THE ECONOMICS OF REDUCING ANTIBIOTIC USE TO REDUCE ANTIMICROBIAL RESISTANCE

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Human consumption of antibiotics is only beneficial to societal welfare when the correct antibiotics are used and they are given at the right dose for the optimal length of time and only to those who need them. There are many cases in which these circumstances do not occur, thereby increasing the risk of adverse outcomes. One of the most important for public consideration is antimicrobial resistance (AMR). Therefore, the discussion of the economics of efforts to control AMR will be considered in terms of the cost of managing production and consumption of antibiotics because this factor is so intimately and inextricably related to the development of AMR.

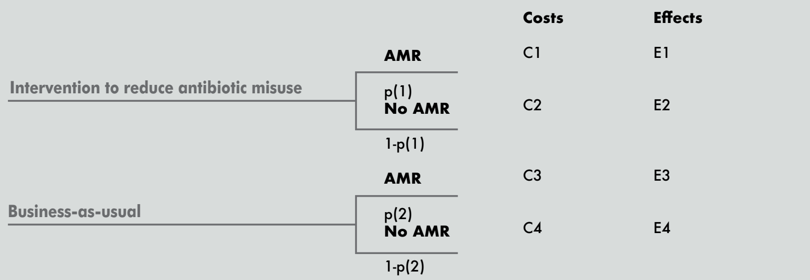
Shortly after the first widespread use of antibiotics for human health in the 1940s, there was already evidence that targeted pathogenic agents could develop resistance to an antibiotic and the realization that further use of any antibiotic agent would cause antimicrobial resistance (AMR) as a natural part of the Darwinian evolution of living organisms *(1, 2)*. Economic theory predicts that, without market distortions and if given accurate information, we would be compelled to stop using antibiotics in the current way they are being used when the adverse consequences of AMR are considered too great to accept the status quo. However, we know of many distortions that exist in this market and therefore we observe that overall the "bads" of AMR are not accounted for fully compared to the perceived "goods" of antibiotics as used in their current fashion. There is still widespread overuse or misuse. Correcting market distortions would then allow us to accurately answer the question of the level of resources we should to allocate to improving antibiotic use and therefore decreasing the risk of AMR. This article discusses market distortion, then examines interventions to decrease the risk of AMR and consider what economic factors need to be considered before attempting to implement them in specific settings.

An externality is a consequence of an economic activity experienced by unrelated third parties, and they can be positive or negative. A person taking less than the full course of an inexpensive first-line antibiotic prescribed for their condition may cause the organism infecting them to become resistant to that antibiotic. If that AMR organism then infects another person and they then need to purchase more expensive second-line antibiotics, this is a negative externality because the first antibiotic consumer is not paying the additional cost the second infected person must then pay.

Another negative externality of AMR occurs when a food or animal producer uses antibiotics to increase the productivity of their food production/livestock operation. They may reap the extra profits from the greater productivity but they are not paying the price of treating the AMR infections that their antibiotic use has caused.

To avoid market distortions caused by negative externalities

Figure 1: Cost-effectiveness decision tree and formula



$$\text{Incremental cost-effectiveness ratio} = \frac{\text{Difference in costs of the 2 scenarios}}{\text{Difference in the effects of the 2 scenarios}}$$

$$= \frac{[(p(1) \times C_1) + (1\text{-}P(1) \times C_2)] - [(p(2) \times C_3) + (1\text{-}P(2) \times C_4)]}{[(p(1) \times E_1) + (1\text{-}P(1) \times E_2)] - [(p(2) \times E_3) + (1\text{-}P(2) \times E_4)]}$$

from AMR, either the producers or consumers in the transaction above should pay for the externality, thereby "internalizing" it *(3, 4)*. If the food/animal producer or the meat/product consumer paid for the consequences of development of AMR from such agricultural antibiotic use and other antibiotic misuse, the market forces would then cause a correction towards much better antibiotic stewardship. Accounting for these factors could see the reallocation of up to US$ 35 billion in the United States alone *(5, 6)*.

