



MALCOLM WILLET

HEALTH SYSTEMS PERSPECTIVES

Stoking the antibiotic pipeline

New antibiotics to tackle multidrug resistant bacteria are much needed. **Chantal Morel** and **Elias Mossialos** show how financial incentives might be used to persuade drug companies to develop them

Multidrug resistant bacteria pose a major health problem.^{1,2} In the European Union alone infections with these bacteria cause around 25 000 deaths a year.³ The economic burden associated with these infections is immense. One estimate suggests a total yearly loss of \$21bn-\$34bn (£14bn-£22bn; €15bn-€25bn) in the United States.⁴ Two thirds of deaths are due to infection with Gram negative bacteria, including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and Enterobacteriaceae such as *Escherichia coli* and *Klebsiella pneumoniae*.

New antibiotics to tackle resistant bacteria are urgently needed. Yet a recent report from the European Centre for Disease Prevention and Control and European Medicines Agency warns of an almost empty pipeline.³ Only two new drugs are under development; both are in the early stages when failure rates are high.

Six months ago, the Council of the European Union called on the European Commission to

develop proposals to promote the research and development of new antibiotics for multidrug resistant Gram negative pathogens,⁵ and the EU and US have set up a transatlantic taskforce on antimicrobial resistance.⁶ We analyse some of the mechanisms that could be used to stimulate drug companies to research and develop new antibiotics and suggest which are the most promising. Further analysis is available in the report commissioned by the Swedish presidency of the European Union.⁷

Why the antibiotic pipeline is dry

Industry has been reluctant to invest in research and development of antibiotics. In 2004, only 1.6% of drugs in development by the world's 15 largest drug companies were antibiotics.⁸ The lack of investment is due to several factors. Firstly, there are many generic antibiotics on the market that are still effective (to varying degrees) for most infections and public health authorities advocate these

as first treatment. New, more effective antibiotics are usually saved for severe infections. This sends a message to industry that any new antibiotics developed will be dispensed infrequently and used only in the last resort, even if rates of resistance to widely used antibiotics are high.

Secondly, the limited duration of antibiotic regimens, along with the fact that they are curative treatments (rather than used to mitigate symptoms of a chronic disease), makes them less profitable than drugs in other therapeutic areas. One estimate gives the risk adjusted net value of an antibiotic as 100, which compares with 300 for a cancer drug, 720 for a neurological drug, and 1150 for a musculoskeletal drug.⁹

Thirdly, rapid growth of resistance could, in theory, shorten clinical lifespan sufficiently to affect financial returns. Fourthly, negotiations with public purchasers don't tend to take into account the relative health gain from effective antibiotic treat-

Box 1 | Incentives to encourage drug company investment in antibiotics ¹⁵⁻¹⁹**Push mechanisms (early research subsidies)**

- *Grants and fellowships*—Funding for capacity building and training of both new and experienced researchers
- *Funding for translational research among academic laboratories*—To promote multidisciplinary collaboration to help tie basic research with drug development and medical practice: “from bench to bedside”
- *Support for open access research*—Funding for publicly accessible data repositories such as molecule libraries
- *Tax incentives*—Tax related privileges tied to early research activities
- *Product development partnerships*—Collaboration between public (or quasi-public) organisations with private developers to combine funding and expertise to bring a product to market.

Pull mechanisms (outcome based rewards)

- *Lump sum monetary prizes*—Large financial reward on development and authorisation of a product with specified characteristics
- *Milestone monetary prizes*—Incremental awards for reaching specified milestones in product development
- *Optional rewards system*—On completion of product with specified characteristics a developer can choose between maintaining the patent for that product or having the patent bought out with a financial reward
- *Research tournaments*—Competitions to be the first to develop a product to specified stages
- *Advanced market commitments*—Early commitment to purchase a drug at a pre-agreed price and volume once it is developed

Lego-regulatory mechanisms (market based outcome rewards)

