Should rare diseases get special treatment?

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ABSTRACT

Orphan drug policy often gives 'special treatment' to rare diseases, by giving additional priority or making exceptions to specific drugs, based on the rarity of the conditions they aim to treat. This essay argues that the goal of orphan drug policy should be to make prevalence irrelevant to funding decisions. It aims to demonstrate that it is severity, not prevalence, which drives our judgments that important claims are being overlooked when treatments for severe rare diseases are not funded. It shows that prioritising severity avoids problems caused by prioritising rarity, and that it is compatible with a range of normative frameworks. The implications of a severity-based view for drug development are then derived. The severity-based view also accounts for what is wrong with how the current system of drug development unfairly neglects common diseases that burden the developing world. Lastly, the implications of a severity-based view for current orphan drug policies are discussed.

Rare diseases, by definition, have small patient populations. As a result, drugs for these diseases (also called orphan drugs[i]) have small potential markets. This entails weak incentives for pharmaceutical companies to invest in orphan drugs. Much time, money and effort is put towards developing treatments and preventive or diagnostic interventions for common conditions, even if they are not serious and even if other effective treatments already exist. In contrast, even life-threatening or severely disabling rare diseases remain largely neglected.

Since the 1980s, however, activism by rare disease patient groups has increased public attention to what many view as an unfair situation for people who have such diseases. This has led the USA, the European Union and other countries to offer tax and regulatory incentives for the development of orphan drugs. These incentives are credited with more such drugs reaching the market.

When an effective treatment for a rare disease reaches the market, manufacturers' need to make a profit from a small number of patients results in a high price per patient,or per quality-adjusted life-year (QALY), or per some other unit of health benefit. In health insurance systems that take some form of cost-effectiveness assessment into account,[ii] the prices of these drugs often exceed the amount the insurer is usually willing to pay for the benefits provided. The result is a new situation in which there is an effective treatment for a rare disease but insurers refuse to cover it, leading to patients either being unable to access needed care due to inability to pay or facing a high financial burden in addition to their burden of ill health. This raises the question of whether public insurers should be willing to treat orphan drugs differently when making coverage decisions. Proposed methods for how public insurers might decide when and how much to pay for costly orphan drugs include increasing their willingness to pay proportionately as disease prevalence decreases, and setting aside a separate budget for orphan drugs only, thereby removing them from 'competition' for funds with drugs for common diseases.

In my view, rarity itself is not an appropriate basis for treating some diseases as exceptional cases[iii] in insurance funding decisions. I will argue that appeals for added priority for funding for orphan drugs may have merit—not on account of rarity, but because they may also involve severity, an attribute that tends to receive less priority than it should.

TWO VIEWS ON PRIORITY SETTING

When it comes to making choices in order to allocate a limited budget, a utilitarian ethical view supports relying heavily on cost-effectiveness. This *maximising view* is appealing in its impartiality, as its goal is to obtain as much health benefit as possible for the entire population, regardless of who gets it. The practical corollary of this approach, the imperative to get the best value for money, also makes the maximising view attractive in the context of allocating scarce public resources.

Paying higher prices per QALY for orphan diseases does not accord to this maximising approach.[1 2] Policies that assign higher value to some QALYs than to others originate from a different view, in which all patients have just as strong a claim on societal assistance as any other patient and we ought not to ignore these claims even if they are costly to attend to. I will call this vaguely defined general sense the *equal claims view*. The widely held belief that strict maximisation of health benefit leads to

[i] Throughout this paper I use this term to refer only to drugs for rare diseases, and not to drugs for neglected tropical diseases.

[ii] I focus exclusively in systems that give some role to cost-effectiveness in priority setting, particularly publicly funded health insurance systems in the developed world.

[iii] My contention that rarity is not an appropriate basis for differential treatment of some diseases applies only to insurance funding decisions. Rarity clearly is relevant in the clinical sphere, since it is precisely because of the rarity of some diseases that physicians are not used to encountering them, which makes it more difficult for patients with rare diseases to be accurately diagnosed or find the clinical expertise they need. In the evidence context, it is also rarity that makes it impossible for treatments for rare diseases to be put through trials similar to those required of drugs for common diseases. These two contexts are examples of settings where rarity is an appropriate basis for differential treatment of some diseases.