When considering the cost-effectiveness of health interventions, the analyst must consider what two or more scenarios are being compared and what are the possible outcomes and their probabilities of occurrence. Then the expected costs and effects of the different scenarios can be compared. Decision trees are used to show the comparison: a simple model for comparing an intervention to reduce inappropriate antibiotic use to a business-as-usual scenario is given in Figure 1. The two scenarios are compared in terms of the costs and effects expected, which are determined by the probabilities of the events given in the model. In the scenario where the "Intervention to reduce antibiotic misuse" is used, there is a certain probability that AMR will develop, depending on how successful the intervention is. There is a different probability that AMR will develop in the business-as-usual scenario where the intervention is not implemented. Derived from this basic model is the equation for the incremental cost-effectiveness ratio or simply the cost-effectiveness of the intervention compared to business-as-usual.

The cost-effectiveness economic analyses of the possible interventions to decrease AMR that are discussed in this article can be conducted using this simple model as a basis. It provides a useful framework for determining the relative economic efficiencies of different approaches to addressing AMR. When the result of cost-effectiveness calculations are negative costs for positive health consequences, the intervention is considered "cost-saving", meaning the intervention improves health while saving money. On economics alone, such interventions must be implemented.

One change in antibiotic use for reducing the risk of AMR to consider is improving the prescribing practices of medical professionals. It is clear that physicians and other prescribing professionals give their patients antibiotics even when the available medical evidence does not support such use *(7, 8)*. They may do this because they do not have the best available evidence to prescribe medications correctly, because they succumb to patient expectations for such prescriptions or because they are influenced by outside incentives from the producers or purveyors of such drugs. There is evidence that interventions implemented in several settings to improve physician prescribing practices have been successful and that they can actually be cost-saving to the health system even without consideration of the adverse economic consequences of AMR *(9-12)*. The costs of such intervention should include the following:

- Training of clinicians:
  - time of the trainers;
  - opportunity costs of clinicians not providing their usual services while involved in the training;
  - associated costs of preparing for and conducting the training.
- Economic benefits to consider include:
  - reduced expenditure for antibiotics that are not indicated;
  - reduced costs of managing adverse events from inappropriate antibiotic consumption;
  - reduced lengths of stay in hospital for patients, if this occurs;
  - associated improvements in other aspects of physician behaviour to be better-aligned with evidence-based medicine.

All economic analyses presented here must take into account, to the greatest extent that evidence allows, the economic consequences of the AMR that the intervention is seeking to minimize or eliminate.

Another intervention to reduce AMR risk by changing antibiotic use is education of healthcare consumers such that they take a more rational approach to their use of antibiotics. It may be more difficult to measure the effects of such interventions and there are fewer evaluations of such initiatives available *(13-15)*. The economic consequences of these interventions should include:

- Public behaviour change communication:
  - development of communication materials;
  - cost of media resources to distribute the information to the public.
- Economic benefits should include:
  - Reduced expenditure for inappropriate antibiotic purchases;
  - reduced costs of managing adverse events from inappropriate antibiotic consumption
  - possible reduced cost of unnecessary medical consultations for self-limiting conditions.

A third intervention for changing antibiotic consumption to reduce AMR risk is related to the first two demand-side interventions but this one addresses the supply of the antibiotics market and it involves regulation of that market. In some countries, especially low- and middle-income countries, there are few regulations on the supply of antibiotics and all types may be available in the free market *(16-18)*. Therefore, consumers with no scientific knowledge of the type/dose/route of administration or duration of the course of antibiotics for a specific condition nor their side-effects or contra-indications, are free to purchase and consume essentially any antibiotic commercially available as long as they can afford the price. It is often patients with no access to a qualified professional medical for consultation because they cannot afford the high price, who are left to purchase whatever medication they can afford in the free market *(19)*. In such cases, it is highly likely that the antibiotic purchased and used by such a consumer would not be the correct type for the condition or not taken appropriately and the risk of AMR would therefore be higher. This problem could be curtailed with regulation of the pharmaceutical marketplace to restrict the availability of antibiotics only to those patients with a prescription from a qualified medical practitioner with the knowledge, skills, willingness and responsibility to order only appropriate antibiotics. Adequate enforcement of the regulations must also be applied. It is also possible that application of such regulations may reduce the risk of counterfeit antibiotics becoming available in the marketplace (*20, 21)*. The economic consequences of these interventions should include:

- Preparation of regulations through a jurisdiction's mechanism:
  - scientific and pharmaceutical industry consultation;
  - cost of lobbying legal entities to implement new regulations;
  - cost of training all stakeholders in the new regulations;
  - cost of enforcement through active, effective policing;
  - cost of additional medical consultations from those who previously purchased antibiotics without prescriptions.
- Economic benefits should include:
  - reduced expenditure for inappropriate antibiotic purchases;
  - reduced costs of managing adverse events from inappropriate antibiotic consumption;
  - possible reduced costs of unnecessary medical consultations for self-limiting conditions.

