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Antibiotic resistance – why is the problem so difficult to solve?

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Antibiotic resistance has been increasing along with antibiotic use. At the same time, the supply of new drugs to replace those rendered inefficient by the development has been dwindling, leading to concerns that we may soon lack efficient means to treat bacterial infections. Though the problem has received considerable interest, there are no indications that the situation is about to change. The present review maintains that this is because the two objectives - preserving the efficiency of existing drugs and increasing the supply of new ones - are partly opposing. Hence, creating an incentive structure compatible with both of them is not easy. Nevertheless, it is suggested that levying a fee on the use of antibiotics, and earmarking the proceeds from this fee for subsidizing development of new antibiotics, would be an important step towards increasing incentives for a better antibiotic stewardship while preserving incentives to develop new substances.

Keywords: *global problem*; *incentives*; *antibiotic stewardship*; *drug development*; *fees and regulation*

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It has been said that the discovery of antibiotics has changed medicine from a diagnostic to a therapeutic discipline (1). Certainly, several procedures, such as organ transplants, chemotherapy for cancer and orthopaedic surgery would entail high (possibly prohibitive) risks without the availability of effective antibiotics (2–4). Access to efficient antibiotics is, therefore, of crucial value to society. However, for quite some time it has also been known that all use of antibiotics leads to bacteria developing resistance (3, 5–9). Until the late 1980s, the problem was not perceived as very significant as new substances were developed and brought to market when resistance rendered existing drugs inefficient but, as few new antibiotics have been introduced since the 1990s, views have changed (1, 4, 10–12). Accordingly, several studies have pointed to the possibility that we in a not so distant future may lack effective means for treating bacterial infections and suggested ways to address the problem (1–4, 7, 8, 11, 12). Still, there is little indication that the spread of resistance has been contained or of an increase in the number of newly developed antibiotics. The purpose of the present paper is to discuss why this is so in the light of existing knowledge.

Scope of problem

One problem may be that it is difficult to present a comprehensive picture of the scope of the problem assessable to other than clinical experts. Resistance is a global phenomenon involving many types of infections, bacteria and substances and data are scarce, particularly so in developing countries. Nevertheless, using data from the European Antimicrobial Resistance Surveillance System (EARSS), the European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMEA) issued a report in 2007 on the situation in the EU, Norway and Iceland for six commonly isolated, often multi-resistant, bacteria (4). For the US, information on resistance in, more or less, the same bacteria are available from intensive care units (11, 13). Though the figures for the EU and the US are not quite comparable, Table 1 gives an indication of the prevalence of resistance in these two regions.

It should be noted that, for the European countries, there are large differences in the shares of resistant isolates in Table 1. In particular, there seems to be a north-south gradient, suggesting that they are less frequent in the Scandinavian countries and Iceland, and more frequent in the Mediterranean countries. It has been suggested that these differences can be partly explained by differences in antibiotic use between countries (9).

As to trends in resistance, the findings in the ECDC/EMEA joint technical report indicate that, for Europe as a whole, shares of resistant isolates, despite some variation from one year to another, have been fairly constant

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Table 1. Shares of resistant isolates in selected bacteria in the EU, Norway and Iceland and in the US

Bacteria	EU, Norway, Iceland (%)	The US (%)
Methicillin-resistant *Staphylococcus aureus* (MRSA)	22	60
Methicillin-resistant coagulase-negative *Staphylococci*	N.a.	89
Vancomycin-intermediate resistant *Staphylococcus aureus*	0.1	N.a.
Vancomycin-resistant *Staphylococcus aureus*	0	N.a.
Vancomycin-resistant *Enterococcus faecium* (VRE)	8	28
Penicillin-resistant *Streptococcus pneumonia*	4	11
3rd generation cephalosporin-resistant *Escherichia coli*	8	7
3rd generation cephalosporin-resistant *Klebsiella pneumonia*	19	20
3rd generation cephalosporin-resistant *Pseudomonas aeruginosa*	N.a.	30
Carbapenem-resistant *Klebsiella pneumonia*	<1 in most countries 42 in Greece	N.a.
Carbapenem-resistant *Pseudomonas aeruginosa*	18	22
Quinolone-resistant *Pseudomonas aeruginosa*	N.a.	33

Sources: Data for the EU, Norway and Iceland are from EARSS and refer to 2007 (cf. reference 4). Data for the US are from CDC National Nosocomial Infections Surveillance System and refer to 2002/2003 (cf. references 11 and 13).

over time for most of the bacteria in Table 1. Exceptions are MRSA, which declined from 2004 to 2007, and 3rd generation cephalosporin-resistant *Escherichia coli* isolates, which have been rising steadily since 2002. Again, there are differences between countries. For instance, despite the decline in the overall European share of MRSA isolates, two of the 28 countries reported increasing shares.