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unacceptable results that overlook some such claims[3–5] is (part of) the motivation for the development of methods for incorporating a variety of criteria into priority-setting processes,[6–9] constraining maximisation.

Motivated by a concern for equal claims, current orphan drug regulations constrain maximisation of aggregate health by giving special consideration to interventions based on the prevalence of the diseases they treat. Current orphan drug regulations and incentive schemes are evidence that policymakers are already motivated to recognise the equal claims intuition. I will therefore assume that priority-setting will incorporate some concern for equal claims, taking into account at least some criteria other than cost-effectiveness and discuss only what follows from that. My goal in this paper is to show that this move from the equal claims view to prevalence-based orphan drug policies is mistaken.

In the following section, I will discuss some common arguments for treating rare diseases as an exception to usual funding decision rules, and argue that they fail to justify this special treatment. Section 3 presents my own view, which emphasises severity as an important factor for priority setting and justifies special treatment of (some) rare diseases (as well as other severe diseases). Sections 4 and 5 test the plausibility of my view and discuss the normative frameworks supporting it. Section 6 expands my account to the stage of drug development, and section 7 briefly discusses its policy implications.

SHOULD RARITY MATTER?

Current orphan drug policies distinguish between rare and non-rare diseases, implying that society ought to value a QALY more highly if it is gained by treating a rare disease than if it is gained by treating a common disease. To investigate whether there is justification for this distinction, I identified potential reasons, proposed in the literature, why rarity should matter for policy. I will not review this literature here, but rather discuss arguments that are particularly prominent or interesting. The literature suggests moral reasons to value rarity, as well as practical, or instrumental, reasons. I will start with two of the latter:

The Citizens Council of the UK's National Institute for Health and Care Excellence (NICE) cites the value of *new scientific knowledge and technological innovation* as a reason to devote additional resources to orphan drugs.[10] Gericke and coauthors appeal to 'a professional obligation to advance medical science'.[11] These considerations do not seem appropriate to the decision of how to allocate a healthcare budget that has the function to improve population health. The professional obligation to advance science may apply to scientists, but policymakers in charge of allocating resources to promote population health have no such obligation. Scientific innovation certainly has social value, which may justify setting aside some public resources to invest in scientific research. But by using innovation as a criterion to choose between groups of patients we fail to show equal concern towards the needs of all. We could not justify our decision to a patient whose treatment was not funded because it was less innovative than other drugs. This is irrelevant to the patient's claim to assistance. Taking indirect costs and benefits (not only innovation, but also productivity, tax revenue or provision of care to infants or the elderly) into account gives us reasons to choose patients on the basis of how 'socially useful' they are. This leads to morally unappealing results. For instance, it gives us reasons to choose whom to help based on their economic productivity, which correlates with socioeconomic status and other forms of advantage.

NICE's Citizens Council also raises the concern that, due to their small numbers, *patients with rare diseases are less likely to be well-represented in the decision-making process*, and therefore should get special attention.[10] If it is true that smaller patient groups tend to be overlooked, we ought to make sure their voices are given space and consideration in the decision process. However, a reason to ensure that minority groups receive fair consideration in a decision-making process is in no way a reason to believe that society ought to take the actions advocated by these groups.

In any case, it is not necessarily true that diseases with the greatest number of patients get better representation, as a small number of patients may be easier to organise around common interests. Moreover, proposals to allocate more resources to rare diseases or a particular rare disease do not specify where these funds would come from, so that even if patients with common diseases were equally well organised, there would be no way to know which common diseases would be affected. Whether patients with rare or common diseases get their voices heard more easily is an interesting empirical question and beyond the scope of this discussion.

