NEW DRUGS TO TACKLE ANTIMICROBIAL RESISTANCE

ANALYSIS OF EU POLICY OPTIONS

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OHE Research
Office of Health Economics

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ABBREVIATIONS

ACE	Antibiotic Conservation and Effectiveness
AMC	Advance Market Commitment
AMR	Antimicrobial Resistance
ARI	Acute Respiratory Infections
CBRN	Chemical, biological, radiological and nuclear agents
CGD	Center for Global Development
COA	Call Option for Antibiotics
EARSS	European Antimicrobial Resistance Surveillance System
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EFPIA	European Federation of Pharmaceutical Industries (EFPIA)
EMA/EMEA	European Medicines Agency
ESAC	European Surveillance of Antimicrobial Consumption
EU	European Union
FDA	Food and Drug Administration
FDMA	FDA Modernization Act
FP7	Framework Programme No 7
FTO	Fast Track Option
GAIN	Generating Antibiotic Incentives Now
GSK	GlaxoSmithKline
HHS	Department of Health and Human Service
HTA	Health Technology Assessment
HTS	High throughput screening
IDSA	Infectious Disease Society of America
IMI	Innovative Medicines Initiative
IOM	Institute of Medicine
IP	Intellectual Property
IRR	Internal Rate of Return
LSE	London School of Economics and Political Science

ABBREVIATIONS

MDR	Multi-drug resistance
MRSA	Methicillin-resistant *Staphylococcus aureus*
NDM-1	New Delhi metallo-β-lactamase 1
NPV	Net Present Value
ODA	US Orphan Drug Act
PAMTA	Preservation of Antibiotics for Medical Treatment Act
PDP	Product Development Partnership
PIP	Paediatric Investigational Plan
PRV	Priority Review Voucher
QALY	Quality Adjusted Life Year
R&D	Research and Development
SPC	Supplementary Protection Certificate
SME	Small to Medium Enterprises
STAAR	Strategies to Address Antimicrobial Resistance Act
TATFAR	TransAtlantic Task Force on Antimicrobial Resistance
UK	United Kingdom
US	United States
WHO	World Health Organization

KEY CONCEPTS[1]

Advance Market Commitment (**AMC**) is a commitment by a government or a private/international organisation to purchase a specified quantity of a drug or vaccine that meets criteria that has been pre-specified by the purchaser, at a pre-determined price. It is an example of a pull incentive.

Antibacterials[2] are more commonly referred to as antibiotics. They are medicinal or natural products which can kill or inhibit the growth of bacteria.

Antimicrobials are medicinal products that kill or inhibit the growth of living micro-organisms including bacteria, fungi, viruses and parasites. Antimicrobials include antibacterials.

Antimicrobial resistance is a naturally occurring phenomenon whereby micro-organisms develop the ability to survive and replicate during the course of treatment.

Bacteria are microorganisms that can be classified into categories using a number of criteria. One way to classify them is based on staining. This divides most bacteria into two groups, Gram-positive and Gram-negative, based on the properties of their cell walls.

Broad Spectrum antibacterials are active against a wide range of bacteria, compared to narrow spectrum, which target a specific group.

Call Option for Antibiotics (**COA**) is a **hybrid incentive** that is based on the principles of a call option in equity markets. A potential purchaser buys the right, during drug development, to purchase a pre-determined quantity of the drug at a discounted price when and if it makes it to the market.

Clinical trials are research activities that involve the administration of a test regimen to humans to evaluate its efficacy and safety.

Data exclusivity bars the use of clinical trial information for the regulatory approval of generic equivalents of a drug, even after patent expiry.

A **Fast Track Option** (**FTO**) can be purchased by a company for a drug of its choice. This allows the company to expedite the development and regulatory review of a drug in their pipeline, getting it onto the market more quickly. The funds raised as result are used to support public sector R&D. In this way, an FTO functions as a push mechanism, however, the option to fast track a drug as reward for the successful development of a needed drug or vaccine can act as a pull incentive for companies as well.

Gram-positive bacteria are bacteria that are stained purple as a result of Gram staining. Examples of Gram-positive strains include *Bacillus, Listeria, Staphylococcus, Streptococcus,* and *Enterococcus.*

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[1] References: Mossialos et al, 2009; EMEA/ECDC, 2009

[2] For consistency, we use the term antibacterial throughout the paper, unless specifically referencing an idea or a piece of work that uses "antibiotic" instead. The two terms are interchangeable.

Gram-negative bacteria are bacteria that do not retain the purple stain of Gram staining and are stained pink as a result. They are more problematic to treat than Gram-positive bacteria because they have an outer cell wall which makes them difficult to attack. Examples of Gram-negative bacterial strains include *Escherichia coli, Helicobacter, Moraxella, Pseudomonas, Salmonella,* and *Shigella*.

Hybrid incentives combine the use of push and pull incentives (see below). An example of a hybrid incentive is the Orphan Drug Act in the US-it includes grants for clinical research (push) as well as market exclusivity (pull).

Intellectual property (IP) right or protection is a type of legal monopoly where the inventor(s) of an invention with social value are granted exclusive rights. These rights allow the owner of the IP to earn monopoly profits. In the case of pharmaceuticals, IP protection is exerted primarily through the patent system.

IP extensions increase the amount of time a drug is protected from generic competition allowing prices and sales revenue to remain high. One form of IP extension is a patent extension. IP extensions are an example of a pull incentive.

Market exclusivity bars the entry of therapeutic substitute(s), unless there are provisions that limit the period of exclusivity if and when therapeutic substitutes offer improvements (in terms of both efficacy and safety) over the existing available drug.

Net Present Value (NPV) describes the relationship between project costs and revenue in terms of discounted cash flow.

Non-inferiority study[3] determines whether or not an experimental drug is similar in efficacy to a comparator drug, neither or which are tested against a placebo. Non-inferiority studies are used in the approval process of new antibacterials.

Orphan disease in the US is defined as a disease or condition that affects less than 200,000 people or affects more than 200,000 but for which there is no reasonable expectation that a pharmaceutical company will recover its research and development costs through sales. In the EU, an orphan disease is defined as a life threatening or chronically debilitating condition that affects a maximum of 5 in 10,000 people.

Orphan drug legislation has been implemented in the US and EU, among other countries, and is used to stimulate R&D for rare diseases and conditions. It is an example of a hybrid incentive.

Open source drug discovery is based on the concept of "open source" used in technology and software development. As it applies to pharmaceuticals, it usually refers to the use of web-based tools and software to increase access to and facilitate the sharing of information and ideas to stimulate innovation. An issue in pharmaceuticals, given the importance of IP, is whether open source arrangements enable innovators to get a reward for their efforts.

[3] Choffnes et al, 2010

Priority Review Voucher (**PRV**) is a pull incentive. They are awarded to the successful developer of a drug or vaccine. The PRV allows the company to receive priority review on any drug in their portfolio and gets it on the market, on average, six months earlier.

Product Development Partnerships (**PDPs**) are a type of public-private partnership that focus on the development of health technologies, such as drugs. PDPs, like public-private partnerships, generally involve collaboration between public and private partners. PDPs are an example of a push incentive.

Project BioShield is a drug and vaccine acquisition programme introduced in the US in 2004. Similar to an AMC, its purpose is to spur the development of countermeasures against chemical, biological, radiological and nuclear threats. Unlike an AMC, however, Project BioShield includes milestone payments during the development phase, and hence is hybrid incentive.

Pull incentives pay for research outputs. They reward R&D effort if it results in a product that can (or does) deliver health gain, i.e. the successful development of a new drug.

Push Incentives pay for research inputs. They fund or reward R&D effort irrespective of the outcome.

Tax incentives can incentivise research. One type is a tax credit on R&D which reduces the after-tax cost of R&D and thus functions as a type of push incentive.

Transferable IP Extensions, also referred to as **wildcard patent extensions**, are a reward for the development of a needed drug or vaccine. The developer is awarded a patent extension on another drug in its portfolio.

EXECUTIVE SUMMARY

Introduction

Antimicrobial resistance (AMR) is becoming a major global public health threat, contributing to the growing problem of drug resistance, a naturally occurring consequence of treating infectious diseases with antimicrobial agents. Recently, AMR has begun to command attention from European policy makers whose focus has moved towards addressing the lack of new antibacterials in the pharmaceutical industry R&D pipeline.

In 2009 the EU focused on the need for the development of new antibacterials to fill the pipeline and for the introduction of appropriate incentives to stimulate research and development (R&D) for novel antibacterials. A Report commissioned from the London School of Economics (LSE) examined appropriate ways to stimulate the development of new antibacterials. Its findings and other material were discussed at a conference in Stockholm in September 2009, titled "Innovative Incentives for Effective Antibacterials".

The outcome of the conference was that the Council of the European Union formally adopted the conclusions of the Swedish conference in December 2009. The Council has been called upon to come up with a proposal for stimulating antibacterial R&D by the end of 2011.The purpose of this paper is to contribute to the discussion that began in Stockholm by presenting policy makers and other relevant stakeholders with a short list of feasible and realistic solutions for Europe to stimulate R&D.

Understanding the Problem

Antimicrobial resistance is a global problem affecting both the developed and developing world alike. The Center for Global Development (CGD) finds that the developing world faces the following challenges (Nugent et al, 2010; Nugent et al 2008):

- Up to 53 million people are carriers of Methicillin-resistant *Staphylococcus aureus* (MRSA).
- Acute respiratory infections are responsible for more than 3 million deaths each year among children under five. *Streptococcus pneumoniae* is believed to be responsible for nearly 70% of these infections but the number of *S pneumoniae* strains susceptible to penicillin has decreased significantly.
- All four species of Shigella, a highly contagious and deadly diarrheal pathogen, have shown resistance to antibacterials.

The clinical outcomes of AMR are increased morbidity, resulting in longer hospitalizations and increased mortality. There are also significant costs associated with AMR. Not only have treatment costs increased, but there are increasing societal costs as well. For example, a study by Noskin et al (2007) estimates that the total economic burden of *S. aureus* in the US increased from $8.7 billion in 1998 to $14.5 billion in 2003 for all inpatient stays and from $7.6 billion to $12.3 billion for surgical stays. The Institute of Medicine (IOM) in the US has estimated that the financial burden of AMR (including direct and indirect costs) may be as high as $30 billion per year.

In the EU, Iceland and Norway, the European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC) estimated that resistant strains of *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 (EMEA/ECDC 2009).

Similarly, outpatient costs were estimated at €10 million, the productivity loss due to absenteeism was calculated to be over €150 million per year and the total productivity loss due to infection mortality was estimated to be €450 million per year. Overall, the EMEA/ECDC (2009) calculated the total societal costs of infection due to resistance from these selected pathogens to be €1.5 billion per year. The biggest cost of all however is the 25,000 deaths that occurred in Europe in 2007 as a result of AMR.

The causes of antimicrobial resistance

Bacteria have developed resistance to almost every antibacterial developed in the past 50 years or so starting with Penicillin. Bacterial resistance is a naturally occurring, evolutionary phenomenon which can be exacerbated in a number of ways:

- There is a positive correlation between the use and prevalence of resistance
- Inappropriate prescribing of (i) antibacterials for viral infections and (ii) broad spectrum antibacterials rather than targeted narrow spectrum antibacterials
- Patient non adherence to the treatment regime
- The misuse of antibacterials in farming and fishing

The current state of the pipeline

For nearly 40 years, between the 1940s and the end of the 1970s pharmaceutical companies produced a steady flow of new antibacterials. In the past 30 years, however, only two new classes of antibacterials have been discovered. This decline reflects the fact that in the 1990s the number of large pharmaceutical companies involved in antibacterial research began to decrease significantly. This was partly due to a number of mergers and acquisitions that occurred between companies, but for many, it was a conscious decision. For example, in 2001, Eli Lilly and Bristol-Meyers Squibb exited the market altogether, while Roche spun-off its antibacterial unit into a separate company, Basilea.

The overall impact was that in 1990 there were 18 large pharmaceutical companies involved in antibacterial R&D, however, by 2005, Power (2006) estimates that only eight companies had in-house R&D capacity for antibacterials and the Infectious Disease Society of America (IDSA) counts only five major companies as still actively involved in antibacterial R&D.

The EMEA/ECDC (2009) identified only 15 antibacterials in development in 2008 that had new mechanisms of action or targets and with the potential to meet the challenge of drug resistance. Boucher et al (2009) conducted a similar study and found 16 antibacterial compounds in Phase II or later. The likelihood that the majority of these candidates succeeds however, is low.

The reasons for pharmaceutical companies exiting antibacterial R&D

1. Low returns in the market

Despite a large market size, there are a number of forces that exert downward pressure on revenues resulting in reduced commercial prospects for antibacterials. The most commonly used hospital and community antibacterials are generics. Competition from generics keeps prices low. The few new antibacterials that are still on-patent are predominantly used in hospitals as second or third line treatment, thus keeping their use low. The pricing problem is further compounded by the growing use of health technology assessment (HTA) by many European governments. In

principle this should make it easier to charge higher prices when there is value to society, and HTA should also take into account the consequences of AMR. It does not appear to do so, however, as prices for newly approved antibacterials remain relatively low.

Given that drug development is estimated to cost between $802 million and $1.7 billion, companies need to maximise the returns from their R&D budget. Unfortunately, as can be seen from the table below taken from Projan (2003), antibacterials are not an attractive investment relative to projects in other disease areas. This is because, unlike chronic diseases where treatment can last for months or years, most antibacterials are for short course therapy only. Thus low prices are not offset by high volumes of use/sales. As a result, it is more profitable for companies to invest in drug discovery for chronic diseases.

Therapeutic Class	Risk Adjusted NPV $m
Musculoskeletal	1,150
Neuroscience	720
Oncology	300
Vaccines	160
Injectable antibacterial (Gram-positive)	100

Source: Projan (2003)

2. Scientific difficulties surrounding antibacterial development
The main challenge to antibacterial discovery is finding a lead compound that can act as an antibacterial agent. It has been estimated that an average of 20 drug candidates are needed to yield one marketable drug. While it was hoped that the complete sequencing of the bacterial genome would result in an abundance of targets, that has not been the case. The result is that although new targets are still being explored, in some cases, antibacterial discovery research has shifted back to pre-genome tried and tested approaches. In addition to looking for novel targets, pharmaceutical companies are also developing new versions of existing classes of antibacterials, however, as the underlying mechanism of action remains unchanged, resistance to these new generation antibacterials in known classes may develop more quickly than for novel agents.

3. The regulatory environment
A number of regulatory issues are currently causing problems for the pharmaceutical industry, notably the standards for proving non-inferiority (where proposals for change led to some firms exiting R&D) and the problems of different regulatory and clinical trial requirements across countries.

4. Restrictions on antibacterial use
There is an inherent tension between the two aims of antibacterial management. On the one hand, policy makers rationally want to restrict the use of existing antibacterials to prevent the spread of resistance, while on the other, they want to promote the development of novel antibacterials to combat resistance. But restrictions on use reduce the expected returns from

innovation, decreasing the number of antibacterials being developed. As a result, health care systems become more dependent on existing antibacterials, which many no longer be as effective, accelerating the development and spread of resistance.

Modelling the Impact of Incentives on the NPV

To date, there has been no attempt to determine the size of the various incentives needed to make the NPV for antibacterial development more competitive relative to other disease areas. Doing so will help policy makers and industry leaders shorten the long list of potential incentives down to a more manageable and realistic few.

To do this we selected incentives that have been implemented or discussed in regards to addressing disincentives and market failures in other markets: neglected diseases, orphan drugs, countermeasures against chemical, biological, radiological and nuclear (CBRN) agents, and evidence for paediatric drug use.

These incentives can be divided into two categories: push and pull. Push incentives lower the cost of R&D for drug development and thus lower a potential barrier to entry while pull incentives seek to mimic the market incentives that exist for commercially lucrative pharmaceutical products. Both push and pull incentives have their advantages and disadvantages. As a result, there is growing recognition that neither alone may be able to cost-effectively stimulate antibacterial R&D. The consensus at the Stockholm conference was that a hybrid approach will be necessary. The table below lists the incentives discussed in the paper.

Type of Incentive	Incentive
Pull	• Advance market commitments (AMC) • Priority review voucher (PRV) and the fast track option (FTO) variation of PRV • Patent extensions • Transferable patent extensions
Push	• Product development partnerships (PDPs) • Tax incentives • Direct funding of R&D • Funding and regulatory support for pre-competitive consortia
Hybrid	• The call option for antibiotics (COA) • Orphan drug legislation • Vaccines and drugs to counter chemical, biological, radiological and nuclear (CBRN) threats. This includes Project BioShield

The baseline case for the development of an antibacterial used data from publically available, peer reviewed literature. Where possible, antibacterial specific data was used, otherwise antibacterial data was assumed to be similar to that of the average new molecular entity.

Section 3.3 of the paper discusses the model in more detail. Using risk adjusted NPV estimates from Projan (2003) we set a target NPV for antibacterial R&D of $200 million or €147 million. At this level, investment in antibacterial R&D would be competitive with other therapeutic areas that currently attract higher investment from the pharmaceutical industry. We then determined the size of the various incentives that would be needed in Europe to increase the baseline NPV for antibacterial R&D to that level, and examined the impact of certain incentives on the NPV to assess their effectiveness.

The model only considered the impact of incentives implemented in Europe. Based on IMS data, we assumed that the European market makes up 40% of the relevant global market for antibacterials (IMS 2010). Sales and costs in other markets are not altered by any of the incentives, although the global nature of the problem is discussed later in the paper.

The baseline NPV calculated for an antibacterial was -€38.15 million and the IRR was 10% (below our assumed cost of capital of 11%) which goes some way to explaining the current lack of commercial investment.