The ECDC/EMA-report also presents estimates of the consequences of resistance in terms of annual number of infections, additional deaths, extra hospital days and societal costs (direct health care costs and the value of productivity lost) caused by the selected bacteria (cf. Tables 2 and 3).

Data for the US are more scattered and often concern effects of all infections caused by resistant bacteria in singular hospitals (14) or, alternatively, the consequences of all hospital acquired infections (which may not necessarily have been caused by resistant bacteria) (15). However, there are studies reporting that MRSA caused 250,000–300,000 hospital acquired infections, about 2.7 million hospital days, and 12,000 deaths annually, resulting in annual costs of about US $9.5 billion (€10.1 billion) in the early 2000s and that VRE caused about 26,000 infections in US hospitals in 2004 (16, 17).

Regarding the development of new antibiotic substances, the ECDC/EMEA joint technical report (4), as well as successive reports from the Infectious Diseases Society of America (IDSA) (1, 11, 13) and Institute Of Medicine of the National Academies (IOM) (12), reveal that few new drugs have been forthcoming since the 1990s. Moreover, most of them do not represent a novel mode of action associated with a new chemical structure (18). Reviewing what is presently under development (phase II–III), ECDC/EMEA and IDSA concluded that expectations for a rapid change are low. In particular there seems to be a lack of new antibiotics expected to be effective in resistant gram-negative bacteria (3rd generation cephalosporin resistant *E. coli* and *Klebsiella pneumonia*, and carbapenem resistant *Pseudomonas aeruginosa*). A further cause for concern is the fact that pharmaceutical firms seem to have reduced investment in R&D for antibiotics in favour of other drugs with more promising financial incentives (1, 18–25).

Table 2. Number of infections, deaths and hospital days caused by resistant bacteria in the EU, Norway and Iceland 2007

Bacteria	Infections	Deaths	Hospital days
Methicillin-resistant *Staphylococcus aureus* (MRSA)	171,200	5,400	1,050,000
Vancomycin-resistant *Enterococcus faecium* (VRE)	18,100	1,500	111,000
Penicillin-resistant *Streptococcus pneumonia*	3,500	N.a.	N.a.
3rd generation cephalosporin-resistant *Escherichia coli*	32,500	5,100	358,000
3rd generation cephalosporin-resistant *Klebsiella pneumoniae*	18,900	2,900	208,000
Carbapenem-resistant *Pseudomonas aeruginosa*	141,900	10,200	809,000

Source: EARSS (cf. reference 4).

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Table 3. Societal costs of infections caused by antibiotic resistant bacteria in the EU, Norway and Iceland 2007 (million €)

Bacteria	Hospital costs	Out-patient costs	Productivity losses (absence from work)	Productivity losses (deaths)	Total
MRSA and VRE	424.7	5.5	91.1	145.6	666.9
3rd-generation cephalosporin-resistant *Escherichia coli* and 3rd-generation cephalosporin-resistant *Klebsiella pneumoniae* and carbapenem-resistant *Pseudomonas aeruginosa*	503.1	4.5	59.3	300.3	867.2

Source: EARSS (cf. reference 4).

Thus, although the data above do not present an encompassing picture of the resistance problem, they do suggest that it is significant and causes substantial societal costs. The question is, then, what remedies there are.

Suggested remedies – and their problems

On a general level, there seems to be consensus that there is a need for doing two things (1) preserve the efficiency of present substances by restricting use and, (2) increase the supply of new substances brought to the market (1, 4, 12). Unfortunately, as preserving the efficiency of present substances entails restricting use, the two objectives are partly opposing and not easy to achieve simultaneously. The discussion below uses examples from human medicine and there are concerns that the use of antibiotics in veterinary medicine may be an equally large problem. Moreover, resistance to drugs used in veterinary medicine may potentially affect resistance to drugs used in human medicine, and vice versa. However, as the problem is similar, the measures to address it will also be similar.

Measures to preserve efficiency of present substances

To preserve the efficiency of existing drugs, the need for guidelines for good antibiotic stewardship has been emphasised. Such guidelines have also been developed in several countries, although their implementation is not straight forward (26–30). They include, inter alia, recommendations to increase hygienic measures to control resistance in hospitals and community homes, to condition all use of antibiotics on prescription, to restrict use to bacterial infections only, and emphasise the importance of choosing the optimal therapy with regard to substance, administration, dosage and duration (27–35).

