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Review

Preserving the 'commons': addressing the sustainable use of antibiotics through an economic lens

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ABSTRACT

Background: As the growth of antibiotic resistance has resulted in large part from widespread use of antibiotics, every effort must be made to ensure their sustainable use.
Aims: This narrative review aims to assess the potential contribution of health economic analyses to sustainable use efforts.
Sources: The work draws on existing literature and experience with health economic tools.
Content: The study examines some of the weaknesses in the health, regulatory, and industry arenas that could contribute to inappropriate or suboptimal prescribing of antibiotics and describes how economic analysis could be used to improve current practice by comparing both costs and health outcomes to maximize societal wellbeing over the longer-term. It finds that economic considerations underpinning current antibiotic prescribing strategies are incomplete and short-termist, with the result that they may foster suboptimal use. It also stresses that perverse incentives that drive antibiotic sales and inappropriate prescribing practices must be dis-entangled for sustainable use policies to gain traction. Finally, payment structures can be used to re-align incentives and promote optimal prescribing and sustainable use more generally. In particular, eliminating or altering reimbursement differentials could help steer clinical practice more deliberately towards the minimization of selection pressure and the resulting levels of antibiotic resistance.
Implications: This work highlights the need for appropriately designed cost-effectiveness analyses, incentives analysis, and novel remuneration systems to underpin sustainable use policies both within and beyond the health sector. **C.M. Morel, Clin Microbiol Infect 2017;23:718**

Introduction

As antibiotics are a public good, their preservation for future generations through 'sustainable use' should be at the forefront of public policy [1]. Sustainable use implies optimal prescribing and consumption of these drugs in a way that slows the growth of overall pathogen resistance, thereby maximizing the wellbeing of humans now and in future. It also encompasses lowering both 'appropriate' and 'inappropriate' demand for antibiotics. The first involves infection prevention and control, vaccine campaigns, investment in new vaccines, and other preventive or curative technologies. The second can be achieved through public awareness, stewardship initiatives to better guide prescribers, limits on agricultural use of antibiotics, rapid point-of-care diagnostics, and improved guidelines and treatment algorithms where appropriate [2]. As such, sustainable use requires a society-wide, public health, long-term, 'OneHealth' approach [3]. It necessitates careful consideration of a number of complex social and time-related trade-offs such as: i) present-day antibiotic use vs. future efficacy; ii) treatment of individual patients vs. wider public health goals; and iii) the present vs. the future cost of antibiotic resistance.

In view of the trade-offs involved, the sustainable use of antibiotics implies an optimization across both space and time. By measuring utility, or wellbeing, and allowing quantitative comparisons of health states and investments, economic analysis is the ideal way to achieve this optimization. This study describes how the implicit economic analysis that underlies current policies and

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regulations is flawed. It also shows how a more holistic approach, one that takes into account the incentives of key actors in different sectors, can bring to light critical inconsistencies and ultimately help bring policies into line with sustainable use goals. It is only through coherent sustainable use policies that we have any chance of slowing the growth of antibiotic resistance. See Table 1 for a summary of the review's recommendations.

More appropriate use of economic tools

Protecting the efficacy of antibiotics requires minimizing the emergence, growth, and transmission of pathogen resistance. This can be achieved through complementary practices by physicians and patients, such as using prior microbiological diagnosis when possible, choosing the antibiotic with the most narrow spectrum that covers the causative pathogen, lowering selective pressure on any one drug through broader prescribing strategies (weighing long-term public health costs against individual patient benefits), and adherence with treatment regimens. Although definitions vary, optimal use definitions that function as the basis of antibiotic stewardship programmes seek to optimize clinical outcomes while minimizing the unintended consequences associated with antibiotic use, such as toxicity, the selection of pathogenic organisms, and the emergence of resistance. In theory such policies may also have a secondary goal of reducing healthcare costs without harming the quality of care (definition adapted from [4]). In many cases, however—especially in the treatment of uncomplicated infections—the cost component is fairly prominent when choosing among alternatives. Indeed the World Health Organization defines appropriate use as 'the cost-effective use of antimicrobials which maximizes clinical therapeutic effect while minimizing both drug-related toxicity and the development of antimicrobial resistance' [5].

