IMI’s New Drugs for Bad Bugs (ND4BB) programme

IMI’s public-private partnership model is based on a 50:50 partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA). Any IMI project is based on the commitment by pharmaceutical companies to contribute to a certain topic (EFPIA in-kind contribution). The EFPIA companies’ commitment is matched with IMI JU funding (coming out of the European Commission framework programme FP7 or in the future Horizon 2020) that goes to beneficiaries. Beneficiaries are selected through a competitive call process and can include academic teams, hospitals, patient organisations, small- and medium-sized companies, regulatory agencies, public health institutes, etc. EFPIA companies do not receive funding in the IMI model.

In March 2012, the Innovative Medicines Initiative (IMI) launched its first call for proposals under the ‘New Drugs for Bad Bugs’ (ND4BB) programme, a major public-private partnership effort to address bottlenecks in the discovery and development of new antibiotics. Seven ND4BB projects with a total committed budget of more than €600 million have since either started or are in preparatory phases. Four of the ND4BB projects are aiming at facilitating the clinical development of later-stage assets (decreasing risk and investment for the pharmaceutical industry sponsor), whereas the other three have the following principal aims:

1) To advance our understanding of the underlying science, notably penetration barriers and efflux mechanisms in Gram-negative bacteria & to build an ND4BB Information Center (Translocation)
2) To progress promising novel hit or lead molecules into early clinical development (ENABLE); and
3) To develop options for novel economic models of antibiotic R&D and responsible use of antibiotics (ND4BB Topic 4, likely project start October 2014).

These three projects might be the most relevant to the meeting on May 13 as they represent unprecedented models of collaboration to address the two main challenges of antibiotic R&D: the scientific challenge and the return on investment challenge.

1. Translocation (basic research + information/data sharing):

In Translocation, academic and industry experts join forces and share their experience, expertise and knowledge to advance our understanding of efflux mechanisms and penetration barriers in Gram-negative bacteria. The goal is that the results generated from the basic research conducted should translate into new knowledge to inform antibiotic drug design.

In addition, Translocation has a second important objective, the creation of an ND4BB Information Center where antibacterial R&D information and data (including legacy data from pharmaceutical companies) is shared. Every project under ND4BB is expected to contribute to the Information Center and explore ways to make use of it. Translocation partners are investigating ways for sharing
data and accessing data, with the goal to make as much information as possible accessible not only to ND4BB partners, but to the scientific community outside ND4BB as well.

2. ENABLE (discovery)

This public-private partnership project represents a unique model of collaboration in the field of competitive drug discovery. Pharmaceutical industry antibiotic R&D experts collaborate with owners of promising new molecules from the academic and SME sectors and with experts from specific backgrounds to jointly advance the most promising molecules towards early clinical stages. In addition, large pharma companies are collaborating on their assets - discovering their historically different approaches.

The project has sufficient funding to work on up to eight hit-to-lead programmes from the academic and SME sector and on up to three lead-to-clinical candidate programmes, and potentially up to 2 Phase 1 clinical trials.

The ENABLE model of collaboration is based on an unprecedented intellectual property agreement that was tailored to meet the needs of the project. Partners in ENABLE work collaboratively on competitive assets and have found an agreement that makes it attractive both for hit owners and for those who contribute to further progress the molecule to participate in the project.

Importantly, the governance structure of ENABLE ensures that only the best hit-to-lead projects out there in Europe get funded, and each programme accepted for funding gets re-evaluated on a regular basis.

The ENABLE model could prove inspirational for R&D collaborations in other disease areas.

3. ND4BB Topic 4 (return-on-investment & responsible use):

This three-year project is expected to start in October 2014. The project’s goal will be to propose options for a new economic model of antibiotic R&D and responsible use of antibiotics. The different building blocks for a new economic model will be investigated, such as new commercial models, a definition of ‘responsible use’ of antibiotics, quantification of the economic burden of resistance, definition of the clinical impact of emerging multi-drug resistant pathogens, and quantification of the value of a new antibiotic.

The different concepts will then be assembled into options for a new economic model, and these options will be tested against several requirements for success such as the legal, political and regulatory feasibility, geographical reach and differences, the impact of evolving medical practice, and the impact on real-life antibiotics in development by innovator companies.

Key for success will be the engagement of stakeholders (patients, clinical societies, SME’s, large pharmaceutical companies, healthcare payers, public health officials, government officials) as well as dissemination of information to policy makers and the wider public community.
Towards a sustainable model of antibiotic research, development and commercialization

Manos Perros, Head of Infection Research and Early Development, AstraZeneca

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 that 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

The “Antibiotic Health Impact Fund”: A Proposal
Kevin Outterson, Thomas Pogge, Aidan Hollis

The Antibiotic Health Impact Fund (aHIF) is designed to achieve two core goals:

1. the availability of effective, safe antibiotics over the long run
2. access to such antibiotics by patients regardless of their income.

Achieving the first goal is compromised by the development of resistance. Solutions to the resistance problem involve (a) successful stewardship programs to minimize the development and spread of resistant organisms and (b) investment in R&D for new antibiotics.

