The economics of antibiotic resistance: a claim for personalised treatments

F. Antoñanzas¹ · H. Goossens²

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Concept and epidemiology

Antimicrobial resistance (AMR) is the ability of microbes to grow in the presence of a chemical (drug) that would normally kill them or limit their growth. Antimicrobial resistance makes it harder to eliminate infections as existing drugs become less effective. In 1945, Alexander Fleming already warned that misuse of antibiotics could result in the selection of resistant bacteria. AMR is a growing public health threat, and many governments have adopted policies to combat it as in the future common infections could become fatal. According to the World Health Organization (WHO), “the development of resistance is a normal evolutionary process for microorganisms, but it is accelerated by the selective pressure exerted by widespread use of antibacterial drugs. Resistant strains are able to propagate and spread where there is non-compliance with infection prevention and control measures” [1].

Unless action is taken, it is estimated that by 2050, up to ten million additional lives will be lost prematurely each year because of AMR. From European Antimicrobial Resistance Surveillance System (EARS-Net) data collected in 2015, the European Centre for Disease Prevention and Control (ECDC) estimated 670,000 infections with antibiotic-resistant bacteria, and these infections accounted for an estimated 33,000 attributable deaths and 870,000 disability adjusted life years (DALYs). The burden for the EU and European Economic Area has increased since 2007 and was highest in Italy and Greece [2]. In the USA, resistant bacteria are believed to affect approximately 2 million people and could annually cause more than 23,000 deaths [3].

There are epidemiological, economic and health care organisation factors which contribute to the emergence of antibiotic-resistant bacteria: social mobility and concentration of population in urban areas facilitate transmission of infections and bacteria carrying antibiotic-resistant genes; cheap antibiotics (many antibacterial groups cost less than half a Euro a day), the growth of per capita income in many countries, and the consideration of health as a high income-elasticity good (increasing income drives a higher demand for drugs in general and antibiotics in particular). These are all economic factors that drive higher antibiotic consumption. Health care organisation also influences antibiotic consumption depending on how patients access the system and whom they are referred to for treatment.

The ECDC estimates that 30–50% of all antibiotics prescribed in Europe do not benefit patients and thus simply increase the risk of harm to individuals, society, and future generations. For example, of all patients consulting for an acute cough, which is one of the most important reasons for consultation, experts estimate that only 10% should be prescribed an antibiotic, whereas the actual proportion of prescribed antibiotics in EU countries was 50% overall with a range from just over 20% to 80% [4, 5].

Several researchers analysed antibiotic consumption trends and worldwide distribution. In a recent publication by Klein et al. [6], it was found that during the period 2010–2015, the increase of consumption, measured as the number of defined daily doses (DDD), in the 76 countries analysed increased 65% (from 21.1 to 34.8 billion DDD), and the antibiotic consumption rate increased 39% (from 11.3 to 15.7 DDD per 1000 inhabitants per day). As a general result, high-income countries average about 25 DDD per 1000 inhabitants per day with a slightly negative trend during that period, while low and middle-income countries average about 15 DDD per 1000 inhabitants per day with a strong positive trend, which may lead to a convergence in consumption in the near future.

✉ F. Antoñanzas
fernando.antonanzas@unirioja.es

¹ Department of Economics, University of La Rioja,
26004 Logroño, Spain

² Laboratory of Medical Microbiology, Vaccine and Infectious
Diseases Institute, University of Antwerp, Antwerp, Belgium

Economics

The ECDC estimated at almost €1.5 billion per year during last decade the direct cost of infections caused by some of the most important antimicrobial-resistant bacteria in the EU, Iceland and Norway [7]. A similar study in the USA that included both direct and indirect costs gave a figure of \$55 billion for the year 2013 [3]. Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most common bacteria causing hospital-acquired infections. According to the EARS-Net data there is a gradient across Europe in the sense that Northern countries have lower proportions of MRSA (about 20%) while Mediterranean countries account for rates of about 50%. A similar gradient can also be observed with other antibiotic-resistant bacteria.

The economic analysis of AMR has adopted different approaches to get a better understanding of the impact of the problem for the health care sector and for society as a whole, usually segmenting it by type of resistant bacteria, by jurisdiction or by antibiotic family. There is an abundance of economic literature in this area. For MRSA infections, these analyses show a wide range of values depending on their methodology, but the main conclusions are that MRSA infection increases the length of hospital stays between 2 and 10 days, and direct costs are 1.5–3 times greater (in the range of €1,200–€50,000 more) than the cost with no infection. Other studies have focused on the efficiency of several policies (prophylactic, early diagnosis, fast diagnostic techniques, changing health care organisation, isolation policies, etc.) and have performed economic evaluations of different modalities which could be useful for managing AMR. Again, figures vary widely from one study to another, making generalisations difficult [8].