Model Results

The main results of the modelling exercise are summarised in the table:

Incentive	Size of incentive (€)	New NPV (€)
1 year AMC	985 million	147 million
5 year AMC	1.4 billion (275 million per year)	150 million
PRV	221 million	8 million
6 month Transferable IP Extension	800 million	147 million
2 years Transferable IP Extension	840 million (420 million per year)	147 million
5 year Transferable IP Extension	975 million (195 million per year)	147 million
Higher prices	300% increase in antibacterial revenue in Europe	149 million

In addition, we found:

- The effects of six month and two year and five year (non-transferable) IP extensions for antibacterials on the NPV were minimal.
- The Fast Track Option was modelled as both a pull and push incentive in the form of direct funding of R&D. As a pull mechanism, the FTO is unable to increase the NPV to a competitive level. As a push mechanism, the results showed that direct funding at the earlier stages of R&D, i.e. preclinical and Phase I, have a significant impact on the NPV. For example, €27 million per year to fund preclinical development increased the NPV from

-€38.15 million to €68 million and increased the IRR to 15%. These results highlight the value of push incentives, and give policy makers a sense of the amount of funding needed for PDPs. They further suggest that pull incentives alone may not address the fundamental lack of commercial attractiveness of the antibacterial market.

Recommendations

The focus of this paper is, as we noted earlier, to move the discussion in Europe forward by presenting policy makers and stakeholders with a short list of feasible and realistic solutions to stimulate R&D to fight AMR in Europe. We note that the EU Commission has been tasked to come up with a comprehensive proposal by the end of 2011 at the latest.

Our recommendations are as follows:

Our preference is for a hybrid policy treating drugs for AMR in a similar way to orphan drugs. Such a policy could be combined with push initiatives in the pre-competitive stages of R&D. Examples of such push initiatives are currently being pursued through the IMI and through FP7.

Such a policy should include some of the components of the actual 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 antibacterial problem. Additionally, this policy should also include some type of fast track or priority review for new antibacterials developed. It would reward successful companies with priority review for a drug tackling AMR not only at the EU/EMA market authorisation level but ideally would also accelerate the pricing and reimbursement decision at the Member State level.

Another critical element within such a package, as with orphan drugs, will be the market power that such a measure would bring. In the case of orphan drugs, there is a market exclusivity provision. Market exclusivity might not be appropriate for new antibacterials, 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.

Of more importance is the willingness of Member States to accept significant price premiums. Member States might resist on grounds of cost and of cost-effectiveness. It would be important that there was a Member State consensus around the importance of taking into account the growing costs of AMR in any assessment of value.

We recognize, however, that such a hybrid might 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 may be ways to avoid any adverse consequences. **Any incentive package should include measures to ensure and encourage appropriate use and stewardship. Therefore, an important emphasis should be placed on the development of rapid point of care diagnostics to ensure that drugs are only used on patients for whom they will be effective. There needs to be a review of the challenges of getting more point of care diagnostics developed and used in clinical practice.** Such a review is needed as a matter of urgency.

An alternative package could include an upfront payment for registration (rather than for volume of use) in the form of an AMC "prize" or a Transferable IP Extension. Both incentives would reward the launch of an effective drug rather than actual volumes of use. The advantage of this type of approach compared to a "reward for use" approach is that it is able to balance the inherent tension between the public health goals of policy makers, i.e. to slow the growth and spread of resistance and encourage the development of new antibacterials, and the need for companies to generate attractive returns on their R&D investments.

However, AMCs are expensive and will require upfront funding from Member States. Added to this, a new AMC will have to be established for each new antibacterial needed or one much larger AMC with a more complex specification of types of qualifying drugs will need to be established in order to lead to a sustainable pipeline.

Transferable IP Extensions are not likely to be popular options. The biggest strike against them is that some patient advocate groups and politicians believe that they pass the burden onto others in the form of extended patent protection leading to delayed generic entry. In most Member States, 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 an IP extension and therefore the length of the extension. Limits on the number of extensions triggered could be accomplished by having a product specification hurdle similar to that which would be required for an AMC.

Another important issue would be the price at which the product was made available once licensed. The higher the value of the AMC or transferable IP extension the closer, in theory, the selling price could be to the generic price. It would be important to ensure use of the product was managed, ideally through the use of diagnostic tests to target treatment.

A European PDP for antibacterial drugs is a potentially attractive option, given its success in the area of neglected diseases, but also by looking at the impact of early stage R&D funding on the NPV for antibacterial development. In spite of this, we believe that the absence of commercial incentives is a more significant problem, especially when companies are deciding whether or not to begin the costly Phase III trials. In theory a European PDP could help fund Phase III trials however, it would make more sense to let the full cost and risk lie with the company. It is for this reason that we advocate for an increase in price, or an AMC or Transferable IP Extension linked to the licensing of a new antibacterial.

An area worth further research is how many lives would be saved by bringing new antibacterials to the market. While there are excellent monitoring and surveillance systems in place to track the emergence and spread of resistance, such as the European Antimicrobial Resistance Surveillance System (EARSS) and the European Surveillance of Antimicrobial Consumption (ESAC), there are few systems in place to measure the burden of resistance. This information gap must be filled. Policy makers and all stakeholders need a better sense of what the pay-off would be for investing in antibacterial R&D. If this was known, it might help to put the cost of potential incentives into perspective.

The dialogue between the US and European government agencies (TATFAR) is very important and should be continued. It offers an opportunity for comparable incentives to be

put in place on both sides of the Atlantic, especially if the EU chooses incentive mechanisms that could, in principle, be replicated by the US. The advantage of implementing the same or complementary incentives in both the EU and US is that the size of the incentives needed would be considerably smaller as the burden would be shared between the two. The other crucial role that TATFAR can play in the area of R&D incentives 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 different regulatory and clinical trial requirements across countries. The EMA and FDA have a strong tradition of dialogue and collaboration and the Task Force provides another area in which important progress could be made between the two regulatory bodies.

It is important to note that antibacterials developed in Europe and the US will also have value and be effective in other countries in which resistance is emerging, such as India and Pakistan. As in Europe it will be important to find ways of ensuring appropriate use without denying access to those in need. There is scope here for more work to be done on how to slow the development and spread of AMR due to inappropriate use in emerging markets. **There needs to be a global dialogue as to how the build-up of resistance to drugs is to be tackled. Without such a dialogue, the value of new drugs to the EU health care system will be eroded by a build-up of resistance to these drugs outside of the EU.**

The Commission has a deadline of the end of 2011 but should act now. **Our recommendation to the Commission is to establish a task force whose membership includes some Member States, key players from the pharmaceutical industry, EMA, ECDC, academia, microbiologists, and clinicians.** The task force will then be charged with working through these issues, as well as coming up with proposals for implementing incentives for antibacterial R&D.

1 INTRODUCTION

1.1 The Problem of AMR and the Purpose of the Paper

The growth of antimicrobial resistance (AMR) in Europe has commanded increasing attention from European policy makers. The emphasis has increasingly moved towards the lack of new drugs in the R&D pipelines of the pharmaceutical industry.

Antimicrobial resistance (AMR) is a growing global public health threat. It reduces the chances of successfully treating patients with infectious diseases, increasing the probability of complications, morbidity and mortality (Mossialos et al 2009). Infectious diseases remain important in both rich and poor countries. The World Health Organization (WHO) estimates that not only are infectious and parasitic diseases the second leading cause of death world-wide, but they are the third leading cause of death in the European Union (EU) and all developed countries (WHO 2004, Projan 2003, Mossialos et al 2009).

The problem of drug resistance is a natural and unavoidable consequence of treating infectious diseases with drugs (Beith 2008). As an increasing number of people have access to lifesaving treatments for other infectious diseases such as HIV/AIDS, Malaria, Tuberculosis, resistance to these drugs has increased. Antibacterial resistance is one part of the larger problem of AMR.

The focus of this paper is to move the discussion forward in Europe by presenting policy makers and stakeholders with a short list of feasible and realistic solutions to stimulate research and development (R&D) to fight AMR in Europe. We begin, however, by putting the issues in Europe in the context of what is a global phenomenon. Consider the recently published study (Kumarasamy et al 2010) tracking the discovery of New Delhi metallo-β-lactamase 1 (NMD-1) in 2008 among patients in the United Kingdom (UK) who had recently travelled to India or Pakistan. Given the close links between the UK and both of these countries, India and Pakistan's new superbug should be, and is, of great concern to public health officials in the UK. Of course, addressing the global dimension is not just about tackling cases that "arrive" in Europe, as we discuss later.

We note that the EU Commission has been tasked to come up with a comprehensive proposal by the end of 2011. We hope that our paper will provide an input into this process which will, hopefully, not take until the end of 2011.

1.2. Policy Impetus within the European Union, the US and the TransAtlantic Task Force on Antimicrobial Resistance

Developments in Europe

Three recent presidencies of the EU have placed a major focus on AMR and examined, successively, issues relating to: (i) the appropriate use of antibacterials; (ii) the threat of bacterial resistance to patient safety; and, most recently, (iii) the need to stimulate R&D for novel antibacterials using appropriate incentives. To that end, the LSE was tasked to examine appropriate ways to stimulate the development of new antibacterials. Its findings and other material were discussed at a conference hosted by the Swedish Presidency in Stockholm in September 2009, titled "Innovative Incentives for Effective Antibacterials". The outcome of the conference was that 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: "...review and consider options to strengthen incentives to conduct research and development of new effective antibiotics within the academic as well as the pharmaceutical sector as a whole, taking into account the situation of 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…"

Developments in the US

The past few years has also seen a wave of AMR-related activity at the policy level in the United States (US). Among them are three bills that have been introduced to Congress. The first two, the Preservation of Antibiotics for Medical Treatment Act (PAMTA)[4] and the Strategies to Address Antimicrobial Resistance (STAAR) Act[5] sought to address the non-therapeutic use of antibacterials in animal husbandry by limiting or ending the practice altogether, as the EU did in 2006, and by improving monitoring and surveillance of antibacterial use and new infections. Related to this was the publication of draft guidance by the Food and Drug Administration (FDA) in June 2010 stating that the agricultural use of antibacterials should be limited to therapeutic uses and that veterinarians should be involved in their administration (Harris 2010, FDA 2010). The third bill was more recently introduced and is titled the Generating Antibiotic Incentives Now (GAIN) Act of 2010. Briefly, this bill calls for five year IP extensions on antibacterials, priority review vouchers, fast tracking and revision of existing clinical trial guidelines for antibacterials[6]. Finally, at the Federal level we should note that the Institute of Medicine (IOM) and the Department of Health and Human Services (HHS) held a workshop in February 2010 to examine federal policies that affect the discovery, development and approval of medical countermeasures including new antibacterials (HHS 2010).

The 10 by 20 Initiative and the TransAtlantic Task Force on Antimicrobial Resistance

The Infectious Diseases Society of America (IDSA) established the 10 by 20 Initiative. The aim is to create a sustainable R&D enterprise with the ability to develop 10 new antibacterials by 2020. IDSA believes that the antibacterial pipeline problem can be solved by bringing together a range of global stakeholders and 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).

In line with IDSA's 10 by 20 initiative is the creation of the TransAtlantic Task Force on Antimicrobial Resistance (TATFAR) established in 2009 by US President Barack Obama and Swedish Prime Minister Friedrik Reinfeldt (when Sweden held the EU Presidency) on behalf of the EU. The purpose of the Task Force is to focus on solutions to the antibacterial pipeline problem, and strengthening infection control interventions and antimicrobial stewardship practices in both human and veterinary settings (Gilbert et al 2010).

[4] http://www.govtrack.us/congress/bill.xpd?bill=h111-1549&tab=summary
[5] http://www.govtrack.us/congress/bill.xpd?bill=h111-2400&tab=summary
[6] http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=111_cong_bills&docid=f:h6331ih.txt.pdf

2 UNDERSTANDING THE PROBLEM

In setting out the nature of the problem we draw from a number of sources, in particular:

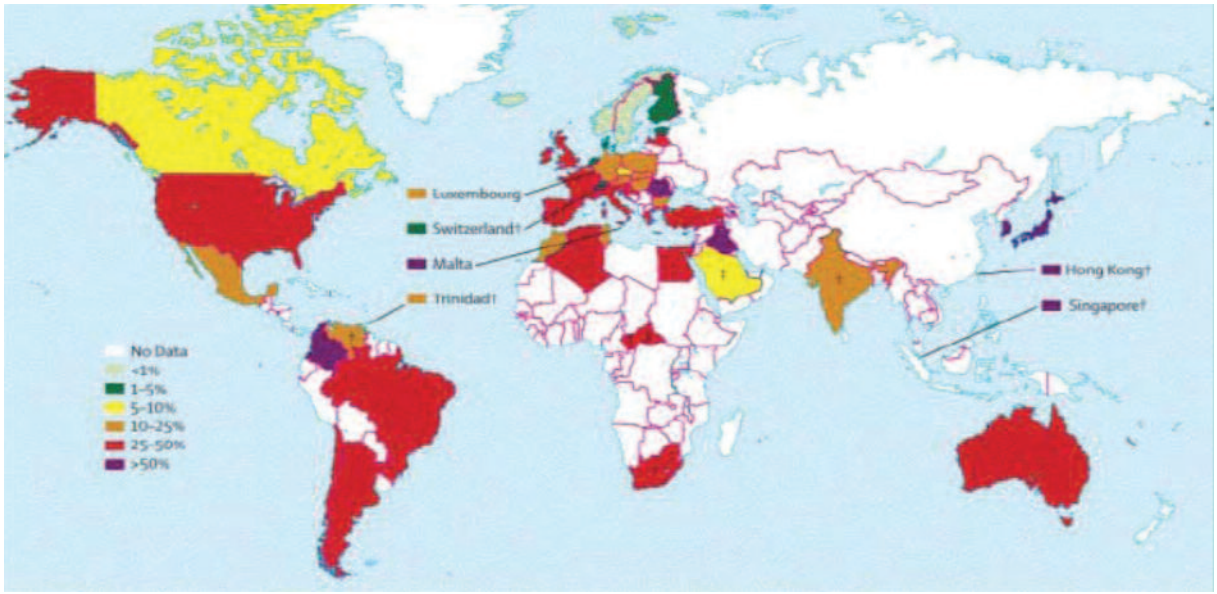
- The report of the European Centre for Diseases Prevention and Control (ECDC) and the European Medicines Agency (EMA) on the scale of the problem in the EU (EMEA/ECDC 2009);
- The work of the London School of Economics (LSE) team commissioned by the EU to explore incentives for R&D, (Mossialos et al 2009, Morel and Mossialos 2010);
- Earlier literature on the type of incentives that can and have been used to incentivise R&D for neglected diseases (Kremer 2000, Kremer 2001, Barder et al 2005, Towse 2005);
- Papers on the issue of AMR and drug development (Laxminaryan and Malani 2007, Power 2006, Projan 2003, Payne et al 2007).

2.1 The global burden of antimicrobial resistance

According to the Center for Global Development (CGD), developing countries face a number of challenges as a result of AMR including the following (Nugent et al 2008; Nugent et al 2010):

- Up to 53 million people are carriers of Methicillin-resistant *Staphylococcus aureus* (MSRA) Figure 1 provides a picture of the global prevalence of MRSA;
- Acute respiratory infections (ARIs) are a leading cause of death among children under five, killing more than 3 million children every year in developing countries. *Streptococcus pneumoniae* is believed to be responsible for nearly 70% of these infections. This pathogen can also cause otitis media, bacteraemia and bacterial meningitis. Unfortunately, the number of *S pneumonia* strains susceptible to treatment by penicillin has decreased to between half to two-thirds of all strains in many countries, and as low as a quarter in others. Strains resistant to penicillin are also likely to be resistant to other antibacterials as well;
- Shigella is a highly contagious and deadly diarrheal pathogen and all four species of Shigella (*dysenteriae*, *flexneri*, *boydii*, and *sonnei*) have shown resistance to antibacterials. For example, less than 40% of Shigella flexneri isolates are susceptible to cheap and safe antibacterials in the majority of Latin America. Further, in Asia, Shigella has been found to be resistant to trimethoprimsulfamethoxazole (81%), tetracycline (74%) and ampicillin (53%). There is also evidence of increasing resistance to ciprofloxacin, the WHO recommended treatment for Shigella.

Figure 1 Map of the global prevalence of MRSA (Grundmann et al 2006)



The clinical outcomes of AMR are increased morbidity and mortality. Several studies have shown that patients infected with a resistant strain of bacteria are likely to require longer hospitalization and are at increased risk of mortality. For example, the risk of mortality among patients infected with MRSA is double that of patients infected with non-resistant strains of *S aureus*.

There are other consequences as well. Treatment costs associated with certain conditions have increased. For example, it was estimated that in the US the cost associated with treating ear infections increased by 20% or $216 million between 1997 and 1998 because of increases in resistance. In the UK, drug resistance has increased the cost of treating urinary tract infections by 70%. In the developing world context while the prices of many first line treatments has fallen, thanks in part to donor financing and increased generic competition, the price for second and third line drugs are still high. In countries with inadequate resources, not everyone who needs these drugs will be able to access them. Lack of data means that the economic cost of AMR in developing countries is not easily measured.

The US has one of the highest rates of MRSA in the world. Approximately 60% of patients infected with *S aureus* in intensive care units in US hospitals cannot be treated with Methicillin (Laxminarayan and Malani 2007). Compared to Europe, only Romania and Malta had higher rates of MRSA than the US. Taiwan, South Korea and Japan, however, had higher rates of MRSA than the US because of their high antibacterial use, as did Argentina, Brazil and Columbia.

Unsurprisingly, the increased number of hospitalizations, morbidity and mortality also places an economic burden on hospitals, health care systems and the countries themselves. Roberts et al (2009) estimated that the medical and societal costs of AMR for *one* hospital in Chicago were between $10.7 and $15 million. They estimated that the additional medical costs attributable to patients with AMR are between $18,588 and $29,069 per patient, and the excess length of stay due to infection was anywhere from 6.4 to 12.7 days.

Noskin et al (2007) estimate that the total economic burden of *S aureus* in the US increased from $8.7 billion in 1998 to $14.5 billion in 2003 for all inpatient stays, and from $7.6 billion to $12.3 billion for surgical stays. The IOM estimates that the financial burden of AMR in the US (including direct and indirect costs) may be as high as $30 billion per year.