Successful stewardship is challenging. Generally, neither the patentee of an antibiotic, nor its potential present users find it in their interest to limit its use as such restraint entails immediate and uncompensated losses for them: the patentee loses highly profitable sales, and the users (e.g., farmers foregoing antibiotic prophylaxis in their herds) lose the immediate benefit of keeping infections at bay. Both parties derive only a small fraction of the benefits of their forbearance, which mostly accrue to users and generic providers of the antibiotic in the future. As a result of these unfortunate incentives, there is too little investment in protecting and preserving the efficacy of antibiotics in the absence of some outside intervention.

A further problem is that, even if successful stewardship programs could somehow be imposed upon the patentees of antibiotics, this would undermine private incentives to research and develop new such antibiotics by diminishing the prospect of large sales volumes during the patent period. And, finally, there is also the global scope of the collective action problem: bacteria spread worldwide, and successful stewardship programs in any one country will therefore often seem pointless as their wholesome effects are so easily undermined by the massive promiscuous use of the same antibiotics (esp. in agriculture) in other countries.

The aHIF proposal builds on the Health Impact Fund proposal (www.healthimpactfund.org). The central idea is that a fund supported by governments would reward the development of new antibiotics that are safe, effective, and successfully conserved. Companies could obtain a share of the fund’s annual payouts by registering qualifying products with the aHIF. Any new antibiotic obtaining regulatory approval could qualify. Registered products would be subject to pricing constraints and availability requirements; in exchange, the registrant would be compensated through payments conditioned on the health benefits generated by the drug as well as on the product’s sustained efficacy over time. Health benefits could be measured by the number of infections treated appropriately with the drug multiplied by the average effectiveness of the drug as measured in clinical trials and as observed in the product’s actual practical use. The sustained efficacy would be measured by the extent to which the drug continues to work against the pathogens for which it is indicated. Both of these reward components would be precisely specified and laid down in an explicit agreement.

Given rewards for both appropriate use and sustained efficacy, the patentee would have balanced incentives for the drug to be used and for its efficacy to be preserved and protected against the development of resistance. Assuming an appropriate balance between these two
rewards, the patentee would wish to promote the antibiotic in those uses that deliver the most benefit to patients, while perhaps trying to limit other uses with relatively low health impact. Low value uses would be unattractive since they would bring relatively little revenue to the patentee while creating more opportunities for resistance to develop. Rewards could be paid out over a period of time longer than the patent exclusivity afforded to the product; if generics entered, the registrant would continue to obtain rewards based on health impact and sustained efficacy.

We have left somewhat ambiguous the precise pricing constraints a registrant would have to accept for its registered products. The reason is that there are two options: in the standard Health Impact Fund model, the price should be capped at the cost of manufacturing, so that the registrant obtains all its profits from rewards from the Fund. Such a low price ceiling assures access for even very poor patients, which is especially important in the poorer countries. However, in the case of antibiotics, it is not obvious that such a uniform low price is the optimal strategy – a higher price in the more affluent countries may help deter lower-value uses and preserve the product’s efficacy. It is important to consider this trade-off, which might support a regime of differentiated prices, based on national income.

The advantages of the aHIF approach to rewarding new antibiotics is that it would

(1) increase incentives for patentees to try to preserve the efficacy of their new antibiotics; and nonetheless
(2) enable widespread access to new antibiotics where needed and
(3) strengthen incentives to develop new antibiotics.

We believe that an appropriate source of funding for the aHIF would be user fees placed on sales of antibiotics for non-human uses. Such non-human uses create resistance in bacteria that affect humans, but the value of these uses tends to be relatively low. A user fee could generate substantial resources to support a reward mechanism such as the aHIF, while also discouraging undesirable non-human uses of antibiotics.

References


Chatham House Working Group on New Business Models for Antibiotics

By: John-Arne Rottingen
Director, Division of Infectious Disease Control,
Norwegian Institute of Public Health

Since the summer of 2013, the Chatham House Centre on Global Health Security has been working to articulate new business models for antibiotics, particularly delinkage mechanisms to remove any incentive for volume-based sales, which are particularly problematic for antibiotics due to resistance. In October 2013, a roundtable was organized at Chatham House to discuss all known antibiotic delinkage models. A follow up working group (WG) has been established and intends to identify a workable breakthrough approach rather than extensions or modifications of the reasonably well-understood existing business models.

Building on those discussions, in February 2014, Chatham House released a WG Paper: New Business Models for Sustainable Antibiotics, which summarized the nine existing models and related concepts. Many of the models are similar, or share overlapping features and functions, making it difficult to compare the strengths and weaknesses of each one.