When the *small budget impact* of funding a drug for a rare disease is considered in a decision, the low total cost of covering a costly drug for very few patients may count in its favour. Zallen puts the argument as follows: 'Since people with rare diseases are geographically dispersed, no single government or insurance company is overwhelmed by the cost of orphan drugs. In fact, insurers admit that they could save more money by shaving a half-penny off the price of a popular cholesterol drug than by slicing a few thousand dollars off the price of an orphan drug'.[12] Wales' decision to fund the drug laronidase was partly based on evidence of its small budget impact, since only two patients in the country would be eligible for the treatment.[13] Small budget impact is also given as a reason to fund drugs for rare diseases by Dear and colleagues,[14] and by NICE's Citizens Council.[10]

Budget impact is a legitimate concern in funding decisions, since even the most cost-effective drug can be unaffordable if the patient population is large enough, or the amount of resources available is small enough (see for example Urrutia and coauthors on the case of antivirals for hepatitis C).[15] However, it is problematic to apply this reasoning backwards and count small budget impact as a reason in favour of funding a drug. If this principle is applied consistently, these small costs can easily add up to a large part of the available healthcare budget. Having a lot of the budget spent in a cost-ineffective way would lead to unacceptable opportunity costs, as even interventions for severe common diseases become unaffordable. In addition, as technological advances make it possible to increasingly personalise treatments, more and more common diseases will be 'broken into' a number of rare diseases. Accepting small budget impact as a reason to fund cost-ineffective interventions is therefore unsustainable.

Practical reasons, then, do not seem to provide a satisfactory justification for valuing rarity. Potential moral reasons for valuing rarity include the rule of rescue, priority to identified victims and personal responsibility.

The rule of rescue, the imperative to save those who are in immediate danger, is the most common principle underlying arguments for treating rare diseases differently. For the sake of argument, I will assume that the rule of rescue has normative force rather than being a psychological tendency that may or may not lead us into error. If immediate danger is what causes the rule of rescue to apply to a case, then it fails to distinguish between rare and common diseases, since the prevalence of a

condition has no bearing on the immediacy of the danger faced by any particular patient. Therefore, if we understand it as a response to immediate danger, the rule of rescue cannot justify differential treatment to rare diseases.

When describing the conditions under which the rule of rescue applies to the orphan drugs debate, Hughes and coauthors explicitly mention 'a small number of cases',[13] which does single out rare diseases. Why would the number of cases be relevant for the rule of rescue to kick in? The argument might go as follows: if there are few cases, the public can 'put a face to' those patients while not putting a face to those who would otherwise benefit from the resources. If this interpretation is correct, Hughes is describing a *preference for identified over statistical victims* rather than a preference for helping those in immediate danger. The term rule of rescue is used in a few different ways in the literature, so this interpretation seems plausible. Can this new interpretation of the rule of rescue tell us something about rare diseases? I do not think so.

In their investigation of our tendency to prefer identified to statistical victims, Jenni and Loewenstein conclude that it is a response to the concentration of risk within a reference group,[16] by which our concern increases as the concentration of risk increases. An identified victim has the highest possible concentration of risk (p=1) and thus commands our attention more than any statistical victim ever could. This seems like a plausible explanation of the psychological mechanism underlying our preference for identified victims, but not an appropriate normative rule for policy decisions. Healthcare professionals necessarily encounter identified victims, and have responsibilities towards particular identified patients created by their professional relationship. In order to fulfil these responsibilities, clinicians must act in the best interest of their own particular patients within the legal and resource limits set at the population level. By contrast, population-level decision-makers should ideally not respond to particular cases, to knowledge of the identities of the particular people who would be affected by a decision. The obligations of the population-level policymaker are to each member of the population equally.

In any case, the number of patients that exist with a given condition has no bearing on whether a single patient or group of patients becomes identifiable. Rare disease patients may be more likely to attract public attention to the extent that the rarity of their condition is deemed 'newsworthy', but many features of patients with common diseases may make them the focus of public attention. To count such visibility as a reason for helping some rather than others is at best arbitrary and at worst discriminatory, depending on the reasons why the visible victims came to be visible while others did not.

Lastly, the fact that patients have *no responsibility* for how rare their diseases are may be seen as a reason for making rare diseases an exception in the discussion of the equal claims view above. Personal responsibility, by itself, does not distinguish rare from common diseases that all happen to the patient due to factors outside their control. The appeal to rare disease patients having no responsibility for their plight may be rooted in the thought that having a rare disease is even worse brute luck (to borrow the language of luck-egalitarianism) than having an otherwise identical common disease. But it is not clear that this is the case, as far as the disease itself goes. It may be argued that, *on top of* the disease itself, the rare disease patient faces the additional bad brute luck of having been born into a system that prioritises common diseases, which differentiates them from a patient with an otherwise identical common disease for whom it is good brute luck to have been born in such a system. This argument is compelling, but it applies to the drug development stage rather than to coverage decisions. It is the current system of drug development that neglects rare diseases in favour of larger markets and puts high prices on orphan drugs in search of returns on investment. I will return to this argument in section 6, which discusses drug development.

