Towards a sustainable model of antibiotic research, development and commercialization

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Despite the alarming increase in the prevalence of drug-resistant bacterial infections, the number of new antibiotic approvals in the last decade has declined from the peak of NDA or MAA approvals in the 80s, to only three systemic antibiotics having been approved in the last five years (1). The situation is particularly alarming for Gram-negative bacteria, many of which have been designated as “Urgent” in the latest report by the CDC (2). Both the rapid emergence of resistance, as well as the paucity of new antibiotic approvals, has frequently been attributed to the pharmaceutical R&D model, which requires early adoption of new drugs and large volumes of sales to drive revenue. The calls for the establishment of a new commercial model for antibiotics in order to revitalize R&D have multiplied in the past year, with several opinion leaders (from both the pharmaceutical industry and public health sector) advocating delinking reward for antibiotic R&D from the volume of sales (3).

Unfortunately, the solution is unlikely to be as simple. The paucity of new antibiotic approvals is the tip of the iceberg, with corrective actions needed from basic research, pharmaceutical R&D, to regulatory requirements and to clinical use. Thanks to sustained efforts from both industry and regulatory agencies, there has been promising progress on new regulatory paths both in the US and Europe. However little progress has been made in the three other areas.

Basic research in pathogenic bacteria has suffered a double blow of chronic underfunding and misdirection. First, public under-funding relative to other major diseases (e.g. HIV/AIDS, which is often taken as an example of how pharmaceutical innovation can transform a disease) has limited the generation of new knowledge in this space. PubMed queries with the keywords “Pseudomonas aeruginosa” returned 2,425 publications in 2013, “Acinetobacter baumannii” 568, whereas “HIV” returned 14,791 hits. One could reasonably advocate that a small proportion of the $2.9 billion of public money spent on HIV/AIDS R&D in the US alone, should be diverted to fund research into pathogenic bacteria that kill 23,000 Americans each year. Public funding of basic research must increase.

The lack of new antibiotics being generated in biotech and pharmaceutical companies has prompted a number of academic laboratories and research institutes to engage in antibiotic drug discovery. Although this is understandable given the urgency, few groups are left which focus exclusively on basic research. We must re-direct our basic research to answer fundamental unknowns (e.g. molecule transport across the bacterial cell wall, immune control, virulence) and help us better understand the organisms we’re fighting, so we can develop new therapeutic modalities.

Pharmaceutical R&D has also suffered from the paucity of new knowledge and technology available for antibacterial drug discovery. The incremental differentiation of recently approved or late-stage development agents reflects that. Recent public-private initiatives (e.g. IMI’s New Drugs for Bad Bugs) aiming at building stronger links amongst pharma companies and with academia are laudable, but stronger links are inconsequential if no new knowledge is generated. We must sharpen the focus of public-private initiatives to ensure they foster ground-breaking basic research, which industry groups can then translate into new approaches, rather than substitute for pharmaceutical R&D funding. The second challenge for the industry R&D groups is funding. Pharmaceutical and biotech executives have a fiduciary responsibility to their investors. Big pharma’s decision to focus R&D resources in areas of equally high medical need but greater profitability is a translation of that responsibility. To draw private funding away from those more profitable areas and back into antimicrobials, we must develop a model which returns a profit that is competitive with those achieved in other diseases. Public partnerships such as IMI in Europe, or BARDA and...
NIH in the US are helping offset some of the R&D costs, particularly in late-stage development (“push mechanisms”). But a “not-for-profit” (or “low profit”) model will not draw the kind of resources needed to combat multiple and diverse pathogens, which develop resistance rapidly and spread globally.

Clinical use and prescription practices must also evolve. The decade-old habit of using broad-spectrum antibiotics empirically is not sustainable: Patients infected with drug-sensitive strains are treated with a new broad-spectrum antibiotic “on suspicion”. This not only accelerates the emergence of resistance against the new agent in this particular pathogen, but also in all other commensal or bystander bacteria. The approach of “reserving” the new drug for later use is not only dangerous to seriously ill patients, but is of limited impact once resistance starts to spread. To take a recent example, in its latest guidance (4) the CDC recommended discontinuation of cefixime as a first-line treatment for *Neisseria gonorrhoeae*, at a time when >90% of patients in the US are infected with drug-susceptible strains. Technologies are now available which can be rapidly developed and adapted to diagnose not only the infecting pathogen, but also whether it carries some of the known resistance markers. Rapid molecular diagnostics coupled with pathogen-targeted agents would restrict the use of the new drugs to those patients who need them, taking the guesswork out of the decision process and limiting use of new drugs without artificially “reserving” them, while slowing the emergence of resistance. Pathogen-targeted drugs have other advantages, in terms of accessibility in discovery (it might be easier to optimize an agent against a single pathogen or class of pathogens) and development (more rapid clinical trials and accelerated regulatory paths).

This “personalized care” approach poses once again the fundamental problem of profitability. Put simply, the use of pathogen- (and resistance-) targeted treatments, fragments the patient population. To offset this, such novel treatments will have to be priced at a premium, as has been the case in e.g. oncology. Premium pricing of those new life-saving treatments is more likely to generate an economic incentive comparable to that in other profitable therapy areas, than “delinked” commercial models would. Pricing would be structured on the same pharmaco-economic principles which drive drug pricing in other low-volume therapy areas (5). Most importantly, the use of such drugs will also be gated by diagnostics which will restrict them to patients who need them, with others being treated by inexpensive yet still effective generic broad-spectrum antibiotics. This approach is also in line with critical antibiotic stewardship initiatives.

**Action plan:**

- Drastically **increase the funding for basic research**, and focus those efforts on knowledge generation and technology development.
- **Continue funding through public-private partnerships to facilitate knowledge sharing** and offset the cost of clinical development.
- **Foster the development and adoption of rapid diagnostic technologies**, including those that can discern resistant from susceptible strains, and pathogen-targeted antibiotics for high medical need infections.
- **Facilitate registration, reimbursement and adoption of premium-priced, pathogen targeted antibiotics** for serious infections, in order to evolve a more sustainable clinical practice and create a commercial incentive for fresh investment in the pharmaceutical industry.

2. CDC Antibiotic/Antimicrobial Resistance, Threat Report 2013