The WG has now received an Inception Paper that approaches delinkage in a new way, by articulating the six essential features that must be evaluated in any antibiotic delinkage model. This approach avoids focusing too much on labels and too little on substance. The six functional issues are:

1) **Structuring the innovation reward** (methodology: population-based payment based on health impact, broader valuation strategies, “insurance” models, or other measures; length of the payment period (single year, multiple years or perpetual); value of current v. future needs;
2) **Geographic scope** of the model (single country, regional, global, or a select group of countries based on interest; how is the model scalable and coordinated);
3) **Product scope** of the model (all anti-infective technologies (including vaccines & diagnostics), all antimicrobials, only systemic antibiotics, or just highly effective new antibiotics);
4) **Financing** mechanisms (refundable tax credits, health insurance payers, user fees (Pigouvian taxes) on agricultural and human antibiotic sales, general taxation);
5) **Ownership of the intellectual property** (private, public, private-public partnership, or administered by a third party); and
6) **Control of marketing and utilization** (restrictions on sales and trade, requirements for prescriptions, strong regulations (e.g. like narcotics), etc.).
The WG will work through these six functional questions from April until October 2014, at which point a final report will be issued. The Innovative Medicines Initiative has issued a call under its New Drugs for Bad Bugs programme (ND4BB) for work on new business models. The final report from the Chatham House WG intends to inform that work and other policy processes,

A consortium has been formed to conduct this work, the DRIVE-AB project, which will further develop the models, by mixing and matching the analysis of the six functional areas and include an analysis of experiences from other business sectors. Out of this analysis, existing models can be logically examined as well as new models potentially developed. Once the most promising models have been identified, they will be simulated to calculate the public health benefit against anticipated earnings (net present value). This analysis will be reviewed and validated by policymakers, industry experts, academics, donors and other stakeholders.
New open innovation business model for the development of antibiotics.

James Love, Knowledge Ecology International

There is a high level of awareness of the exigent need to develop new antibiotic drugs, and also the fact that antibiotic drugs present unique challenges for both innovation and use, including in particular the need to reconcile developer incentives with the conservation of the resource.

KEI (and others) have proposed new open innovation business model for the development of antibiotic drugs.

The KEI proposal, first presented as a WHO CEWG demonstration project, endorsed the WHO EURO region, has two stages of implementation.

The first stage involves the creation of a new governance structure, initial funding commitments, and the adoption of initial policies and norms, and the use of grants and innovation inducement prizes to stimulate innovation.

The second stage involves the implementation of a new fee or tax on the use of antibiotic drugs, with the revenue from the fee or tax used to partly or completely fund the grants and innovation inducement prizes, and to discourage low value uses of antibiotic drugs that generate significant negative externalities.

Taken together, the project would replace the current system of temporary monopolies as the reward for the development of new drugs, with a new system with the following features:

1. The creation of new financial innovation incentives that are delinked from drug prices.
2. The elimination of perverse incentives for drug developers to promote inappropriate or low value use of drugs, particularly where there are significant negative impacts on the conservation of the antibiotic resources.
3. The creation of economic incentives to induce the open sharing of knowledge, data, materials, and technology relevant to the development of new products.
4. The competitive production of generic supplies of products at affordable prices.
5. The transfer of technology to drug manufacturers in developing countries.
6. Opportunities for researchers, institutions and both small and large businesses to participate as suppliers of innovations, in both developed and developing countries.
7. A sustainable system of financing for open source development of new antibiotics.

Mechanics
An Antibiotics Innovation Funding Mechanism (AIFM) is created.

In Stage 1, the AIFM provides a combination of grants and innovation inducement prizes.

Among the innovation inducement prizes are (1) end product prizes, (2) interim results prizes, and (3) open source dividend prizes that reward the open sharing of knowledge, data, materials, and technology relevant to the development of new antibiotic drugs.

The AIFM would operate under policies that condition grant and prize money to the licensing of rights in inventions, data, and other intellectual property. These rights would be managed according to policies set out by the public sector entities providing funding for the grants and prizes.

In Stage 2, the AIFM would be engaged in the development of multilateral norm setting as regards the levels of funding for the innovation grants and prizes, the implementation of a system of fees or taxes on the use of antibiotic drugs, and the norms and objectives as regards the conservation of antibiotic drugs.

Prize Design

The use of innovation inducement prizes to stimulate R&D for new drugs, vaccines or diagnostics has been widely discussed, but antibiotics pose unique health challenges, and require somewhat different challenges for the prize designs, particularly for end product prizes, where nearer term utilization may be negatively correlated with the lifecycle value of the drug. Given the need to be brief, we won’t go into the all of the prize design details now, but note that the value of end product prizes can be significant even when current consumption is zero or close to zero.

Funding

As noted above, a new Antibiotic Innovation Funding Mechanism (AIFM) would be set up, and initially resourced at whatever level was available from governments willing to become donors. Donors would have the flexibility to fund grants, and/or the innovation inducement prizes, including prizes that would reward upstream innovations and interim results, as well as end product prices. In Stage 2 of the project, a system of user fees or taxes would be evaluated, as a system of sustainable funding.

For prizes with high standards to qualify, donors could commit funding contingent upon a successful project (a pure pay-for-success commitment), buy insurance that would pay off in the event of a successful project (in some cases a less expensive obligation), or otherwise put money in escrow, to be returned if no one is able to achieve the standard during the period of the prize offer.