In in-depth discussions of philosophical arguments for prioritising rare diseases, Juth[17] and Albertsen[18] also fail to identify an argument that justifies giving added weight to rarity per se. If we have not, so far, found a practical or moral argument that justifies prioritising rare over common diseases, is there anything else that might?

THE SEVERITY VIEW

In public debate about rare diseases, our attention is focused on the suffering endured by patients, often throughout their lives, and on how a high-cost drug may relieve it. In my view, it is the high burden imposed by severe rare diseases on each individual patient that makes it morally unacceptable for these patients to go without treatment even though greater benefits could be obtained in the aggregate by spending healthcare resources elsewhere. In other words, the problem is not that our system neglects *rare diseases*, but that it neglects *severe diseases that happen to be rare*.

This view seems to account for the fact that advocacy groups, the academic literature and regulations aimed specifically at rare diseases all seem to refer to conditions that are not only rare but also severe. Some of these policies, like the European Council's regulation on orphan medicinal products,[19] explicitly require that a disease be severe in order for research and treatments to qualify for incentives, while rarity itself is not always required. NICE's Citizens Council recommended that decisions about orphan drugs take into account not only prevalence, but also the severity of a disease, whether it is life threatening, and the expected benefit of treatment.[10] The US Orphan Drugs Act does not require any degree of severity for a drug to qualify for special treatment, but the text of the law begins with a list of severe rare diseases that appear to have motivated the Act ("Huntington's disease, myoclonus, ALS (Lou Gehrig's disease), Tourette syndrome and muscular dystrophy"),[20] so severity seems to have at least some role in the justification for the policy. A review of regulations in 35 countries enumerates prevalence, severity and existence of alternative therapies as the most typical factors used to designate a drug as orphan.[21]

To avoid confusion, it is important to distinguish a few concepts related to rarity and severity that are distinct but sometimes get conflated in everyday speech. Rarity, or prevalence, is how frequently a given condition occurs in a population. It is distinct from the size of a health benefit, which may be individual (how much health improvement a treatment is expected to bring to a patient) or aggregate (the sum of the individual benefit sizes for the entire population). The size of the aggregate health benefit tends to increase as prevalence increases, but this is not necessarily the case. The size of a health benefit is also distinct from the severity of a condition: while the *potential* for individual and aggregate health benefit tracks the severity of a current and fully reversible health state, that is not necessarily the case for the expected individual and aggregate benefit of specific treatments, as treatments for severe diseases do not necessarily restore patients to full health or to their previous health state.

The concept of severity combines at least four distinct ideas: *how badly off a patient has been in the past*, *how badly off a*

patient is now, *how badly off a patient is expected to become if not treated* and *how soon they need treatment in order to avoid a bad outcome*. Severity can, at least, refer to any one of these, or to some combination.

Experts have disagreed about the normative content of the concept and its helpfulness for policymaking[22–24]; citizens may also refer to this concept to convey a complex range of ideas.[25 26] Studies of public views on whether and to what extent severity should increase willingness to pay per QALY have been carried out in many publics (for the most part, in developed countries), and generally show public support for severity as a factor attracting at least some priority.[27–31] However, specific conclusions are difficult to draw from this large and heterogeneous body of literature, since studies differ in how they define severity,[28] and responses have been shown to depend a lot on framing effects.[32 33] See[27] for a discussion. Rarity, by contrast, seems to be presented to the public less often in such studies,[28] and to attract less support as a priority-setting criterion.[31 34]

Here, for simplicity, I am thinking of severity as the current state of a patient and assuming this condition will not change unless the patient is treated[iv]. Severity refers to past, present and future states of health in the absence of treatment, while the size of a health benefit is the health gain expected to accrue from treatment.