A fourth intervention to decrease the risk of AMR involves the supply of new pharmaceutical agents to ameliorate the problem. Development of new antibiotic agents is disadvantaged relative to development of many other types of pharmaceutical agents, particularly those that are used to treat chronic conditions rather than acute infections. For example, pharmaceutical companies make substantively greater profits from developing new products for diabetes treatment compared to new antibiotics *(22)*. Not enough new antibiotics are being discovered to counteract the rate of development of AMR to existing antibiotic formulations *(23)*. Economic incentives could be provided to universities, private research companies and pharmaceutical companies to develop and bring to market new antibiotic agents for eventual introduction into the market. As a greater number of such agents are developed there could be a regular rotation of the agents into and out of widespread production and distribution so that the infectious pathological agents they are developed to work against do not have an adequate opportunity to develop biological defence mechanisms that would render them resistant to antibiotics in current circulation.

Such an intervention could only be effective if there was widespread buy-in from entities that fund academic and commercial pharmaceutical development and it would likely need to be combined with regulation of antibiotic use to a degree that many political and industrial entities may find unacceptable. The economic analysis evaluating the consequences of interventions to promote pharmaceutical innovation include:

- Incentives for pharmaceutical development:
  - scientific and pharmaceutical industry consultation;
  - cost of lobbying policy and industry entities to develop acceptance of incentives;
  - cost of administrating the incentive programme to ensure its appropriate application;
  - cost of the incentives (e.g., industry tax payment changes, grant making);
  - cost of additional medical consultations from those who previous purchased antibiotics without prescriptions.
- Economic benefits should include:
  - profits resulting from development of new antibiotic products;
  - economic implications of use of the innovative products that are possibly more effective than existing pharmaceuticals.

The economic definition of a public good is one that individuals can consume without diminishing its availability for consumption by others and one for which consumers cannot be excluded by others. In this context, the general effectiveness of antibiotics (or the absence of AMR) can be considered a public good. As such, its protection is not supported by normal market mechanisms and it is generally undersupplied in the free market. Given the strong association between antibiotic use and AMR, the antibiotic market cannot be considered in the same light as other pharmaceutical products, such as medication to treat diabetes or cardiovascular disease, where their overconsumption would not have such an adverse effect on human welfare. Therefore, it must be protected with outside intervention. The four interventions described here have been considered in isolation but in practice may have a more profound effect on controlling AMR if implemented in one of various combinations. For example, changing physician practice done simultaneously with public campaigns for social and behavioural changes to reduce public demand for antibiotics in cases where they are not indicated, is likely to have a greater effect than either intervention working alone. When such a combined implementation is applied, the economic evaluation becomes more complex but the basic principles of robustly determining all relevant costs and effects and modeling them over an appropriate time period in a decision tree still applies.

As discussed previously in this article and elsewhere in this volume, antibiotics are used in food animal husbandry to treat or prevent infectious disease among livestock or to promote growth and thereby improve the productivity of the food production. AMR can become a problem for human health if the resistant bacteria are transmitted to humans and cause disease. The additional cost of treating those with AMR compared to those with antibiotic-susceptible infectious agents has been reported in different settings *(24-26)*. Reductions in the use of antibiotics in this setting should be considered in light of the increase in treatment costs of human diseases and how these costs may escalate considerably in the future as the consequences of resistance – the severity of the diseases, the difficulty in treating the conditions, and the number of people infected – increases with time. Internalizing the externalities of AMR, as discussed above, is crucial.

Conclusion

Negative externalities of AMR from antibiotic use must be internalized to prevent market distortions. Economic principles can help determine the optimal level of resources to be allocated to reduce the risk of AMR in a given setting. The economic modeling used for this relies on the costs of the intervention, its economic consequences and the economic consequence of AMR itself in that setting. It is also a function of the risk of AMR both with and without the intervention under consideration. The higher the risk or AMR, the greater its negative economic consequences and the more effective the intervention, the more likely it will be seen to be cost-effective. Considering the high cost of AMR, interventions to reduce its risk may be cost-saving. ■

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