Governance
The governance of the AIFM would be, at a high level, through a committee of donors, voting either by membership, or some modified system, such as half by membership and half in proportion to (the square) of their contributions. The committee of donors would contract with a third party to provide a secretariat, and with various parties that could manage different aspects of the operations, such as the licensing of intellectual property, or the management of portfolios of grants or prizes.

Delinkage of R&D costs and product prices

All funds allocated for grants or cash prizes would be conditioned upon licenses to use all patents, knowhow, data and other intellectual property rights, in the field of use of antibiotics for humans and animals. The AIFM would operate under policies that condition grant and prize money to the licensing of rights in inventions, data, and other intellectual property, according to policies set out by the public sector entities funding the grants and prizes.
Developing and Conserving Innovative Antibiotics – De-Linking Volumes from Sales

James Anderson, Government Affairs, Public Policy, Patient Advocacy, GSK

Executive Summary

The threats to public health from increasing bacterial resistance and a dearth of new antibiotics in development are increasingly recognised and debated globally. A globally coordinated, multi-faceted policy approach is urgently needed to address each of the challenges contributing to resistance. GSK welcomes the recent activity from leading governments and international fora such as WHO and we are committed to help developing solutions to meet the needs of all stakeholders.

Bacteria will continue to develop resistance to therapies, so a regular supply of new antibiotics is essential for society. The industry should play a key role in developing new treatments, but investment in antibiotic R&D is relatively unattractive: a new model is urgently needed to redress this issue. The dynamics of the value and use of antibiotics are unique. The use of antibiotics should be minimised to slow development of resistance, and yet prescribing is empiric and therefore challenging to control. People are dying from over- and under-use of antibiotics within the same country. The slow adoption of new antibiotics may be appropriate for public health maximisation, but it is a key factor that drives the poor economics for companies. A model that de-links the volume of sales from the reward paid for a new antibiotic could encourage investment, while reducing pressure to pursue higher volumes. The challenge gets harder post patent-expiry as multiple manufacturers will compete for volume.

GSK recognises these unique challenges which undoubtedly contribute to the lack of new products. We also recognise that unique solutions such as de-linkage are needed. We are already working more collaboratively with partners and stakeholders in this area to improve efficiency of R&D (e.g IMI & BARDA partnerships). We welcome the opportunity to work closely with stakeholders to design solutions that will work for us all.

The need for a new model

Antibiotic development is challenging and revenues are low and uncertain, making financial investment in antibiotic R&D relatively unattractive. Many companies have stopped investing in this area altogether, despite the high need for new antibiotics. Recognised as a market failure, a new economic model to incentivise investment in antibiotic R&D is needed to reverse the trend. Private investment will be attracted by predictable returns on investment (ROI). There are several causes for the current poor ROI in antibiotics, including: the low value placed on antibiotics; the reserved use of new therapies (resulting in slow adoption and low volumes); scientific and development challenges and the unpredictability of use as resistance evolves. In addition to the value of a new antibiotic in treating infections, significant value comes from preventing infection (e.g in surgery) and being prepared to treat emerging resistance.

The new model should not only address the market failure, but it also needs to reduce the incentives for companies (and doctors and pharmacists) to pursue greater volumes of product use, which can accelerate the development of resistance. A model that de-links the volume of sales from the reward paid for a new antibiotic would achieve this. We recommend a model based on a series of fixed payments to the innovator, that reflect the societal “insurance” value of a new antibiotic. This would better align incentives for all actors, with public health conservation goals. In the extreme case, a new product may provide most value to society by not being used at the time it is approved but preserved until resistance to existing products increases.

Finally, the model needs to facilitate access to all patients with infections resistant to other antibiotics, no matter where they are being treated around the world.

How it Could Work

A combination of push incentives (PPPs such as IMI, tax credits, public support for research, BARDA), efforts to reduce the costs of development and pull funding is needed. All are important parts of the model and help improve ROI, but the economic market failure remains the critical gap for attracting new investment. The de-linked model would fill this gap.

A guaranteed series of payments should be negotiated between the innovating company and payers. The payments could be structured to reward successful development (not failure) and appeal to large and small companies (and other institutions developing new antibiotics). The negotiation would be agreed during mid-stages of development, to encourage companies to make the large investments in late clinical studies. Value would be created for companies by
reducing commercial uncertainty and for payers by reducing budgetary uncertainty, for example in the event of an MDR outbreak. We recommend 5-10 fixed annual payments.

The payments should provide an ROI to the company at a sufficient level to attract further investment into antibiotic R&D. The payers would gain the right to use the product and have full control over the volume and geographical location of use. The company should supply the product at cost price, according to a manufacturing service agreement. Other important elements of product management (including pharmacovigilance, maintenance of Regulatory files, clinical investigation, distribution and physician education) need to be considered as part of the agreement.

While clear signals of a willingness to pay higher prices would be likely to attract investment, price alone will not deliver a sustainable model. Higher prices would increase unpredictability for companies’ and payers’ forecasting alike. For example, an outbreak in a local hospital would trigger significant unplanned expenditure. High prices would also be challenging to implement globally, within current national HTA and pricing systems. Finally, companies would be tempted to invest more in sales and marketing, whereas payers would want to control volumes tightly.

