [([1,919,206 × 0.000024914] × 0.0000303) × 0.1] = 43

Definitions of function variables

Variable	Definition
I	Incidence proportion (percentage of newly diagnosed individuals per number of live births in the total population per current year) in the general population
I'	DA-adjusted incidence proportion
M	% mortality in prevalent population
N	Population of interest
P1	Incidence-derived prevalence
P1′	DA-adjusted prevalence
Peak	Peak uptake (achieves 100% when a drag factor has reached full DA in the field)
Time i	Time of measurement of current incidence I
Time 0	Function starting point (defined by the date on which the disease was first described)
Time 1	Time to peak (time between a modifier's inception and peak) in years
Value 1	Defines the modifier's sigmoidal gradient reflecting the rate of uptake
Value 2	Defines the modifier's peak uptake

DA, diagnostic awareness; DS, Dravet syndrome.

Incidence-Derived versus DA-Adjusted Prevalence of DS

In the DA-adjusted prevalence model (using the DS drag factors described in Table 1), DA-adjusted prevalence (using the Swedish study's incidence) was 43 pediatric patients and 213 patients in total, which more closely approximates the Swedish study's diagnosed prevalence of 42 (pediatric population) and 104 (the total Swedish patient population extrapolated from the Buskerud County study), respectively (Fig.3).

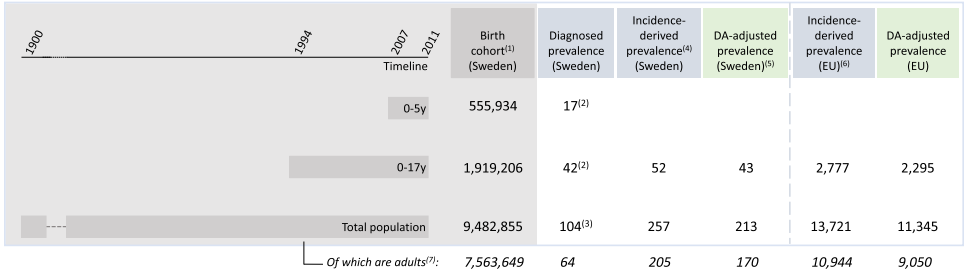

Fig. 3 – Cases of DS in Sweden in pediatric and adult populations on the basis of incidence-derived prevalence and DA-adjusted prevalence. 1) On the basis of the National Census of the Swedish population who were known to be alive on December 31, 2011 (Rosander and Hallböök [28]); 2) Prevalence in Sweden reported by Rosander and Hallböök [28]; 3) Expected prevalence in Sweden on the basis of diagnosed prevalence (1 in 90,742: 3 patients with DS in a population of 272,228 on January 1, 2014) in Buskerud County in Norway reported by Syvertsen et al. [39] in 2015; 4)Incidence-derived prevalence in Sweden on the basis of incidence of 2007–2011 cohort reported by Rosander and Hallböök [28]; 5)DA-adjusted prevalence: calculated prevalence of DS (assuming 10% mortality and incidence of 1 in 33,000 live births) using drag factors (modifiers a–d); 6)Assuming 10% mortality, an incidence of 1 in 33,000 live births, and population data from 2011 for the European Union (total population of 515,596,077); 7) Calculated by subtracting the pediatric population from the total population. DA, diagnostic awareness; DS, Dravet syndrome.

The approximation of the DA-adjusted prevalence to the prevalence reported in the Swedish study demonstrates that the incorporation of drag factors in the DA-adjusted prevalence model may be useful for estimating the diagnosed prevalence of rare diseases in large populations where the size of the required epidemiological studies would be inconceivably large. Thus, using the aforementioned assumptions (an incidence of 1 in 33,000 live births and population data from 2011) in the conceptual model, the incidence-derived prevalent DS population in the EU (total population 515,596,077) was calculated as 13,721 in the total population and 2,777 in the pediatric population, and the DA-adjusted prevalence as 11,345 in the total population and 2,295in the pediatric population (Fig.3).

