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Incentives for R&D for New Antimicrobial Drugs

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Abstract

Antimicrobial resistance (AMR) is becoming a major global public health threat and has begun to command attention from European and US policy makers. An initial focus on monitoring AMR and conserving existing treatments by cutting down on misuse has been complemented by moves towards addressing the paucity of new drugs in the R&D pipeline of the pharmaceutical industry. We identify five economic challenges: the utilisation externality; the lack of incentives for R&D arising from use restrictions, low prices, and scientific and regulatory challenges; the global joint sunk nature of R&D cost; the need for access to drugs in middle and low income countries; and failures in the market for point of care diagnostics. We analyse “push,” “pull” and hybrid incentives and conclude that higher prices linked to targeted use with diagnostic tests and/or an AMC-based “prize” for registering (but not necessarily using) desired new drugs would be effective, and could be linked to push measures. US and European collaboration on incentives would be desirable, but not if achieving agreement leads to delays. Action on conservation needs to be global and linked to use of new products. This will not be easy given TRIPS provisions and national sensitivities on this issue as seen in the 2010 reaction to evidence on the origins of NDM-1.

Introduction

Antimicrobial resistance (AMR) is becoming a major global public health threat, alongside that of resistance to treatments for infectious disease, including HIV/AIDS, malaria and tuberculosis. AMR has begun to command attention from European and US policy makers. An initial focus on monitoring AMR and conserving existing treatments by cutting down on misuse has been complemented by moves towards addressing the paucity of new drugs in the R&D pipeline of the pharmaceutical industry.

This paper sets out:

- the context, in terms of the burden of disease, lack of drug pipeline, and the policy interest;
- the economic issues arising from the 'externality' of resistance and the lack of R&D;
- proposals to stimulate R&D including the results of modelling we have undertaken in the context of the European debate;
- options for the way forward.

The global burden of antimicrobial resistance

Infectious diseases remain important in both rich and poor countries. The World Health Organization (WHO) estimates that infectious and parasitic diseases are the second leading cause of death world-wide, and the third leading cause of death in developed countries (WHO, 2004; Projan, 2003, Mossialos, et al., 2009). The Center for Global Development (CGD) found, for example, that more than 50 million people worldwide are carriers of one important type of AMR, Methicillin-resistant *Staphylococcus aureus* (MRSA) (Nugent, et al., 2010; Nugent, et al., 2008). The US has some of the highest rates of MRSA in the world. Approximately 60% of patients infected with *S aureus* in intensive care units in the US hospitals cannot be treated with Methicillin (Laximinarayan and Malani, 2007). A study conducted in the US found that MRSA was responsible for 125,969 hospitalizations between 1999 and 2000. Europe has lower rates. However, a number of major countries in Asia (Taiwan, South Korea and Japan) and in South America (Argentina, Brazil and Columbia) have higher rates of MRSA than the US. This is linked to high antibiotic use.

In the EU, Norway and Iceland, the European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC) estimated that drug resistant strains of six microbes (*Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecium*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*) were responsible for 2.5 million extra hospital days that cost over €900 million in 2007 (ECDC/EMA, 2009).

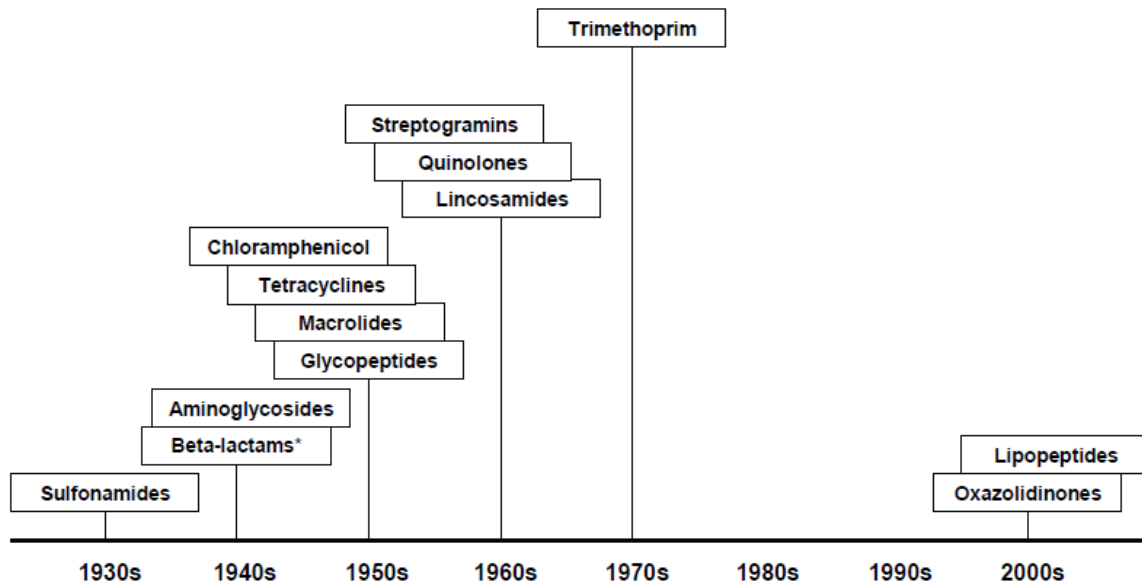
It is important in this context to weigh the costs against the benefits that will result from the discovery and development of a new antimicrobial. For example, a report by the ECDC/EMA (2009) estimated that AMR resulted in approximately 25,000 deaths in 2007 in the EU alone. If we use the bottom end of the €1-2 million range for the value of a statistical life recommended for European Commission Impact Assessments (European Commission, 2009), then the total cost of these deaths is €25 billion. An R&D incentive that reduced mortality in the EU in one year only by five per cent would, on this basis, be "worth" €1.25 billion.

