Innovating for Antibacterial Resistance

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Antibiotics are losing their effect at an alarming pace. Estimates from South Asia alone show that a young infant dies every second minute, as a direct consequence of treatment failure due to antibiotic resistance.(1) In European hospitals, methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant, Gram-negative bacteria are important causes of nosocomial infections. (2, 3) The public health consequences are severe. Without effective antibiotics, we risk rolling back major achievements of modern medicine, such as the successes of organ transplantation and certain types of cancer treatment, and the work towards improved child survival in the developing world is severely threatened.

Antibiotic resistance comes as no surprise. Already in 1945, Alexander Fleming warned in his Nobel speech that inappropriate use of antibiotics could lead to resistance problems. (4) Even earlier, microbiologist René Dubos predicted that bacterial resistance to antibiotics should be expected as a consequence of bacterial adaptation. (5) But we did not heed such warnings. Extensive overuse of antibiotics - abetted by the naïve reliance on the pharmaceutical industry to continuously provide new drugs when the old ones lose their effect - has led to the situation we see today.

As increasing resistance rates are reported from all parts of the world, (6) development of new antibiotics is steadily declining. More than a dozen new classes of antibiotics were developed in the 1930's through the 1960's, but since then, only two new classes have come to market. (7) Nor does the trend of declining innovation seem to be reversing. In a study of the pipeline of the top 15 pharmaceutical companies, only 1.6% of drugs in development (five out of 315) were antibacterials, none of which were for novel classes. (8) Results from a deeper analysis performed in 2005 of the entire industry were not encouraging, showing that most of the candidates targeted only Gram-positive bacteria, (9) leaving needs unmet for the increasing threat of multi-resistant, Gram-negative infections.

An emerging coalition to combat antibiotic resistance: www.reactgroup.org

Fully combating antibiotic resistance requires a multi-tiered approach, including significantly improved use of antibiotics and increased monitoring to prevent and detect emerging resistance. In addition, new approaches are also urgently needed to stimulate innovation of new antibiotics before resistance overtakes all available treatment options.

The lack of antibacterial innovation stems from the low priority of antibiotics in private sector pharmaceutical research and development (R&D). In selecting therapeutic candidates for research, companies weigh costs of innovation with expected payoff of a successful drug. As an example, musculoskeletal drugs promise a potential return ten times that of an injectable antibiotic. (10) Short treatment length, high therapeutic competition, treatment guidelines which rightly discourage first-line use of new drugs, and the eventual emergence of resistance all contribute to the lower expected payoff for antibacterials. (10, 11)

New approaches to antibacterial innovation

With existing incentives, current levels of innovation are clearly inadequate, but some alternatives have been proposed to redress the dearth of therapeutic innovation and are summarised below. However, no matter how innovation is accelerated, the use of these new antibacterials must be safeguarded by regulations and practices that encourage prudent use. In addition, a gap analysis of the present pipeline *versus* current resistance patterns and trends should be performed, to give priority to the most urgently needed antibiotics before any public involvement is concerned.

Product development partnerships

Product development partnerships (PDPs) are arrangements between public organisations and private companies to develop drugs that have been neglected by the existing system of innovation. For instance, between 1974 and 1999, only (16) new drugs for tropical diseases were approved, around 1% of all approved drugs. (12) Currently, there are 63 neglected disease products in the pipeline, and the majority of these drugs are being developed under PDPs. (13) By combining the respective advantages of drug development from the public and private sectors, PDPs offer one potential model that might stimulate innovation where markets otherwise fail to meet public health priorities.

Push mechanisms

Various proposals put forth for improving innovation for neglected diseases in developing countries may also apply to antibiotics. 'Push' mechanisms improve R&D by reducing the financial, transactional and time-intensive costs of the development process. Push mechanisms commonly include government grants and R&D tax subsidies, but more creative approaches are also possible. Public compound libraries might enable access to and screening of proprietary collections of compounds for antibacterial properties, increasing the probability of success of development. Upstream along the R&D pipeline, pooling of intellectual property can lower the transactional costs of cross-licensing, building blocks of knowledge or research tools essential for innovation. Downstream along the R&D pipeline, pooling can facilitate the development of fixed-dose drug combinations.

