ReAct
Action on Antibiotic Resistance

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Antibiotic Innovation

An eventful year is drawing to a close; a year which has seen the mounting of several interesting processes. In this edition of ReAct Quarterly, we sum up of some of the major developments that came about during the fall and winter. A certain emphasis has been placed on antibiotic innovation issues, not least in the article by Anthony So and Neha Gupta. But first, a quick summary of the past few months.

On the 17th of September, the Swedish presidency of the European Union hosted an invitational expert conference entitled **"Innovative Incentives for Effective Anti-bacterials"** in Stockholm.

The conference brought together a unique mix of representatives from science, health care, policy and industry. The objective was to explore ways of creating incentives for the development of new drugs, including changes in regulatory mechanisms and use of innovative financial instruments. Conference report available here>

Photo: Leif R Jansson/Scanpix

Elias Mossialos, Bo Aronsson, Dominique Monnet and Otto Cars, at the conference

ReAct, Action on Antibiotic Resistance, was deeply involved in the entire process leading up to and during the Conference.

In 2007 ReAct initiated discussions with the European Medicines Agency (EMEA) and the European Centre for Disease Prevention and Control (ECDC) on the need to document the gap between the frequency of multidrug-resistant bacterial infections and the, practically non-existent, R&D pipeline of new antibiotics.

An EMEA-ECDC joint working group was established to conduct research that would allow deter-mination of reasonable predictions of the extent of this gap in the coming years. ReAct played a substantial role in the development of the scientific methodology for the study and performed part of the actual pipeline analysis. The result is the report; ***"The Bacterial Challenge – Time to React"***

The EU efforts under the Swedish EU presidency have sparked a number of valuable spin-offs, even on the other side of the Atlantic. Most notably, the EU-US Summit agreement to establish a transatlantic task force on antimicrobial resistance. More about the task force on reactgroup.org>

And on the 1st of December, the health ministers of the 27 European Union member states adopted council conclusions concerning innovative incentives for effective antibiotics.

These conclusions comprise measures ranging from national level strategies to ensure awareness among the public and health professionals to union level efforts to promote public-private partnerships to facilitate research into new antibiotics, diagnostic methods and strategies for use of currently available antibiotics. Council conclusions available here>

Speaking of antibiotic innovation, one could say that the 2009 Nobel Prize in chemistry was timely; Venkatraman Ramakrishnan, Thomas Steitz and Ada Yonath were awarded the prize for mapping the atoms that make up ribosomes.

Nobel Prize laureate Ada Yonath.

As stated in the press release from the Royal Swedish Academy of Sciences, the three laureates "have all generated 3D models that show how different antibiotics bind to the ribosome. These models are now used by scientists in order to develop new antibiotics, directly assisting the saving of lives and decreasing humanity's suffering."

Following below, Anthony So and Neha Gupta, of ReAct policy unit, Duke University, provide an overview of the scientific and economic barriers to innovation of new antibiotics, but also some promising ideas on how to overcome similar problems in neighboring fields.

Barriers to overcome

by Anthony So and Neha Gupta

While emerging and existing resistance to antibiotics increasingly threatens to give way to a future without effective antibacterial agents—a problem which affects all medical practices, from cancer treatment to transplants—little progress has been made in recent R&D for new antibiotics.

Indeed, among the top 15 pharmaceutical companies—which accounted for 93% of antibiotics placed on the market between 1980 and 2003—only 1.6% of the drugs in their R&D pipelines are anti-bacterials.[i] The past thirty years have seen the development of only two new classes of antibiotics: oxa-zolidinones and cyclic lipopeptides, neither of which is effective against Gram-negative bacteria.

This alarming reality is in part because of scientific challenges specific to antibiotic R&D, but also because of economic barriers and obstacles within traditional R&D models. However, a multitude of op-portunities exist for pharmaceutical firms to overcome, and in some cases help solve, these problems.