- *Accelerated assessment*—Faster assessment process offered to highly desired products. In Europe this shortens assessment time by about 60 days
- *Accelerated approval*—This includes allowing some or much of phase III trials to take place after marketing. Examples include conditional and exceptional circumstances approval
- *Vouchers for accelerated assessment*—Accelerated assessment privileges that are transferable to other products within a company or to other companies
- *Pricing and reimbursement adjustments*—Reforms to better align prices to the value of the product, complemented by minimum purchase agreements in systems where volume measures are part of price negotiations
- *Antibiotic conservation and effectiveness programme*—Value based pricing, reimbursement for antibiotic surveillance and infection control; market exclusivity provisions tied to continued drug effectiveness; limited antitrust waivers; payments to hold a few drugs in reserve
- *Intellectual property extensions*—Extension of the period of market or data exclusivity
- *Wildcard patent extensions*—Patent right extensions that are transferable to other companies
- *Anti-trust reform*—Relaxing of anti-trust law to allow for effective collusion among developers with products with similar resistance related characteristics in order to reduce resistance arising from competition between drugs under different patents for the same condition

Combination mechanisms

- *Call options for antibiotics model*—A mechanism that allows an investor to purchase the right to buy a specified amount of an antibiotic for a specified price once it is developed. The earlier the purchase of the option in the development process, the lower the price
- *Orphan-like special designation status*—Drugs for rare diseases are currently given orphan status. In Europe orphan drugs receive help with protocols, tax incentives at country level, fee reductions before and after authorisation, and 10 year market exclusivity. Legislation to give similar help for antibiotics is under development

Box 2 | Characteristics of ideal incentive mechanism

- Is funded at a global or international level
- Rewards only true innovation
- Discourages over-marketing or over-consumption
- Shares some of the risk associated with development between developers and funders
- Allows for limited control over prices such that richer and poorer markets can be segmented
- Avoids complicated partnerships



ment, often granting higher prices to drugs (such as cancer drugs) that offer only a few months of additional life.¹⁰

Regulatory hurdles are also a deterrent.¹¹⁻¹² It can be difficult to recruit a sufficient number of participants in trials because of a lack of point of care diagnostic tests to identify them and there is a lower tolerance for adverse side effects within some indications of antibiotics than within other classes of drugs.¹³ Furthermore, the shifting of approval requirements (for example, from non-inferiority to superiority trials for some indications), the lack of clinical trial guidelines for many indications, and the ambiguity surrounding the acceptability of model based evidence to prove safety and efficacy further discourage developers.¹⁴

Mechanisms to stimulate investment

Box 1 sets out a range of mechanisms to encourage drug companies to develop new antibiotics.¹⁵

“Push” incentives lower the cost of research and development for the developer, thereby lowering barriers to entry (table). They may come from public or private sources such as venture capitalists or large philanthropic donors. Push incentives are particularly useful for attracting small and medium enterprises with limited funds.²⁰ However, developers paid through push mechanisms may lack the motivation to move into the later phases of production. There is also a risk of dampening entrepreneurialism. In addition, researchers (who are better informed than donors) may paint an overoptimistic picture of the potential of their work, which exaggerates the merits of up front investment. The funder therefore bears most of the risk with push mechanisms.

In contrast to push mechanisms, “pull” mechanisms grant financial rewards only after a technology has been developed. They tend to be larger than push incentives in order to lure investment through the more expensive later stages of development (table). As profits increase with decreasing development costs, pull incentives minimise inefficiencies. However, if the incentive relies only on the promise of rewards (as opposed to a fully earmarked fund), pull mechanisms are at the mercy of the changing political and budgetary tides. Financial rewards are reaped only after product development and so the developer bears all the risk.

Determining the size of a reward before drug development and subsequent use is difficult. It is hard to predict how effective and widely used a drug may eventually turn out to be, especially given that the long term resistance profile is highly unpredictable.

It is important not to overemphasise the lack of potential profitability in the antibiotic market. There is certainly a profit to be made from sales in developed countries

Lego-regulatory mechanisms are intended to lure development of new drugs to market with the promise of enlarged rewards through higher prices or extended effective patent life. They use the market to determine reward size. This gets round the problem of determining reward before the drug is marketed.