**Challenges for Implementing a De-Linked Model**

The proposed model of fixed payments draws from elements within and outside current healthcare purchasing systems. The result has not yet been applied to medicines purchasing and creates several implementation challenges that need to be resolved between stakeholders. The risks of unintended consequences must be carefully considered. For example, Advance Market Commitments have been used to encourage companies to invest in vaccine development, by guaranteeing a certain level of revenue. Contracts are agreed between Governments and other industries designed to deliver levels of ROI that encourage companies to invest, for example in needed infrastructure such as toll roads and power stations. GAVI provides a global model for managing appropriate distribution of valuable medical products. Lessons can also be learned from malaria, HIV and TB.

The key potential areas of challenge for implementation include: roles and governance, geographical scope, funding mechanisms and amounts, product scope and IP issues.

**Roles and governance**

A body with a strong public health mandate is needed to govern and run the process, by publishing the priority product targets (based on predicted areas of medical need), assessing products against those criteria, negotiating the purchase agreements and managing the ethical and practical challenges of global use. Clear and transparent decision-making rules will be needed. It is recognised that certain decisions may be controversial, for example where prioritisation between different product targets and/or restrictions to use of products in certain countries are required.

For example, countries would request an annual amount of the product to meet their needs. Demand should be moderated globally towards the highest need. Product supply to certain countries could be conditional on implementation of processes to ensure appropriate use (eg within the WHO GAP framework).

**Geographical scope**

Resistance is a global issue and the new model needs to deliver globally. Drug development is also undertaken globally. However, patterns of resistance vary significantly (between and within countries). A multi-lateral solution delivers a pooling of risks of resistance and economies of scale. Countries need to recognise that the value they receive from this solution is a type of insurance and, as such, they may never need to use the resulting products (ie a particular country may avoid a particular strain or outbreak).

All countries should be able to access the product whether or not they contribute funding (see below). The goal should be that as many countries as possible contribute. However, achieving a global agreement is practically challenging, so it may need to be driven initially by a coalition of willing governments. The terms of access would be decided by the fund itself, but should reflect countries’ ability to pay.

**Funding Mechanism and Amounts**

We support a GAVI-like model under which Governments contribute to a pooled fund. The fund would negotiate with and pay the company. Appropriate government commitments would be needed to guarantee longer-term agreements (eg annual payments for 10 years). The fund would be the sole purchaser for antibiotics under the agreement. The company would not be allowed to sell the product to others.
To qualify for supply of a new product, governments may be required to take measures to ensure appropriate use (WHO GAP will provide guidance). A local supply price set by the government and paid by the hospital would be a logical component. This would help avoid over-use of a new product, driven by the financial incentives of hospitals (and doctors and pharmacists). It would also off-set the governments’ commitment to the global fund. Taxes on sales of all antibiotics would achieve a similar effect.

Negotiating the level of the payments is critical: too low and companies will continue to disinvest from antibiotic R&D; too high and payers may leave. Therefore, a joint approach to financial modelling will be needed involving companies and payers, and a level of trust, transparency and realistic expectations from all parties. Only five hospital antibiotics sell >£500m per year globally; only two are still patent protected. Where public money directly supports R&D for a product, it should reduce the level of payments needed to deliver ROI.

Product scope

Deciding which products to include under a global programme is one of the most challenging design issues. Decisions are needed which can address different geographical needs and priorities, timescale (ie today’s resistance or tomorrow’s), the optimal number of products and how to manage products that are not selected. There is no simple answer to these questions, but global programmes for influenza, GAVI show that open dialogue between experts from different stakeholder groups can reach consensus and create practical approaches to move forward. A similar mechanism is needed for antibiotics.

Intellectual Property issues

We do not believe changes to the IP system should play a role in solving the challenges inherent in AMR. IP rights are needed during development to protect the investments being made. However, once the purchase agreement is signed, IP becomes somewhat less relevant, as purchasers and the manufacturer are contractually bound to each other for the duration of the agreement. It is interesting to consider how the purchase and use of the product should be controlled after the initial agreement (and the patent) expires. The fund should continue to act as sole purchaser, but can choose suppliers of the necessary services and manufacturing. Again, IP doesn’t play a key role, as long as the purchasing systems are adhered to. If not, competitive, volume-based direct supply by multiple manufacturers would be likely to increase volumes.