It is, however, difficult to get a true sense of the actual burden of AMR from much of the available literature. For example, estimating and quantifying the impact (both clinical and economic) of resistance in a hospital setting requires separating two confounding effects: the first is the fact that a longer length of stay increases the likelihood of becoming infected with a resistant infection and the second is that infection then increases the overall length of stay.

In addition, many studies estimating the economic burden of resistance often only look at direct medical or hospital related costs and do not take a societal perspective looking at indirect costs such as productivity losses and, most importantly, at the *value* of health loss in terms of increased morbidity and mortality.

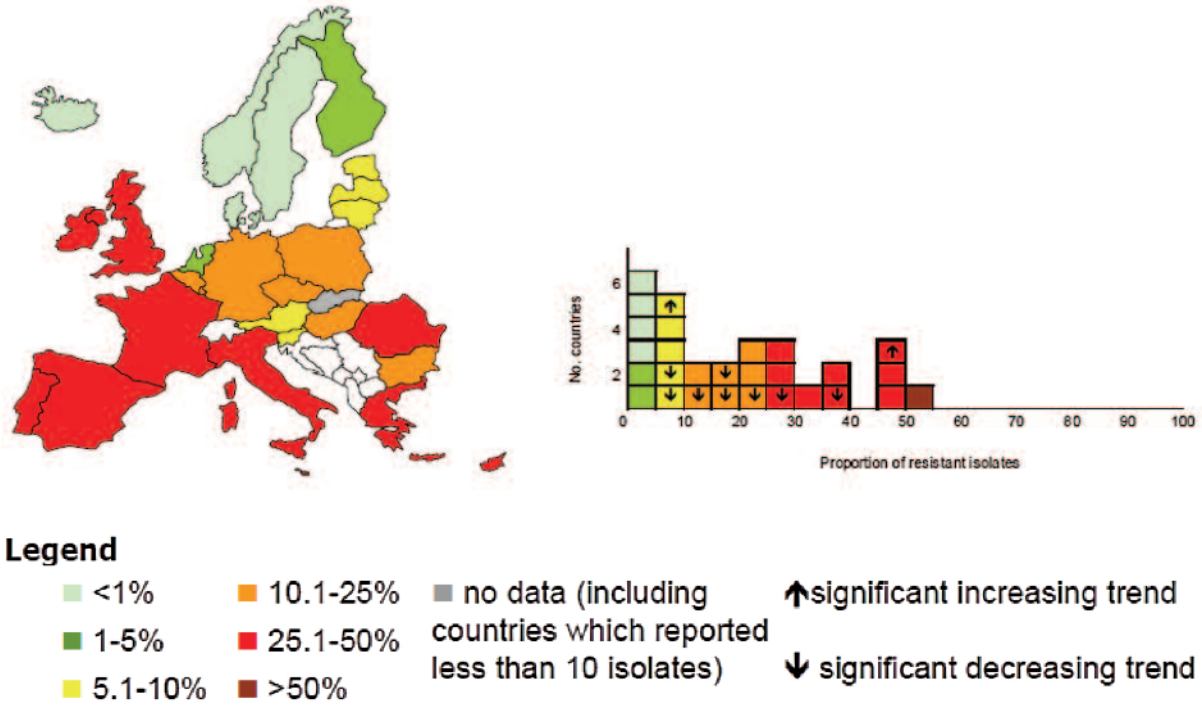
2.2 The European burden of antimicrobial resistance

Within Europe, AMR tends to be more prevalent in the South than in the North, a trend driven primarily by the use of antibacterials, defined as daily doses/1000 inhabitants/day. A 2009 report found that there were large variations in resistance between countries. For example, whilst the average proportion of MRSA in the EU, Iceland and Norway was 22%, the variation between countries was high, with less than 1% in Denmark, Iceland, Norway and Sweden, and over 25% in 10 countries, see Figure 2 (EMEA/ECDC 2009).

In the EU, Iceland and Norway, infection from the following six resistant strains of bacteria led to 2.5 million extra hospital days: *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecium*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. The costs of extra hospital days and in-hospital treatment were estimated to be over €900 million in 2007. Similarly, outpatient costs were estimated at €10 million and the productivity loss as a result of absence from work due to infection was calculated to be over €150 million per year.

Productivity loss due to infection mortality was estimated to be approximately €450 million per year. The EMEA/ECDC (2009) calculated the total societal costs of infection due to AMR from selected resistant bacteria (see list above) to be €1.5 billion per year. The biggest cost of all, however, are the approximately 25,000 patient deaths that resulted from resistant infections in 2007 in the EU, Iceland and Norway. Importantly, two-thirds of these deaths were due to Gram-negative bacteria. We estimate the cost of this as up to €25 billion, as we discuss later.

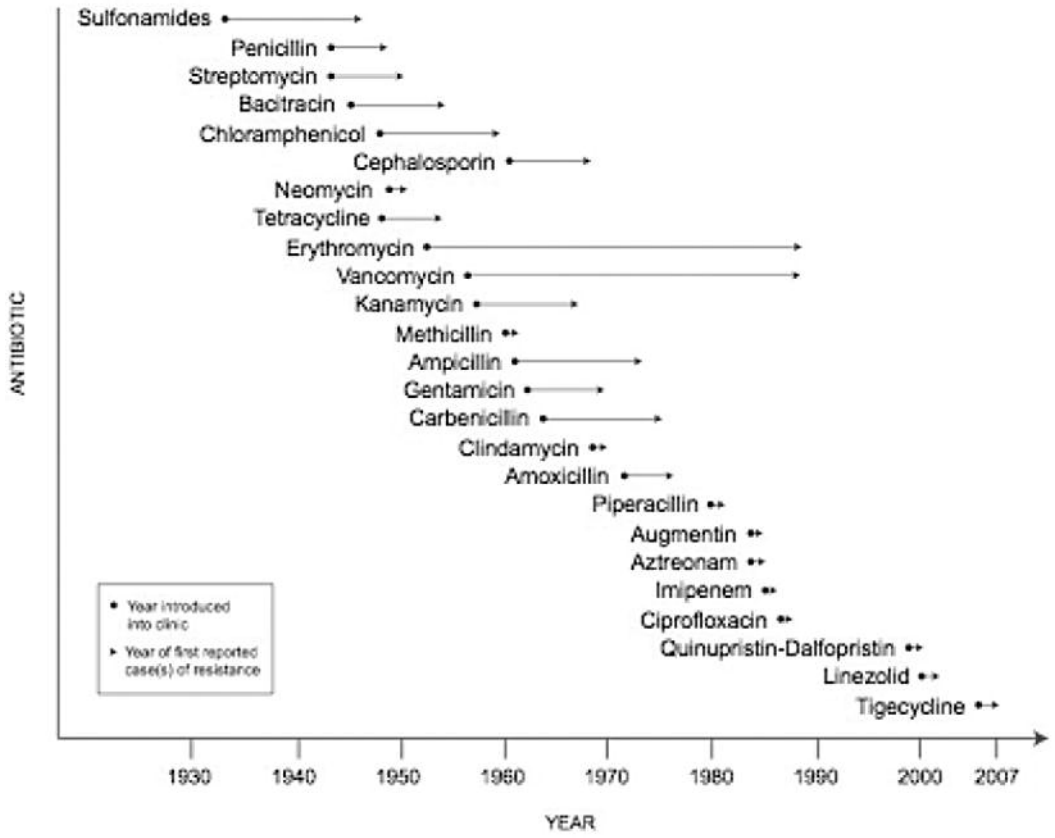
Figure 2 MRSA-resistance in Europe (EMEA/ECDC 2009)



2.3 The causes of antimicrobial resistance

Bacteria have developed resistance to almost every antibacterial developed in the past 50 or so years starting with penicillin which was first introduced in 1940. As early as three years later, cases of penicillin resistant *Staphylococcus aureus* infections were being reported. Figure 3 provides a timeline of the introduction of new antibacterials and the approximate year of the first reported cases of resistance. The rate of bacterial resistance to new antibacterials is increasing rapidly.

Figure 3 Timeline of the emergence of resistance (Pray 2008)



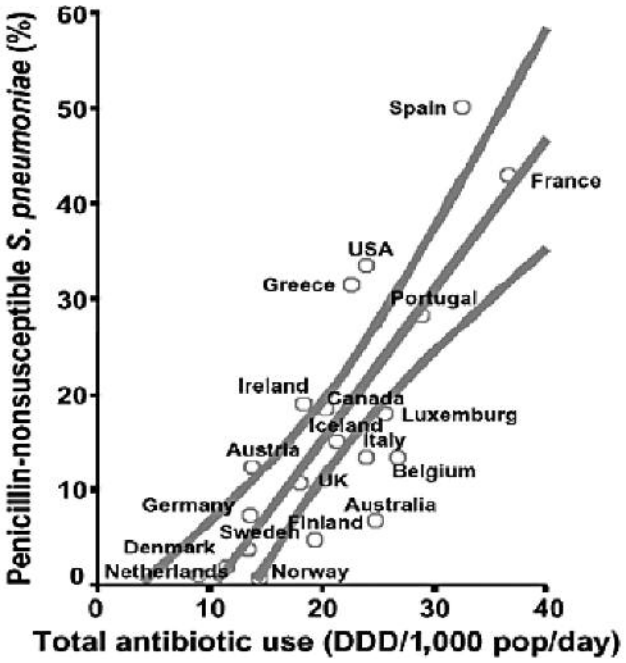
Although bacterial resistance to antibacterials is a naturally occurring, evolutionary phenomenon, resistance can be exacerbated in several ways.

Firstly, there is a well-documented positive correlation between antibacterial use and the prevalence of resistance. Higher rates of resistance are seen in countries with higher antibacterial consumption. Figure 4 shows the correlation between penicillin use and the prevalence of penicillin non-susceptible *S pneumoniae*.

This is linked to a second problem, that of inappropriate prescribing. This is one of the major facilitators of AMR and it has two different causes. One is that physicians often prescribe antibacterials for viral infections such as the common cold or flu. For example, a study conducted in 2001 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 cause 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, and that 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 test results that can often take days to come back, but err on the side of caution by prescribing broad spectrum antibacterials or combinations of antibacterials.

Figure 4 Correlation between penicillin use and prevalence of non-susceptible S pneumoniae (Albrich et al 2004)



A third problem is patient non-adherence to the regime. This is a particular problem in developing countries where social and environmental factors can lead to non-adherence. These include the cost of transportation to the clinic or pharmacy, the lack of food to take with medication, or the inability to afford a full therapeutic course of antibacterials (Nugent et al 2008). It is a problem in developed countries as well. Patients feel better and discontinue their treatment.

The fourth major problem is the misuse of antibacterials in farming and fishing. It has been estimated that approximately 70% of all antibacterials consumed in the US and 50% globally are given to livestock for non-therapeutic purposes (Union of Concerned Scientists, no date). The result is that AMR linked to animals is increasing. For example, Campylobacter is a poultry bacterium that can cause diarrheal disease in humans. Severe cases are treated with antibacterials from the quinolone class, such as Ciprofloxacin, which have been effectively used to treat infections in humans since the 1960s. However, since this class of antibacterials was approved for use in poultry husbandry in the 1990s, quinolone resistant strains of Campylobacter have begun to emerge (The Humane Society of the United States, no date). The EU banned the use of antibacterials in farming in 2006 and the US is now taking steps to better regulate its agricultural use.

2.4 The current state of the pipeline of antibacterial development

For nearly four decades between the 1940s and the end of the 1970s pharmaceutical companies produced a steady flow of new antibacterials, many of which had new mechanisms of action, to help slow the pace of resistance. By the early 1970s there were eleven distinct classes of antibacterials and over 270 different drugs in clinical use. In the past three decades, however, only two new classes of antibacterials have been discovered: oxazolidinones in 2000 and cyclic lipopeptides in 2003. Figure 5 tracks the timeline of the discovery of new classes of antibacterials.

More worryingly, in its technical report, the EMEA/ECDC (2009) identified only 15 systemically administered antibacterials (i.e. administered intravenously) with new mechanisms of action or targets that have the potential to meet the challenge of multi-drug resistance (MDR) under development in 2008. Of these fifteen, only eight had activity against Gram-negative bacteria, several of which such as *Acinetobacter species* and *P aeruginosa* are become increasingly problematic around the world.

The change reflects the fact that in the 1990s the number of large pharmaceutical companies involved in antibacterial research began to decrease significantly. By 1991 approximately half of them had cut or reduced funding for their infectious disease R&D programs. There was a temporary resurgence after 1991 as companies restarted their antibacterial research programs to address the emergence of AMR, but this was short-lived.

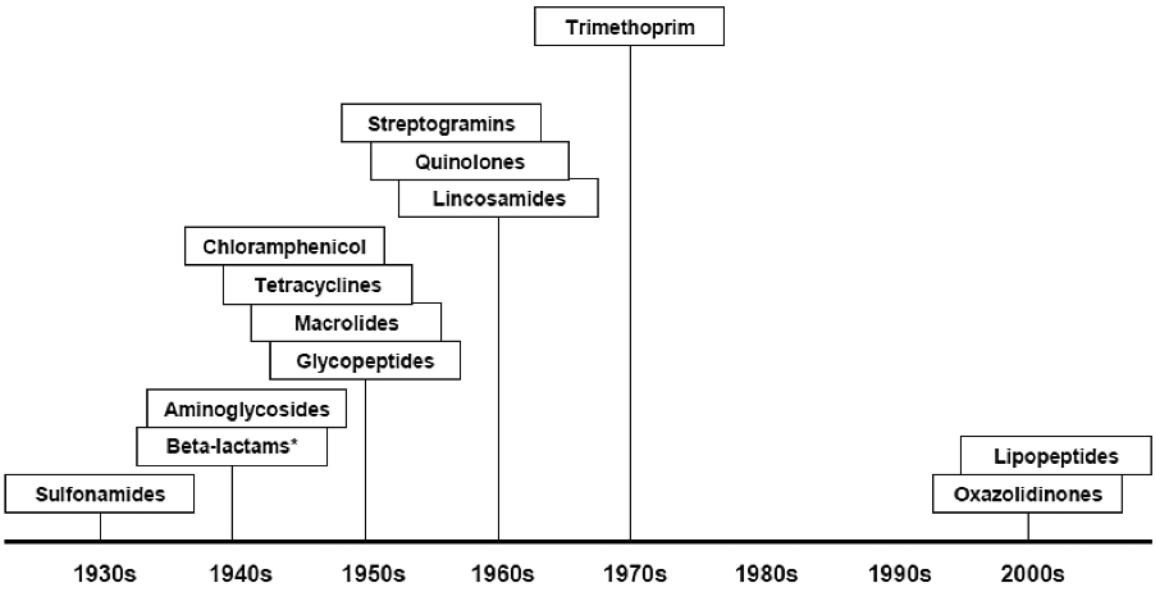
Part of the downsizing of antibacterial R&D was because of portfolio reviews following mergers and acquisitions. However, for some, it was not part of a broader review. In 2001 both Eli Lilly and Bristol-Meyers Squibb exited the market altogether, while Roche spun-off its antibacterials unit into a separate company called Basilea (Power 2006, Mossialos et al 2009). In 1990, there were 18 large pharmaceutical companies active in antibacterial R&D (Shlaes and Projan 2009). By 2005, Power (2006) estimates that the number of large pharmaceutical companies that had in-house R&D capacity for antibacterials had dropped to eight while IDSA estimates that currently only five major companies are actively involved in antibacterial R&D: GlaxoSmithKline (GSK), Novartis, AstraZeneca, Merck and Pfizer.

The gap left by the exit of larger pharmaceutical companies has, to some extent, been filled by biotechnology companies and smaller pharmaceutical companies - 'small to medium enterprises' or SMEs. Mossialos et al (2009) caution, however, that SMEs will not be able to fill the gap without help. The majority of products currently under development by SMEs were licensed from larger pharmaceutical companies who were downsizing their own antibacterial programs. These 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 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.

In the US, Boucher et al (2009) conducted a similar study of antibacterial candidates that were in the development pipeline. They focused on drugs that had successfully progressed to Phase II or III. They found 16 antimicrobial compounds in Phase II or later stages of development. Of these 16, eight were found to have activity against Gram-positive pathogens and the other eight had activity against both Gram-positive and negative pathogens. Additionally they found several

drug candidates in the early stages of development that had the potential to address the unmet need for Gram-negative pathogens. It is of course likely that many of these candidates will fail to make it to the market.

Figure 5 Timeline of new antibacterial class discovery (Singh and Greenstein 2000)



These results of the EMEA/ECDC report (2009) confirm what Boucher et al (2009) observed in the US. The number of antibacterials to make it through the development process and receive approval by the FDA has decreased significantly over the past 25 year. Overall, Boucher et al (2009) estimated a 75% decrease in the number of systemic antibacterials approved by the FDA between 1983 and 2007. They further found evidence of a continuing drop in approvals in the last five years of their study period (2003-2007). In order to effectively tackle the problem of AMR, this trend needs to be reversed and pharmaceutical companies need to be incentivised to not only develop new antibacterials, but novel antibacterials that address the areas of unmet need, in particular Gram-negative bacteria.

2.5 The reasons for pharmaceutical companies exiting antibacterial R&D

In order to address the problem one needs first to understand the major reasons why companies are exiting the market.

Low returns in the market

Although the market for antibacterials remains large there are a number of forces that exert downward pressure on market revenues leading to reduced commercial prospects for new antibacterials. The most important of these is the availability of generics. The majority of antibacterials commonly used in both hospital and community settings are generic. The most commonly prescribed class of

antibacterials, cephalosporins, are off-patent, with a few exceptions. The same is true of the penicillin and macrolide classes. There are new antibacterials being used in hospitals that are still protected from generic competition, such as Zyvox (Linezolid) and Tygacil (tigacycline), however these are predominately used as second or third line treatment and their use is low compared to that of generic competitors. This type of competition keeps prices low as generic manufacturers do not have to recoup the significant costs involved in R&D. The pricing problem for new entrants is compounded by the growing use of health technology assessment (HTA), including cost-effectiveness analysis, by many European governments. 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 appear do so, as prices for newly approved antibacterials remain relatively low (Kesselheim and Outterson, 2010). Additionally, the "non-inferiority" nature of clinical trials for antibacterials, described later in this section, provides payers with a disincentive to value new antibacterials above the generic comparator. Thus new antibacterials can expect to be priced below their true social value reducing the opportunity for companies to recoup their R&D investment.