The basic elements of push and pull mechanisms can also be combined to create combination mechanisms. Early stage, upfront funding provides the financial space to explore new pathways and ideas; the promise of larger and delayed rewards persuades companies to undertake the later phases of drug development. The advantage of combining push and pull incentives in this way is that it spreads the risk between the funder and the developer. This is especially important for antibiotics given that the development of an entirely new product is a big technical challenge and thus presents a high level of risk.

Size of incentive

It is not easy to calculate what level of reward should be offered to encourage development of new antibiotics. The award has to be high enough to attract researchers with the necessary skills but not so high that it wastes scarce public or private resources. Achieving this balance is crucial, and several considerations must be taken into account.

The size of the reward would need to compete with the financial gains to be made from making drugs for chronic conditions. Most proposals suggest that judgment on who should be the winner of a prize or how prize funds should be distributed between companies should be linked to the scale of the innovation or the clinical benefits the drug brings. One proposal from Outterson is to award \$3bn to the first effective treatment for a high priority pathogen.²¹

The problem of going down this route is that there is a risk that society will end up paying more for an innovatory product than it is worth. It is, therefore, important not to overemphasise the lack of potential profitability in the antibiotic market. There is certainly a profit to be made from sales in developed countries. In addition, the developer of a new antibiotic may have their public reputation boosted if they bring a life saving product to market.²² Although these advantages are clearly not sufficient to drive the desired level of research into new antibiotics, they should be considered in the calculation of an appropriate award. The political palatability of paying out large sums given competing priorities within the public sector is also important. Pragmatically, it can be argued that

Advantages and disadvantages of different types of incentives

Advantages	Disadvantages
Push mechanisms (early research subsidies)	
Require smaller financial outlays	Risk of funding unsuccessful research
Remove barriers to entry	Funder and developer don't have the same level of information, allowing developer to act in its own interests
Attract small and medium enterprises	Risk is borne almost entirely by funder
Useful for encouraging discrete steps in research and development	Risk of dampening entrepreneurial momentum
Pull mechanisms (outcome based, extra market determined rewards)	
Reward only successful research	Risk is borne entirely by developer
Minimise developer inefficiencies	Attract only developers with substantial funding
More likely to encourage development of final product	Promise of large reward may lack credibility because of political and budgeting changes during product development
	Difficulty in predicting appropriate award size
Lego-regulatory mechanisms (outcome based, market determined rewards)	
Reward only successful research	Risk is borne entirely by developer
Maintain some link between product use and reward size	Attract only developers with substantial funding
Minimise developer inefficiencies	May impede competition
More likely to encourage final product development	

incentives that avoid overtly calculating reward size may receive less opposition as the high cost of drug development can be hidden.

Partnerships between industry and academic institutions

Some experts suggest that the key strategy for the promotion of drug discovery will be focused cooperation between academic institutions and small and medium enterprises.¹³ Indeed, the smaller companies are already starting to fill the gap left by the larger companies that have pulled out of antibiotics. Smaller companies require substantially lower annual sales to recoup investments (perhaps \$100m-\$200m a year) compared with \$500m-\$800m for large companies.²³ Precedent now exists for a relatively small company to acquire a promising molecule and carry it through development and to market.

In theory, a collaborative approach would be taken between the public sector and industry to allow for better control over prices and sales volumes (to minimise growth of resistance). However, complicated partnerships or shared rights could put participants off collaborative ventures based on incentive schemes. This is especially true for financially self sufficient large companies, which are traditionally autonomous. Previous public-private partnerships have shown that negotiations over rights can be long and wearing for all parties when the product in question has a market in both developed and developing countries. Antibiotics—a therapeutic area that lacks the positive public relations image of neglected diseases—would be even less likely to persuade large drug companies to accept shared rights agreements. This means that

options for partnerships are twofold: either limit industry participation to smaller companies, which can provide most if not all the necessary expertise and resources, or avoid partnerships and attract large drug companies.

The way forward

The characteristics of an ideal incentive mechanism (see box 2) and the desire for an equitable approach that engages developers of all sizes would suggest that neither push, pull, nor lego-regulatory mechanisms would be optimal to spur the desired investment in antibiotics for Gram negative pathogens. Rather, elements of each should be combined. The exact shape of the ideal package is, however, as yet unclear.