Extended IP protection has been proposed to encourage companies to conserve their products more actively and the GAIN Act in US includes 5 years extra data exclusivity. Modelling suggests that these extensions do not have a sufficient impact on ROI and we don’t believe they will impact companies approach to conservation.
WHO White Paper on Innovative Models to Enhance Antibiotic Development

Description of BARDA/BSA program

The Biomedical Advanced Research and Development Authority (BARDA), part of the United States Department of Health and Human Services, seeks to enhance national preparedness for chemical, biological, radiological, and nuclear threats, pandemic influenza, and emerging infectious diseases by supporting innovation, developing and acquiring medical countermeasures, and building manufacturing infrastructure. BARDA’s Broad Spectrum Antimicrobials (BSA) program was established in June 2010 with the goal of re-vitalizing the antimicrobial pipeline through the support of advanced research and development of novel antimicrobial drugs. BARDA recognizes that new antimicrobials are needed immediately to address the increasingly prevalent public health threat of antibiotic resistance, as it is likely to complicate standard treatment of a wide array of infections. At the same time, BARDA acknowledges that antimicrobial resistance can complicate the response to a public health emergency (natural disaster, flu outbreak, etc.). Through the establishment of innovative public-private partnerships, BARDA hopes to help revitalize the antimicrobial pipeline by providing incentives for pharmaceutical and biotechnology companies to engage (or reengage) in antimicrobial development.

By engaging with BARDA in a contract/agreement, our industry partners are able to receive funding and expert technical advice from BARDA for nonclinical studies, clinical studies (Phase 1-3), manufacturing, and regulatory activities. Unlike the interaction that typically occurs when researchers are supported by grants, BARDA engages its industry partners in a more comprehensive and holistic manner. BARDA provides technical support and guidance on all facets of drug development and works with its industry partners as true collaborators.

The BSA program's non-dilutive funding strategy provides our partners with capital to support product development and supplement existing equity. BARDA has successfully established public-private partnerships with industry partners to further the development of novel antimicrobials and anticipates a long-term commitment to this therapeutic area. BARDA has consistently seen the companies we partner with raise additional funding in private markets, become more attractive targets for purchase, enter into co-development arrangements and/or move forward with Initial Public Offerings (IPOs). While there are factors that impact each business decision our partners have made, it is clear that those that have partnered with BARDA have continued to achieve important technical and business milestones. Securing technical guidance and financial resources through a BARDA partnership is more frequently viewed by investors as a step to mitigate drug development risks. In addition, it frees up additional resources to help a company to grow and diversify. BARDA is seen by our partners, and their investors, as a collaborator that mitigates regulatory uncertainty as a result of our direct involvement with multiple antibiotic development programs. If antibiotics supported under a BARDA partnership are seen to advance more rapidly through drug development, and ultimately result in approved products, then BARDA’s technical guidance could become as important as our non-dilutive funding.

In May 2013, BARDA further exemplified our ability, and commitment, to innovatively interact with companies when we entered into a strategic alliance with GlaxoSmithKline to launch a “Portfolio Partnership.” Instead of focusing the program on a single antimicrobial candidate, an entire portfolio of candidate antimicrobial therapies is supported. This “Portfolio Partnership” is a 5 year $200M agreement that utilizes a unique authority within the United States Government called Other Transactional Authority. This authority allows HHS to enter into an Other Transaction (OT) Agreement. An OT Agreement is essentially an agreement that is formed between the government and an industry partner (or partners) that is constructed de novo, free from many regulations present within Federal
April 19, 2014

Acquisition Regulations. The agreement with GSK possesses three central tenets: 1) flexible technical scope, 2) cost sharing, and 3) joint strategic oversight. The agreement is flexible as it allows for candidates to be incorporated, or removed, from the portfolio over the course of the agreement. It allows for the level of resources invested in each candidate product to be adjusted in real-time and the development plan for each candidate to be modified or revised, as needed. The agreement is governed by a Joint Oversight Committee (JOC) that consists of senior leadership from both GSK and BARDA. The JOC meets approximately every six months and makes all major decisions on the composition of the portfolio and the activities that are to be performed during the subsequent six month period. Overall progress on the agreement is monitored by BARDA’s In-Process Reviews using federal interagency subject matter experts and leaders to deliberate and provide recommendations on overall BARDA funding for the agreement periodically. This type of long-term partnership sends a strong signal of commitment to industry, as the agreement is able to withstand the potential attrition of candidates that is commensurate with traditional pharmaceutical development.

Under the BARDA-funded programs, our partners are able to receive reimbursement for drug development activities in real-time. This is in contrast to a model where reimbursement is only provided after the purchase of product, as an advanced market commitment, or a milestone or prize payment upon advancing a candidate antimicrobial to a certain developmental point. The near real-time direct reimbursement for drug development activities is a preferred structure, as it shares the financial risk with the government. The non-diluted funding provided by BARDA to support development activities does not need to be repaid and does not dilute shareholder’s equity. Further, the funding favorably impacts the net present value calculation of our partners by reducing their upfront costs. BARDA’s support also does not require future royalty payments. The growth of the BSA program from one partnership in September 2010 to six antibacterial development partnerships today, with three of our partner’s having antibiotics in Phase III, we believe validates our model.