The decline in the pipeline for antimicrobial drug development

Between the 1940s and the end of the 1970s pharmaceutical companies produced a steady flow of new antimicrobials, many of which had new mechanisms of action, to help counteract resistance (ECDC/EMA, 2009). By the early 1970's there were 11 distinct classes of antimicrobials

and over 270 different drugs in clinical use (Power, 2006). In the past three decades however, only two new classes of antimicrobials have been discovered: oxazolidinones in 2000 and cyclic lipopeptides in 2003 (ECDC/EMA, 2009). Figure 1 provides a timeline of the discovery of new antimicrobial classes.

Figure 1 Timeline of new antibacterial class discovery (ECDC/EMA, 2009)



The ECDC/EMA (2009) identified only 15 systemically administered antimicrobials (i.e. administered intravenously) under development in 2008 with new mechanisms of action or targets that have the potential to meet the challenge of AMR. Of these 15, only eight are likely to be effective against Gram-negative bacteria such as *Acinetobacter species* and *P aeruginosa*, which are becoming increasingly problematic around the world. A similar study by Boucher, et al., (2009) of antibacterial candidates found 16 antimicrobial compounds in Phase II or later stages of development. It is of course inevitable, as in any drug development pipeline, that a significant proportion of these candidates will fail to make it to the market.

This decline in the R&D pipeline reflects the fact that in the 1990s the number of large pharmaceutical companies involved in antimicrobial research began to decrease significantly (Mossialos, et al., 2009). By 1991 approximately half of them had cut or reduced funding for their infectious disease R&D program. There was a temporary resurgence after 1991 as companies restarted their antimicrobials research program to address the emergence of AMR, but this was short lived (Projan, 2003). In 2001 Eli Lilly and Bristol-Myers Squibb exited the market altogether, while Roche spun-off its antimicrobials unit into a separate company called Basilea (Power, 2006). In 1990, there were 18 large pharmaceutical companies active in antimicrobial R&D (Shlaes and Projan, 2009). By 2005, Power (2006) estimates that this had dropped to eight, while the Infectious Disease Society of America (IDSA) estimates that currently only five major companies are actively involved in antimicrobials R&D (Boucher, et al., 2009).

The gap left by the exit of larger pharmaceutical companies has been filled, to some extent, by biotechnology companies and small or medium sized enterprises (SMEs). Mossialos, et al. (2009) caution, however, that the majority of products currently under development by SMEs were licensed from larger pharmaceutical companies that were downsizing their own antimicrobial programmes. The smaller companies have not done any in-house discovery of targets. SMEs also have limited financial resources to meet the high costs of taking a drug to the market. It is worth noting that more than 90 per cent of the new antibacterials marketed between 1980 and 2003 were developed by large pharmaceutical companies.

The policy impetus in the European Union and the United States

In recognition of the increasing burden of AMR and reductions in pipelines for new drugs, policy developments in the EU and the US have shifted over time from an emphasis on conservation of existing antimicrobials to implementing incentives to create new ones.

EU Policy Developments

Recently, the EU has focussed on new drugs for AMR. Previously the focus was on: (i) the conservation of the effectiveness of existing drugs through their appropriate use and (ii) the threat of microbial resistance to patient safety. But now the emphasis has shifted towards the need to stimulate R&D for novel antimicrobials.

The findings of an EU-commissioned London School of Economics (LSE) report (Mossialos, et al., 2009) were discussed at a 2009 conference (Swedish Presidency, 2009). The Council of the European Union formally adopted the conclusions of the Swedish Conference (Council of the European Union, 2009) in December 2009. These included calls upon:

- The Member States to: "...consider options to strengthen incentives to conduct research and development of new effective antibiotics within the academic as well as the pharmaceutical sector ... taking into account ... small and medium-sized enterprises."
- The Member States and the Commission to "...explore ways to promote further public-private partnerships ... to facilitate research into new antibiotics, strategies for use of currently available antibiotics and diagnostic methods;"
- The Commission to "...within 24 months, [i.e. by the end of 2011] develop a comprehensive action-plan, with concrete proposals concerning incentives to develop effective new antibiotics..."
- The Commission to "...consider using experience regarding relevant procedures from previous specific EU legislation on orphan drugs and drugs for paediatric use..."

US Policy Developments

In the US initial emphasis was also on conserving the effectiveness of existing antimicrobial drugs. Some of the earlier legislation introduced into Congress, the Preservation of Antibiotics for Medical Treatment Act (PAMTA) and the Strategies to Address Antimicrobial Resistance (STAAR) Act, sought to limit antimicrobials use to slow the growth of resistance. Emphasis was placed on eliminating non-therapeutic use of antimicrobials in animal husbandry, a proposal the Food and Drug Administration (FDA) has endorsed (Harris, 2010; FDA, 2010). The EU banned the use of antimicrobials in farming in 2006. In September 2010, however, the Generating Antibiotic Incentives Now (GAIN) Act was introduced into Congress (H.R. 6311). Unlike the previous two bills, the purpose of the GAIN Act is to stimulate the development of new antimicrobials.

The IDSA launched a "10 by 20" Initiative aiming at creating an R&D environment with the ability to develop 10 new antimicrobials by 2020. IDSA has been seeking to bring together a range of global leaders from policy, academia, industry, intellectual property, medicine, and philanthropy to develop creative incentives to stimulate antibacterial and diagnostic R&D (Gilbert, et al., 2010).