Additionally, unlike chronic diseases, where treatment can last for months or even years, most antibacterials are used for short course therapy only. Low prices are not offset by high volume sales. As a result, it is often more profitable for pharmaceutical companies to invest in drug discovery for chronic diseases. In order to achieve a commercially attractive return on antibacterials, pharmaceutical companies would need to charge what payers may regard as unreasonably high prices in comparison to existing antibacterials. Estimates of the current cost of developing a new drug range from $802 million to $1.7 billion. With such significant investment costs at stake, pharmaceutical companies need to optimise the use of their R&D budget and competing projects must be prioritized relative to each other. One way of doing this is according to each project's net present value (NPV). Simply, the NPV describes the relationship between the projected costs and revenues in terms of a discounted cash flow. Table 1 below shows the NPV of a number of different therapeutic classes, including antibacterials. From the Table, it is clear that antibacterials are not particularly attractive relative to projects in other disease areas.

Table 1 NPV of drug development by therapeutic class

Therapeutic Class	Risk Adjusted NPV[7] $m
Musculoskeletal	1,150
Neuroscience	720
Oncology	300
Vaccines	160
Injectable antibacterial (Gram-positive)	100

Source: Adapted from Projan 2003

[7] NPVs were risk adjusted with increased risk associated with projects at the earlier stages of drug development (Projan 2003).

Scientific difficulties surrounding antibacterial development

The main challenge to antibacterial discovery is finding a lead compound that can act as an antibacterial agent. It has been estimated that for antibacterials an average of 20 drug candidates are needed to yield one marketable drug. It was hoped that the complete sequencing of the bacterial genome would result in an abundance of targets, however, that has not happened. For example, Payne et al (2007) report that GSK's success rate for antibacterial high throughput screening (HTS) was four to fivefold *lower* than for 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, although novel targets are still being explored, in some cases antibacterial discovery has shifted back to pre-genome sequencing tried and tested approaches. In addition to looking for novel targets, pharmaceutical companies are also developing new versions of existing classes of antibacterials with new properties, instead of novel antibacterials. The interaction between these drugs and the target is still altered somewhat as compared to the original antibacterial, but the underlying mechanism of action is unchanged. Resistance to these new generation agents in known classes could develop more quickly than for novel agents.

This problem is not unique to the larger pharmaceutical companies. Smaller biotechnology companies that tend to specialise in innovative research approaches, such as Essential Therapeutics and Cubist, have ended their target-based discovery programs because they were unproductive. What makes antibacterials unique is that, for example, when attempting to find a broad spectrum antibacterial, what is needed is a single molecule that can inhibit a group of related targets as opposed to a single target. One compound must be able to inhibit the growth of many different Gram-positive and negative bacterial species, all of which have different molecular targets, different membrane permeabilities and different metabolic pathways.

A number of other unique approaches to antibacterial discovery are also being pursued. Examples include open source drug discovery and exploring the potential of "shelved compounds" and/or existing drugs for antibacterial potential. All of these efforts, however, require funding and resources.

The regulatory environment

Regulatory agencies such as the FDA in the US or the EMA in Europe can have a direct impact on antibacterial R&D. Not only do these agencies set the criteria by which drugs are evaluated but they also determine the parameters by which they can be marketed. The "delta issue" provides an example of the magnitude of the impact that the regulatory environment can have on antibacterial R&D.

In 2001 both the FDA and the EMA changed the requirements for clinical trials involving antibacterials. New antibacterials are required to show non-inferiority compared to a currently registered antibacterial. The issue is how to statistically prove non-inferiority. Prior to 2001, regulatory agencies normally used a delta value of 15% for antibacterials to determine non-inferiority. In other words, trials should be powered such that the new drug could be up to this amount lower in efficacy than the reference drug and still be deemed to be non-inferior within the lower limit of the 95% confidence interval (or 97.5% confidence interval for a single-tailed test).

The FDA had two particular concerns with this approach. Firstly, it believed that as a result of this approach successively less effective comparators were being selected and this was leading to a presumed equivalence of what were in reality statistically and clinically inequivalent products. This is a phenomenon known as bio-creep. In other words, drugs that were inferior were being classified as non-inferior. Secondly, the effectiveness of (comparator) products changes over time as resistance patterns change and new information is gathered. Typically the comparator becomes less effective. To address these issues, the FDA and the EMA recommended the use of a delta value of 10%. While this was 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. The cost of running larger trials and the length of time needed would have (a) significantly increased the costs of developing an antibacterial and (b) substantially delayed the point of entry into the market. Recruiting a larger number of patients for clinical trials would have been difficult, taking time because of a lack of diagnostics with which to identify eligible patients and also requiring recruitment from many more centres around the world. This would have required additional infrastructure to be set up, further increasing costs and time. It was feared by industry 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 and by clinicians.

Projan (2003) estimates that if the tighter statistical parameters had been adopted, the effect would have been to reduce the risk adjusted NPV for a novel, Gram-positive antibacterials from $100 million to $35 million. The effects of the proposed changes were dramatic. A number of pharmaceutical companies put their antibacterials programs on hold and the exit of Eli Lilly and Bristol-Myers Squibb from the field of antibacterials occurred around this time. As a result of these unintended consequences, the FDA held a meeting with the Pharmaceutical Research and Manufacturers of America and the IDSA. The outcome of the meeting was that the proposed 10% delta value was dropped and it was agreed that delta values would be chosen on a case by case basis. The meeting successfully defused the immediate crisis, but there were some lasting effects, including the delayed development of a number of new products and uncertainty still remains around the requirements for clinical evaluation.

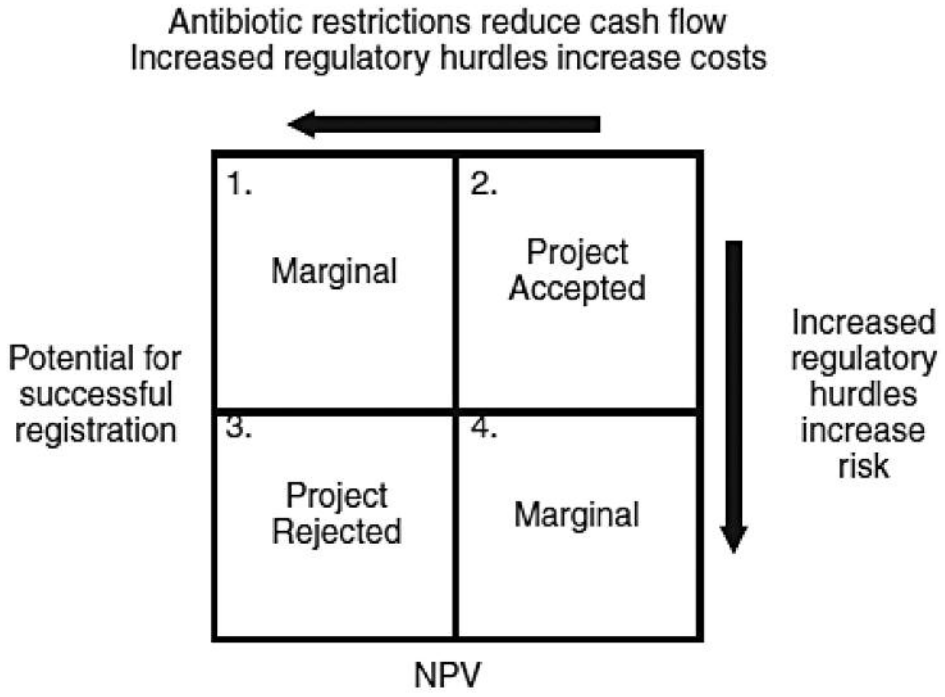
Restrictions on antibacterial use

A number of polices have been implemented to curb the use of antibacterials. For example, in an attempt to reduce physician prescribing in Belgium, the government launched a campaign that included the release of a position paper in a professional journal, sending letters to all family practitioners and to pharmacists, and providing family practitioners with feedback about their prescribing practices. Simultaneously a number of patient awareness initiatives, to lower expectations about receiving antibacterials, were put into effect including the distribution of booklets, the use of television and radio spots, and the creation of a website. The campaign was successful at decreasing the rates of antibacterial consumption: total sales decreased by 11.7% and 9.6% respectively during the 2000-2001 and 2001-2002 campaign periods.

This, however, also highlights a tension between two aims of antibacterial management. On the one hand, policy makers want to restrict the use of antibacterials to prevent the spread of resistance, while on the other, they are trying to promote the development of novel antibacterials

to combat resistance. The result is what Power (2006) describes as a vicious cycle. Market restrictions stifle innovation decreasing the number of antibacterials being developed. As a result, health care systems become more dependent on existing antibacterials which may no longer be as effective. Dependency on (and therefore use of) existing drugs accelerates the development and spread of resistance.

Figure 6 The relationship between the NPV, successful registration, regulatory hurdles and antibacterial restrictions.



Source: Power 2006

Figure 6 taken from Power (2006) shows the relationship between the NPV and the impact of both regulatory factors and use restrictions on the likelihood of a company proceeding with a project. Restrictions on the use of antibacterials decrease the potential for profit while increased regulatory hurdles increase development costs and decrease the chance of successful registration, pushing a project from "accepted" to "marginal". Of course, an antibacterial 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 resistance over 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, 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.

Philipson and Mechoulan (2003) and Philipson, Mechoulan and Jena (2006) set out the problem of the "negative externality" of resistance as current consumption produces AMR as a negative side-effect that lowers the value of future consumption. This is assumed to dominate the classic positive external effects of treating infectious diseases (Philpson 2000). However, they note that limiting use of antibacterials to slow the build-up of AMR discourages R&D into new antibacterials to replace those for which resistance is building. These "dynamic costs" (the health and economic consequences of less R&D) may exceed the short term benefits of restricting use of current antibacterials "even though such limits are the appropriate policy in the absence of technological change," i.e. the development of new antibacterials (page 4, Philipson and Mechoulan, 2003). They argue that "a single instrument is not sufficient to appropriately control R&D incentives *ex-ante* and externalities *ex-post*" (page 31) and any policy must tackle both. In other words:

- Restricting use of existing antibacterials makes sense as we do not know how many new antibacterials we will get, and when a new antibacterial appears it will be subject to restrictions, as we do not know when the next one will be developed;
- Another strong policy lever is therefore required to stimulate R&D, as use restrictions reduce R&D incentives.

Thus, two separate policy instruments are required.

3 MODELLING POTENTIAL SOLUTIONS

3.1 Related Disincentives and Market Failure in Other Pharmaceutical Markets

Many of the disincentives that pharmaceutical companies face in the market for antibacterials are not unique. Similar disincentives are observed in the markets for neglected diseases in developing countries, orphan drugs in developed countries, countermeasures for chemical, biological, radiological and nuclear (CBRN) threats, and for evidence collection on the effects of drugs in paediatric use. The implication in all cases is that policy makers, on behalf of their populations, want to address the failure of the market by providing incentives that companies can respond to. The policies enacted or put forward in an attempt to provide appropriate incentives will be discussed in the next section as possible solutions to the decline in antibacterial R&D. We initially set out the similarity of the challenges in other markets.

Neglected diseases
Neglected diseases such as malaria, tuberculosis and diarrhoeal diseases account for 90% of the world's health problems but only receive 10% of health related R&D funding (Hecht et al 2009). As a result, the health gap between developed and developing countries is increasing. There are a number of reasons why large pharmaceutical companies find markets for neglected diseases unattractive, but the most important is that these markets have low returns because the people who need the drugs cannot afford to pay for them and nor, in most cases, can their governments. As a result, companies are unable to recoup their R&D costs and so do not invest in programmes to tackle neglected disease (Wheeler and Berkley 2001, Hecht 2009).

Orphan drugs
The main problem with orphan diseases is the low number of potential patients, reducing expected returns on R&D investment. In the US, an orphan disease is defined as a condition which either afflicts less than 200,000 people or, although it affects more than 200,000 people, is one for which there is no expectation that a manufacturer would be able to recoup R&D investment through sales revenue. In the EU, an orphan disease is one that affects a maximum of 5 in 100,000 people. Because of the time, cost and risk associated with drug development, pharmaceutical companies have more incentive to invest in medicines that will be more widely used (Gluck 2002).

Countermeasures against chemical, biological, radiological and nuclear (CBRN) agents
Following the anthrax attacks in the US in 2001, the creation of countermeasures against CBRN agents became a top public health and defence priority. Unfortunately, large pharmaceutical companies view the US Federal Government as offering an uncertain (high risk) and low profit market.

Evidence for paediatric drug use
Up to 80% of prescriptions for children in hospital and general practice are for off-label use, i.e., outside of the product license. Most are not licensed for use in children at all. In 2007, only 35% of commercially available drugs in Europe were authorized for use in children. There are a number of ethical, scientific and commercial reasons why children are not recruited to participate in trials, notably: (i) it is considered unacceptable to treat children with drugs that have not been properly tested on adults, and hence such a programme would have to be

undertaken separately, after the drug has been licensed for use in adults, adding to cost and reducing the time available within patent life to get a return on investment; (ii) response in children is more unpredictable and poor results risk undermining the attractiveness of the product for the adult market; and (iii) the market is too small to justify such an investment (Boots 2007, Grieve et al 2005). Pharmaceutical companies need to be separately incentivised if society wants them to perform additional paediatric studies.

3.2 Solutions to address market failures

A number of solutions have been proposed to correct for the lack of incentives identified above. Many, if not all, have also been: proposed as solutions to the antibacterial problem; discussed in great detail in the literature; and put forward as solutions at the 2009 Stockholm conference. To date, however, there has been no attempt, to our knowledge, to narrow this list down, prioritising them in terms of their impact or of the size needed to incentivise companies to undertake antibacterial R&D.

In an attempt to fill this gap, we conducted a modelling exercise. The details of the model and the results are presented in the following section (as well as in a separate annex), and the implications of the results are discussed. The objective of this paper is to help move the AMR discussion forward by presenting a realistic and feasible short list of incentives. The incentives we modelled were selected for this exercise because they have already been implemented to address the market failures discussed in the previous section, or have been extensively discussed in the literature and are believed to be realistic solutions to the antibacterial R&D problem. They are listed below in Table 2.

Table 2 List of incentives discussed in the model

Type of Incentive	Incentive
Pull	• Advance market commitments (AMC) • Priority review voucher (PRV) and the fast track option (FTO) variation of PRV • Patent extensions • Transferable patent extensions
Push	• Product development partnerships (PDPs) • Tax incentives • Direct funding of R&D • Funding and regulatory support for pre-competitive consortia
Hybrid	• The call option for antibiotics (COA) • Orphan drug legislation • Vaccines and drugs to counter chemical, biological, radiological and nuclear (CBRN) threats. This includes Project BioShield

These incentives can be broken down into "push" and "pull" categories. The main difference between them is that push incentives pay for research *inputs*, funding or rewarding R&D effort *ex ante*, i.e. irrespective of the outcome, and pull incentives pay for research *outputs*, rewarding R&D effort *ex post*, if the outputs of R&D result in a health gain. Push incentives lower the cost of R&D for drug development and thus lower a potential barrier to entry while pull incentives seek to mimic the market incentives that exist for commercially lucrative pharmaceutical products. We use the term "hybrid" to refer to proposals that seek to combine elements of both push and pull incentives.

Push incentives can be attractive, particularly to SMEs because they typically have limited resources and funding 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, they have a number of disadvantages. For example, they are subject to information asymmetry which can lead to principal-agency problems such as adverse selection and moral hazard (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. The developer may then lack the motivation to put effort into continuing the development once they secured the push funding. With push incentives the funder bears the majority of the risk, as there is no guarantee of a successful payoff (Brogan and Mossialos 2006).

Pull incentives avoid some of the pitfalls of push incentives because they only reward success. The information asymmetry does not give rise to principal-agency problems. Because developers only receive a reward after a product has been developed, they have a strong incentive to be realistic about their prospects and, as a result, to either abandon a project or to put effort into seeing the project through to the end of the development stage. Although the developer bears the majority of the risk, this can be partially offset with the awarding of milestone payments. Kremer (2001), however, argues that milestone payments could, as a de facto form of push funding, lead to principal-agency problems with wasteful investments in research lines which the developer knows are not likely to yield a viable product but which will reach the threshold for the milestone payment. If the payment is greater than the cost of conducting the research, there might be a profit incentive to reach the milestone even if the developer knows it is a dead end. In these circumstances a pull incentive can begin to suffer from the same problems as a push incentive.

There are also additional challenges in organising a pull incentive. These include (a) the fact that it is hard to prospectively determine the size of the reward needed to incentivize R&D – too much risks overpaying, too little means no one may invest; (b) pull rewards must be larger in both nominal and real cash amounts than push rewards in order to reward investors for the risk of failure and the opportunity cost of having R&D funds tied up for a long period; and (c) a pull incentive requires pre-specification of the output before it has been developed. The credibility of the pull funder is important as companies will not invest in costly R&D if they do not believe they will be rewarded at the end. This is partly a time inconsistency problem (policy makers would be better off if they changed their minds about rewarding R&D once companies had made irrevocable commitments to invest, i.e. if they were able to behave opportunistically) which can be tackled by pre-commitment, and partly about the likelihood and ability of the funder(s) to honour the pre-commitment (Grabowski et al 2008).

There is growing recognition that neither push nor pull incentives alone may be able to cost-effectively stimulate antibacterial R&D. It may be, for example, that pull incentives are better at addressing the commercial uncertainty (given a drug what are the chances of achieving the sales needed for a return in 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 likely success criteria?). The consensus coming out of the conference in Stockholm was that a hybrid approach will be necessary to stimulate and foster R&D for antibacterials. Hybrid incentives 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.