All three dimensions of severity and the size of the expected benefit are important for the decision of which treatments should get funded. Here, I am discussing priority setting in decisions between *effective* treatments competing for insurance funding, and trying to establish that severity-we-can-do-something-about, severe health impairment that is avoidable or at least amenable to relief, is a reason to give priority to a severe claim over other claims of lesser severity. I am leaving benefit size aside in order to discuss how to prioritise claims, rather than claim–treatment pairings. At the funding stage, there is no reason to prioritise a severe condition for which no health gain is possible. Severity regardless of attainable gain is a consideration more appropriate for research-agenda-setting decisions.

TESTING THE SEVERITY VIEW

Whenever a treatment for a very severe disease goes unfunded, it is implicitly being compared with all the treatments that are funded, including the many interventions that relieve smaller burdens for greater numbers. To test the plausibility of the idea that severity, but not rarity, should matter for priority setting, I will compare four imaginary cases. In each case, we must choose one of two interventions to fund. Insurance would cover the cost for each intervention for the entire population with the disease, and that population would be restored to full health by the intervention. The same total amount of funds would be expended to cover each patient population, but the intervention for the larger population would always generate greater aggregate benefit than the intervention for the smaller group simply because the former group has more people.

(Case 1) *Mild common disease versus mild rare disease:* in this case, there appear to be no plausible grounds for choosing the rare over the common disease. A defender of the equal claims view may not object to this and happily choose the common disease, as in this case the situation of whichever group is not funded will be equally (and not very) bad. Since each individual has an equally strong claim on social assistance, it is hard to see why not meet as many of those claims as possible[v].

(Case 2) *Severe common disease versus severe rare disease:* here too the equal claims view would either choose the common disease or prioritise both equally (eg, by splitting the funds, setting up some sort of lottery or weighted lottery). It would be difficult to make an argument for choosing the rare disease, since there is no question of less important claims of each of the many outweighing larger claims of each of the few.

(Case 3) *Severe common disease versus mild rare disease:* treating the severe common disease maximises aggregate benefit, and treating the rare disease would leave the larger group in a dire situation. It is difficult to find any consideration that would favour treating the mild rare disease over the severe common disease.

(Case 4) *Mild common disease versus severe rare disease*: while a maximiser would choose the larger group so as to achieve the greatest aggregate benefit, the equal claims view would consider it unacceptable to allow the severe rare disease to go unfunded. The equal claims view would choose to treat the rare disease, even though it costs more per patient and per QALY, in order to attend to the greater claims of the severely ill.

The equal claims view only diverges from the maximising view in case 4. In all other cases it must side with maximisation and choose the common disease, or defend implausible conclusions. If rarity was truly driving these judgments, then in cases 1 and 2, when all else is equal, rarity would have to at least provide some sort of consideration in favour of choosing the rare disease.

Even an equal claims proponent who did not at all value maximising the good and was indifferent in cases 1 and 2, or a strong non-maximiser who preferred the rare diseases in cases 1 and 2, would run into trouble in case 3. In case 3, the same consideration that supports choosing the rare disease in case 4 now favours the common disease: without help, this group will be left in a dire situation, while the same is not true of the group with the rare condition. Therefore, it would be inconsistent for the equal claims view to choose the rare disease in case 3. Thus, a consistent equal claims view would choose the rare disease in case 4, and the common disease in case 3. A consistent equal claims view that also gives some value to the aggregate benefit would choose the rare disease in case 4 and the common disease in cases 1, 2 and 3.

These cases demonstrate that it is severity, and not rarity, that is driving the judgments of the equal claims view. The most severe condition takes priority; if severity is equal the choice that maximises aggregate benefit takes priority. The move from an equal claims view to a policy of giving extra weight to treatments according to the prevalence of the disease is, therefore, confused. This confusion may arise from comparing the serious rare diseases we hear about with less severe ailments for which public health insurance normally provides care, and then mistakenly attributing the resulting sense of unfairness to a rare disease being overlooked for more common ones, rather than to a severe

[iv] This assumption needs to be challenged, and the relationships between justice in allocation and how badly off a patient has been, how badly off a patient is now, how badly off a patient is expected to become and the urgency of their condition need to be analysed separately, and public views on these different dimensions need to be elicited separately. Here I only aim to make the point that severity should play a role in priority setting.

