Rare DISEASE DAY 2023

DOLON

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Why do rare diseases warrant special treatment?

While the burden imposed by rare diseases and extent of unmet needs is clear, some question the need to make special adaptations (in law, access frameworks, or healthcare spending) for rare diseases – on the basis of ethics, affordability concerns, or scepticism as to the uniqueness of rare diseases.

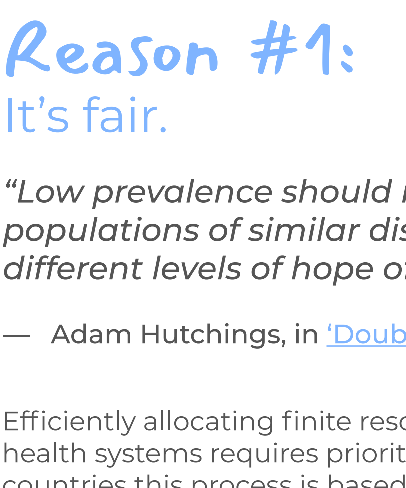
Yet there is a strong moral, economic, and pragmatic case to treat rare diseases differently. In recognition of Rare Disease Day 2023, we explore four key reasons why rare diseases warrant special treatment. These reasons are summarised below, building on published work by Dolon team members.

#1 It's fair.

#2 It's needed.

#3 They're fundamentally different.

#4 We can afford it.



Reason #1:
It's fair.

"Low prevalence should not be a reason why two patient populations of similar disease severity should have markedly different levels of hope of ever being effectively treated."[1]

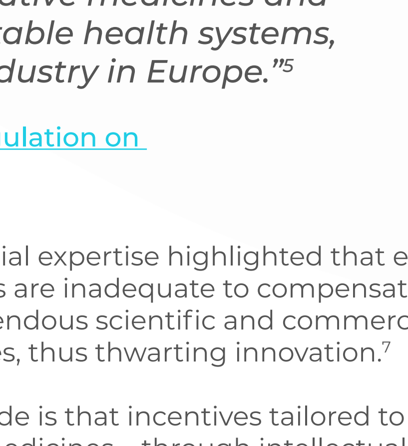
— Adam Hutchings, in 'Double bad luck: Should rare diseases get special treatment?'

Efficiently allocating finite resources within health systems requires prioritisation. In many countries this process is based in utilitarianism, a philosophy that focuses on maximising benefit in aggregate.[2] Utilitarianism is not concerned, however, with distributing that benefit: 'a QALY is a QALY is a QALY', regardless on whom it falls. Under this view, rare diseases are generally neglected, as they affect a smaller number of people and often cost more per patient.[3]

A recent article in the Journal of Medical Ethics neatly summed up this line of thinking, arguing that healthcare resources should be prioritised by disease severity, but not by rarity.[4] The author argued that rarity doesn't matter *conceptually*. This may be true, but – as Adam pointed out in his published commentary on the article – *in practice*, it matters tremendously.

This is because the size of the population has a direct and proportionate impact on the likelihood of a medicine being developed (see *Reason #2: 'It's needed'*). The author of the original article viewed this as 'bad brute luck' for rare disease patients: that they are unfortunate enough to be born with a severe disease, and then doubly unfortunate that they are born with a disease for which an effective treatment is unlikely to be developed.

But 'bad luck' is often a policy choice. Rarity does matter, and along with severity, should be accounted for in the frameworks that determine where investment happens. Goals of efficiency and equity are not binary: for the sake of rare disease patients, we must strike a fair balance.



Reason #2:
It's needed.

"Maintaining a positive incentive framework is essential to advancing therapeutic innovation towards effective preventative medicines and treatments for rare diseases, strengthening equitable health systems, and fostering a productive biopharmaceutical industry in Europe."[5]

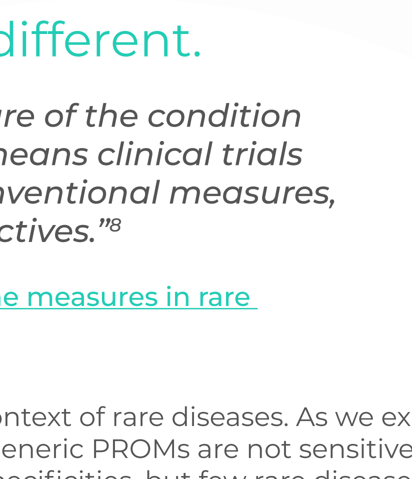
— Emilie Neez, in 'Estimated impact of the EU Orphan Regulation on incentives for innovation.'

The economics of rare disease innovation are tough. Small populations mean more complex and risky development programmes, as well as smaller returns if a medicine is approved. Our analysis of the economic viability of orphan medicines in Europe suggested that for the more prevalent rare diseases the economics were currently marginal; for the very rare, they are unfeasible. [5]

Therefore, if rare disease innovation is not incentivised, research investment will go elsewhere. That is exactly what was observed before the enactment of US (1983) and EU (2000) orphan legislation: industry R&D focused on prevalent diseases and only a handful of rare disease treatments were available.[6] This is still happening in many extremely rare or paediatric-onset rare diseases. In a workshop we organised for EFPIA, pharmaceutical executives with R&D, clinical, strategy, and commercial expertise highlighted that existing incentives are inadequate to compensate for the tremendous scientific and commercial challenges, thus thwarting innovation.[7]

The flip side is that incentives tailored to orphan medicines – through intellectual property, tax and P&R systems – can sufficiently level the economic playing field to ensure that innovation does happen. Case in point: we estimated that the European Orphan Regulation doubled the amount of innovation that would have been expected without dedicated incentives.[5]

The relationship is simple: no special economic treatment means few medical treatments for rare disease patients. But if, as a society, we are serious about addressing unmet needs in rare diseases, we need to put our incentives where our mouth is.