3.3 Modelling the NPV of antibacterial development

To date, there has been no attempt to determine the size of the various incentives needed to make the NPV for antibacterial development more competitive relative to other disease areas. Doing so will hopefully help policy makers and industry leaders shorten the laundry list of incentives down to a more manageable and realistic handful, helping to move the dialogue forward. Armed with a better sense of what an AMC for antibacterials would cost, or what the economic burden of a Transferable IP Extension is, will help ensure that all parties have the information they need to start thinking about how best to tackle the problem of stimulating R&D against AMR.

In this section we set out the baseline model, how it was developed and the assumptions that were made. We then consider the main push, pull and hybrid candidates that have been discussed and use the model to gain an understanding of the costs that might be involved in using a particular incentive. Later in the paper we discuss the implications of the results and make outline recommendations for Europe.

The baseline case for the development of an antibacterial[8] was modelled using data from publically available, peer reviewed literature. Where possible, antibacterial specific data was used, otherwise antibacterial data was assumed to be similar to that for an "average" new molecular entity. The detailed assumptions about R&D costs and failure rates and about sales and operating costs are set out in Annex 1. The baseline NPV calculated for an antibacterial was -€38.15 million and the internal rate of return (IRR) was 10%.

Advance Market Commitments (AMCs)

An AMC is a commitment by a government or a private/international organisation to purchase a specified quantity of a drug or a vaccine that meets certain criteria pre-specified by the purchasers at a pre-determined price (Glennerster and Kremer 2001). AMCs work primarily by increasing the size of, and reducing the uncertainty of the market associated with drugs or vaccines. Put forward for neglected diseases an AMC can, if large enough, ensure that developers are able to achieve a reasonable return on their R&D investment and thus create similar incentives for commercial investment as the developed world market for drugs (Batson 2005, Brendt and Hurvitz 2005). The larger the commitment, the more R&D is stimulated, increasing the chance of a successful pharmaceutical product being developed. Acemoglu and Linn (2004) found that a 1% increase in the potential market size for a drug category increases the number of new drugs in that category by 4-6%.

[8] The antibacterial specific data used for the model is for antibacterials in general. Policy makers are, however, most likely to be interested in Gram-negative antibacterials. It is unclear how this might affect the model and any of its results. Our initial view is that costs may be similar, but revenues may be lower.

AMCs can correct the time inconsistency problem that occurs because developer and purchaser decisions are made at different times. The developer wants to ensure that they will receive a return on R&D comparable to what they would receive with more a lucrative product. However, there is potential for opportunistic behaviour on the part of a dominant purchaser, who has an incentive to buy the final product at as low a price as possible, pushing price towards the marginal cost of production (Report to the G8 Finance Ministers 2005). Prices that only cover the variable costs of production are not high enough to allow companies to recoup their R&D costs and will deter them from investing.

An AMC corrects this by stipulating a pre-determined price at which a quantity of the vaccine or drug will be purchased. The purchaser can agree to either fully or partially finance the purchase of the drug or vaccine. Recipient countries then can purchase the product at a discounted price, closer to the marginal cost, and the purchaser tops up the difference to the guaranteed price (Report to the G8 Finance Ministers 2005).

The strength of an AMC as an incentive for R&D hinges on the credibility of the purchaser. To that end, all commitments must be legally enforceable to assure developers that purchasers will not renege on their commitment once R&D has begun or a product has been successfully developed. At the same time, however, any AMC must be flexible enough to allow for any unforeseen contingencies that may arise during the drug development process. Similarly the developer must pre-agree to sell the vaccine or drug at a sustainably low price once the AMC has expired. An Independent Adjudication Committee would be needed to oversee the arrangements.

There are two approaches to an AMC: the "winner takes all" approach or the "multiple winners" approach. The "winner takes all" approach is easier to administer and is much more streamlined. The prospect of 100% of the reward is a powerful incentive for a pharmaceutical company to begin investing in R&D. It could, however, discourage participation as there is no incentive to begin or to continue R&D if a rival company is thought to be ahead, close to completion, or has successfully developed a drug or vaccine. A winner takes all approach is ill-suited to the process of drug development. Typically an underlying scientific breakthrough in the understanding of a disease, or of the potential therapeutic benefits of a particular compound, will lead to a number of companies racing to develop products each with different risks and benefits. Only some of these will get to market. This scientific process rarely results in the product that happens to be first being clinically more effective or safer for all patients than products that follow. If a superior product was subsequently developed and the AMC was already pre-committed to provide a clinically inferior product then a major practical and ethical problem would appear (Berndt and Hurvitz 2005).

The "multiple winners" approach allows any product meeting the quality specification for AMC reimbursement to obtain the premium price until the cumulative volume guaranteed by the AMC has been reached. This better encourages competition by increasing the probability of a company receiving some reward. But by decreasing the strength of the R&D incentive it may potentially act as a disincentive from participation by some companies. The maximum size of the reward each product can receive is smaller, with an unclear impact on the *expected* reward (i.e. the probability of success multiplied by the size of the reward).

An AMC does not necessarily need to specify a quantity of product to be purchased. The main benefit of doing so is to reduce demand uncertainty. However, a pre-specified quantity leads to the substitution of the market preference for the purchaser's preference and could result in the development of a suboptimal product that does not meet market demand. Specifying a quantity for purchase is more difficult to combine with a multiple winners approach (Berndt and Hurvitz 2005).

It is important that an efficient price is chosen. If the price is too high, it could result in a waste of resources, although a higher price could accelerate the development of a drug or vaccine by ensuring increased returns to the first developer, albeit resulting in the faster depletion of the AMC. If the price is too low it will not provide enough of an incentive for companies to begin investing in R&D. Front-loading the price (paying a higher price for a small initial quantity of a product or for a finite period of time) means early developers receive more reward than later developers, providing a strong incentive for developing a product quickly, while still encouraging competition as later developers will be rewarded. Efficient pricing seems to suggest front-loading as it helps to align the reward with social value. The development of the first product is highly valuable to society if there are no other products available (Berndt and Hurvitz 2005).

As a pull mechanism, AMCs link payment to quality and success. They allow the private sector to decide independently which projects to pursue as a reaction to the market forces created by the AMC (Glennerster and Kremer 2001). Similarly, decisions regarding how to divide R&D tasks are left to the private sector as they have better information and knowledge about skills and complementary research being conducted by other companies (Kremer, Towse and Williams 2005). Finally, because payment is linked to success, developers have a strong incentive to focus on the successful creation of a drug or vaccine and not be distracted by other projects (Glennerster and Kremer 2001).

We can see that determining the size and price of an AMC are the most difficult and critical tasks. The overall size of the AMC must be large enough to stimulate R&D but not be so large that purchasers' end up paying more for the product than it is worth or than they need to (Report to the G8 Finance Ministers 2005). The CGD AMC Working Group proposed that the optimal size of an AMC is $3.1 billion, based on the sales revenues of successful products. The first AMC has now been set up as an incentive for neglected disease R&D. In 2007 the GAVI Alliance received $1.5 billion in pledges from Canada, Italy, Norway, Russia, the UK and the Bill and Melinda Gates Foundation for a pneumococcal vaccine AMC (Berndt et al. 2007). Less money is needed than the CGD estimate because it is aimed only at incentivising later stage activities. It is not a "winner takes all" scheme, any product meeting the quality specification will receive the price premium until the "pot" is exhausted. The AMC is still in its pilot stage. How well it works and how it overcomes the challenges outlined above remains to be seen.

Establishing an AMC for antibacterials in the EU will perhaps not be as straightforward as establishing the pneumococcal AMC as it will require the participation and cooperation of all of the Member States. As a first step, and this holds true for all the incentives discussed in this section, target pathogens must be identified by policy makers, clinicians and public health specialists. This would represent areas of unmet need and be the target for the AMC or any of the other incentives. We assume these would, in the first instance, be Gram-negative as this has already been highlighted as an area of unmet need.

Because the AMC would apply to the whole of the EU, all Member States would, ideally, need to contribute in some way to the final pot. One method of determining each country's contribution is to base it upon the burden of resistance to the pathogen being targeted. This would ensure that countries who have the highest rates of resistance, and thus are likely to benefit the most from the AMC, will contribute the most. Exceptions could be made, however, if countries with the highest burden are unable to pay their proportionate share. Some of these countries with high incidence of AMR are among the lower income countries in the EU. In such cases, the other countries could help top up the pot by contributing the difference. Indeed, another basis for contributions is, of course, on a per capita income basis. Administration of the AMC could take place at the EU level, conducted by an independent committee with the ability to make binding decisions on behalf of the funders. Its responsibilities would include determining if antibacterials meet the criteria outlined by the AMC and dispute resolution.

One final point is that any AMC for antibacterials should resemble a prize more than an AMC for a neglected disease because the aims of the two are different. An AMC for a neglected disease links price to volume or use as the goal is to increase access to a drug or vaccine. In the case of an AMC for an antibacterial, the aim would be to reward the successful development and registration of a new antibacterial rather than increased use, so the price/reward offered should be decoupled from the volume sold or amount used.

Modelling Results for the AMC

Two versions of an AMC were modelled. In both versions we assume, for simplicity, a "winner-takes-all" approach. The first version is a one year AMC, in which the reward is given as a lump sum to the developer at launch (in year 1). Because the AMC was applicable only in Europe and the antibacterial was available for sale in the rest of the world, European sales were set to zero for the duration of the AMC. Sales and marketing costs were reduced by 40% for the length of the AMC. Once the AMC expired, as with AMCs for neglected diseases, the developer agrees to sell the new antibacterial in Europe at cost. Thus once the AMC for the antibacterial expired, sales in Europe followed the sales curve for antibacterials set by DiMasi et al (2004) but were decreased by 50% to reflect the lower price.

The second AMC modelled was for five years. In this case, the reward was given to the developer over five years after launch. As with the one year AMC, sales in the rest of the world were unaffected, European sales were set to zero and the sales and marketing costs were reduced for the length of the AMC. Once the AMC had expired, sales followed the DiMasi et al (2004) curve with sales in Europe reduced by 50%. The results of the modelling exercise for the one and five year AMCs are shown in Table 3.

Table 3 Results for AMCs

	Size of AMC (€)	Baseline NPV (€)	New NPV (€)
1 year AMC	985 million	-38.15 million	147 million
5 year AMC	1.4 billion (275 million per year)	-38.15 million	150 million

The results of the modelling exercise suggest that the size of the incentive can be smaller than the CGD AMC Working Group estimate of $3 billion or approximately €2.2 billion, primarily because there are substantial sales from non-European markets, notably the US. However, several different pathogens may need to be targeted requiring multiple AMCs or a much larger, more complex AMC for multiple pathogens.

Priority Review Vouchers and the Fast Track Option

The priority review voucher (PRV) is an incentive for R&D for neglected diseases and was implemented in the US in 2008 (FDA 2008). It is awarded by the FDA to a company that has successfully developed a pharmaceutical product for a neglected disease. The voucher entitles the holder to a priority review by the FDA for another drug in its portfolio or it can sell it to another company to use (Ridley et al 2006, Grabowski et al 2008, FDA 2008). Priority review shortens the FDA review time from an average of 18 months to approximately six months.

An FDA "priority review" is normally only for drugs that treat a life-threatening condition, therefore access to it for a drug that would not otherwise qualify is potentially very valuable. Estimates of the value of getting a top-selling drug to market a few months earlier range from over $100 million to $322 million. The true value of the voucher will depend on whether the FDA approves the drug or if it is returned to the sponsor to address any concerns or problems, and how well the drug will do once it enters the market (Grabowski et al 2008, Ridley et al 2006). A disadvantage of the PRV from the point of view of patients is that it can create distortions in the market to which the voucher is applied and may cause other companies to pull out of R&D in this area. A disadvantage to companies is that in order to use it, the voucher holder must notify the FDA 365 days in advance of filing the new drug application (Grabowski et al 2008). This means that:

- Either the company must use the voucher on a product that has already completed its Phase III trials (and so the time saving is lost as the company would be ready to file within that 12 months in any case);
- Or the company must use the PRV on a drug that has not yet completed Phase III trials and so there is a risk that the drug may fail to show value in those trials.

To date, Novartis is the only company to have been awarded a PRV for the successful approval of CoArtem, an antimalarial. The voucher has yet to be used or traded.

Modelling the PRV

Ridley and Sanchez (2010) outlined how a PRV could potentially work in Europe. Briefly, this voucher would be awarded by the EMA or EC to the successful developer of a novel antibacterial. Use of the voucher for an unrelated product would provide an accelerated review at the EMA market authorization level for that unrelated product, as well as at the Member States level where decisions about pricing and reimbursement are made. Overall, Ridley and Sanchez (2010) determine that such a voucher would, on average, allow a drug to be launched six months earlier. The results of this are twofold: (1) there is a time benefit as take up of the drug begins six months earlier, and (2) it spends an additional six months on the market before it goes off patent, earning on patent revenue. Ridley and Sanchez (2010) estimate that the value of shifting the sales curve forward (effect 1) is $20 million per month while the net present value of the extended patent life (effect 2) is approximately $30 million per month. In total then, the six months saved by using a PRV is worth $120 million from earlier sales plus $180 million in additional sales under the extended effective patent life, a total of $300 million (€221 million).

We use Ridley and Sanchez's (2010) estimate of the value of a PRV to determine its impact on the NPV for antibacterial R&D. Because the value is discounted, if we assume that the blockbuster drug being priority reviewed goes on the market the year after the antibacterial, we can attribute the €221 million to the second year profit stream for the antibacterial, i.e. there is a lump sum cash input in year 2 which represents either the present value of another drug in the company's portfolio being priority reviewed as a result of the successful development and registration of a novel antibacterial, or the resale value of the PRV if the antibacterial developer sold the PRV to a third party.

The results of the model indicate that a PRV would increase the NPV of antibacterial R&D to €8 million, well below the €147 million target. The new IRR is 11%. It thus achieves "breakeven" but does not meet the target return.

The Fast Track Option (FTO)
A variant of the PRV is the Fast Track Option (FTO), a means of getting to market more quickly through an expedited development and regulatory process.

As initially put forward by Moran (2005) the FTO was an R&D funding mechanism, rather than an incentive, for neglected disease R&D. Companies would be allowed to purchase an FTO for a drug of their choice and the funds raised as a result are used to support public sector neglected disease R&D, for example through a PDP. Like the PRV, the FTO is also tradable to other companies. To optimize the prices of FTOs, Moran suggested a limited number (one or two vouchers each year) could be sold via an auction.

An FTO could also operate as a pull mechanism in the same way as a PRV. A company bringing an antibacterial to the market could receive a tradable FTO. As with the PRV, it is easier to see how such an incentive could apply in the US than in the EU. Unlike the EMA, the FDA has had a formal "fast track" program in place since 1993 (Moran et al 2005). It was initially used to allow drugs for serious and life-threatening diseases to reach the market sooner, and was later expanded to include drugs for chronic conditions such as diabetes and obesity.

To understand the potential value of an FTO in a US context we can note that the Tufts Center for the Study of Drug Development (CSDD, 2003) found that between 1998 and 2003 the average clinical development time for fast track drugs was 2 and 2.5 years shorter than for non-fast track standard and priority drugs. The majority of drugs that were fast tracked also received priority review. Taken altogether, the total time saved was around 3 years: 2-2.5 year reduction in clinical development and a 13 month reduction in approval time. While the FTO proposed for neglected disease would not include R&D shortcuts, there is still a substantial time gain of anywhere from 6 months to 2.5 years (Moran 2005).

Modelling the effect of an FTO
There are two ways to model an FTO. First we model it as a push incentive for a PDP and then as a pull incentive for pharmaceutical companies.

Moran et al (2005) estimate that the discounted value of an FTO ranges between $270 million to $520 million. We assume that companies are willing to pay around $200 million for an FTO and thus the sale of a single FTO could potentially raise over $100 million per year for R&D.

For our modelling of an FTO as a push incentive we assume that a pharmaceutical company has paid $200 million to purchase an FTO for a drug in its portfolio. All of this $200 million or €147 million is used to fund early stage antibacterial R&D being conducted by a PDP, i.e. preclinical and Phases I and II. We illustrate using the money at different stages of development from preclinical through to Phase II and for each phase the money is assumed to be distributed equally across the entire length of the phase. The results are presented in Table 4.

Table 4 Results for an FTO with €147 million for PDP funding

Development phase	Length of phase (years)	Size of incentive/ year (€)	Baseline NPV (€)	New NPV (€)
Preclinical	5.5	27 million	-38.15 million	68 million
Phase I	1.5	98 million	-38.15 million	38 million
Phase II	2.5	59 million	-38.15 million	21 million

The results of the model for FTOs show that funding early stage research has a large effect on the NPV. This is primarily due to the effect of discounting. Similarly, even though the NPV never reaches the target of €147 million, it is still possible to see that the size of the incentives needed to increase the NPV to a competitive level would be significantly less than the size of the PRV or AMC needed to achieve the same goal. These figures also give policy makers a sense of the sums that would be required for PDP push funding. Importantly, these costs take into account the failure rate as well, but there are no guarantees. Push funding is paying for effort. Pull funding is paying for success.

As a pull incentive, the FTO more closely resembles a PRV, in that it is awarded to a company upon the successful launch of a novel antibacterial. To model this effect of an FTO on the NPV for antibacterial R&D we used Moran's (2005) risk adjusted and time discounted estimates of the potential returns to Eli Lilly had they been able to fast track Prozac®. Moran (2005) estimated that they would have earned $470 million (€346 million) after-tax or $521 million (€384 million) after-tax, depending upon the stage of development that the fast tracking could have taken place. We assume that the FTO is awarded (and sold) at launch of a new antibacterial and is modelled as a lump sum cash input in year 1. The results are presented in Table 5.

Table 5 Results for a "pull" FTO

FTO gains	Baseline NPV (€)	New NPV (€)
€346 million	-38.15 million	42 million
€384million	-38.15 million	51 million

The results indicate that as a pull incentive, FTOs can have a significant impact on the NPV for antibacterial R&D but not enough to increase it to competitive levels. Importantly, these estimates were calculated using sales data for a top decile drug so the impact would be lower for less lucrative drugs.