[v] There is a complex body of literature on whether and to what extent the number of individuals in each population should determine such a choice. For a discussion, see Otsuka.[35]

disease being overlooked for less severe ones, which is what is truly objectionable.

Looking back at case 2 above with this view in mind, we would choose to treat the common severe disease, while recognising that it is profoundly unfortunate that it is not possible to also treat the equally severe rare disease. The fact that some patients are having their needs met while others have equal needs that remain unmet can be a reason for having more resources allocated to healthcare, or taken from less severe diseases, in order to cover the severe rare disease. This reason seems especially compelling considering that, by deciding to treat the larger group, we have already recognised that a disease at this level of severity gives individuals a claim to assistance that society ought to attend to. But there is no justification for prioritising the rare disease over an equally severe common disease.

If my view is correct, then we have reasons to treat the financing of treatments for severe diseases differently from non-severe diseases, regardless of prevalence. The group of severe diseases will include, but not be limited to, the rare diseases that currently benefit from orphan drug policies. Rather than raise the cost-effectiveness threshold according to prevalence, then, the appropriate way to recognise the morally relevant consideration would be to vary the threshold according to the severity of diseases.

NORMATIVE FRAMEWORKS SUPPORTING THE SEVERITY VIEW

This discussion takes some form of an equal claims view for granted, taking no stance on why we do (or ought to) hold this view. A number of ethical theories can give rise to concerns for equal claims, and to concerns for severity specifically, and consequently support my account of the role that severity should play in priority setting in healthcare.

A concern for severity will often stem from a concern for the worst off. Egalitarian or prioritarian views naturally lead to a concern for severity through this path. Egalitarianism, if focused on the health sphere, gives us reason to prioritise improving the health of those with severe diseases, since the more severe the disease the greater the gap in health between the patient and most others. Egalitarian views that focus on welfare may well come to similar judgments due to the negative impact that severe disease has not only on health but also on many other dimensions of welfare. For Hausman, other dimensions of welfare can compensate for losses caused by less severe diseases, but severe diseases cannot be compensated for in this way and therefore should be of concern to welfare egalitarians.[36] The same reasoning applies to prioritarian views. Whether focused on welfare or on health, and whether health is measured in life-years,[37] or QALYs,[38] those with severe diseases are likely to be among the worst off in a relevant way.

Attention to equal claims can also be founded on ethical views that are concerned about how people stand in relation to one another, rather than about particular goods or distributional outcomes. Daniels' view of health as a component of fair equality of opportunity, which a just society should provide to all,[39] is compatible with the severity view. More severe diseases will usually cause greater departure from the normal range of opportunities and thereby place more restrictions on one's ability to formulate and pursue a life plan and participate in social cooperation as a free and equal citizen. All else being equal, then, orphan drugs that can bring patients who start out with greater opportunity restrictions closer to normal functioning have greater value than interventions that help patients who already start out closer to the normal opportunity range. Thus, prioritising severity promotes fair equality of opportunity, an important dimension of equal standing.

In Scanlon's contractualism, the concern for equal standing is expressed by the requirement that right actions be guided by principles that no one could reasonably reject based on its effects on any single person.[40] It seems reasonable for a few with severe diseases to reject a principle that leaves each of them with a great burden so that many others can each be relieved of a smaller burden. It seems more reasonable to ask each of the many to accept a smaller burden in order to help others with more severe conditions.

DO WE HAVE REASONS TO OFFER INCENTIVES FOR THE DEVELOPMENT OF DRUGS FOR RARE DISEASES?

The discussion in the previous sections, about how to deal with drugs for (severe) rare diseases at the funding stage, presupposes that such drugs exist. Given the lack of incentives for manufacturers to develop these drugs, however, such drugs are less likely to come into existence than drugs for common diseases. As mentioned above, some developed countries have addressed this problem by giving rare diseases a different kind of special treatment: subsidies for research and/or favourable approval and market entry processes for drugs targeting rare diseases.

This type of special treatment operates differently and has different consequences than raising the cost-effectiveness threshold, and poses some distinct ethical and political questions. Yet, at a general level, both types of special treatment can be described as putting more of society's resources towards rare diseases than would be the case if we stuck to a strict QALY-maximising strategy. Given this similarity, I believe that a focus on severity can also explain what seems wrong about our current drug development system in the absence of such subsidies, and therefore why this second type of special treatment is justified as a way to correct this wrong.