Other Models Proposed by Industry and Academic Groups

Some experts have recommended advanced market commitments, where the government would commit, in advance, to purchase a prescribed number of novel antibiotics. This would be utilized particularly for antibiotics that would be reserved for very limited use against the most dire, untreatable infections. There is some concern over the long-term sustainability of this model. First, there is concern that the government would not be able to put up enough of an investment to actually change the economic model. The level of market share committed would need to be substantive enough to entice developers while considering financial principles like present value, specifically the need to “discount” a future guaranteed purchase to the present value. Estimates commonly provided suggest that a market commitment between $250-500M per candidate product would be required. Such a commitment would represent a government investment of several billion dollars to ensure there was a sufficient market share for each company. If BARDA moved to this type of model, it would likely require a move away from our current funding strategies of reimbursement in real-time for drug development activities. Second, is the long term concern that the government would be creating a market where the major driver for profitability is directly proportional to the level of government subsidization. Third and most important, BARDA purchases of antibiotics for biothreats are tied to PHEMCE requirements and the level of preparedness that HHS senior leaders are able to accommodate amidst competing budget priorities and constraints. The quantities of antibiotics purchased by BARDA under Project BioShield may be less than that estimated by industry to make this approach feasible.
Antimicrobial stewardship will be critical as new drugs come to market. Various experts have proposed a need to move away from an economic model that is based on units sold as the driver of profitability. This would require a market adjustment where antimicrobial drugs that possess narrow label indications command much higher prices and target patients with the most dire, untreatable infections. The clear mortality benefit of antibiotics to treat multi-drug resistant (MDR) infections could be a major factor that could justify pricing reforms. Oncology therapies, which often command prices significantly higher than antibiotics, often only extend quality life years and are often not curative. Thus, therapies that provide a clear mortality benefit against untreatable infections should be priced similarly to oncology therapies. Barriers to this include whether payers will allow these pricing reforms to occur. Ultimately, it is unlikely that substantive market reforms will transpire until the prevalence of MDR infections reaches a level of greater crisis that necessitates immediate action.

Alternatively, other experts propose providing institutional licenses for antibiotic use/prescription as a means to ensure use in limited populations where the medical need is greatest. Tracking of antibiotic use could be a requirement of the licensing agreement and monitoring and enforcement of prudent use would be conducted by the company. This model would effectively remove units sold as the primary driver of profitability. However, the number of licenses sold would remain a constant force in commercialization of the product.

Overall, it is clear that multiple and coordinated incentives need to be established or sustained to bolster the pipeline of candidate antimicrobial therapies. Further, reforms to the commercial market are necessary to alter the commercialization path for new antimicrobial therapies particularly to account for preserving new antimicrobial therapies for the treatment of the direst resistant infections. Sustainability of any potential incentives needs to be a primary consideration.
ANTIMICROBIAL RESISTANCE R&D

Research and development (R&D) is what has moved society from the pre-antibiotic era, when over 40% of all deaths were due to bacterial infections, to today, a society in which the largest majority of bacterial infections can be treated with antibiotics, saving millions of lives each year. As these antibiotics are gradually rendered obsolete by the emergence of resistance, continued development of novel antibiotics becomes absolutely essential. Hence, R&D is critical to ensure that healthcare professionals are armed with the tools they need to tackle infection.

Despite the clear need for innovation, antibiotic R&D faces a set of hurdles that reduce private interest for the space and discourage investment. These hurdles are four:

■ Limited public and private funding for basic microbiology research; this places more, and the more risky part, of the R&D burden in the private sector
■ Challenging regulatory requirements with a high bar for improvement versus the standard of care make R&D into new molecules for ‘old diseases’ difficult
■ Reduced patient populations and short treatment courses result in limited commercial potential for antibiotics
■ Commoditized market (low prices compared to other therapeutic areas) compounding the effect of reduced patient populations and short treatments

As a result of these hurdles it is unclear how long the large and mid-sized pharmaceutical companies that still do research and development in infectious diseases, and particularly in antibiotics, will remain in the area. To tackle this lack of incentives, a solution should:

■ Encourage basic research by both academic and private sector laboratories
■ De-risk private sector R&D from a financial standpoint OR increase the probability of positive financial return OR increase the size of financial return
■ Engage governments and regulatory authorities to ensure the products of the R&D effort will be evaluated with a framework appropriate for antimicrobial resistance (AMR) research and not the regular novel drug regulatory paradigm
■ Couple the support to R&D with mechanisms to guarantee the appropriate use of antibiotics developed through the R&D efforts, e.g.,
  – Support the co-development of rapid diagnostics to reduce empirical use
  – Limit production volumes to match epidemiological needs
  – Advocate for policies to restrict resistance-fostering practices like non-prescription sales, veterinary use, etc.
■ Ensure the financial incentives for private sector R&D do not prevent drug accessibility by developing countries, e.g., like a mechanism based on overall price increases would do

A potential solution for AMR R&D

Decouple sales from R&D to separate the incentive to innovate from the incentive to sell while allowing for investor returns. Main characteristics of the proposed solution:

■ An entity created to incentivize R&D through
  – Grants to academic institutions to focus in basic microbiology
- Research and drug development grants to private sector institutions to de-risk AMR research
- Funds for clinical research organizations to conduct clinical trials on the results of the AMR R&D supported or other promising candidates that could be acquired or in-licensed

■ The *entity* invests in promising assets in which it is able to have significant stakes in the intellectual property (IP) generated