However, hygienic measures to control resistance in the institutional setting are not without costs to hospitals and nursing homes. Restricting use to bacterial infections and choosing the optimal therapy requires access to quick and reliable diagnostic facilities which may be a problem outside the hospital setting. Thus, faced with concerned patients presenting symptoms not easily diagnosed, physicians may have incentives to prescribe broad spectrum antibiotics with potential adverse effects on resistance. Informing the public on the issues involved might make a decision not to prescribe (until test-results are available) more acceptable, but this is by no means certain as the individual patient, while gaining the full benefit if treatment is effective, will not bear the full (societal) costs of increased resistance if it is not (36–38). Note that the opposite problem applies to hospitals and other institutions when determining if the implementation of stricter hygienic procedures is worthwhile (i.e. the institution will bear the full costs of the procedures in question while sharing the benefits with society at large).

To provide patients and institutions with incentives to consider the full societal costs of antibiotic use, it has been suggested that a fee corresponding to the expected costs of resistance should be levied on the use of antibiotics (1, 38). One problem with this solution is that the fee's demand-constraining effect may be limited if expenses for antibiotics are covered by insurance- or other third party payer systems. This could, of course, be overcome by exempting antibiotics from such schemes. However, that could raise concern regarding the access to antibiotics for less affluent patients (and countries) and, therefore, not be acceptable to policy makers.

Another problem is the determination of the size of the fee. The optimal fee should equal the expected marginal costs of resistance caused by antibiotic use (39). If it is set higher, demand will be reduced by too much (i.e. the health benefits from a marginal increase in use will exceed the expected costs of resistance caused by that marginal increase in use) and, if it its set lower, demand will be reduced by too little (health benefits from a marginal increase in use will be smaller than the expected costs of resistance caused by that marginal increase in use). As the effects of use on resistance are not fully understood, and may differ between substances, optimal fees cannot be expected.

One might consider determining the fee on the basis that it, for a given antibiotic, should generate enough returns to finance the development of a successor during

the period it takes until resistance becomes a problem for that substance. This requires information on development costs and time until resistance becomes a problem which is likely to depend on the antibiotic in question. However, some knowledge may be gained from past experience. While development costs are the property of pharmaceutical firms and, therefore, not easily accessible, some estimates do exist (40–44). Similarly, there are estimates of the time from introduction to detection of resistance for several substances (45). To determine the fee per unit of substance required to raise the necessary funds, information on the annual amounts consumed of different substances would also be needed. This information may be available from pharmaceutical statistics at least for some countries.

A fee determined in this way is of course unlikely to be optimal in the sense defined above. However, it is also unlikely to be too high since one result from studies estimating development costs is that these have been rising continuously since the 1970s. Accordingly, while it may not be large enough to achieve an optimal reduction in antibiotic consumption from the perspective of preserving efficiency, it may at least go part of the way. On the other hand, if the consumption of antibiotics is reduced, this could increase the problem of achieving the other objective – increasing the supply of new antibiotics.

Measures to increase the supply of new antibiotics

The supply of new antibiotics is dependent on research and development (R&D) to discover and market them. The outcome of this process depends on how difficult it is to identify substances with the desired characteristics. This, in turn, is a function of our understanding of the biological mechanisms involved, and of the requirements of the approval procedure. The less that is known about the biological mechanisms, the more resources are needed to uncover the issues involved. Similarly, the stricter the requirements for approval, the more resources are needed to satisfy them. More resources imply higher R&D cost. As to antibiotics, our understanding of the biological mechanisms is imperfect (not least regarding the mechanisms causing resistance), suggesting that R&D costs may be substantial. However, the literature does not indicate that they are significantly higher than for other types of pharmaceuticals (46). The bulk of the R&D work is carried out by pharmaceutical firms that depend on sales revenues for financing their operation. Of course, the larger the costs of R&D are in relation to the (expected) revenues, the smaller the incentives for pharmaceutical firms to engage in the process. The revenues are a function of the amounts sold and the price of the drug in question. Here, there are indications that revenues from antibiotics may be lower than those from other classes of pharmaceuticals that are prescribed for longer periods (18, 20, 25). Accordingly, it appears that insufficient financial incentives to engage in R&D is an important reason for the paucity of new antibiotic substances.

Several measures to increase the supply of antibiotics by changing incentives, ranging from changing the requirements for approval of new drugs, over tax-credits for research and public-private partnerships, to prolongation of patent duration, have therefore been discussed and suggested (1, 13, 18, 19, 46).