The TransAtlantic Task Force on Antimicrobial Resistance

The EU-US 2009 Summit Declaration established the TransAtlantic Task Force on Antimicrobial Resistance (TATFAR) to address issues relating to the appropriate therapeutic use of antimicrobial drugs, and strategies for improving the antimicrobial pipeline. A final report was due in March 2011.

The Economic Problem

There are five related economic challenges to stimulating an efficient R&D response to AMR.

The utilisation externality

The first is that the development of AMR is linked to the use of antimicrobial drugs. Philipson and Mechoulan (2003) and Philipson, Mechoulan and Jena (2006) set out the problem of resistance as a “negative externality.” Current utilisation produces AMR as a negative side-effect, decreasing the value of future use as antimicrobials lose their effectiveness. This is assumed to dominate any positive external effects of treatments for infectious diseases by reducing the number of infectious carriers who might otherwise infect other people (Philipson, 2000).

The problem of AMR is not new. Bacteria have evolved resistance to every antibacterial developed. As early as three years after the introduction of penicillin in the 1940s, cases of penicillin resistant *Staphylococcus aureus* infections were reported. However, the rate of resistance to new antimicrobials is increasing rapidly and there is a positive correlation between antimicrobial drug utilisation and the prevalence of resistance. Higher rates of resistance are seen in higher use countries.

This is linked to the problem of inappropriate prescribing, a major facilitator of AMR. There are two aspects. Physicians prescribe antibacterials inappropriately for viral infections such as the common cold or flu. A study by the University of Colorado Health Sciences Center suggested that approximately 55% of all the antibacterials prescribed in the US for upper respiratory infections were unnecessary (Taubes, 2008). The second aspect is that physicians often prescribe broad spectrum antibacterials rather than more effective and targeted narrow spectrum antibacterials.

There is a shared underlying reason for both aspects of inappropriate prescribing, which is that rapid point of care diagnostics are not readily available to physicians to determine if the pathogen is viral or bacterial, and in the case of a bacterial infection, which bacterium is the culprit. The result is that most physicians, faced with evidence of an infectious disease, do not wait for the results of tests that may require days to be completed, but err on the side of caution by prescribing broad spectrum antimicrobials or combinations of antimicrobials.

A second major problem is patient non-adherence to the regime, a particular problem in developing countries where social and environmental factors can lead to non-adherence. These include transportation costs to the clinic or pharmacy, lack of food to take with medication, or inability to afford a full therapeutic treatment course (Nugent, et al., 2008). Non-adherence is a problem in developed countries as well. In some cases patients may simply feel better and stop taking their medicine.

Finally, we have noted the misuse of antimicrobials in farming and fishing for non-therapeutic purposes. The result is that AMR in humans is linked to drug use in animals is increasing. For example, since the quinolone class of antimicrobials was approved for use in poultry husbandry in the 1990s, quinolone resistant strains of *Campylobacter* (a poultry bacterium that can cause diarrheal disease in humans) have begun to emerge (HSUS, 2007).

We can think of the externality arising from use of a drug as leading to an erosion in the effectiveness of the drug. The per-patient health gain achieved depreciates over time. The rate of depreciation is a function of the cumulative use of the product. This rate of depreciation also depends on the nature of that use which reflects characteristics of the health care system, for example, the incentives faced by prescribers.

As Philipson and Mechoulan (2003) note, fear of depreciating effectiveness leads to policies to restrict the use of existing antimicrobials. When a new antimicrobial appears, it too will be subject to restrictions, because we do not know when the next one will appear. The most cost-effective outcome from the health care system’s point of view maybe that a new drug is only used in patients with infections resistant to all existing treatments. This does not create an attractive market for new entry.

Lack of incentives for R&D

The second problem is low expected returns to R&D investment. Estimates of the average cost of developing a new drug range from \$802 million to \$1.7 billion (DiMasi, et al., 2003; Paul, et al., 2010). With such significant investment costs at stake, pharmaceutical companies prioritize competing projects according to expected net present value (NPV). Table 1 below shows Projan's estimated outturn NPV of a number of different therapeutic classes, including antimicrobials. From Table 1, it is clear that antimicrobials are not particularly attractive relative to projects in other disease areas.

Table 1 NPV of drug development by therapeutic class (adapted from Projan, 2003)

Therapeutic Class	Risk Adjusted NPV "x\$1,000,000
Musculoskeletal	1,150
Neuroscience	720
Oncology	300
Vaccines	160
Injectable Antibacterial (Gram-positive)	100

There are a number of reasons for the relatively low profitability of antimicrobial drugs.

Restrictions on antibacterial use

Restrictions on use by payers and providers (for example, through the use of clinical protocols) to delay the build up of resistance are one important part of reduced incentives to develop new antimicrobials. The other major problem is that a key benefit of a new drug – its future potential to replace current drugs as their effectiveness declines – is not factored into pricing as we discuss below.

One public policy prescription for addressing consumption externalities in a market is to use measures such as a tax (Philipson and Mechoulan, 2003) that can raise the price paid by the user to one that reflects the full social cost. The tax revenues raised also can be used to tackle the externality either by paying compensation to those affected or by investing in alternatives. In the case of AMR, it is unlikely to be politically feasible to tax the use of existing antibiotics. Non-price based conservation efforts to slow the growth and development of resistance have been used. These involve limiting utilisation by controlling access and use.