The unfairness I identified in following a strictly maximising criterion for funding decisions is that the cost-effectiveness threshold did not respond appropriately to the burden that each disease imposes on an individual. Similarly, what seems unfair in our current system for developing and marketing drugs is that it does not respond to severity in the way it ought to.

Our current system of drug development gives great weight to potential profits when setting priorities for pursuing research. This system has its upsides, such as a high incentive to innovation and efficiency, but also downsides such as greater sensitivity to the size and wealth of a drug's potential market than to the severity of the disease to be targeted or to the overall burden of disease. This results in a systematic de-prioritisation of severe diseases with small patient populations only because they happen to be rare, in favour of minor conditions affecting large numbers, preferably in rich countries. It also leads to the neglect of common, often severe diseases that burden the developing world. Since, as I have argued here, prevalence is not morally relevant and severity is, this is unjust.

The practice of choosing which drugs to invest in by the size and wealth of the potential market discriminates on morally irrelevant grounds, namely prevalence and ability to pay. Just as varying the cost-effectiveness threshold according to severity is a means to make the results of funding decisions align more closely with the intuitive judgments revealed by the cases in part 4, offering incentives for research based on severity would affect manufacturers' calculations so as to make the results more similar to what we consider fair.

The current system for drug development and marketing is historically contingent, it evolved organically over time. The observed neglect of severe rare diseases, and severe neglected diseases in the developing world, are an accidental result of how research funding and returns on investment currently work, not a feature deliberately put in place for reasons that need to be overridden by patients' claims to assistance. On the contrary, if arbitrary features of the system cause unjust outcomes, we have a pro tanto duty to alter the system so as to remedy the injustice. Providing incentives for research on severe diseases that is not encouraged by the market alone (due to a small potential market or to other reasons, such as high cost and complexity of research) corrects the unresponsiveness of the system to severity, while keeping its desirable features of innovativeness and efficiency.

If my view is correct, then, here too we have reasons to treat severe diseases differently, regardless of rarity. The appropriate special treatment would shift the system's priorities towards severity, or at least make the system behave as if severity was its priority.

As mentioned in section 3, there is one rationale according to which, arguably, low prevalence matters in this context. The current incentives for drug development make it the case that having a rare disease is bad brute luck over and above the bad brute luck of the disease itself, of having to endure the pain, suffering and loss of opportunities that the disease causes. The latter brute luck is identical for identically severe diseases, but the nature of our current research and development system puts the additional burden of neglect on those with rare diseases. Since the prevalence of a patient's condition is in no way under their control, the current system creates an injustice against those with rare diseases. This suggests that we have a duty to compensate for this bad brute luck by giving rarity itself some weight in priority setting. If we were persuaded that rarity matters in this context for this reason, we could still prioritise addressing the most severe cases of brute luck (the most severe diseases) if we could not address them all, but would presumably have to pick a rare disease over a common one when severity is equal, the implausible response to case 2 in section 4 above. Importantly, the burden of neglect does not fall only on those with rare diseases, as demonstrated by the case of neglected tropical diseases, which are severe and common. Rarity, therefore, still fails to track this additional burden.

POLICY IMPLICATIONS

The crucial policy implication of the view I defend here is that severity, rather than prevalence, should determine the decision of whether to allocate additional resources towards funding treatments for diseases that the current system does not adequately serve. This contradicts some existing orphan drug laws, which define which diseases are eligible for special treatment based on a prevalence cut-off below which diseases are considered rare. Besides the arbitrariness of this cut-off and the sharp discontinuity in treatment that this approach introduces between the most common disease below the cut-off and the rarest disease above it, there is the more fundamental problem that, to the extent that they respond to prevalence, these policies fail to respond to what is actually morally relevant, and may overlook severe diseases that are expensive to treat for reasons *other* than low prevalence. In an analysis of egalitarian arguments for accepting higher costs per QALY for treatments for rare diseases, Juth and coauthors[41] also conclude that rarity is not morally relevant, although they allow for the possibility that it can be used in policy as a weighting factor to compensate for morally relevant factors.