Priority Review Vouchers versus the Fast Track Option
The time savings gained from a PRV are less than under an FTO. A PRV expedites the review process after a drug has been developed but does not allow sponsors to benefit from any of the efficiency gains during the development process. Ridley et al (2006) estimate for Europe a 6 month time gain compared to standard review. An FTO, however, could potentially yield 1-2.5 years saved (Moran 2005).

In a European setting both would only lead to earlier sales if Member States acted to a provide priority pricing and reimbursement review. Health systems would be required to purchase these drugs earlier. This imposes an additional cost burden to the health care system. If one assumes, however, that health care systems will only use drugs that bring value (in terms of patient and other benefits) relative to price, then early use will bring net benefit to the health care system. However, any uncertainty as to whether Member States would in practice use the product earlier would reduce the value of an FTO option.

A criticism of fast tracking and priority review is that rapid review comes at the expense of safety. Philipson et al (2005), however, find that the net effect was a gain to the consumer. The authors estimated that faster approval resulted in 180,000-300,000 life-years saved compared to lower implicit safety standards which cost a maximum of 56,000 life-years. Philipson et al (2005) further calculated that these changes increased the private returns of developers, and thus incentives for innovation by $11-$13 billion (Laxminarayan and Malani, 2007).

Intellectual Property (IP) extensions
Because companies apply for patents early on in the drug development process, the effective patent life (i.e. the life of the patent remaining when the product is licensed to be sold) is much lower than the nominal length of the patent, hence the importance of IP extensions.

In the EU, there are several types of IP extensions that pharmaceuticals can qualify for. These include Supplementary Protection Certificates (SPCs), market exclusivity under orphan drug legislation (discussed below), paediatric drug legislation and various forms of data exclusivity provisions. SPCs were implemented in 1993 and allow manufacturers to recoup patent time lost in development and in regulatory review. They come into effect once the original patent has expired and provide protection for a specific active ingredient that has received market authorization. To calculate the period of extended exclusivity the time between the filing of the patent until market authorization is reduced by five years. The period of extended exclusivity cannot exceed five years and total market exclusivity for a product is capped at 15 years. The added protection of an SPC was found to increase sales revenues for high selling drugs. For example, 80% of Prozac® sales in Europe, over the last 10 years of effective patent life were in the five years covered by the SPC.

In 2007, the EU implemented paediatric drug legislation. Companies applying for marketing approval for a new drug can submit a Paediatric Investigational Plan (PIP), which must include information on the timing and method of testing the quality, safety and efficacy of the drug in a paediatric population. Newly approved drugs can have their SPC extended by six months if the company has filed a PIP and orphan drugs can receive up to two years of extended exclusivity. Drugs that are exclusively for paediatric use or all age paediatric formulations that were launched prior to 2007 are also eligible for a Paediatric Use Marketing Authorization which grants ten years of market exclusivity. However, these drugs cannot already be covered by a patent or SPC.

In the US, there are four programs that can provide pharmaceuticals with IP extensions:

- The 1984 Drug Price Competition and Patent Term Restoration (Hatch-Waxman) Act lowers the barriers for generic market entry but also increases patent times for new drugs that have been delayed by FDA regulation. In particular, the Hatch-Waxman Act restores half of the time spent in clinical testing and all the time spent in the marketing application process, up to a maximum of five years. Total patent time cannot exceed 14 years after marketing approval (Mossialos et al 2009).
- The QI Program Supplementary Funding Act provides three years of exclusivity for the approval of a new indication for an already approved antibacterial and five years for the approval of previously unapproved older antibacterial (Grabowksi and Vernon 1996).
- The FDA Modernization Act (FDAMA) included a six month IP extension on all approved indications of a drug to companies who performed paediatric studies approved by the FDA (Gluck 2002). Exclusivity is granted depending on the quality of the submitted study report (Grieve 2005). The reward is for conducting paediatric trials, regardless of the outcome. The prospect of an IP extension for the adult indications drives companies to conduct the research necessary to explore the potential benefits in children. Paediatric exclusivity demonstrates the possible effect of exclusivity which is transferable beyond the indication for which it is being sought.
- The Orphan Drug Act (ODA), discussed below.

Modelling IP extensions

Three different IP extension scenarios were modelled. The first was a six month extension, similar to the extension available on an SPC if a company has filed a PIP, the second a two year extension that is available to companies who file a PIP on an orphan drug, and finally, a five year extension. In this case, rather than trying to determine how to increase the NPV with an IP extension, the purpose was to determine the effect of these extensions on the NPV. Of interest was by how much did the NPV increase and was it enough of an increase to make antibacterial R&D competitive.

An IP extension delays competition from generics (and in the case of orphan drug market exclusivity follow-on drugs as well), thus the sales earned by the drug on patent are higher than off. To model a patent extension, the decline in European sales after the drug comes of patent in year 13 is delayed by the duration of the extension, i.e. the sales curve is elongated by the duration of the IP extensions: six months, two years and five years. Because the IP extension is only applicable in Europe, only European sales are affected by the IP extensions. This is also true for Transferable IP Extensions, discussed next. Table 6 presents the model results for IP extensions.

Table 6 Results for IP extensions

	Baseline NPV (€)	New NPV (€)	Size of effect on NPV (€)
6 month IP extension	-38.15 million	-37.99 million	0.16 million
2 year IP extension	-38.15 million	-37.35 million	0.8 million
5 year IP extension	-38.15 million	-33.26 million	4.89 million

IP extensions seem to be ineffective at increasing the NPV to a competitive level and none of the IP extensions succeeded at making antibacterial R&D a worthwhile investment compared to other disease areas. This is primarily due to the effect of discounting as a result of the timing of the incentive, i.e. it impacts sales towards the end of the product life. It also reflects low revenues at peak sales. Higher prices would increase the value of a patent extension.

Outterson et al (2007) argued against IP extensions in part because antibacterials decrease in clinical effectiveness over time. Furthermore, sales from the additional patent life will be depressed by resistance and competition from other follow-on drugs. Additional patent protection provides little incentive to conduct antibacterial R&D. They believe that the prospect of antibacterial patent expiry provides a strong incentive to produce a new blockbuster drug. However, this confuses the pressure to undertake some R&D to replace revenues arising from loss of patent expiry with the decision as to where R&D should take place in order to best generate replacement revenues. Our modelling suggests patent extensions for antibacterials will not provide a strong incentive for antibacterial R&D, but not for the reasons Outterson et al (2007) suggest.

Transferable IP Extensions

Transferable IP Extensions are also sometimes referred to as "wildcard" patent extensions. The idea is often attributed to Jonathan Mann, the late founding director of the WHO Global Program on AIDS, who suggested that the developer of an HIV vaccine should be compensated with a ten year patent extension on another pharmaceutical product (Kremer 2000). In this case, a pharmaceutical company who successfully develops a new antibacterial is granted a patent extension for another drug in its portfolio. The patent lengths suggested range from six months to two years in the US and up to five years in the EU. Proponents of the Transferable IP Extension believe that it provides pharmaceutical companies with a significant incentive to invest in antibacterial R&D, irrespective of their size. For large pharmaceutical companies, the prospect of extending a patent on a best-selling drug is very appealing as additional sales could be in the billions of dollars (Kremer 2000). Using 2007 US sales data for Lipitor®, Sonderholm (2009) estimates that if sales remain constant at $6.17 billion per annum until patent expiry in 2010, a six month extension would be worth $3.1 billion to Pfizer. For smaller (or larger) companies without a blockbuster drug nearing patent expiry, selling the IP extension to another larger company could be highly profitable.

Transferable IP Extensions are also potentially appealing from an EU Commission perspective as they do not require additional public funding "up front" and, given the size of the potential incentive, they are likely to engage the private sector in the development of new antibacterials. Despite the appeal, Transferable IP Extensions are extremely controversial. There are currently no Transferable IP Extension schemes in either the EU or the US. The US Biodefense and Pandemic Vaccine and Drug Development Act of 2005 (BioShield II) originally included a Transferable IP Extension provision. Strong opposition on the part of generic companies supported by health care insurers ensured that it was removed from the original bill before it was signed into law.

One criticism of Transferable IP Extensions is that they are associated with significant costs to society. Outterson et al (2007) contend that IP extensions function as a tax on consumers by charging higher prices during a drug's patent life and are an inefficient method of subsidizing antibacaterial research. They believe that Transferable IP Extensions will cost between $8.7 and $11.9 billion per newly developed antibacterial. This far exceeds current estimates of $0.8 billion - $1.9 billion (Mestre-Ferrandiz et al 2011) required to develop a new molecular entity.

A number of authors including Sonderholm (2009) and Spellberg et al (2007) take issue with the Outterson et al (2007) calculation of the cost of a Transferable IP Extension. For example, Outterson et al (2007) assume a two year extension, however, the period of extension can be shorter. Consider, for example, what happens with a six month period of Transferable IP Extension. This would cut the societal costs by 75% to $2.2 billion. This new figure could be even lower as it still includes tax credits and government grants for R&D. Furthermore, a six month Transferable IP Extension could still be attractive as an incentive to companies.

A second common criticism is that Transferable IP Extensions are inequitable and unethical because they transfer the cost of developing a new drug onto patients with another disease (Outterson et al 2007). It acts as a tax, and a high tax on a narrow tax base is an inefficient way to raise revenue as it distorts the consumption away from the taxed good and prevents some patients from accessing the treatment they need (Kremer 2000). Sonderholm (2009) argues that this criticism does not hold and that everyone, and not a select sick few, pay for antibacterial R&D under a Transferable IP Extension programme. For example, in the US, if the price of a drug increases, premiums for all enrolees in the insurance plan increase, not just those who need the medication. Likewise, in European tax-based and social insurance based systems, the cost increase will be passed onto the health care system and not the patients using the drug that attracts the IP extension. Of course if health care expenditure is limited at least in the short run then there may be consequences for other health services.

Modelling Results for Transferable IP Extensions

The Transferable IP Extension was modelled as if it was applied to a blockbuster drug just coming off patent as the antibacterial was being launched. Any profit generated by the extension is attributed to the first few years the antibacterial is on the market. Three different lengths of extension were modelled to determine the approximate amount of profit that is needed under each to increase the NPV to €153 million: six months, two years and five years. It is important to note that because the IP extension only applies to the European market, the profit necessary to increase the NPV must be generated from sales in the European market only. No structural changes were made to the model for this incentive. The results are presented in Table 7.

Table 7 Results for Transferable IP Extensions

	Size of incentive (€)	Annual size of drug sales in Europe (€)	Baseline NPV (€)	New NPV (€)
6 month Transferable IP Extension	800 million	3.2 billion	-38.15 million	147 million
2 year Transferable IP Extension	840 million (420 million per year)	840 million	-38.15 million	147 million
5 year Transferable IP Extension	975 million (195 million per year)	390 million	-38.15 million	147 million

Despite being contentious, Transferable IP Extensions could be a very effective and feasible incentive for antibacterial R&D. A six month Transferable IP Extensions is likely to be an unrealistically low incentive because no drug currently on the market earns enough in European sales to fill the gap in profit. Longer IP extensions, while perhaps less popular, would be strong incentives to more companies as the size of the profit and annual European drug sales required to adequately reward antibacterial R&D is more achievable. Indeed, any one of the top 10 best-selling drugs in 2009 earns more than is required in Europe to make a Transferable IP Extensions appealing over this period. These extensions would also appeal to SMEs as they would be able to sell them to larger companies.

PDPs and other Push Incentives

We can think of push incentives as being discretionary (in which the donor is choosing which "winners" to back), or non-discretionary, i.e. they are available to any body meeting the qualifying hurdles. The most common non-discretionary incentive is the tax based incentive. Tax credits on pre-specified types of R&D expenditures are the most commonly used form (Mossialos et al 2009). The effect of tax credits is to boost R&D expenditures at the margin and reduce the after-tax cost of R&D (Kremer and Glennerster 2004, Mossialos et al 2009).

However, there are some disadvantages to using tax incentives. They only appeal to companies that have tax liabilities and this would exclude those biotechnology companies not yet generating profits (Kremer and Glennerster 2004). A second disadvantage is that there is the potential for abuse which requires governments to spend money on monitoring. In an EU context an additional problem is that taxation issues are reserved to Member States.

Most push incentives are discretionary. The greatest innovation of the last decade has been the Product Development Partnership (PDP), a concept developed by the Rockefeller Foundation but made possible by the funding from the Bill and Melinda Gates Foundation. PDPs are not-for profit organizations whose main function is to promote R&D for neglected diseases (Moran 2005). Examples of PDPs include the International AIDS Vaccine Initiative and the Medicines for Malaria Venture. The classic model is a partnership in which the public partner provides the funding, while the private partner provides the skill and expertise needed to conduct R&D

(Moran et al 2005). PDPs bring together health actors from government, academia, large and small pharmaceutical and biotechnology companies (Mrazek and Mossialos 2003, Moran 2005).

The key innovation of PDPs is an arms-length portfolio approach. The PDP manages a mix of projects which it has chosen, rather than donors funding specific projects. This enables the PDP to be held accountable for the outcome of a programme rather than for each specific project. Of course there are incentive problems. The PDP has an incentive in the short term to ensure it has a full portfolio of projects (irrespective of the quality) to impress donors. However, in the longer term it will be expected to deliver effective new products.

The two main advantages of PDPs are that they reduce the risk associated with R&D by spreading risk across a portfolio of products and they provide subsidies for R&D, both in cash and in-kind, to its partners at the various stages of drug development, thus reducing the overall cost of conducting R&D (Buse and Walt 2000).

Government funding of R&D has typically been a simple push mechanism. In both the EU and the US there is a long history of government funding of scientific research. The US government funnels the majority of its funds through organizations such as the National Institute of Health and the Center for Disease Control and Prevention. In the EU, the main current funding mechanism is the Framework Programme No.7 (FP7), which includes a programme dedicated to addressing the problem of AMR (Mossialos et al 2009). However, there is a question as to whether or not a government or the European Commission is best suited for determining the viability of a project or projects beyond the basic and earliest stages of translational research, especially given the information asymmetry that is inherent with push incentives.

Funding and regulatory support for pre-competitive research consortia is an alternative to direct government funding of R&D. An example of such a consortium is the Innovative Medicines Initiative (IMI) launched by the European Commission and the European Federation of Pharmaceutical Industries (EFPIA). The rationale for establishing and funding such initiatives is that in small markets where R&D levels are likely to be low, pre-competitive research consortia can create a common platform from which different companies can tap into, increasing the likelihood that competitive R&D will take place. Government funding and regulatory support create push effects by lowering the out-of pocket expenditures and opportunity costs associated with R&D.

The push results for the FTO highlight the value of push incentives. We can reinterpret the results in Table 4 as indicating the potential value of a PDP with €147 million to invest. If the money was put into early stage projects then it could be expected to achieve an approved new antibacterial. The results suggest that any early stage funding or support could go a long way towards impacting the NPV for antibacterial R&D.

Orphan Drug Legislation

Orphan drug laws were implemented to stimulate R&D for rare diseases and conditions where small numbers of patients made R&D commercially unattractive. Table 8 provides an outline and comparison of their design and impact in the US and the EU. Other countries with orphan drug legislation include Japan, Australia and Singapore.

The US ODA has been a success. Since it was enacted in 1983, over 200 drugs and biological products for orphan diseases have been brought to the market, providing treatment for an estimated 9 million people (Grabowski 2003, Milne et al 2001). The EU Orphan Medicinal

Products Regulation was implemented in 2000. The purpose was to implement a common policy on orphan drugs within the EU and establish incentives for orphan drug R&D (Milne et al 2001, Rinaldi 2005). The EU legislation was largely based on its US counterpart and includes similar push and pull incentives (Rinaldi 2005, Heemstra et al 2008). The main incentive is a ten year period of market exclusivity. Also available are tax credits (at the discretion of the Member States), grants for clinical research , fee reductions or waivers for marketing approval, direct access to centralised procedure for EU marketing authorization, and scientific, protocol and technical assistance (Rinaldi 2005, Milne et al 2001, Heemstra et al 2008).

Table 8 Outline and Comparison of EU and US Orphan Drug Legislation (Adapted from Mossialos et al 2009 and Rinaldi 2005)

	US	EU
Administrative Body	FDA/Office of Orphan Products Development (OOPD)	EMEA/Committee For Orphan Medicinal Products
Legislation	Orphan Drug Act (1983); Orphan Drug Regulation (1993)	Regulation (CE) No. 141/2000 (2000)
Eligibility Criteria	7.5 per 10,000	5 per 10,000
Market Exclusivity	7 yrs.	10 yrs.
Data Exclusivity	5 yrs. (NCE), 3 yrs. (non-NCE)	10 (+1) yrs. NCE
Funding	Grants for clinical research	Framework programmes for research and national measures
Tax Credits	50% of clinical costs	Managed by Member States
Protocol Assistance	Yes	Yes
Accelerated Review	Yes	Yes
Reconsideration	No	Yes (every 6 yrs.)

As of 2007, there have been over 500 EU orphan designations and approximately 45 products have received marketing approval. 53% of the orphan designations are for novel or innovative products and an estimated 85% of them are from SMEs (Heemstra et al 2008).

The success and appeal of orphan drug legislation in the EU and the US is often attributed to the "pull" of the market exclusivity incentive, considered to be the most important aspect of both programs (Grabowski 2003). However, many of the "push" incentives are important. Tax credits appeal to large and small companies, but especially to large companies who already have the

capacity and resources available to carry the majority of orphan products through to approval (Milne et al 2001). Yin (2008) found that grants and technical assistance are much more useful to smaller companies. In the US, these incentives have encouraged smaller and less experienced companies to seek approval for orphan products. Indeed, between 1998 and 2000 nearly 40% of orphan designations went to small companies. Access to early regulatory advice is important. There is a strong proven correlation between scientific support and success (Moran 2005, Tickell 2005).