Of course, a drug to which resistance will develop quickly will have a shorter clinical life compared to one for which resistance is slower to develop. In theory an innovation could benefit from restrictions on use that slow the spread of AMR in a particular time period if overall long term sales were much higher. This would depend on the extra length of life, the length of the patent, the price of the drug, and the likelihood of competitive entry eroding that price or market share. If, however, as seems plausible, the build-up of resistance is largely a function of the cumulative volume of use of an antibacterial, then delayed sales due to prescribing restrictions will unambiguously reduce market attractiveness for R&D effort.

If, however, restrictions in use were accompanied by a higher price (for example, after the use of a point of care diagnostic to target the drug) then long-term, discounted, on-patent revenues could in principle be higher than in an environment where there were no effective restrictions.

Low prices in the market

The majority of antimicrobials commonly used in both hospital and community settings are off-patent generics, notably cephalosporins and the penicillin and macrolide classes. There are on-patent antimicrobials being used in hospitals, such as Zyvox (linezolid) and Tygacil (tigacycline),

however these are predominately used as second or third line treatment. This is partly to conserve their effectiveness, but also for cost purposes. Cheaper drugs are tried first. Only non-responding patients are put on higher priced drugs.

The pricing problem for new entrants is compounded by growing use of health technology assessment (HTA), including cost-effectiveness analysis, by many governments and payers. Although in principle this should make it easier to charge high prices when there is value to society, and HTA should take account of the consequences of AMR in its calculations, it does not currently do so. Prices for newly approved antimicrobials remain low in Europe and the US (Kesselheim and Outterson, 2010). They can expect to be priced below their true social value, reducing the opportunity for companies to recoup R&D investment.

Additionally, unlike chronic diseases where treatment can last for months or even years, most antimicrobials are used for short course therapy only. Low prices are not offset by high volumes. As a result, it is often more profitable (ignoring differences in the scientific challenge and in clinical development costs) for pharmaceutical companies to invest in drug discovery for chronic diseases. In order to achieve a commercially attractive return, pharmaceutical companies would need to charge what payers may regard as unreasonably high prices in comparison to existing antimicrobials.

Scientific difficulties surrounding antimicrobial development

The main scientific challenge to antimicrobial discovery is finding a lead compound that can act as an antimicrobial agent. Payne, et al. (2007) estimate that for antimicrobials an average of 20 drug candidates are needed to yield one marketable drug. It was hoped that the complete sequencing of a bacterial genome would result in an abundance of targets, but that has not happened. One compound must be able to inhibit the growth of many different bacterial species, presenting different molecular targets, membrane permeabilities and metabolic pathways. Payne, et al. (2007) report that GSK's success rate with antimicrobial high throughput screening was four to fivefold *lower* than with targets for other therapy areas. The authors reviewed the available literature between 1996 and 2004 and found that whilst over 125 antibacterial screens on 60 different targets were used by 34 different companies, none of these screens resulted in a credible development candidate.

The result is that, in some cases, antimicrobial discovery has shifted back to tried and tested approaches. In addition to looking for novel targets, pharmaceutical companies are also developing new "follow-on" drugs in existing classes of antimicrobials, instead of new classes. The interaction between follow-on drugs and the target bacteria is altered somewhat as compared to existing drugs in the therapy class, but the underlying mechanism of action is unchanged. Resistance to new generation agents in known classes could develop more quickly than for agents creating novel therapy classes.

The regulatory environment and clinical development cost and time

New antimicrobials are required by drug regulatory bodies to show non-inferiority compared to a currently registered antibacterial. Prior to 2001, regulatory agencies normally used a "delta value" of 15% for antimicrobials to determine non-inferiority. In other words, trials should be powered such that a new drug could be up to 15% lower in efficacy than the reference drug and still be within the lower limit of the 95% confidence interval and so deemed to be non-inferior.

The FDA and EMA had two concerns with this approach. Firstly, successively less effective comparators could be selected, leading to a presumed equivalence of what were in reality statistically and clinically inequivalent products. Drugs that were inferior were being classified as non-inferior. Secondly, the effectiveness of (comparator) products changed over time as resistance patterns changed, typically becoming less effective. In 2001 both the FDA and the EMA changed the requirements for clinical trials involving antimicrobials, recommending the use of a delta value of 10%. While a seemingly small change, the potential impact on trial size, duration, and cost was substantial. The new delta value would have doubled the number of patients needed for clinical trials. Industry feared that by the time a clinical trial ended, the "standard" therapy (i.e. the

comparator) would have changed and the study results could be deemed irrelevant by the regulator, payers and clinicians. Projan (2003) estimated that the effect would have been to reduce the risk adjusted NPV for a novel, Gram-positive antibacterial from the \$100 million shown in Table 1 to \$35 million, further reducing the relative attractiveness of R&D in this area.

A number of pharmaceutical companies put their antimicrobials programmes on hold and the exit of Eli Lilly and Bristol-Meyers Squibb from the field of antimicrobials occurred around this time. As a result of these unintended consequences, the FDA dropped the proposed 10% delta value, agreeing that delta values would be chosen on a case by case basis. This defused the immediate crisis, but there were some lasting effects, including the delayed development of a number of new products. The case-by-case approach means that uncertainty still remains around the requirements for clinical evaluation.

From the point of view of HTA and Pricing and Reimbursement bodies acting on behalf of payers, equivalence means, at best, the same price as the comparator. To achieve a higher price (or use at a higher price) a product would usually need to show superiority, if not in a “head-to-head” trial then in an indirect comparison.