Policies

Public health policies are difficult to implement for a variety of reasons such as entrenched prescribing habits, increasing consumption trends in society, new access to these drugs in highly populated emerging countries, and the strong business interests of the pharmaceutical and agriculture sectors. In the EU the practice of using antibiotics to promote animal growth is banned since 2006 while in other parts of the world it is still allowed, or countries lack specific legislation on use of antibiotics for livestock. However, due to relaxed trading regulations, meat and fish products derived from animals fed with antibiotic growth promoters is not commonly tracked and their consumption is still allowed within the EU. See, for instance, the work by van Boeckel et al. [9] for a report analysing this important issue.

Thus, while in mostly high-income countries there is an excessive of antibiotics, and therefore they should reduce antibiotic consumption both for humans and animals, many low- and middle-income countries lack of access to these life-saving drugs and we can expect an increase in consumption.

In this context, we propose that policies to cope with AMR should be based on three pillars: innovation, reduction of antibiotics consumption in high-income countries, and development of diagnostic procedures to better target those patients who really need antibiotics.

As bacteria keep developing resistances against existing antibiotics, one potential solution is to develop new antibiotics so that the older ones can be replaced by new ones with a more complex mechanism of action that makes it difficult for bacteria to develop such resistances. Mechanisms of AMR have been studied by microbiologists to enable the design of new antibiotics in the future. However, in spite of the research in this area, during the last 25 years almost no new antibiotics have reached marketing approval. There are several reasons that explain the failure to develop new antibiotics: (1) drug companies do not expect a clear return on their investment in research and development, as existing antibiotics are very cheap (mostly generics) and the potential prices of a new drug if only based on comparative efficacy would not be very high (as it would likely be similar to the existing one); (2) the pharmaceutical industry strives to develop new antibiotics with different resistance profiles, but is uncertain about future rewards by health authorities in terms of price and reimbursement, which reduces its motivation for initiating R&D activities; (3) the duration of antibiotic treatments is short (only for acute processes) which makes its sales pattern totally different from that of a drug targeting a chronic disease; (4) moreover, new antibiotics will likely be prescribed as second-line treatments to patients for whom traditional antibiotics failed, which would shrink its market and, again, the company is uncertain about the sales penetration of the new antibiotic as resistances could quickly appear. In spite of much public funding to incentivise such research (for example, the EU has launched several research and collaboration calls on this topic over at least two decades and has spent hundreds of millions of euros in funding) and improved knowledge of the molecular mechanisms of AMR, so far, pharmaceutical companies have not been able to convert those inputs into new treatments that make it more difficult for bacteria to evolve new resistance mechanisms.

The second pillar must be based on health care systems, which have to establish treatment priorities, rationalise antibiotic prescription with guidelines that define the appropriateness of prescription and find new ways to reorganise the infection management to reduce antibiotic consumption.

The third pillar would be to base prescription on diagnostics. In this sense, it is useful to remember that although

health systems have evolved enormously, antibiotic prescription is still largely practiced as it was 60 years ago [10]; that is to say, community-based prescriptions are issued in a rather empirical way based on clinical criteria, and almost every physician can prescribe most of the therapeutic groups without restriction, with only a few groups reserved for specialised care (some only administered with special authorisation). Rarely are diagnostic tests used to guide the prescription of the billions of doses of antibiotics consumed worldwide each year.

In the new context of personalised medicine, diagnostics tests to guide treatments have made a difference. However, for antibiotic prescription it is not straightforward to use them in the EU due to Regulation (EC) 2017/746 under which candidate diagnostic test that could potentially help addressing this growing catastrophe, should not be introduced into routine care unless there is rigorous evidence, derived in the context where their use is intended, being cost effective and improve outcomes for patients. Critically, new tests should generate ‘actionable information’ that will enhance the quality of antibiotic prescribing decisions for patient benefit and reduce AMR. This regulation is rather strict in its requirements as the research and the evidence of the new tests based on efficiency is very challenging to provide. The efficiency of the diagnostics is complex to demonstrate as the outcomes of AMR reduction may take place in the medium/long-run and consequently the cause–effect relationship is difficult to quantify. This regulation requires thorough research on diagnostic techniques, the modification of prescribing patterns, the implementation of surveillance systems and the collection of economic data to show the efficiency of the whole process or policy.

In conclusion, AMR, like many other challenges to today’s society, is a global problem; and so it must be addressed with an international consensus. Nevertheless, feasible policies can be adopted at a local level to overcome the problems identified above. Such policies must be adapted to the specificities of each health care system to have a chance of success. The economic interests surrounding this matter are paramount and have to be adequately addressed. In this sense, a strategy based on development of new antibiotics together with a compromise to limit their use, so that AMR does not occur soon, could be appealing. These new antibiotics would be only prescribed in situations where

epidemiological data justifies their use. But this strategy has to be agreed upon and, of course, funded. Economic evaluation would contribute to assessing the potential policies for guiding selection of the most efficient ones. The task is huge, but the danger of not having effective treatments to cope with AMR is not potential but imminent.

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