FROM THE ANALYST'S COUCH

Antibacterial R&D incentives

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Resistance to antibacterial drugs — an unavoidable consequence of their use — is a serious problem in many countries. Because the development of new antibacterials may have fallen behind the rate of antibacterial obsolescence, incentives for new drug development are needed. Recent reports have suggested that government incentives are essential to encourage research and development (R&D) for novel antibacterials[1,2]. It is also important that such incentives do not undermine efforts to preserve the effectiveness of existing drugs, and indeed, they could be targeted to promote such preservation. Here, we highlight the objectives of incentives for antibacterial R&D and compare the ability of various incentive policies to address the long-term challenge of antibacterial resistance.

Stimulating antibacterial R&D

New antibacterial drugs should fulfil three criteria: first, they should be drugs to which resistance has not developed and that do not exhibit cross-resistance with other drugs; second, they should have a narrow spectrum of activity to reduce the likelihood of resistance; and third, they should directly address public health needs. The following policies to create incentives for antibacterial R&D vary substantially in their ability to meet these three objectives (TABLE 1).

Financial incentives. Possible financial incentives for antibacterial R&D include tax credits, advanced market commitments for purchase, payments for conservation, call options and orphan drug protection (see below). The best incentives would motivate R&D by pharmaceutical companies and fulfil public health goals. However, the use of public funds to encourage the development of new antibacterials that may be unaffordable to many, even in high-income countries, deserves scrutiny. It is also crucial to bear in mind that such incentives could affect efforts to preserve the effectiveness of existing antibacterials; for example, the threat of market entry by a competitor could prompt manufacturers to promote sales of existing antibacterials, which could deplete their effectiveness. In our view, financial incentives are unlikely to encourage more appropriate use of either existing or new antibacterials.

Priority review vouchers. US legislation enacted in 2007 aimed to provide an incentive to develop drugs for neglected tropical diseases by allowing the US Food and Drug Administration (FDA) to grant companies that obtain approval for a drug for a tropical disease a one-time, transferable priority review voucher for an unrelated future drug. However, without clear eligibility criteria related to novelty and ability to address public health needs, application of a similar scheme for antibacterials might encourage manufacturers to develop 'me-too' antibacterials solely to earn the vouchers, which are economically valuable.

Orphan drug incentives. The 1983 US Orphan Drug Act offers extended tax credits and guarantees 7 years of market exclusivity to developers of drugs for rare conditions that affect fewer than 200,000 patients in the United States. The US Congress could extend the act to cover all new antibacterials or enact a law specifically for antibacterials for certain multidrug-resistant infections.

However, some antibacterials that could qualify for 'orphan drug'-like incentives might be developed anyway. In addition, experience in other therapeutic areas suggests that the prices of such drugs could be very high. There also could be challenges in ensuring that drugs are reserved specifically for those with resistant infections. Importantly, however, the period of protection against competition could give companies a greater incentive to try to preserve the effectiveness of their drugs.

Liability exemption. One proposal is to exempt manufacturers from liability associated with their antibacterials, as for vaccine manufacturers. For example, in the United States, a mandatory federal vaccine injury compensation programme provides a no-fault alternative to litigation against the manufacturer for resolving vaccine injury claims. However, there is much greater scope for the overuse or misuse of antibacterials than for vaccines.

Broadening scope of antibacterial patents. Patent policy could help to resolve the conflict between the private profit motives of companies and the public's interest in conserving antibacterial effectiveness. Patents could be awarded for new 'functional resistance groups' rather than for single molecules[2], where the functional resistance group includes all molecules that are active against bacteria that share a common and novel genetic basis of resistance. There are scientific and legal challenges to implementing such a policy, such as the difficulty of reassigning existing patents. However, changing intellectual property rights would increase both the pay-off for investing in new classes of antibacterials and the incentive to conserve the effectiveness of existing drugs.

Public–private partnerships (PPPs). PPPs reduce participants' costs and risks by sharing funds and expertise among the public, philanthropic and private sectors. In the United States, the Biomedical Advanced Research and Development Authority (BARDA) funds the development of antimicrobials with potential biodefence indications and could extend this funding to antimicrobials for routine indications. However, the BARDA model is relatively new and untested. Government involvement in drug development may counteract industry incentives to oversell antibacterials. Furthermore, PPPs may be able to push in the direction of narrow-spectrum, affordable antibacterials. Giving government a direct role in drug discovery and development has its critics, but the successful experience of the Walter Reed Army Institute for Research in the development of antimalarials offers a strong counterargument.