Summary of the R&D incentives problem

A crucial solution to the AMR problem is the creation of new antimicrobials to replace those to which resistance has developed. But limiting use of antimicrobials to slow down the build-up of AMR discourages R&D because it lowers and delays expected volumes and therefore revenues. These “dynamic costs” (the health and economic consequences of less R&D) may exceed the short term benefits of restricting use of current antimicrobials “even though such limits are the appropriate policy in the absence of technological change” (page 4, Philipson and Mechoulan, 2003). The problem is compounded by the use of HTA which does not in practice (although it could) factor in any future benefits from avoiding the consequences of drug resistance. Difficulties with the science of discovery and regulatory uncertainty add to the unattractiveness of R&D in this area.

Philipson and Mechoulan (2003) argue that “a single instrument is not sufficient to appropriately control R&D incentives *ex-ante* and externalities *ex-post*” (page 31). Solutions to correct externalities can lead to R&D inefficiencies *ex-ante* even if they are efficient *ex-post*, when there is need to stimulate technological change. In other words:

- restricting use of existing antimicrobials makes sense as we don’t know how many new antimicrobials we will get, and when a new antimicrobial drug appears it will be subject in turn to restrictions, because we don’t know when the next one will come along;
- an additional strong policy lever is therefore required to stimulate R&D, as these use restrictions *reduce* R&D incentives. Philipson and Mechoulan (2003) argue that “one needs to break the link between *ex-ante* R&D and *ex-post* output provision” (page 31). Thus any policy addressing the problem of AMR should be a two pronged solution: one arm should address the *ex-post* utilisation externality through the conservation of existing antimicrobials and the other should stimulate *ex-ante* R&D.

The global nature of R&D

The third aspect of the economic problem of responding to AMR is the global joint sunk cost characteristics of pharmaceutical R&D. The benefits of new products, given R&D investment, can in principle be made available in all markets subject to prices exceeding marginal production and selling costs. Danzon and Towse (2003) proposed applying Ramsey Optimal Pricing (ROP) approaches to the problem of recouping the globally joint cost of pharmaceutical R&D across users in different countries through differential pricing. Since both ROP prices and profit maximizing price discrimination imply prices inversely related to demand elasticities, market incentives should lead unregulated price discriminating firms facing competition to set (second best) optimal price differentials across markets, provided they can segment markets.

However, in the context of AMR, as we have noted, health care systems are not currently sending signals of willingness to pay that reflect social value, and negative externalities reduce the social value of increasing access. Differential prices may not reflect these factors. The global public policy challenge is to stimulate an optimal amount of R&D in the absence of clear market signals from payers that reflect social value. National and regional initiatives to stimulate research could lead to too little or much R&D. There is a case for co-ordination of global policy effort, but a risk that this leads to delay and so increases the overall cost of tackling the problem.

Access to new drugs in Middle and Low Income Countries (MLICs)

The fourth element of the AMR economic problem is access to new drugs in MLICs, a number of which have very high rates of resistance to existing drugs in their populations, reflecting high use. The application of differential pricing is designed to increase static efficiency by increasing use in MLICs. It does this by making drugs more affordable with prices close to marginal cost for lower income patients (whether they are buying out-of-pocket or third parties are paying on their behalf). In some cases, the money to pay for these drugs for poorer populations will be funded from overseas aid payments from rich country governments and from donations from foundations. Much R&D for new drugs to meet global health challenges also comes from these sources, reflecting donor desire to contribute to the improved health and wellbeing of poorer people in low income countries. There is also an element of self interest, linked to concerns about the potential global spread of MLIC prevalent infectious diseases.

However, in the case of the use of antimicrobials, additional MLICs utilisation could in turn lead to a build up of global resistance to the new drugs, including amongst patients in higher income countries. We have seen in 2010 the spread of resistance to New Delhi *metallo- β -lactamase 1* (NDM-1) from India and Pakistan to other, mostly European, countries as a result of travel between countries, including for medical treatment.

Any AMR policies implemented in one part of the world therefore will have implications for other parts. For example, incentives to stimulate antimicrobial R&D in (say) the US will benefit everyone, not just patients in the US. Similarly, conservation policies put in place in (say) India and Pakistan will have benefits for patients in Europe and the US as well as in those two countries. The option of seeking a global approach to addressing AMR is attractive if achievable. The Trade Related Intellectual Property agreement (TRIPs) as supplemented by the Doha Agreement allows for compulsory licensing in situations of national health emergency enabling “go it alone” strategies to be adopted in the absence of such an approach. “Go it alone” strategies are unlikely to lead to optimal global outcomes.

Failures in market for diagnostics to target drug treatment

The fifth problem is that the market for point of care diagnostic tests, which enable treatments to be rapidly targeted, suffers from several economic challenges. The use of diagnostic tests presupposes the existence of tests with a good evidence base. In reality there are failures in the market for tests, which reduce incentives for diagnostics R&D. The most important of these is the difficulty of establishing intellectual property rights over a test. Many hospitals have “in-house” capabilities to produce their own “home-brew” versions of commercial tests. For this reason, developers have little incentive to invest in evidence generation, in particular to demonstrate the clinical utility of their tests. This reduces the confidence of health care payers and providers that drug-test combinations really do deliver better health care outcomes. Of course, the drug developer can fund test development, and this is happening in stratified medicine more generally. Drug-test combinations are used in Phase III trials to provide an evidence base for product registration linked

to the use of a test. However, in the case of antimicrobials there is no current incentive for a drug company to invest in restricting its sales volume.