The call options for antibiotics model (box 1) is a combination method that provides investors with an option to buy rather than a commitment to buy and thereby places substantial risk on the developer. However, as the purchaser pays the developers a premium early on in the development phase this compensates for some of the risk. The call options model also spreads out the cost of drug purchase, which may be more fiscally feasible. The model's purchasing framework would make it relatively straightforward to set different prices for richer and poorer markets. However, the success of the call options model hinges on thorough evaluation of potential new antibiotics, which is difficult given that the developer knows much more about the merits of the drug than the investor.

Orphan legislation has been successful in stimulating drug development for rare diseases through national and European push incentives and an extension of market exclusivity. Similar legislative

options are being explored for antibiotics. Another approach would be to provide grants for capacity building of new and experienced researchers (who have switched to other therapeutic areas due to lack of funding), open access molecule libraries, and encourage translational research. At the very least, further progress must be made towards providing developers with clear and consistent guidance for conducting the required clinical trials.

Reforms that clearly link pricing and reimbursement to therapeutic benefit are also likely to lure developers back to antibiotics. Such reforms would have the additional benefit of aiding antibiotic conservation efforts as appropriate prices would be likely to lead to more careful prescribing (at least in systems with a public payer). That said, given the fragmented approach to pricing and reimbursement among European countries, achieving a common approach is clearly a long term goal.

At present, the proposals in box 1, which include value based pricing,¹⁵ seem to provide the most holistic lego-regulatory plan to align incentives within healthcare settings and promote the development of new drugs. However, the proposals require major reforms in several sectors, currently include many practical unknowns, and will take time to implement.

Conclusions

In view of the rapid growth of antibiotic resistance among Gram negative pathogens, the intricacies of the antibiotics market, and the cost savings from improved treatment, there is a public health as well as economic justification for intervention. Incentives to develop new antibiotics should be designed with some early funding to ignite interest and appropriate rewards for the high risks of research and development. Such action needs to be accompanied by parallel efforts to redress and dismantle incentive structures that lead to over-use of antibiotics, which is currently fuelling the spread of resistant bacteria.