Despite available targets, recent efforts to identify lead compounds with novel mechanisms of action have proved disappointing. Low yields from high-throughput screening[ii] demonstrate that perhaps the screening of natural products is a path researchers should pursue.

Also, compound libraries structured around the Lipinski Rule of 5 may not be optimal for discovering new antibacterial drugs, which often have different chemical properties, such as greater polarity, than other therapeutic agents.[iii]

Furthermore, agreements to share proprietary compound libraries or create open-source libraries, complete with annotations, would increase opportunities for drug discovery. This would also facilitate the entry of small and medium size pharmaceutical firms in search of a commercializable drug candidate.

In addition, the relatively low net present value of antibiotics has driven pharmaceutical companies to invest in other, more profitable areas of research. Bristol-Myers Squibb, Eli Lilly, Wyeth and Procter and Gamble all ended their discovery work on anti-infectives in the 1990s.[iv]

Photo: SPL/Nordic Photos

Indeed, potential returns from a new musculoskeletal drug are ostensibly greater than those that would be de-rived from a new antibiotic product. Not only are antibiotic treatment cycles shorter, but drug resistance itself makes the effective lifespan of an antibiotic uncertain.

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Further, competing within a market saturated with generic products to promote increased use of antibiotics would further promote drug resistance, compounding research challenges.

Public and philanthropic funds provide a push mechanism to drive research. These efforts, such as the Wellcome Trust's Seeding Drug Discovery Initiative—a five-year, UK£91 million effort—have expanded to include some funds for antiinfectives.

European org-anizations like the Innovative Medicines Initiative (IMI) and TI Pharma combine the efforts of academic and industry resear-chers in the pre-competitive stages of antibacterial R&D. However, financial barriers seem to remain in moving drug candidates across the valley of death from pre-clinical to clinical trials, keeping potentially promising treatments from reaching the market.

Over the past decade, product development partnerships (PDPs) have emerged to fill the R&D gaps. While largely focused on neglected diseases, the experience of these PDPs may offer lessons for antibiotic R&D.

By mobilizing public sector resources complemented by private sector expertise, PDPs might rekindle interest in the development of new antibacterials by lowering the risks of R&D, enabling access to compound libraries and other research tools, and bringing synergy from partners that might make complementary contributions to R&D.

Pull mechanisms pay for the outputs of R&D. From prizes to advance market commitments (AMCs), some have experimented with this approach. The Global Alliance for TB Drug Development offered prizes for finding simpler and safer methods for making a Phase II TB drug candidate PA-824, and attracted a number of proposals, two of which won US $20,000 for their promising ideas.[v]

An AMC piloted by the Bill and Melinda Gates foundation along with Canada, Italy, Norway, Russia, and the United Kingdom pledged $1.5 billion to ensure a guaranteed market for a pneumococcal vaccine adapted to developing country strains.[vi].

As the vaccine had already reached phase 3 clinical trials, the pilot did not test the AMC's ability to pull a product through the R&D pipeline. However, the AMC may help secure corporate commitments to scale up production for the developing world.

A significant share of future bilateral aid commitments to the Global Alliance for Vaccines and Immunizations was locked into the AMC, so it remains to be seen whether this approach can be repeated or whether it puts at risk other pressing priorities that beckon for such funding.

A hybrid model of push and pull incentives might offer a more optimal balance, ensuring capacity building among potential con-tributors to the R&D pipeline while reducing the uncertainty of the antibiotic marketplace. The dearth of antibiotics with novel mechanisms of action suggests that scientific obstacles may pose as great a challenge as financial ones. Reengineering the value chain of R&D may also be necessary.

Enhancing scientific exchange upstream through open source approaches might catalyze R&D efforts. Watching efforts like India's Open Source Drug Discovery Initiative for TB drugs may provide useful clues.

Patent thickets or holdouts may block research efforts, particularly where the profit potential of the end-product may not justify the transaction or licensing costs to overcome such barriers.

The urgent need for novel antibiotics certainly calls for testing out new approaches in pharmaceutical innovation.

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