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CORRESPONDENCE

Reply to E. Vicente et al.

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To the Editor:

Thank you to Mrs. Vicente, Pruneda and Ardanaz for their comments on our publication 'Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database'. We hope, as you do, that both publications stimulate discussion about the standardization of rare diseases and prompts other groups to futher refine the estimates we have presented.

We would like to clarify some points that your letter raises.

With regards to the consideration of only prevalent diseases in our analysis, this was not to negate the contribution of incident rare diseases such as cancers, tropical diseases and infections to the human toll of rare diseases, but rather the inaccuracy of combining statistical analyses of incident and prevalent conditions. Orphanet does record conditions with epidemiological indicators related to incidence [1], but for consistency these were excluded from our analysis. The contribution of incident diseases such as rare cancers has been considered in other publications referenced in our article [2].

The second issue raised is that there is a large geographic disparity in prevalence of different rare diseases. We have mitigated this as much as possible in our analysis by exclusion of prevalences reported on population isolates and founder populations, and selected those representing the widest geographic representation possible: one value was selected in the order of preference: worldwide; or European (EU, Russia, Turkey, and Iceland). If no point prevalence was available from these regions then a USA point prevalence figure was used if it did not exceed the European threshold definition of 5/10,000 [3]. Disorders that did not have a prevalence value reported in any of these geographic areas were excluded. The Orphanet's literature search for epidemiological indicators takes place on a disease-by-disease basis [1]. All epidemiological indicators are collected, irrespective of whether the disease has a 'rare' designation in that country. Orphanet's standardization of a rare disease list by the European definition of five cases per 10,000 permits pan-European interoperability despite inter-country differences.

The third issue raised is the defining rare diseases as to whether they are 'serious'. While 'life-threatening' may be more numerically defined, the impact of rare diseases has been shown to be medical, psychological, financial, social as well as time-consuming [4–6]. The United Nation's Sustainable Development Goals call for effective global action to ensure that no one is left behind. The UN Political Declaration on Universal Health Coverage adopted in 2019 [7] includes "rare diseases" not "serious rare diseases". In all EU legislations, EU Member states legislation and policies, legislation in the USA, Australia and China, rare diseases are inclusive of all people with rare diseases, without any reference to severity.

We do agree with the authors that the consideration of prevalence class data is less than ideal and may create overestimation or underestimation if the underlying true values are not distributed evenly within the classes, but instead are clustered at the boundaries of the classes. This is a limitation of the data available—for many diseases no representative point prevalence is available in the literature, and instead a prevalence class has been assigned by consultation with an expert. This highlights the scarcity of reliable rare disease epidemiological indicators in the literature, and highlights the need for future population research.

There is no doubt that the estimate we derive is just that—an estimate, and susceptible to the variability in the heterogeneous methods used to collect the primary data and inadequate to capture the natural variability in population prevalences of rare diseases. In order to provide as robust an

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estimate as possible, only diseases with prevalence as an epidemiological indicator were selected, and using prevalence values from a wide geographic area were incorporated. While our resulting estimate of 3.5–5.9% does seem high compared to the 0.6% for the Veneto region derived from 331 disorders and groups of disorders from which some prevalent diseases (i.e., cystic fibrosis) are excluded [8], higher figures have been reported in other countries. Walker et al. [9] and Chiu et al. [10] report prevalences of 2% in Western Australia and 1.5% in Hong Kong respectively, using linked hospital data capture of 467 diseases of the >6000 rare diseases on Orphanet. A recent retrospective national cohort study in Ireland found that at least 4% of Irish born in the year 2000 have a rare disease (100% diseases on Orphanet) by age 16 (E. Gunne, personal communication).

The challenge now lies with countries to implement thorough and widespread data capture systems in registries or within electronic healthcare records so that data about rare diseases can be recorded and used to inform health and social care policy for people with rare diseases. We fully recognized the limitations of our study, but hopefully its impact will be sufficient to motivate further, more precise research on this topic. As rare diseases are a global health policy issue, we also hope that our work will contribute feeding discussions on a commonly accepted definition framework of rare diseases.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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