Payers will look at the cost effectiveness of the use of diagnostic tests. The gain from using tests to target treatment has to exceed the cost of testing (Danzon and Towse, 2002). Patients who have a different infection to that anticipated can now be treated in a different way. This gain could have three elements:

- There is greater health gain by matching treatment to those patients who can benefit.
- The build up of resistance is delayed.
- The out-of-pocket costs of treating patients with inappropriate drugs are avoided.

Use of point of care tests also can help in the development of new drugs. Without rapid diagnostics it is difficult and time consuming to identify patients who are infected with the targeted microbes as current tests can take days to produce results. These diagnostics can help companies conducting clinical trials recruit patients reducing the length and cost of trials, and making it more feasible to run higher powered trials, for example, to show superiority.

Incentives for antimicrobial R&D

The disincentives that pharmaceutical companies face in the market for antimicrobials are not unique. Similar disincentives of low prices and low volumes are observed in the markets for: numerous neglected diseases in developing countries (Kremer, 2001); orphan drugs in developed countries; countermeasures for chemical biological, radiological and nuclear (CBRN) threats; and for evidence collection on the benefits of drugs for paediatric use. The policies proposed or enacted in an attempt to correct these market failures have also been proposed as solutions to the AMR problem. More detailed discussion is available in Sharma and Towse (2011).

Incentives for R&D to supplement or replace market demand can be broken down into “push” and “pull” categories. The main difference between them is that push incentives pay for research *inputs* by funding or rewarding R&D effort *ex-ante*, i.e. in expectation of successful outcomes but not conditional on them, and pull incentives pay for research *outputs* rewarding R&D effort *ex-post*, if the outputs of R&D (be they drugs, vaccines, or diagnostic tests) result in a health gain and/or the achievement of other health system goals. In other words, in the context of drugs to counter AMR, push incentives lower the cost of R&D for drug development while pull incentives seek to mimic the market incentives that exist for other pharmaceutical products. The term “hybrid” is used to refer to proposals combining elements of both push and pull incentives. Table 2 provides a list of some push, pull and hybrid incentives commonly discussed in the literatures. Sharma and Towse (2011), and Mossialos, et al. (2009) provide more detailed discussions of these incentives in the context of their potential application to R&D for drugs to tackle AMR.

Table 2 Examples of push, pull and hybrid incentives

Type of Incentive	Incentive
Pull	Advanced market commitments Priority review vouchers (PRV) and the fast track option (FTO) variation of PRV Patent extensions Transferable Intellectual Property (IP) Extensions
Push	Product development partnerships (PDPs) Tax incentives Direct funding of R&D Funding and regulatory support for pre-

Hybrid

competitive consortia

Orphan drug legislation
Vaccines and drugs to counter chemical, biological, radiological and nuclear (CBRN) threats, including Project BioShield

Push incentives can be attractive, particularly to SMEs with limited resources for R&D, but can also enable larger companies to maintain programmes that would otherwise not have the expected return to justify any allocation of funds. However, information asymmetry can lead to principal-agency problems (Grabowski, 2005). Because the developer knows more about the project than the funder, the developer can overstate the prospects of a project in an attempt to get funding. Having secured push funding, they may subsequently put in little effort if they are not expecting to get through to the next stage. The funder bears the majority of the risk with no guarantee of a successful payoff.

Pull incentives avoid this problem because they reward only successful products. The information asymmetry does not give rise to principal-agency problems. Developers have a strong incentive to be realistic about their prospects, abandoning unpromising projects to put effort into seeing good projects through development.

There are four challenges, however, to organising pull incentives. It is hard to determine prospectively the size of the reward needed to incentivize R&D – too much risks overpaying, too little means insufficient investment. This challenge is linked to the question of how to divide the reward between first, second and subsequent entrants. Secondly, pull incentives appear to cost more. The reward has to explicitly take account of the risks of failure, and it is paid at the end of the development process, leading investors to want a return that takes account of the delay. Of course, a push incentive spent on a failed project is, in reality, a lot more expensive for a donor than the zero cost they would incur with a pull incentive when a project failed. Thirdly, a pull incentive requires pre-specification of the output before it has been developed. There is a risk of “agency capture” by companies seeking a lower hurdle. Fourthly, there is a time inconsistency problem. Policy makers would be better off in the short run if they changed their minds about rewarding R&D once the companies had made irrevocable commitments to invest. This can be tackled by contractual and political pre-commitment (Grabowski, et al., 2008) as in the case of GAVI’s Pneumococcal Vaccine AMC.

It may be that pull incentives are better at addressing the *commercial* uncertainty (given a drug that meets the desired criteria, what are the chances of achieving the sales revenue needed for a return on investment?) whereas push incentives are better at helping to address early stage research *scientific* uncertainty (what are the chances of getting to a drug candidate that meets the desired success criteria?). There appear to be both commercial and scientific challenges in the area of drugs to tackle AMR. The consensus coming out of the 2009 conference in Stockholm was that a hybrid approach will be necessary. These combine both push and pull incentives and thus can in theory complement the advantages and disadvantages of both types of incentive. Perhaps most importantly, however, they spread the risk between the developer and funder.

Examples of hybrid approaches include orphan drug legislation, which has been successful (combining market exclusivity with regulatory support and, in the US, additional R&D tax breaks), and Project BioShield and the related CBRN counter-measures in the US, which have not been successful, in part because the federal government and Congress keep changing the rules.

Which types of push and pull incentives may be appropriate for R&D against AMR?