Crucially the cost-effectiveness considerations underlying current prescribing policies do not include comprehensive, time-dynamic economic analyses but rather are based on intuitive assessments of the short-term costs and benefits of individual drug treatments. For example, they ignore any potential population-level gains associated with prescribing different products for the same indication to different patients at the same time, or with strategically rotating drugs for a given indication over time. The question posed in current practice is essentially 'amongst the drugs that are largely efficacious, which are the cheapest?'. The cheapest drug thus makes up the initial treatment of choice (at least for uncomplicated infection) and ends up being used most of the time. Alternatives are principally used when treatment fails for an individual patient, or treatment fails consistently within a given population and the first line drug is abandoned for another one.

The underlying assumption of current practice is that minimizing exposure to the more expensive antibiotics helps minimize selection pressure on those, usually newer molecules, thereby preserving their efficacy for use as a last resort or for the future when the cheaper alternatives have been exhausted (there is, of course, also a dynamic effect in that the prices of all drugs are likely to decrease after their patent life if there is some form of competition). This approach has obvious intuitive appeal but may not be optimal. An explicit, economic-based analysis may reveal other strategies that more efficiently alleviate the build-up of drug resistance and potentially provide a larger number of efficacy-years or of effectively treated episodes across the population over time.

From the perspective of economic analysis the short-term nature of these informal assessments ignores the future cost of resistance and how this cost may be affected differently by different prescribing strategies. Unfortunately, these limitations are reflected in treatment and health policies more broadly. Optimal selection among antibiotic alternatives may in some instances require prioritizing wider and longer public health interests (e.g. the overall minimization of selection pressure through time) over those of the individual patient. Indeed the re-orienting of antibiotic use towards sustainable use goals could require a discussion of the level of side effects that are acceptable for the sake of public health. Of course this must include the ethical considerations of putting long-term public health ahead of certain individual patient gains (e.g. possibly slightly longer morbidity for the individual patient).

An additional problem is the absence of long-term perspective in current practice which ignores dynamic effects such as the relative impact of future innovation. Different prescribing strategies affect demand for antibiotics differently and thereby affect the effectiveness of 'pull' within the R&D market to varying degrees. For example, a prescribing strategy that explicitly varies the use of equally efficacious products could, in theory, create more market space than one that concentrates use on individual products through to exhaustion. The inclusion of market dynamics in the overall assessment of prescribing practices is presently lacking.

Acknowledge resistance as a safety issue within regulation

Unfortunately, the short-termist approach to the antibiotics problem is re-enforced by the very nature of current regulations. Agencies such as the US Food and Drug Administration and the European Medicines Authority—which are mandated with assessing safety ('risk') and efficacy (pertaining here to non-inferiority, 'benefit') of medicines—only consider the short-term safety to the individual patient, in conjunction with trial evidence of efficacy provided by the developer. In general, the longest time horizon

Table 1
Summary of recommendations

Recommendation	Audience
The choice of antibiotic prescribing strategy should be made on the grounds of health economic analyses that take a longer-term perspective and more explicitly take into account costs, risks, and effects associated with resistance as well as the impact of different prescribing strategies on innovation within the market	Health economists supporting guideline committees, Health Technology Assessment and reimbursement agencies, etc.
Acknowledge resistance as a safety issue within regulation, using a longer time horizon to capture resistance-related safety risks leading to more restrictive labelling	Market authorization agency (e.g. EMA, FDA)
Reward pharmaceutical innovation independently of unit sales	Governments and international bodies via innovation funds
Ban marketing of antibiotics, replacing their role in the transfer of essential product information (e.g. regarding safety and appropriate use) to other actors such as public health authorities or academic detailers	Regulators
Directly align industry incentives with public health objectives such as sustainable use and infection control through bonus payments tied to outcome such as antibiotic susceptibility over time	Governments, international bodies, public health authorities via innovation funds
Use mediated end price differentials to further motivate optimal prescribing	Public health authorities, payors, providers
Remove perverse incentives that could lead to inappropriate prescribing of antibiotics	Public health authorities, payors, providers