Reason #3:
Rare diseases are fundamentally different.

"The high unmet need, severe and disabling nature of the condition and scarcity of adequate data for rare diseases means clinical trials need creative and pragmatic supplements to conventional measures, to capture treatment effects from patient perspectives."[8]

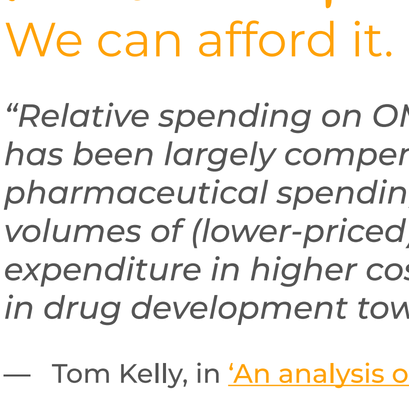
— Amanda Whittal, in 'The use of patient-reported outcome measures in rare diseases and implications for HTA.'

Today, a significant number of rare disease patients cannot access existing treatments that could benefit them. This is in large part because the rarity of these conditions makes it difficult to produce the standard of evidence required for treatments to be reimbursed. For example, rare disease trials generally enrol fewer patients than non-rare ones (thus limiting statistical power to detect meaningful outcomes), are more likely to be single-arm and open-label, and more often rely on surrogate endpoints.[9-10]

The only ones who can fill the gap where more conventional evidence is lacking are rare disease patients and carers themselves, with their lived experience of the disease and understanding of how a potential treatment may alter their lives. Despite this critical role, the integration of patient perspectives into assessments of new treatments can be challenging, is often inconsistent, and in some cases is not present at all.[11-12]

Patient reported outcomes measures (PROMs), for instance, are a potential solution to better understand disease and treatment impact, but simultaneously embody the challenge of measuring drug effectiveness within the unique context of rare diseases. As we explain in a paper, generic PROMs are not sensitive to rare disease specificities, but few rare diseases have disease-specific instruments available. Even when they do, these may not be validated and thus not acceptable as supportive evidence.[8] This reflects the lack of natural history data from which to inform PROM design, and the difficulty of statistically validating a questionnaire in small patient populations with significant disease heterogeneity. Add to this the fact that patients are often children, and sometimes have cognitive impairments associated with the disease, making it difficult or impossible for them to self-report their health state.

The very essence of rare diseases – rarity – makes them fundamentally different in terms of the efficacy evidence that can be produced. This should not create a barrier to patient access. It is essential that traditional value assessment frameworks are adapted to the specific challenges of evidence generation in rare diseases and that the invaluable patient perspective is routinely and effectively incorporated in reimbursement processes.



Reason #4:
We can afford it.

"Relative spending on OMPs has increased over the last 20 years, but this has been largely compensated for within the current allocation of total pharmaceutical spending by flat expenditure for non-OMPs and increased volumes of (lower-priced) generics/biosimilars, reflecting a shift towards expenditure in higher cost, lower volume patient populations and a shift in drug development towards more specialised targeting of diseases." [13]

— Tom Kelly, in 'An analysis of orphan medicine expenditure in Europe: Is it sustainable?'

'We can't afford to pay such high prices' is a common objection to prioritising treatments on the basis of rarity. Concerns surround both the prices of individual medicines (the 'sticker shock') and the cumulative drug expenditure across rare diseases.

Yet looking at individual prices or even aggregate spending on rare diseases ignores the broader dynamics of pharmaceutical expenditure. There are built-in stabilisers for drug spending in the form of genericisation, competition, and savings realised through improved patient outcomes.

We studied whether these budgetary guardrails worked in modulating holistic pharmaceutical expenditure in the context of growing spending on rare diseases, and they did. Increased spending on orphan medicines in Europe between 2010-2017 was offset by greater use of lower-priced generics and biosimilars in more prevalent conditions.[13] The major pharmaceutical cost drivers of the 1990's – atorvastatin, clopidogrel, etc. – lost patent in the early 2000's, exactly the moment that orphan medicines began to be approved. In the 2010's, biosimilars for large molecule blockbusters, such as rituximab, created further savings.

This reflects the bigger story of drug innovation and progress over the last 30 years: expenditure has followed the unmet need. Effective medicines have transformed the prognosis of many highly prevalent conditions; as those medicines lost patent, savings have been increasingly directed towards areas of high unmet need, often in small populations.

The positive cycle is set to continue. In 2017, generics were already available for 23% of FDA-approved orphan medicines.[14] More first-wave orphan medicines will be reaching the stage of patent expiration in the coming years. Imatinib and lenalidomide – two orphan medicines associated with tremendous patient benefit and significant costs – have seen prices in Europe fall more than 75% since going generic.[13,15] IQVIA predicts €54bn in European savings from biosimilars over the rest of this decade.[16]

Healthcare systems can afford to continue to invest in rare diseases that have until now missed out on innovation. Whether they do so is a policy choice. For the reasons we've highlighted this week, we believe they should.

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