Orphan drug legislation is not without its criticisms. A common one is the high price of orphan drugs, which can reach several hundred thousand dollars per year in some cases, reflecting the market power granted by market exclusivity. Some drugs that were originally approved in the US as orphan drugs went on to become top-sellers either because their patient population grew to exceed 200,000, as happened with HIV/AIDS, or they were found to be effective for other more common, non-orphan indications (Rinaldi 2005, Gluck 2002). Critics believe that in these cases their orphan status should be revoked. In the EU it is possible to shorten the exclusivity period to six years, if at the end of the fifth year the product has become sufficiently profitable that it no longer requires market exclusivity. There is currently, however, no definition of "sufficiently profitable," and use of this regulation in a way that sent unclear signals for its future use could have a dampening effect on the strength of the incentive, considering how important market exclusivity is to many companies (Rinaldi 2005).

As the EU already has orphan drug legislation in place, it might be relatively straightforward to implement a similar programme for antibacterials. Target pathogens could be identified and any resulting antibacterials would be subject to appropriate push and pull incentives. The list of pathogens should be updated as resistance patterns change or new resistances emerge over time. This would give companies a certain amount of market power however its value might vary from country to country as is the case with orphan drugs. For example, France fast tracks pricing and usage decisions about orphan drugs but England and Wales do not, applying the same criteria to orphans as to any other drug, hence orphan drug status is more valuable in France than in England and Wales.

Modelling Market exclusivity under an Orphan Drug type Incentive

The success of orphan drug legislation in both the EU and the US is linked to the periods of market exclusivity granted under both programs. In the EU, ten years of exclusivity is granted to the developers of an orphan drug. This is modelled here as an increase in European profit. Specifically, of interest is the percentage increase in European profit needed during this ten year exclusivity period to increase the NPV to €147 million. To determine this, the profit line was separated into two according to market share: Europe (40%) and the rest of the world (60%).

Sales in the rest of the world are unaffected by this period of exclusivity. A further assumption is that the volume of antibacterials sold has not changed. Rather than looking at increased sales volume in Europe, the purpose is to model an increase in price as a result of market exclusivity or payer reimbursement that was more in line with the societal value of antibacterials. However, it is likely in reality that an increase in price will decrease sales volume.

The results of the model indicate that prices for new antibacterials in Europe must increase 4.1 times, i.e. an increase of 300%, in order to make antibacterial R&D competitive. Doing so increases the NPV to €149 million. Whether this is politically feasible or not will depend upon how willing policy makers are to accept increased prices to ensure this level of return. Additional

"push" support including quicker regulatory review would add to the value of an orphan type antibacterial scheme.

Project BioShield and CBRN legislation in the US

We can contrast the success of orphan drug legislation with that of CBRN countermeasure legislation in the US. Following the anthrax attacks in the US in 2001, President Bush proposed the creation of Project BioShield, designed to encourage the development of countermeasures to protect against CBRN agents. It was passed into law on July 21, 2004.

"Project BioShield" usually refers to the acquisition programme which is similar to an AMC. Special Reserve funds are released if the Secretaries of the Departments of Homeland Security and of HHS, as well as heads of other federal agencies determine that there is a CBRN threat. The Secretary of HHS is then required to determine if a countermeasure is necessary to protect public health and if an appropriate countermeasure is available for acquisition. This evaluation is based on current and available evidence on prospective countermeasures that would be ready for licensure within 8 years. In order to qualify for Project BioShield, a product must be far enough along in its development that an accurate assessment of its licensability can be made, products in the pre-clinical phases, therefore, are excluded. The release of funds requires final approval by the President. Payment is withheld until a minimum portion of the countermeasure is delivered. Under this scheme, the manufacturer assumes a portion of the financial risk (Russell 2007).

The purpose of enacting Project BioShield and the creation of a Special Reserve Fund, was to change large pharmaceutical companies' perception of the federal government as an uncertain and low profit market. By establishing the federal acquisition program, the government hoped to incentivize manufacturers to create countermeasures against CBRN threats and reduce the overall uncertainty of the market (Russell 2007). In 2005 Congress passed the Pandemic and All-Hazards Preparedness Act which implemented a number of changes to Project BioShield, in particular giving the HHS authority to award milestone payments, not exceeding 50% of the total contract, to countermeasure developers, thus supporting costlier late-stage R&D and reducing the risk of failure (Russell 2007; Matheny et al 2007).

Project BioShield has come under criticism for a variety of reasons. Firstly, critics argue that the contracts awarded by Project BioShield are too small to motivate large pharmaceutical companies to compete for funding. Consider that only $5.6 billion has been allocated for use over 10 years, for 14 different CBRN threats. Expected revenue from Project BioShield contracts will thus fall short of the CGD AMC Working Group estimated $3 billion per drug mark and indeed of our own estimates of between €985 million to €1.4 billion. As a result, Project BioShield has attracted smaller pharmaceutical and biotech firms, who have lower revenue expectations (Matheny et al 2007).

The dominance of biodefense by small companies is not necessarily problematic. If these companies are successful this could increase the manufacturing capacity and expertise of the pharmaceutical industry as a whole. This does become a problem, however, if these companies need more technical assistance and oversight to ensure that contract requirements are met and that the risk of failure is reduced (HHS 2007). This can make the entire process more costly and time intensive.

A second criticism is the lack of liability protection for manufacturers in the event of adverse reactions to the countermeasures. This is particularly important given the fact that

countermeasures can be used, in an emergency, regardless of whether or not they have been approved by the FDA. Large pharmaceutical companies fear that a lawsuit, no matter how meritless, could be permanently damaging to their reputation (O'Reilly 2006).

The failure of Project BioShield's first and largest contract provides a case study of some of the politics involved and the hurdles to its success. In November 2004, the HHS awarded VaxGen, Inc an $877.5 million contract for 75 million doses of an anthrax vaccine to be delivered within 3 years. This contract drew criticism from Emergent BioSolutions, the manufacturer of a previously used and already licensed anthrax vaccine. The VaxGen contract was terminated on December 2006. According to the HHS, VaxGen failed to meet a key milestone. According to VaxGen, the HHS was at fault for changing the contractual requirements (Grotton 2007). Subsequently, Emergent BioSolutions was awarded a contract for 10 million doses of their already licensed anthrax vaccine. No new vaccine was developed.

The experience of Project BioShield suggests that a central procurement framework which invites a high degree of political lobbying is unlikely to provide strong consistent incentives to engage major pharmaceutical company R&D.

The Call Option for Antibiotics (COA)

Mossialos et al (2009) describe a Call Option for Antibiotics (COA) as a hybrid incentive that is loosely based on the principles of a call option in equity markets. The COA model is based on the Call Option for Vaccines model first proposed by Brogan and Mossialos (2006) in which a potential purchaser buys the right, during the development of a drug, to purchase a pre-determined quantity of the drug at a discounted price, when and if the drug makes it to the market. If the drug fails to gain marketing approval, the purchaser will not exercise the right to buy but has lost the premium, i.e. the price of the option paid to the "seller" (the developer).

The initial investment or investments by the purchaser act as a push incentive while the option to purchase is the pull incentive. In this case, both the developer and the purchaser bear some risk. The developer because they are agreeing to supply at a discounted price, and the purchaser because if the drug fails to gain marketing approval they have lost the premium they paid for the option.

The premium paid to the developer is integral to the success of the call option. In the extreme the premium is high and covers all R&D costs. It is a pure push mechanism. If the "discounted" price is high, including a return on R&D, then the COA has more of the characteristics of a pull mechanism. Through one means or another, the COA will need to cover a share of R&D costs. An appropriately priced premium offer could spur a development race as companies seek to gain "first mover advantage" to ensure that their product is invested in. If the premium is too high, it is unlikely to attract investors. If the premium is too low, it will erode the profitability of the project for the developer and will not incentivize the company to continue development of the drug. Finding a way to correctly value the option presents a practical challenge to implementing the COA as with other incentives.

Many of the features of the COA exist, in some form, in the incentives already discussed. For example, the investment payments during development are similar to the milestone payments in the BioShield legislation or direct funding of R&D using FTO revenue. The pull effect of the option to purchase is similar to the effect created by an AMC. For this reason, the COA will not be discussed further on its own.

3.4 Economic benefit in Europe of investing in antibacterial R&D

The results of the model only tell us part of the story. We need to look at the costs relative to the gains that could result from investing in programs to stimulate the creation of new antibacterials in Europe. Unfortunately it is difficult to come up with a single value for reduced morbidity and mortality as a result of generating new antibacterials. This is an important area for additional research. As an alternative to a full incremental cost-benefit analysis, we calculate a threshold that could be used to evaluate an antibacterial R&D project.

According to our model, the most costly incentive is a five year AMC. Suppose that €1.4 billion was spent on an AMC for an antibacterial. The question we want to answer is how many lives need to be saved in order to justify spending that amount on an incentive? The EMEA/ECDC report (2009) estimated that resistance to selected bacteria resulted in approximately 25,000 deaths in 2007. 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. Therefore, in order to justify spending €1.4 billion on an AMC, the antibacterial must reduce this mortality by approximately 5.6% or 1400 deaths. A reduction in deaths will also result in additional savings elsewhere such as decreased in-and out-patient hospital costs and increased worker productivity. Investing in incentives for stimulating antibacterial R&D is likely to bring about not only health gains, but also significant cost savings.

Of course, health systems may be underfunded, i.e. there are ways in which 1400 deaths could be avoided for less than €1.4 billion. Where investment is constrained then it is a necessary but not sufficient condition that expected benefits exceed costs. It is also necessary to look realistically at what else could be done with the same resources. Other programmes might deliver more health gain, in this or another area.

More work is therefore required to understand the potential impact of new drugs on the economic and health burden of AMR, and also to understand the opportunity cost attached to the resources that might be used to provide R&D incentives. This will enable a proper assessment of the benefits and costs of providing incentives.

4 RECOMMENDATIONS FOR EUROPE

The focus of this paper is, as we noted earlier, to move the discussion in Europe forward by presenting policy makers and stakeholders with a short list of feasible and realistic solutions to stimulate R&D to fight AMR in Europe. We need therefore to put the issues in Europe in the context of what is a global phenomenon. We note that the Commission has been tasked to come up with comprehensive proposals by the end of 2011 at the latest. We hope that our paper will provide an input into this process.

Given that our recommendations are based on the modelling exercise it is important to recognize its limitations. The model is populated with publically available, peer reviewed data. Where possible, antibacterial specific data was used otherwise data for a new molecular entity was substituted and assumed to be the same for antibacterials. The sales curve, taken from DiMasi et al (2004), is based on IMS data for antibacterials approved in the US between 1990 and 1994, thus it may not accurately characterise sales projections for antibacterials recently launched, such as Zyvox (linezolid). Similarly, many simplifying assumptions were made for ease of modelling.

Despite this, the purpose and value of the model is twofold: firstly, it adds numbers to a debate where there had previously been none, and secondly, it provides a sense of the magnitude of the different incentives needed to stimulate antibacterial R&D as well as illustrate which ones have the potential to be effective and which ones do not. The results of the model should not be interpreted as precise estimates but rather as a starting point for discussions between pharmaceutical companies, policy makers and other relevant stakeholders.

Our recommendations are as follows:

Our preference is for a hybrid policy for example treating drugs for AMR in a similar way to orphan drugs. Such a policy could be combined with some push initiatives in the pre-competitive stages of R&D. Examples of such push initiatives are currently being pursued through the IMI and through FP7.

Such a policy should include some of the components of the actual 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 antibacterials problem. Additionally, this policy should also include some type of fast track or priority review for new antibacterials developed. Such a scheme would be similar to what Ridley and Sanchez (2010) propose however, it would only apply to new antibacterials and not another drug in a company's portfolio. It would reward successful companies with priority review for a drug for AMR not only at the EU/EMA market authorisation level but ideally it would also accelerate the pricing and reimbursement decision at the Member States level.

Another critical element within such a package, as with orphan drugs, will be the market power that such a measure would bring. In the case of orphan drugs, there is a market exclusivity provision. It is not clear how important this provision is in securing market power as it can be challenged when a similar drug produces better effects or has a better safety profile. There are also data exclusivity provisions, which have been used to prevent generic competition. In most cases however, the market power comes from the greater willingness to pay higher prices on the

part of many Member State health systems for drugs treating small populations with debilitating diseases. Market exclusivity might in any case not be appropriate for new antibacterials, 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 reducing the potential growth of resistance.

Our analysis indicates significant price premiums would be required. Member States might resist on grounds of cost and of cost-effectiveness. It would be important that there was a Member State consensus around the importance of taking into account the growing costs of AMR in any assessment of value.

We recognize, however, that such a hybrid might encourage companies to seek sales volume. Use of point of care diagnostics and a recognition of the importance of tight controls on use as part of any premium pricing arrangement may be ways to avoid any adverse consequences. **Any incentive package should include measures to ensure and encourage appropriate use and stewardship. Therefore, an important emphasis should be placed on the development of rapid point of care diagnostics to ensure that drugs are only used on patients for whom they will be effective. There needs to be a review of the challenges of getting more point of care diagnostics developed and used in clinical practice.** Such a review is needed as a matter of urgency.

There is significant variation in the way that orphan drugs have been treated by Member States within the EU. For example, as mentioned earlier, the pricing and reimbursement process for England and Wales does not treat orphan drugs differently than other drugs, while France's HTA body does. A potential difficulty for an EU-wide antibacterial policy would be ensuring that each Member State values antibacterials appropriately as this would not be possible to legislate or enforce at the EU level. There are two aspects to this. Firstly, how the evidence base is assessed. Here it may be possible to reach agreement on relative efficacy. Secondly, the value attached to that relative efficacy. This will involve an understanding of the importance of the build-up of resistance and the extent to which this issue was regarded as a priority by a Member State. Differences are likely to persist on that issue.

An alternative package could include an upfront payment for registration (rather than for volume of use) in the form of an AMC "prize" or a Transferable IP Extension. Both incentives would reward the launch of an effective drug rather than actual volumes of use. The advantage of this type of approach compared to a "reward for use" approach is that it is able to balance the inherent tension between the public health goals of policy makers, i.e. to slow the growth and spread of resistance and encourage the development of new antibacterials, and the need for companies to generate attractive returns on their R&D investments.

However, AMCs are expensive and will require upfront funding from Member States. Added to this, a new AMC will have to be established for each new antibacterial needed, or one much larger AMC with a more complex specification of types of qualifying drugs will need to be established in order to lead to a sustainable pipeline.

Transferable IP Extensions are not likely to be popular options. The biggest strike against them is that some patient advocate groups and politicians believe that they pass the burden onto others in the form of extended patent protection leading to delayed generic entry. In most Member

States, 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 an IP extension and therefore the length of the extension. Limits on the number of extensions triggered could be accomplished by having a product specification hurdle similar to that which would be required for an AMC.

Another important issue would be the price at which the product was made available once licensed. The higher the value of the AMC or Transferable IP Extension the more R&D costs are covered, and the closer, in theory, the selling price could then be to the generic price. It would be important to ensure use of the product was managed, ideally through the use of diagnostic tests to target treatment.

Whilst there is already precedent within the EU to enact hybrid policies, such as for orphan drugs, Transferable IP Extensions have never successfully been implemented in either the EU or the US, and only one AMC exists, for purchasing pneumococcal vaccines from Pfizer and GSK that have already been granted market authorization in more commercially lucrative markets such as North America and Europe. Its ability to stimulate R&D remains untested.

A new approach put forward by Kesselheim and Outterson (2010) also attempts to strike a balance between (a) providing financial incentives to pharmaceutical companies and (b) encouraging conservation of new and existing antibacterials. They favour what they call the Antibiotic Conservation and Effectiveness (ACE) program. The ACE program has four elements which they believe will ultimately realign private incentives more closely with public health goals: 1) value-based reimbursement of antibacterials by public payers; 2) making payments contingent upon meeting public health and conservation goals; 3) regulatory changes that include waivers of antitrust laws to allow for better market coordination for conservation and 4) increased public support for basic antibacterial research.

A European PDP for antibacterial drugs is a potentially attractive option, given its success in the area of neglected diseases, but also by looking at the impact of early stage R&D funding on the NPV for antibacterial development. However, while we recognized that PDPs have been extremely successful at generating pipelines where the science behind drug discovery has been difficult, and this is certainly the case for antibacterials, we believe that the absence of commercial incentives is a more significant problem, especially when companies are deciding whether or not to begin costly Phase III trials. Pharmaceutical companies must be confident that, should they succeed, they will be able to justify their investment. It is for this reason, therefore, that we advocate for an increase in price, or an AMC or Transferable IP Extension linked to the licensing of a new antibacterial. In theory a European PDP could help fund Phase III trials, however, it would make more sense to let the full cost and risk lie with the company.

An area worth further research is how many lives would be saved by bringing new antibacterials to the market. Furthermore, while there are excellent monitoring and surveillance systems in place to track the emergence and spread of resistance, such as the European Antimicrobial Resistance Surveillance System (EARSS) and the European Surveillance of Antimicrobial Consumption (ESAC), there are few systems in place to measure the burden of resistance. This information gap must be filled. Policy makers and all stakeholders need a better sense of what the pay-off would be for investing in antibacterial R&D. If this was known, it

might help to put the cost of potential incentives into perspective. We attempt to do this here however much more research and analysis is needed.

The dialogue between the US and European government agencies (TATFAR) is very important and should be continued. It offers an opportunity for comparable incentives to be put in place on both sides of the Atlantic, especially if the EU chooses incentive mechanisms that could, in principle, be replicated by the US. The advantage of implementing the same or complementary incentives in both the EU and US is that the size of the incentives needed would be considerably smaller as the burden would be shared between the two. The other crucial role that TATFAR can play in the area of R&D incentives 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 different regulatory and clinical trial requirements across countries. The EMA and FDA have a strong tradition of dialogue and collaboration and 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. Other countries and other stakeholders, including the pharmaceutical industry, must be included in this dialogue as well. Without full participation from all concerned parties very little can and will be done to address the growing threat of AMR. It is important to note, for example, that antibacterials developed in Europe and the US will also have value and be effective in other countries in which resistance is emerging, such as India and Pakistan. As in Europe it will be important to find ways of ensuring appropriate use without denying access to those in need. There is scope here for more work to be done on how to slow the development and spread of AMR due to inappropriate use in emerging markets. **There needs to be a global dialogue around how the build-up of resistance is to be tackled. Without such a dialogue, the value of new drugs to the EU health care system will be eroded by a build-up of resistance to these drugs outside of the EU.**

The Commission has a deadline of the end of 2011 but should act now. **Our recommendation to the Commission is to establish a task force whose membership includes not only Member States, but also key players from the pharmaceutical industry, EMA, ECDC, academia, microbiologists, and clinicians.** The task force will then be charged with working through these issues, as well as coming up with proposals for implementing incentives for antibacterial R&D.