It is precisely because prevalence is irrelevant to the individual burden of a disease or to any other factor influencing the strength of a particular patient's claim on societal assistance that it is inappropriate grounds for prioritisation. It is this inappropriateness that makes the incentive problems of the current system and resulting neglect of rare conditions objectionable to begin with. The main goal of a rare disease policy should be to make prevalence irrelevant, and to give rare diseases appropriate priority based on their severity.

Therefore, policies such as setting cost-effectiveness thresholds in inverse proportion to prevalence ('as a disease becomes less common a higher cost per QALY is accepted'[13]) seem inadequate even though they avoid setting an arbitrary prevalence cut-off. Because it treats prevalence as the determinant of how much we should be willing to pay to treat a disease, such a policy seems to require a compelling reason to value rarity by itself. Some of the outcomes of this type of policy would be in line with the judgments we consider plausible. For instance, a treatment for a mild rare disease would still be unlikely to be funded under this policy because the small potential gain in QALYs could not be aggregated across a large patient population as happens for mild common diseases. So some objections that could arise from not taking severity into account could be sidestepped. However, it would still have problematic results, as two rare diseases equal in everything but prevalence would be assigned two different cost-effectiveness thresholds due to one being more rare than the other, even though the more common disease is still rare enough to run into the low incentive and high cost problems and be poorly served by the current system.

Other approaches propose 'ring-fencing' of funds, the creation of separate budgets dedicated to treatments of rare diseases only, to be allocated by a separate process. In England, for instance, treatments for some ultra-orphan diseases are commissioned by a national group instead of by local care trusts, while Scotland has a dedicated New Medicines Fund to pay for rare and end-of-life conditions. Ring-fencing approaches seek to avoid the high opportunity cost that arises when funds from the general healthcare budget are used to fund very costly treatments for some, leaving health gains to others that would be cheaper and greater (in the aggregate) unfunded.

While such a solution effectively removes orphan diseases from a 'competition' with more prevalent conditions that may seem unfair, this appears to be more of a political accommodation than a principled solution to the problem. Since both the general funds and the ring-fenced resources are societal resources allocated to healthcare, spending the ring-fenced funds in expensive treatments has the same opportunity costs as spending general funds on the same treatments. The division between funds for common and for rare diseases is artificial, there seems to be no principled justification to adopt different priority-setting criteria to each of these resource pools. There is a discussion to be had about how to fairly allocate the burden of providing the resources destined for rare diseases and to healthcare in general, but it is a separate question from whether, to what extent and under what circumstances we should be willing to pay more to treat costly severe diseases instead of maximising the health benefits we can obtain from whatever amount of resources we decide should be allocated to healthcare.

An example of a policy consistent with the view I am defending here is the recommendation issued by the third Norwegian Committee on Priority Setting in the Health Sector, which proposed three prioritisation criteria: cost, effectiveness and

the 'health-loss criterion'.[42] The 'health-loss criterion' assigns greater priority to diseases that, on average, cause greater loss of healthy life-years compared with a life expectancy of 80 healthy life-years. This can be understood as an operationalisation of severity that is concerned with the effects of disease over the lifetime—in the terms I used in section 3, this understanding of severity combines a concern for *how badly off a patient has been in the past* and *how badly off a patient is expected to become if not treated*. More generally, Norway and Sweden take severity seriously in healthcare priority-setting[43]—not only in the case of rare diseases—and are currently tackling the challenge of incorporating this complex concept into policymaking.

CONCLUSION

Current orphan drug policies aim to address the lack of access to treatments by patients with severe rare diseases, out of a concern that meeting their claims is as important as meeting claims of patients with common diseases. The prevalence of a disease is irrelevant to the strength of these claims. Accordingly, policies aiming to treat equal claims equally should make prevalence irrelevant to funding decisions. It is severity, not prevalence, that drives our judgments that important claims are being overlooked when treatments for severe rare diseases are not funded. Unlike prevalence, severity is an appropriate consideration for priority setting. Therefore, we have reasons to raise the cost-effectiveness threshold for costly severe diseases, or otherwise give these diseases some form of special treatment, regardless of how rare they are.

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