Discussion

Our review of the literature identified few, yet sufficient, epidemiological studies for DS. The epidemiological data of the nationwide Swedish study were comprehensive enough to show that incidence-derived prevalence overestimates diagnosed prevalence in the adult but not in the pediatric population. This observation fits with a general consensus that because DS is seen as a pediatric syndrome (and diagnosis may not always be considered in adult clinics), genetic testing has led to the increased diagnosis in children rather than adults, who remain undiagnosed, or, more likely, misdiagnosed [40,41]. Assuming that the increased diagnosis in children is real, we can say that there is a trend toward increased incidence and can anticipate a change in prevalence. It would be of interest for future epidemiological studies to look into such trends over time.

Using the DA-adjusted prevalence model, we showed that the mismatch in incidence-derived versus diagnosed prevalence can be reduced by drag factors representing the time it takes the best and latest diagnostic knowledge to become practice in the field. For DS, the genetic diagnosis factor is most relevant to rare diseases because many are monogenic, that is, caused by a single genetic aberration [42,43]. In an era of gene discovery, the genetic characterization of all rare diseases has become a core objective for many in the field [44]. Therefore, it is important to recognize that for any rare disease whose genetic contribution has been recently identified, drag factors reflecting the time it takes for specialist expertise to reach all levels of diagnostic practice in the field may affect diagnosed prevalence. For each mutated gene that is identified as a possible cause for a rare disease, much time-consuming work must be invested in establishing the causal link between the mutation and the disease phenotype. This requires a clearly defined disease phenotype and accurate sequencing techniques, and in the case of DS, the clinical implications of *SCN1A* variants are still being defined [45] and sequencing techniques are not yet fully accurate [32,46]. Such factors contribute to the drag in clinical awareness that is ultimately reflected in undiagnosed or misdiagnosed cases and a lower than expected diagnosed prevalence.

Strengths and Limitations

We show that incidence-derived prevalence more accurately estimates diagnosed prevalence when modified by diagnostic drag factors. For example, using the DS drag factors tested on the Sweden study, the DA-adjusted prevalence of patients with DS in Europe is 11,345 compared with the incidence-derived prevalence of 13,721, amounting to a considerable 17% difference in planning for health service resources and budget. A limitation to extrapolating European patient numbers from the Swedish data is that it does not take into account geographical variations of DS, for which, however, no published reports exist. Further limitations to the conceptual model are that there are insufficient epidemiological data to robustly validate the model or the assumptions made in the development of the inception and peak points relating to the drag factors. Furthermore, when testing the model for the adult population in Sweden, we extrapolated adult prevalence from a Norwegian study, without proof that these populations are directly comparable.

Further Work Indicated

Without clear incidence and prevalence figures it is difficult for companies to develop clinical trials and drug development programs. Understanding patient numbers is an early step even before hypotheses are made about drug development. Importantly, funding agencies need to understand the requirement for better epidemiological studies and accurate prevalence data for rare diseases. Such studies often need international collaborations because patient numbers are so low. Robust medical record databases covering entire populations such as those in Scandinavian nations are valuable because they allow large populations to be studied. Funding could be considered for international platforms that combine rare disease registries from different organizations and researchers across the world using uniform, accepted standards for the collection and organization of these data. Guidelines for disease-specific epidemiological studies, such as those recently published for epilepsy [47], will help to standardize data across studies. Attempts to consolidate prevalence data of all rare diseases have been made, such as the EURORDIS "Rare diseases in numbers" and the Orphanet report on prevalence and incidences [48,49]. Nevertheless, although the reports provide extremely useful summary data, prevalence data are unreferenced and not presented as a range.

Conclusions

Diagnosed prevalence of some rare diseases is likely to be overestimated when calculated using current incidence. Incidence of rare diseases may increase over time as diagnostic definitions, technologies, and expertise develop, diffuse, and are adopted into widespread clinical practice. In this article, we identified potential diagnostic drag factors and propose an outline methodology of how these drag factors could be included into the calculation of diagnosed prevalence to yield more realistic estimates of the actual number of patients living with a rare disease.

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Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at https://doi.org/10.1016/j.jval.2018.03.002 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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