Encouraging strategic antibacterial reserves. Incentive payments for antibacterials could be linked to government-set conservation and resistance targets[3]. Disease incidence and rates of emerging resistance could be tracked and used to set public health goals. Manufacturers would receive market exclusivity as long as resistance rates were on target; that is, a period of market exclusivity lasting as long as resistance goals were met would replace the traditional patent period. This approach encourages both conservation and investment in drugs that have little cross-resistance with existing drugs. It would require further research exploring the relationships between *in vitro* resistance and clinical outcomes in patients. ▸

ANTIBACTERIAL POLICY OPTIONS

Extending the life of existing drugs

Incentive programmes could also be directed at innovative strategies to delay the development of resistance to antibacterials.

Diagnostics. Diagnostics can help clinicians to select the appropriate antibacterial treatment, particularly when treatment alternatives have been narrowed because of drug resistance. Rapid diagnostics exist for infection surveillance and drug sensitivity testing, but are not widely used for technological and economic reasons. For example, a low-cost test to screen hospital patients for methicillin-resistant *Staphylococcus aureus* (MRSA) is not used widely in the United States because of little perceived financial benefit to hospitals, and companies might be unwilling to pair their antibacterials with a diagnostic, as this could reduce sales. Although better diagnostics can more narrowly focus antimicrobial use, they may merely detect the presence of organisms or genes that do not influence outcomes in patients, and if not used appropriately, they might increase antimicrobial use and resistance, with no benefit to patients.

Drug combinations. Drug combinations — such as multiple antibacterials or antibacterials combined with an inhibitor of resistance mechanisms— might extend the utility of existing drugs by reducing the likelihood that a single set of mutations could simultaneously confer resistance to two or more drugs. However, antibacterial combinations may increase the risk to the patient from adverse effects caused by drug interactions, which raises ethical questions about increasing the risk of harm to individuals for presumed societal benefit. In reality, many patients receive multiple antibiotics to guard against the risk of any single antibiotic failing.

Patient adherence and duration of therapy. New delivery vehicles for existing antibacterials could improve patient adherence. For example, single-dose, slow-release formulations could improve patient outcomes while lowering the risk of resistance owing to lack of adherence. Research on shortening the duration of therapy may also help to limit resistance development as well as adverse events.

Vaccines. Vaccines that reduce the prevalence of disease also reduce the need for antibacterials. For example, a significant reduction in resistant *Streptococcus pneumoniae* followed the introduction of multivalent pneumococcal conjugate vaccines to infants and children[4]. A vaccine for MRSA is desirable but faces technical challenges.

Tools for clinical trials. Current trial design in infectious disease studies fails to control for the biases inherent in non-inferiority trials and often uses vague outcome measures, such as 'clinical response', based on clinicians' judgment. For bacterial infections in which the findings of the disease in patients are related primarily to symptoms, patient-reported outcomes could provide a more sensitive method for assessing the benefits of new drugs[5]. Investment in developing better tools for clinical trials of antibacterial drug development is worthwhile, as investigators could apply these measures broadly and policymakers and regulators could compare the effectiveness, risks and benefits of various agents more accurately.

Outlook

The debate about government incentives for antibacterial R&D is currently focused on how best to reward pharmaceutical companies for developing new drugs, but the broader challenge is to build a sustainable model for developing and using antibacterials. Government has a role, because the competitive market's response may fail in three respects: first, it may operate more slowly than society desires; second, new antibacterials are likely to be those that maximize profits for firms rather than those that provide the most value for public health; and third, the industry has little incentive to ensure the appropriate use of antibacterials.

One recent proposal to address these challenges has been the 'Generating Antibiotic Incentives Now' (GAIN) Act, which was introduced into the US Congress in June 2011 (HR 2182). It proposes to extend marketing exclusivity to 5 years for novel antibiotics addressing drug-resistant pathogens of public health importance. The proposed law also provides for priority review by the FDA for such products and calls for a review of FDA clinical trial guidelines for their approval. This legislation would be considerably enhanced if marketing exclusivity were to be made contingent on meeting goals for conserving drug effectiveness. It is also important that modifications of FDA clinical trial guidelines and expedited review do not compromise product safety.

In our view, government intervention through PPPs that are focused on the development of antibacterials with desirable properties, in combination with incentives to encourage the conservation of antibacterials and the achievement of resistance targets, is the best way to tackle the increasingly serious public health threat of antibacterial resistance.

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Competing interests statements
The authors declare competing financial interests: see web version for details.

Table 1 | **Policy options to encourage new antibacterial development**

Policy option	Novel drugs	Affordability	Incentive to protect effectiveness	Recommendation
Financial incentives	Possibly	Unlikely	No	No
Priority vouchers	Unlikely	Unlikely	No	No
Orphan drug protection	Possibly	Unlikely	Some	Further research
Liability protection	Likely	Unlikely	No	No
Patent modifications	Yes	Unlikely	Yes	Further research
Public–private partnerships	Yes	Possibly	Possibly	Yes
Antibacterial reserve	Possibly	Possibly	Yes	Yes