Higher prices that internalise the externality, reflecting the social value of the new product make sense. However, higher prices increase the incentive for the company to add volume and should therefore be conditional on restrictions in use, for example, by requiring the use of point of care diagnostic tests. Restrictions in use could be partially offset with a longer patent life or other form of intellectual property protection.

Payments that are independent of volumes also would make sense, although this would require the specification of required output to be very clear. These could be viewed as lump sum premiums for an insurance policy and would be particularly appropriate for products that were expected to be held in reserve for some time. Such an upfront payment could be for registration (rather than for volume of use) of a product meeting desired characteristics. It could be in the form of an AMC “prize” or a Transferable Intellectual Property (IP) Extension (where the reward is a tradable right to extend the patent life of a best selling drug). Both reward the launch of an effective drug rather than volumes of use. Both face challenges.

AMCs are expensive and require upfront commitments from governments and payers. In order to lead to a sustainable pipeline several AMCs will have to be established for each new antimicrobial needed or one much larger AMC set up with a more complex specification of types of qualifying drugs. Transferable IP Extensions are likely to be unpopular, with patient advocate groups and politicians arguing that they “pass the buck,” prolonging revenues for a best selling drug by delaying generic entry, pushing up health care costs. In most European countries, however, the same third party payer would meet the costs as would fund the other incentives. A more practical challenge is estimating the value of any Transferable IP Extension, and therefore the length of extension that should be included in the package.

Transferable IP Extensions never have been implemented in either the EU or the US. One AMC exists, for purchasing pneumococcal vaccines that have already been granted market authorization in more commercially lucrative markets. The ability of either to stimulate R&D is untested. This is true also of selling rights for FDA priority review (PRV) or a fast track option (FTO) review. The evidence is clear that FDA priority reviews and fast track reviews, along with the EMA accelerated marketing authorisation, all speed up review times. But their potential value as a *pull* incentive in the form of a tradable voucher entitling the holder to obtain rapid review for a new drug in an unrelated area is unknown, even in the case of the PRV, which has been enacted.

Push incentives reduce costs, but do not directly incentivise volume. A Product Development Partnership (PDP) for antimicrobial drugs is a potentially attractive option, given the success of PDPs in stimulating drug and vaccine pipelines in the area of neglected diseases. A PDP to fund earlier stage R&D and other push incentives, such as FDA regulatory priority review, fast track or EMA accelerated market access and tax breaks on early stage R&D, could complement a pull incentive and result in a hybrid proposal.

Modelling Incentives for antibacterial development

In a separate paper (Sharma and Towse, 2011) we undertook a modelling exercise of “push” and “pull” incentives for the European market in order to inform the work of the European Commission, which is required to develop “concrete proposals concerning incentives to develop effective new antibiotics.” Where possible we used data from peer-reviewed publications. Our objective was to identify the size of incentive required to raise the expected NPV to \$200m or €147m.

Model Results

The main results of the modelling exercise are presented in the Table 3

Table 3 Results of the modelling exercise

Incentive	Size of Incentive (€)	New NPV (€)
1 year AMC	985 million	147 million
5 year AMC	1.4 billion (275m per year)	150 million
6 month Transferable IP Extension	800 million	147 million
2 year Transferable IP Extension	840 million (420 million per year)	147million
5 year Transferable IP Extension	975 billion (195 million per year)	147 million
PRV^{III}	221 million	8 million
FTO^{III}	384 million	51 million
Higher prices	300% increase in antibacterial revenue in Europe	149 million
PDP for early stage R&D up to end of Phase II	294 million (varying payments per year)	141 million

The results suggest that:

- Substantial increases in the prices (but not volumes sold) of new antimicrobials as compared to the base case could be highly effective;
- Non-transferable IP extensions for antimicrobials had minimal effects on the NPV. This was because of low revenues and the effect of discounting on additional revenues coming at the “back end” of the product life cycle. Substantial increases in prices would, of course, increase the value of any IP extension;
- Two pull incentives (the AMC and Transferable IP Extension) could be highly effective at increasing NPV, involving payments for R&D success that are independent of the volume of the new drug sold;
- The Priority Review Voucher (PRV) and the Fast Track Option (FTO) (as a pull mechanism, i.e. the right to a fast track review to be sold like the right to priority review with a PRV) were unable to increase the NPV to a competitive level;
- A Product Development Partnership (PDP) providing direct funding at the earlier stages of R&D, i.e. the preclinical to the end of Phase I, has a significant impact on the NPV. Of course, as a push incentive it requires payment irrespective of outcomes achieved.

Although we did not directly model them, incentives that provide regulatory expertise (and so reduce regulatory uncertainty) and that speed up the regulatory review process are likely to be of value if linked to a pull incentive.

Recommendations for the way forward

Our preference is for one of two types of “pull” R&D incentive. The first is for price increases linked to conservation. This is similar to the Kesselheim and Outterson (2010) proposal for “value-based reimbursement.” Our analysis indicates significant price premiums would be required. We recognize, however, that higher prices would encourage companies to seek sales volume. Use of point of care diagnostics and recognition of the importance of tight controls on use as part of any premium pricing arrangement would be ways to avoid any adverse consequences. Therefore, an important emphasis should be placed on the development, reimbursement and use of rapid point of

care diagnostics to ensure that drugs are only used on patients for whom they will be effective. These diagnostics will need to be rewarded and yet be affordable at the point of use, thus ensuring maximum use in all clinical settings in all countries. There is a case for a PDP and/or an AMC for diagnostic tests. Both could help to stimulate research, and an AMC driven by volume uptake (unlike the AMC for the drugs) could stimulate use of a test by separating the price paid by the health care provider from that received by the diagnostic company.