■ The *entity* uses IP rights to have meaningful decision power over registration and manufacturing to
  - Ensure timely access for all countries in need
  - Limit production volumes based on epidemiological needs
  - Control pricing and quality in developing countries through manufacturing licenses

■ The *entity* is created as an independent company where
  - Funding parties, both public and private, buy shares of the entity
  - The *entity* owns a share of the IP generated through its investments but no IP is assigned to a particular funding party
  - Scientific decisions are left to an independent Board of scientific advisors
  - Funding parties participate on the Board of the *entity* but not on managing it
  - Management is left to a small set of professional managers incentivized to develop products, extend the active life of those products, and generate returns

■ Returns are defined for, and together with, each funding party and could take several forms depending on each party’s interests, e.g., financial returns, savings to a health system, savings to a nation, etc.

**Open questions**

■ How to prevent generic players to manufacture and sell large volumes of the products once IP protection expires and in countries where IP rights are not enforced?

■ Can returns be defined in a pragmatic manner to match the KPIs of the entity by selecting the right mix of funding parties?
This proposal focuses on creating a global consortium to coordinate pharmaceutical innovation for antibiotics by taking concerted public sector action. Incentives to drive R&D would be applied through a hybrid model of push and pull financing. Various R&D pathways for innovation would be put at play:

1) At the drug discovery stage, milestone prizes would give worldwide incentive to new groups from academic scientists to small innovative companies, to create promising, “druggable” leads for novel antibiotics, while guarantying access to novel Intellectual Property Rights (IPR) through subscription of options on new inventions potentially leading to discovery of new classes of antibiotics;

2) push mechanisms taking the form of grants for developers (academics, small or large companies) for optimizing the new drugs; or competitive access to contracted services would ensure greater public purchase over the pharmaceutical value chain, both removing the risk and ensuring the certainty of return for antibiotic innovation. Investing across a portfolio of promising drug candidates and approaches also will mitigate the risk of failure;

3) end prizes of significant value (c.a. US$ 2-500 million) would reward proven new molecules, and buy out patent rights on new antibiotic classes within a public sector patent pool. Management of IP rights would ensure that use of the new molecules for human applications;

4) public-sector funded clinical trials would assess safety and efficacy of the new antibiotics (alone or in combination to further decrease the risk of resistance);

5) purchase agreement with industries for the production of set number of treatments per year, would be used under conditions that preserve the new drugs.
Importantly, the proposed financing model would lower the barriers to entry for small and medium size enterprises, for firms in low- and middle-income countries (LMICs) and academic research centers worldwide. The consortium's primary focus would be on antibiotics' development, but complementary technologies, such as a diagnostic to identify rapidly patients with multi-drug resistant disease for clinical trial recruitment, might fall within its mission.

Enriching a public compound library, particularly with natural products sourced from a network of biorepositories, could provide an innovation platform for discovering new classes of antibiotics. Over a third of small molecule drugs over the past three decades have originated from natural products, and among antibiotics coming to market between 1982 and 2002, over three-quarters of the drugs derived from natural products.\(^1\) Repleting the antibiotic R&D pipeline would help address the scientific bottleneck that has stymied the pharmaceutical industry, which has reported very low yields from high-throughput screening of their proprietary compound libraries. One large multinational company conducted seventy screens (67 HTS, three whole cell) from 1995 to 2001 and identified only five lead compounds. The 7% success rate captures the challenge.\(^2\)

Sharing of knowledge could accelerate the pace of innovation. A technology trust could be put in place to facilitate the licensing and patenting of compounds, sharing of preclinical and clinical data and pooling of R&D tools related to the products. The sharing of clinical data could improve the efficiency and effectiveness of medical product development, and public funding of clinical trials would also justify the availability of the data generated as a public good.\(^3\) Efforts in Europe to implement greater clinical trial data transparency have also met with some industry concerns over the protection of commercial interests, but some companies have taken voluntary steps to allow researchers to access data from their studies.

Public funding through push and pull financing mechanisms would also condition access to the resulting end-products, apportioning supply to countries where the public health need exists and making this access contingent upon plans for the rational use of the novel antibiotic are in place. In a publicly financed pharmaceutical value chain, antibiotic production could take place under purchase agreements, where production could be contracted from qualified drug manufacturers. If much of the upstream work were publicly financed and the intellectual property owned by the public sector, technology transfer should be easier to facilitate. These manufacturers would commit to producing a limited volume of drugs, set centrally by the global consortium’s efforts to forecast the antibiotic supply needed for rational use. Through a mechanism like the Green Light Committee and Global Drug Facility, assurances would be provided that plans for and monitoring of the rational use of these novel antibiotics would be in place.

The risks of the antibiotic pipeline could be reduced by strategically applying public support to bottlenecks. Push and pull incentives operate differently, but both might be structured to contribute to delinkage—that is, separating returns on investment from volume-based sales or revenues (Price x Quantity).

---

\(^1\) Pelaez, F. "The Historical Delivery of Antibiotics from Microbial Natural Products—Can History Repeat?" *Biochemical Pharmacology* 71.7 (2006): 981-90.