Pull mechanisms

'Pull' mechanisms create rewards for the products of R&D and may supplement or replace revenues in small or resource-poor markets. For instance, prize funds could provide a cash reward for the development of a product that meets certain therapeutic conditions, such as treatment of specific types of resistant bacteria. Similarly, advance market commitments (AMCs) create a fund that guarantees a certain price for drugs that meet therapeutic targets, provided there is a demand for the drug. A recent example is the pneumococcal vaccine AMC, where the AMC guarantees that it will pay an innovator a pre-determined rate (such as USD 14) for each vaccine that a low-income country decides to purchase at a set low price (such as USD 1). (14) An AMC makes up the difference, thereby providing additional financial incentive. It also enables adoption of superior products subsequently developed because the AMC only subsidises the vaccine purchased by countries, which presumably would be the best available.

Intellectual property inducements

Some proposals have suggested more conventional incentives, particularly intellectual property inducements. One related pair of incentives is patent extensions and marketing exclusivity. These arrangements would increase the anticipated revenue by lengthening the period of patent protection or of exclusivity over data submitted for drug registration. As antibiotics already have small markets and since resistance may reduce further the time that an antibacterial has value in the marketplace, these incentives are likely to do little to stimulate greater innovation for antibacterials. (15)

Despite these drawbacks, some persist in promoting stronger intellectual property as incentives. An example of such a proposal is wild-card patent exclusivity, where innovators of new antibiotics may transfer the grant of patent extension to a drug of their choice. (16) Wild-card patent exclusivity makes the most difference for companies that have blockbuster drugs in their portfolio to which this patent extension could be applied profitably. So this proposal might exacerbate further the mismatch between public health and private sector R&D priorities. Small pharmaceutical companies play a large role in antibacterial innovation, and many of these companies will not have other products to which to apply the wild-card exclusivity. Furthermore, this approach would not only be of little value to small companies, but would put them at a disadvantage compared to larger companies which have blockbuster drugs to leverage investment into antibacterial research. Wild–card patent exclusivity creates unpredictability among existing drug producers, which may have products developed for release pending imminent patent expiration, only to have the patent on that originator drug abruptly transferred from another product and extended. Finally, wild-card patent exclusivity displaces the burden of the cost of R&D onto another patient population at a price that is potentially much higher than the cost of directly financing antibacterial research.

Effective antibiotics – a dying species

Is public investment in antibiotic R&D the solution?

The European Center for Disease Control warns that there is no room for complacency in the fight against the emergence of resistant microbes,[17] but the views within Europe on how to approach this problem are divided. The policy options to combat antibiotic resistance presented from the Scientific Technological Options Assessment Panel (STOA) of the European Parliament urge directing research funding towards the containment of antibiotic resistance, rather than towards new drug leads. The report opines that it is a more cost-effective approach than increased public investment for antibiotic R&D. (18)

In contrast, a recently published report from the European Academies Science Advisory Council (EASAC) highlights the considerable potential for Europe to provide a leadership role in the efforts worldwide to promote anti-infective research and innovation, as well as translating these efforts into sustainable health benefits. (19 EASAC states that reducing inappropriate antibiotic use and improving surveillance of resistance patterns are not measures that alone are enough. This is a message echoed by the European Medicines Agency's (EMEA) final report from the EMEA/CHMP think-tank group on innovative drug development. Here it is also suggested that a gap analysis on the unmet medical needs for antibiotics and a priority list of pathogens could be performed, and more tailor-made requirements could be considered to guide the process. (20)

STOA states that we cannot wait any longer for the discovery of new antibiotic drugs and that antibiotic R&D should not be prioritised. EASAC and EMEA argue that mechanisms to stimulate research for new antibiotics are essential. But while the debate continues, so does the emergence of resistance and the decreasing effectiveness of our antibiotics. We can ill afford not to act decisively to improve upon current incentives for antibacterial R&D. ReAct — an emerging coalition to combat antibiotic resistance (www.reactgroup.org) - believes that the need for new antibiotics is more urgent than ever. Therefore, it is now time to think out of the box. If today's market cannot deliver what the public needs, we must envisage another approach that better engages both public and private sector resources to improve antibiotic innovation.

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