Payers might still oppose higher prices for new antimicrobial drugs on grounds of cost and of cost-effectiveness. It would be important to have consensus (in the EU this would need to be at the Member State level) around the importance of accelerating the pricing and reimbursement decision at the Member State level, and of taking into account the growing costs of AMR in any assessment of value. An important area for further research is how AMR estimates should be built into economic appraisal by HTA and pricing and reimbursement bodies. For an early discussion of value of alternative treatment strategies in reducing the build up of AMR over time, see Laximinarayan and Brown (2000).

Such a policy should include (as suggested by the European Council in its instructions to the Commission) some of the components of the paediatric drug programme (notably a patent extension) and of the orphan drug programme, specifically the incentives around regulatory and technical advice and review. These are especially important considering that a lack of clarity surrounding the requirements for regulatory review and approval has been identified as part of the antimicrobials problem.

A critical element within such a package, combining high prices with conservation, will be the market power that such a measure would bring. Orphan drugs have market exclusivity. It is not clear how important this provision is in securing market power as it can be challenged in both the US and the EU when a similar drug produces better effects or has a better safety profile. In most cases the market power comes from the greater willingness of private and public sector payers to pay higher prices for drugs treating small populations with debilitating diseases. Market exclusivity in a therapy area (as opposed to intellectual property protection for the molecule) might in any case not be appropriate for new antimicrobials, as the objective is not to block follow-on innovation, but to have a number of new products, which can then be used in a targeted way that reduces the potential growth of resistance.

The second “pull” measure would be an AMC in the form of a cash “prize” for registration of products meeting pre-agreed AMR specifications. The AMC should be structured in a way that enables “follow on” products to also achieve a return. However, a condition for accepting the AMC prize could be a willingness on the part of the company to accept that the product may be held in reserve as in the proposal for a Strategic Antibiotic Reserve (Kesselheim and Outterson, forthcoming).

Rather than see the two pull measures as mutually exclusive, it may be that they could be used for different types of drugs. The lower the expected immediate use, the more an AMC would be likely to stimulate R&D rather than a potential high price. It may even be possible to have the company choose which route to follow.

Two policy areas worth further research are (i) to assess the insurance value to health care systems of having the ability to treat patients with AMR (for early estimates of insurance values in pandemic influenza and bioterrorist attack, respectively, see Meltzer, et al. (1999) and Kaufmann, et al. (1997)) (ii) to estimate the health benefits – in particular the life years gained – from bringing new antimicrobials to the market. Policy makers need a better sense of what the pay-off would be for investing in antimicrobial R&D.

As we noted, a PDP for antimicrobial drugs is a potentially attractive option, given the success of PDPs in stimulating drug and vaccine pipelines in the area of neglected diseases. However, given information asymmetries, we believe that the absence of commercial incentives is better directly addressed through a pull incentive, especially when companies are deciding whether or not to begin costly Phase III trials. A PDP could fund earlier stage R&D and other push incentives such as

accelerated market access, and tax breaks on early stage R&D could complement a pull incentive, to result in a hybrid proposal. Push initiatives would reduce the required size of the pull initiatives.

The dialogue between the US and European government agencies (TATFAR) is very important and should be continued. It offers an opportunity for the same or complementary incentives to be put in place on both sides of the Atlantic enabling the burden to be shared between the two. The other crucial role for TATFAR is in the exploration of the regulatory issues that are currently causing concern to industry, for example, surrounding proving non-inferiority and the problems of differing regulatory and clinical trial requirements across countries. The EMA and FDA have a strong tradition of dialogue and collaboration. The Task Force provides another area in which important progress could be made between the two regulatory bodies.

TATFAR is an excellent starting point, but more must be done. An essential area of global cooperation will be around balancing conservation efforts against ensuring access to those in need. The availability of cheap first line antibacterials has significantly improved global health, but also has contributed to the global burden of AMR. The CGD Report (Nugent, et al., 2010) proposes ways to conserve use of existing antibiotics.

Access to new antimicrobials in MLICs through differential pricing needs to be accompanied by measures to ensure appropriate use. Any negative externality will be global. Testing may need to be subsidised. This will be a difficult issue to address as seen in the response to the Kumarasamy, et al. (2010) evidence that NDM-1 originated in India (Guilloton, 2010; Herriman, 2010). Achieving multi-stakeholder agreement to constrain antimicrobial use will not be easy, but is an essential complement to the successful incentivisation of R&D for new drugs to tackle AMR.

Endnotes

- I Strictly it looks at antibacterial classes, also known as antibiotics. For the purposes of this paper we use the term antimicrobials, which includes antibacterials.
- II NPVs were risk adjusted with increased risk associated with projects at the earlier stages of drug development (Projan, 2003).
- III Unlike the other incentives where we wanted to determine the size needed to increase the NPV to €147 million, for the PRV, FTO and IP extensions for antibiotics we wanted to determine their impact on the NPV, i.e. would they be able to increase the NPV to a competitive level and stimulate R&D as the literature suggests. We used Ridley and Sanchez's (2010) estimate of €221 million as the discounted value of the PRV to a pharmaceutical company. When the FTO was modelled as a pull incentive, we used Moran's (2005) risk and time discounted estimates of the potential returns to Eli Lilly had they been able to fast track Prozac. This estimate ranges to €384 million after taxes.

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