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- 1 Infectious Disease Society of America. Bad bugs, no drugs: as antibiotic discovery stagnates a public health crisis brews. 2004. www.idsociety.org/badbugsnodrugs.html.
- 2 Cars O, Diaz Högberg L, Murray M, Nordberg O, Sivaraman S, Stålsby Lundborg C, et al. Meeting the challenge of antibiotic resistance. *BMJ* 2008;337:726-8.
- 3 European Medicines Agency, European Centre for Disease Prevention and Control. Joint technical report: the bacterial challenge—time to react. 2009. http://ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf.
- 4 Foster SD. The economic burden of antibiotic resistance—evidence from three recent studies. 2010 annual conference on antimicrobial resistance, Bethesda, 1-3 February, 2010.
- 5 Council of European Union. Conclusions on innovative incentives for effective antibiotics. 2009. <http://register.consilium.europa.eu/pdf/en/09/st16/st16006.en09.pdf>.
- 6 Swedish Presidency of the European Union. EU and USA initiate cooperation against resistant bacteria. Press release, 4 Nov 2009. www.se2009.eu/en/2.543/2.578/2.737/2.741/1.22026.
- 7 Mossialos E, Morel CM, Edwards S, Berenson J, Gemmill-Toyama M, Brogan D. Policies and incentives for promoting innovation in antibiotic research. www.se2009.eu/polopoly_fs/1.16814/menu/standard/file/LSE-ABI-F-Final.pdf.
- 8 Spellberg B, Powers J, Brass E, Miller L, Edwards J. Trends in antimicrobial drug development: implications for the future. *Clin Infect Dis* 2004;38:1279-86.
- 9 Projan S. Why is big pharma getting out of antibacterial drug discovery? *Curr Opin Microbiol* 2003;6:427-30.
- 10 Outterson K, Samora JB, Keller-Cuda K. Will longer antimicrobial patents improve global public health? *Lancet Infect Dis* 2007;7:559-66.
- 11 Power E. Impact of antibiotic restrictions: the pharmaceutical perspective. *Clin Microbiol Infect* 2006;12(suppl 5):25-34.
- 12 Finch R, Hunter PA. Antibiotic resistance—action to promote new technologies: report of an EU intergovernmental conference held in Birmingham, UK, 12–13 December 2005. *J Antimicrob Chemother* 2006;58(suppl 1):i3-22.
- 13 Chopra I. Treatment of health-care-associated infections caused by Gram-negative bacteria: a consensus statement. *Lancet Infect Dis* 2008;8:133-9.
- 14 Spellberg B, Guidos R, Gilbert D, Bradley J, Boucher HW, Scheld WM, et al. The epidemic of antibiotic resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. *Clin Infect Dis* 2008;46:155-64.
- 15 Kesselheim AS, Outterson K. Improving antibiotic markets. *Yale J Health Policy Law Ethics* (forthcoming).
- 16 Kremer M. Patent buyouts: a mechanism for encouraging innovation. *QJ Econ* 1998;113:1137-67.
- 17 Shavell S, van Ypersele T. Rewards versus intellectual property rights. *J Law Econ* 2001;44:525-47.
- 18 Brogan D, Mossialos E. Applying the concepts of financial options to stimulate vaccine development. *Nature Rev Drug Discovery* 2006;5:641-7.
- 19 Kremer M. Creating markets for new vaccines: part II: Design issues. In: Jaffe A, Lerner J, Stems S, eds. *Innovation policy and economy*. MIT Press, 2001.
- 20 Biotechnology Industry Organization. *Biotech funding crisis*. BIO, 2009.
- 21 Outterson K. Author's reply. *Lancet Infect Dis* 2008;4:212-4.
- 22 Aiello A, King N, Foxman B. Ethical conflicts in public health research and practice: antimicrobial resistance and the ethics of drug development. *Am J Public Health* 2006;96:1910-4.
- 23 Monnet D. Antibiotic development and the changing role of the pharmaceutical industry. *Int J Risk Safety Med* 2005;17:133-45.

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See EDITORIAL, p 1091; RESEARCH, p 1120

Financial incentives for drug addicts



The BMA Medical Ethics team has highlighted the American charity "Project Prevention," which aims to prevent babies being born into drug dependent families by offering drug addicts \$300 to take up long term contraception or to undergo sterilisation. The team asked doc2doc members "Do you think it is ethical to offer drug addicts incentives to be sterilised?"

Tnolan: "Anyone who thinks that a cheque for £200 is all that it takes to get someone off drugs is extremely naïve."

CSM: "Monetary incentives or sterilisation and such coercive means have not only eugenic but also other wide ramifications, such as ethical, religious, financial, legal, and political."

Yoram Chaïter: "This is not the way to battle drug addiction. And it is a violation of the most basic human right."

Andrew Papa: "Ultimately, it is about improving society by reducing the 'aggregate' suffering, and preventing the creation of children who are more likely to have health and social problems and, perhaps, end up as addicts and criminals themselves."

Should we pay drug addicts to be sterilised?

Have your say on doc2doc, BMJ Group's global online clinical community, at <http://bit.ly/cHjfv3>

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Research success and fundholding

Domhnall MacAuley blogs about Roald Bahr's research team and the success that the team achieved in the past decade. His 2005 *BMJ* paper on exercises to prevent lower limb injuries in youth sports "was pivotal in the evolution of sport and exercise medicine research worldwide," says Domhnall. "This randomised controlled trial was of clinical importance in itself but, even more importantly, it showed that it was possible to test the principles of sport and exercise medicine by using the highest quality research methodology." Martin McShane discusses the need for trust between general practices and the rest of the NHS when it comes to fundholding and how practices make and spend money. "Decades after it was introduced, the impact of fundholding still resonates," he says. "Many general practitioners hanker after the influence it brought, the way it made the big providers in the system sit up and take notice of primary care." However, as he points out: "The financial model for general practice is based on profit. That is not necessarily a bad thing, but it creates a perception that general practitioners are motivated purely by money."

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