Fix the antibiotics pipeline

As resistance mushrooms, governments must make development of new antibiotics financially viable for industry, say **Matthew A. Cooper** and **David Shlaes**.

The framework for antibiotic discovery, development and approval is broken — only four new classes of antibiotics have been launched in the past 40 years. The World Health Organization forecasts a disaster due to the rapid, unchecked increase in antimicrobial resistance and has just announced a policy to combat its spread. But antibiotic resistance cannot be eliminated by stewardship alone. There needs to be a sustained effort from government and industry to develop new drugs quickly.

Phase III clinical trials — those on large groups of patients — of an antibiotic in a single disease indication cost about US$70 million. Funding for biotech companies — venture capital or government grants — cannot cover this for a drug that will be sold mainly in short courses, and to which resistance may emerge. Following the global recession, successful stock-market flotations of biotechnology firms remain rare. Many large pharmaceutical companies have abandoned research and development (R&D) on antibiotics, leaving few parties able to register and market new compounds.

Solutions have been debated over the past decade, but no concrete action has been taken. Before the end of 2011, the US government and European Union (EU) need to legislate a solution. Otherwise the hundreds of thousands of people dying each year from drug-resistant infections are likely to become millions.

CARROTS AND STICKS

One solution was suggested in 2009 by the London School of Economics (LSE): a 'push–pull' incentive for investment in potential drugs that meet stringent criteria for medical need and probability of successful registration[1]. The 'push' would involve governments funding the otherwise prohibitively expensive phase III trials for at least one indication.

Push incentives lower the cost of market entry. They attract smaller enterprises with limited funds[2], but such firms may not have sufficient expertise to adequately manage phase III trials and get a drug to market. So a 'pull' is also required to engage larger companies with the necessary expertise and marketing reach.

One such pull suggested in the LSE report is guaranteed government purchase of a defined supply of the antibiotic for national stockpile — as happened for pandemic influenza and anthrax. Another pull is proposed by US congressman Henry Waxman (Democrat, California) in his bill Generating Antibiotic Incentives Now, which is with the House Committee on Energy and Commerce, pending US budget approval. This would give certain antibiotics five extra years of patent protection from generic competition. The bill would also enforce an expedited review of crucial new antibiotics by the US Food and Drug Administration (FDA) and encourages the FDA to designate life-saving antibiotics as a special regulatory class for priority review. Pull-only incentives promise financial rewards after a drug has been developed. Here the developer bears all the risk, because there is normally a decade or more between the decision to engage in R&D and commercial returns. The LSE push–pull incentive, plus Waxman's five-year patent extension, seems to us a clear front-runner. The promise of immediate (stockpile) and sustained (patent lifetime) revenues, plus subsidized phase-III development, would make it easier for small companies to go to the public market. It would also encourage the formation of new biotechnology ventures, providing a healthier climate for fundamental academic research.

Governments would get a significant return on investment. They would make savings, for example, in reductions in the estimated 2 million patients in the EU who catch hospital-acquired infections every year (of whom 175,000 die). Antibiotic resistance has been estimated to cost US hospitals more than $20 billion annually and add one to two weeks in hospital per patient. Subsidizing drug companies may be unpopular in many quarters, but it is necessary to bridge the gap between the high value of new antibiotics to society and the low returns they provide to drug companies.

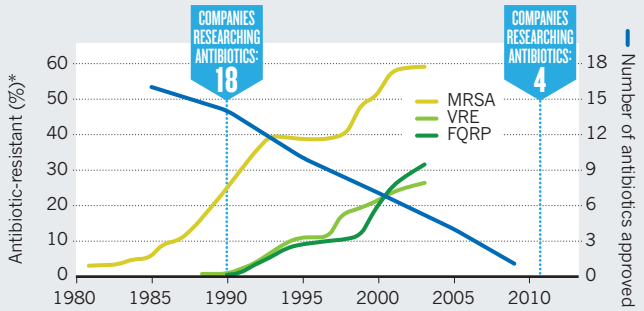
LEADERSHIP NEEDED

Since 2006, the FDA has demanded more costly, larger-cohort studies to prove the non-inferiority of a candidate drug over an existing antibiotic. Without change at the FDA, antibiotic developers, especially smaller companies, may simply ignore the agency. If the European Medicines Agency (EMEA) continues to allow swift, affordable trial designs for key antibiotic indications, a company could use approval in Europe to drive approvals in growing markets such as India, China and Brazil. For example, Johnson & Johnson's doripenem can be used to treat nosocomial pneumonia in almost all countries except the United States.

The Trans Atlantic Task Force on Antimicrobial Resistance prepared a draft proposal[3] for the EU and United States defining areas of future cooperation and policy alignment between industry and governmental agencies. This proposal and the push–pull model above require urgent translation into policy. Antibiotic resistance is a global health crisis. It requires global action before one of the most valuable scientific discoveries of the twentieth century is lost in the twenty-first century. ■

A PERFECT STORM

As bacterial infections grow more resistant to antibiotics, companies are pulling out of antibiotics research and fewer new antibiotics are being approved.



*Proportion of clinical isolates that are resistant to antibiotic. MRSA, methicillin-resistant *Staphylococcus aureus*. VRE, vancomycin-resistant *Enterococcus*. FQRP, fluoroquinolone-resistant *Pseudomonas aeruginosa*.

SOURCE: CDC/IDSA

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D. Shlaes declares competing financial interests: details accompany the full-text HTML version of the paper at go.nature.com/bogtg3.