There certainly appears to be good reason to make adjustments in the requirement for approval. For instance, it is not clear why clinical trials for each infection – pneumonia, urinary tract infection, skin and soft tissue infection, etc. – should be required for approval of the use of a certain drug in their treatment if these infections are caused by the same bacteria. Thus, one suggestion is to condition approval on demonstrated efficacy towards specific organisms rather than specific infections (13, 19). This might also increase incentives for pharmaceutical firms to invest in developing drugs with a narrow spectrum relative to broad spectrum drugs, which would reduce resistance caused by the use of antibiotics.

Tax-credits have been applied to orphan drugs. The evidence is mixed in that, while they do increase incentives, effects appear to be limited since taxes only constitute a small part of the development costs. This is likely to be the case also for R&D in antibiotics.

Public-private partnerships in R&D for antibiotics may be a solution for specific drugs with very limited markets (XDR/PDR *Acineobacter* and *Kleibsella*) but could not, and should not, replace the efforts of private firms in R&D to replace antibiotics not facing these market limitations.

A patent excludes the holder from competition from generic substances which provides a monopoly position with the potential of gaining larger revenues from higher prices. However, patents are often sought early in the development process and, due to the longevity of this process, they may only last for a short period after the drugs are approved and marketed. Increasing the duration of patents for antibiotics might, therefore, provide better incentives for their development. However, the higher prices charged by the monopolist will also affect demand, and it has been shown that this may restrict the use of antibiotics by too much from the societal perspective (47–50). In addition, the revenues obtained may not necessarily be invested in the development of new antibiotics as they compete for resources with other pharmaceuticals that may be perceived to have better net present earnings (18, 20, 25). Finally, strengthening the monopoly position of patent holders may have detrimental effects on competition which could reduce incentives to develop new substances.

An alternative strategy may be subsidies targeted directly at the development of new antibiotics as this

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would compensate for lower expected sales revenues in comparison to other pharmaceuticals, particularly if measures to constrain the use of antibiotics are successfully applied. These subsidies of course needs finance which may be difficult to secure given tight government budgets. However, as noted above, if a fee is levied on the consumption of antibiotics as a measure to preserve the efficiency of existing drugs by containing their use, the proceeds from this fee could be used to finance such targeted subsidies. In this context, it may be noted that the demand-constraining effects of the fee would be less of a problem (i.e. if the fee does not reduce the use of antibiotics very much, the revenues raised and available for the financing of subsidies to develop new substances would be larger). Still, it is important that the subsidies are granted on competitive grounds. That is, the responsible body must have the competence to evaluate the potential of different research ideas, which is a very demanding task.

Discussion

The previous review has, while by no means being exhaustive, pointed at some of the problems in addressing the challenge from antibiotic resistance. Basically, they arise from the fact that the two objectives – preserving the efficiency of existing substances *and* increasing the supply of new antibiotics – are partially opposing. Thus, while several measures to achieve either one of them have been proposed in the literature, each with their own pros and cons that need to be considered, the problem remains that the more successful measures are in achieving one of the objectives, the more difficult will it be to achieve the other. Notwithstanding, the idea of levying a fee on antibiotics and use the proceeds to finance targeted subsidies may, at least partly, reconcile them. Also, measures aimed at facilitating the approval process do not necessarily limit the possibilities of containing the use of antibiotics. This suggests that more resources should be directed to the further development of these two strategies.

A further problem is that, ideally, measures to address antibiotic resistance should be applied on a global basis. This, of course, requires international cooperation which has proved to be complicated in other circumstances. Given the global nature of the resistance problem, as well as the fact that pharmaceutical firms operate on a global basis, the WHO seems to be a natural candidate for shouldering the responsibility of developing solutions to the implementation of the measures suggested in the literature. However, national governments may be reluctant to give up legislative power (which might be called for if principles of good antibiotic stewardship should be equally enforced in all countries) or the control of funds (which may be the implication of using the proceeds from a fee on antibiotics strictly for the development of new substances). Nevertheless, actions taken by national governments may go a long way to reduce the resistance problem, as visualised by the differences between countries in the EU in the magnitude of the problem.

Conclusion

Lack of incentives and awareness are important reasons for why the problem of antibiotic resistance is difficult to overcome. Increasing' incentives for supplying new antibiotics requires funding to subsidise R&D costs. To increase awareness, more information on the scope of the problem is needed which also requires funding. This funding could, at least partially, be provided by a fee levied on the use of antibiotics. As the fee would raise the price of antibiotics, it would also serve as an incentive to reduce antibiotic consumption, thereby contributing to preserving the efficiency of present substances.

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