5 REFERENCES

Acemogly D, and Linn J (2004). Market Size in Innovation: Theory and Evidence from the Pharmaceutical Industry. The Quarterly Journal of Economics 1049-1090.

Albrich WC, Monnet DL, Harbarth S (2004). Antibiotic Selection Pressure and Resistance in Streptococcus pneumonia and Streptococcus pyogenes. Emerging Infectious Diseases 10(3): 514-517.

Barder O, Kremer M, Levine R, et al (2005). Making Markets for Vaccines. Washington, DC: Center for Global Development.

Baston A (2005). The Problems and Promise of Vaccine Markets In Developing Countries. Health Affairs 24(3): 690-693.

Beith A (2008). Mapping Factors the Drive Drug Resistance (with a Focus on Resource-Limited Settings): A First Step Towards Better Informed Policy. Washington, DC: Center for Global Development.

Berndt ER and Hurvitz JA(2005). Vaccine Advance-Purchase Agreements for Low-Income Countries: Practical Issues. Health Affairs 24(3): 653-665.

Berndt ER, Glennerster R, Kremer MR, et al (2007). Advance market commitments for vaccines against neglected diseases: estimating costs and effectiveness. Health Economics 16: 491-511.
Boots I, Sukhai RN, Klein RH, et al (2007). Stimulation programs for pediatric drug research-do children really benefit? Eur J Pediatr 166:849-855.

Boucher HW, Talbot GH, Bradley JS, et al (2009). Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America. Clinical Infectious Diseases 48: 1-12.
Brogan D and Mossialos E (2006). Applying the concepts of financial options to stimulate vaccine development. Nature Reviews Drug Discovery 5: 641-647.

Buse K, and Walt G (2000). Global public-private partnerships: part II-what are the health issues for global governance? Bulletin of the World Health Organization 78(5): 699-709.

Choffnes ER, Relman DA, Mack A (2010). Antibiotic Resistance-Implications for Global Health and Novel Intervention Strategies. Workshop Summary. Washington, DC: Institute of Medicine. Available online at http://www.iom.edu/Reports/2010/Antibiotic-Resistance-Implications-for-Global-Health-and-Novel-Intervention-Strategies.aspx

Council of the European Union (2009). Conclusions on innovative incentives for effective antibiotic s. Available online at http://www.se2009.eu/polopoly_fs/1.26034!menu/standard/file/CC%20effective%20antibiotics.pdf

DiMasi JA, Hansen RW, Grabowski HG (2003). The price of innovation: new estimates of drug development costs. Journal of Health Economics 22:151-185.

DiMasi JA, Grabowski HG, Vernon J (2004). R&D Costs and Returns by Therapeutic Category. Drug Information Journal 38: 211-223.

DiMasi JA, Feldman L, Seckler A, Wilson A (2010). Trends in risks associated with new drug development: success rates for investigational drugs. Clinical Pharmacology and Therapeutics 87(3):272-277.

European Commission (2009). Part III: Annexes to Impact Assessment Guidelines. 15 January 2009.

European Medicines Agency (EMEA) and European Centre for Disease Prevention and Control (ECDC) (2009). The bacterial challenge: time to react. Stockholm: EMEA/ECDC
Food and Drug Administration (2008). Guidance for Industry: Tropical Disease Priority Review Vouchers. FDA.

Food and Drug Administration (2010). The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals. FDA.

Gilbert DN, Guidos RJ, Boucher HW, et al (2010). The 10x'20 Initiative: Pursuing a Global Commitment to Develop 10 New Antibacterial Drugs by 2020. Clinical Infectious Diseases 50: 1081-1083.

Glennerster R and Kremer M (2001). A better way to spur medical research and development. Regulation 23(2): 34-39.

Gluck H (2002). Federal Policies Affecting the Cost and Availability of New Pharmaceuticals. The Kaiser Family Foundation.

Govtrack.us HR1549: Preservation of Antibiotics for Medical Treatment Act of 2009. Available online at http://www.govtrack.us/congress/bill.xpd?bill=h111-1549&tab=summary

Govtrack.us HR2400: Strategies to Address Antimicrobial Resistance Act. Available online at http://www.govtrack.us/congress/bill.xpd?bill=h111-2400&tab=summary

Grabowski H and Vernon J (1996). Longer Patents for Increased Generic Competition: The Waxman-Hatch Act After One Decade. Durham: Duke University (Draft).

Grabowski H (2003). Increasing R&D Incentives for Neglected Diseases-Lessons from the Orphan Drug Act.

Grabowski H (2005). Encouraging the development of new vaccines. Health Affairs 24(3): 697-700.

Grabowski HG, Ridley DB, Moe JL (2008). Priority Review Vouchers to Encourage Innovation for Neglected Diseases. Durham: Duke University.

Grieve J, Tordoff J, Reith D, Norris P (2005). Effects of Pediatric Exclusivity Provision on children's access to medicines. British Journal of Clinical Pharmacology 56(6): 730-735.

Grotton F (2007). Project BioShield: Appropriations, and Policy Implementation Issues for Congress. CRS Report for Congress.

Grotton F (2010) Project BioShield: Appropriations, and Policy Implementation Issues for Congress. CRS Report for Congress.

Grundmann H, Aires-de-Sousa M, Boyce J, et al (2006). Emergence and resurgence of methicillin-resistant Staphylococcus aureus as a public-health threat. Lancet 368(9538): 875-885.

Harris G. Antibiotics in Animals Need Limits, F.D.A Says. The New York Times. June 29, 2010.

Hecht R, Wilson P, Palriwala A (2009). Improving Health R&D Financing for Developing Countries: A Menu of Innovative Policy Options. Health Affairs 28(4): 978-985.

Heemstra HE, de Vrueh RLA, van Weely S, et al (2008). Orphan drug development across Europe: bottlenecks and opportunities. Drug Discovery Today 13(15-16): 670-676.

The Humane Society of the United States. Human Health Implications of Non-Therapeutic Antibiotic Use. Available online at http://www.hsus.org/farm/resources/research/pubhealth/human_health_antibiotics.html

IMS (2010). IMS World Review Executive 2010. London: IMS

Internal Revenue Service (2011). Yearly Average Currency Exchange Rates. Available online at http://www.irs.gov/businesses/small/international/article/0,,id=206089,00.html

Pray, L (2008). Antibiotic R&D: Resolving the paradox between unmet medical need and commercial incentive. Insight Pharma Reports.

Kesselheim AS and Outterson K (2010). Fighting Antibiotic Resistance: Marrying New Financial Incentives to Meeting Public Health Goals. Health Affair 29(9): 1698-1696.

Kesselheim AS and Outterson. Improving Antibiotic Markets for Long Term Sustainability. Yale Journal of Health, Policy, Law and Ethics Volume 11.

Kesselheim AS (2010). Using Market-Exclusivity Incentives to Promote Pharmaceutical Innovation. The New England Journal of Medicine 363(19): 1855-1862.

Kremer M (2000). Creating Markets for New Vaccines. Part I: Rationale. Cambridge: Harvard University (draft).

Kremer M (2001). Public Policies to Stimulate the Development of Vaccines and Drugs for the Neglected Disease. Commission on Macroeconomics and Health Working Paper Series. Paper No. WG2:7.

Kremer M and Glennerster R (2004). Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases. Princeton: Princeton University Press.

Kremer M, Towse A, William H (2005). Briefing Note on Advance Purchase Commitments. Prepared for the UK Department for International Development.

Kumarasamy KK, Toleman MA, Walsh TR, et al (2010). Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. The Lancet Infectious Diseases 10(9): 597-601.

Laxminarayan R and Malani A (2007). Extending the Cure: Policy Responses to the Growing Threat of Antibiotic Resistance. Washington, DC: Resources for the Future. Li JS, Eisenstein EL, Grabowski HG, et al (2007). Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program. JAMA 297(5): 480-488.

Matheny J, Mair M, Mulcahy A, Smith BT. Incentives for Biodefense Countermeasure Development. Biosecurity and Bioterrorism: Biodefense Strategy, Practice and Science 5: 228-238.

Milne C, Kaitin K, Ronchi E (2001). Orphan Drug Laws in Europe and the US: Incentives for the Research and Development of Medicines for the Diseases of Poverty. Commission on Macroeconomics and Health Working Paper Series. Paper No. WG2: 8.

Moran M (2005). A breakthrough in R&D for neglected diseases: new ways to get the drugs we need. PLoS Medicine 2(9): 828-832.

Moran M, Ropars A, Guzman J, et al (2005). The New Landscape of Neglected Disease Drug Development. London: London School of Economics and Political Science, and the Wellcome Trust.

Morel C and Mossialos E (2010). Stocking the antibiotic pipeline. BMJ 340: 1115-1118.

Mossialos E, Morel C, Edwards S, et al (2009). Policies and incentives for promoting innovation in antibiotic research. London: London School of Economics and Political Science.

Nosking GA, Rubin RJ, Schentag JJ, et al (2007). National Trends in Staphylococcus aureus Infection Rates: Impact on Economic Burden and Mortality over a 6-Year Period (1998-2003). Clinical Infectious Diseases 45: 1132-40.

Nugent R, Pickett J, Back E (2008). Drug Resistance and a Global Health Policy Priority. Washington, DC: Center for Global Development.

Nugent R, Back E, Beith A (2010). The Race Against Drug Resistance. Washington, DC: Center for Global Development.

O'Reilly M (2006-2007). The Failures of Project Bioshield and Congressional Attempts to Remedy It. J Health Care L 10(3): 503-512.

Outterson K, Samora JB, Keller-Cuda K (2007). Will longer antimicrobial patents improve global public health? Lancet Infect Dis 7:559-66.

Philpson T (2000). Economic epidemiology and infectious disease. In Handbook of Health Economics, ed Newhouse J, Culyer T. New York: North Holland

Philipson T, Mechoulan S, (2003). Intellectual Property & External Consumption Effects: Generalisations from Pharmaceutical Markets. NBER Working Paper 9598

Philipson T, Mechoulan S, Jena A (2006). Health Care, Technological Change, and Altruistic Consumption Externalities. NBER Working Paper 11930.

Paul SM, Mytelka DS, Dunwiddie CT, et al (2010). How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nature Reviews Drug Discovery 9: 203-214.

Payne DJ, Gwynn MN, Holmes DJ, Pompliano DL (2007). Drugs for bad bugs: confronting the challenges of antibacterial discovery. Nature Reviews Drug Discovery 6: 29-40.

Power E (2006). Impact of antibiotic restrictions: the pharmaceutical perspective. Clin Microbiol Infect 12 (Suppl. 5): 25-34.

Projan S (2003). Why is big Pharma getting out of antibacterial drug discovery? Current Opinion in Microbiology 6:427-430.

Report to the G8 Finance Ministers on Advanced Market Commitments. London, December 2, 2005.

Ridley DB, Grabowski HG, Moe JL (2006). Developing Drugs for Developing Countries. Health Affairs 25(2): 313-324.

Ridely DB, Sanchez AC (2010). Introduction of European priority review vouchers to encourage development of new medicines for neglected diseases. The Lancet 376: 922-927.

Rinaldi A (2005). Adopting an orphan. EMBO Reports 6(6): 507-510.

Roberts RR, Hota B, Ahmad I, et al (2009). Hospital and Societal Costs of Antimicrobial-Resistant Infections in a Chicago Teaching Hospital: Implications for Antibiotic Stewardship. Clinical Infectious Diseases 49: 1175-84.

Russell PK (2007). Project BioShield: What It Is, Why It is Needed, and Its Accomplishments So Far. Clinical Infectious Diseases 45:S68-72.

Shlaes DM, Projan S (2009). Antimicrobial Resistance Versus the Discovering and Development of New Antimicrobials. In: DL Mayers ed. (2009). Antimicrobial Drug Resistance: Volume 1. New York: Humana Press. Ch. 4.

Singh MP, Greenstein M (2000). Antibacterial leads from microbial natural products discovery. Current Opinions in Drug Discovery and Development 3: 167-176.

Sonderholm J (2009). Wild-Card Patent Extensions as a Means to Incentivize Research and Development of Antibiotics. Journal of Law, Medicine and Ethics 240-246.

Spellberg G, Miller LG, Kuo N, et al (2007). Societal Costs Versus Savings from Wild-Card Patent Extension Legislation to Spur Critically Needed Antibiotic Development. Infection 35: 167-174.

Spellberg B (2008) Antibiotic resistance and antibiotic development. The Lancet Infect Dis 8: 211-212. Strongin RJ (2002). Hatch-Waxman, Generics and Patents: Balancing Prescription Drug Innovation, Competition and Affordability. National Health Policy Forum Background Paper. Washington, DC: The George Washington University.

Taubes G (2008). The Bacteria Fight Back. Science 321: 356-361.

Tickell S (2005). The Antibiotic Innovation Study: Expert Voices on a Critical Need. ReAct: Action on Antibiotic Research.

THOMAS (Library of Congress). Generating Antibiotic Incentives Now Act of 2010. Available online at http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=111_cong_bills&docid=f:h6331ih.txt.pdf

Towse A (2005) A review of IP and Non-IP Incentives for R&D for Diseases of Poverty. What type of Innovation is Required and How Can We Incentivise the Private Sector to Delivery It? London: OHE Consulting.

Tufts Center for the Study of Drug Development (2003). FDA'S fast track initiative cut total drug development time by 3 years. Impact Report 5(6).

Union of Concerned Scientists. Preservation of Antibiotics for Medical Treatment Act. Available online at http://ucsusa.org/food_and_agriculture/solutions/wise_antibiotics/pamta.html

US Department of Health and Human Services (HHS) (2007). The Jordan Report. Accelerated Development of Vaccines. HHS.

US Department of Health and Human Services (2010). The Public Health Emergency Medical Countermeasures Enterprise Review. Transforming the Enterprise to Meet Long-Range, National Needs. HHS.

Wheeler C and Berkley S (2001). Initial lessons from public-private partnerships in drug and vaccine development. Bulletin of the World Health Organization 79: 728-734.

World Health Organization (2004). The Global Burden of Disease: 2004 Update. Geneva: World Health Organization.

Yin W (2008). Market Incentives and pharmaceutical innovation. Journal of Health Economics 27:1060-1077.

6 ANNEX 1: MODELLING THE NPV OF ANTIBACTERIAL DEVELOPMENT

Table 9 provides a list of the baseline case variables, their references, and indicates if they were antibacterial specific or not.

Table 9 References used for the baseline model

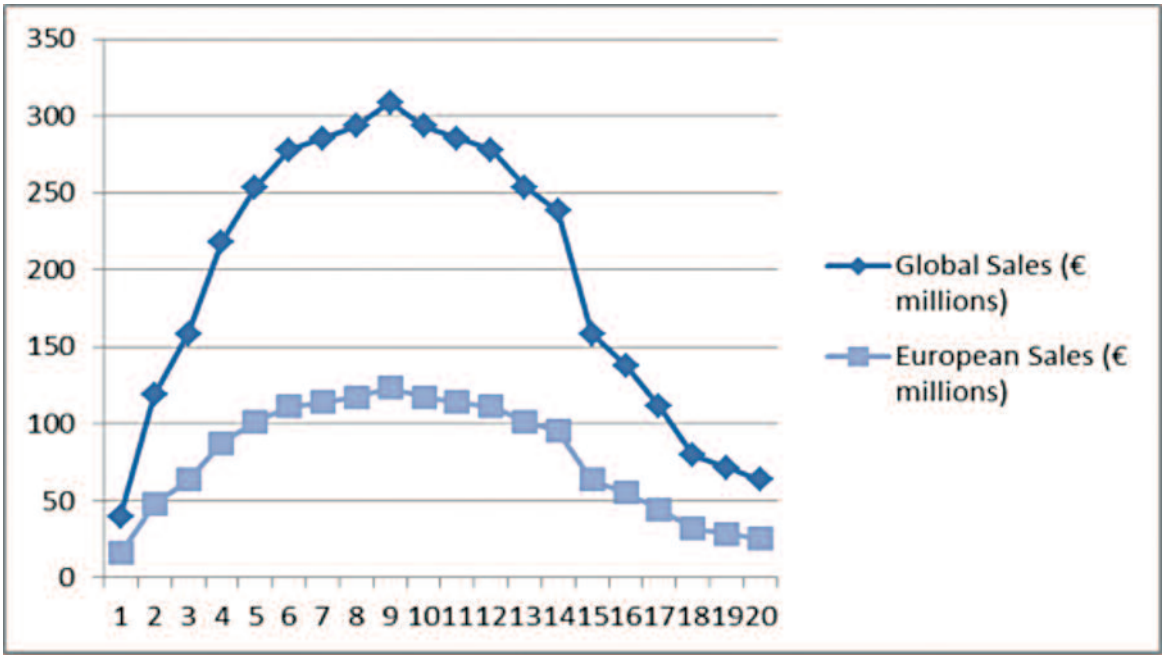
Variables			Reference	Antibacterial Specific
Phase lengths (years)	Preclinical: Phase I: Phase II: Phase III: Approval:	5.5 1.5 2.5 2.5 1.5	Paul et al 2010	No
Cost per Work In Progress (millions €)	Preclinical: Phase I: Phase II: Phase III: Approval	13.63 11.06 29.48 110.55 29.48	Paul et al 2010	No
Probability of Success (preclinical[9])	0.35		Paul et al 2010	No
Probabilities of success (Phase I-Phase III)	Phase I: Phase II: Phase III:	0.582 0.522 0.786	DiMasi et al 2010	Yes
Probability of Success Approval	0.91		Paul et al 2010	No
Sales figures and product life length			DiMasi et al 2004	Yes
Cost of capital	11%		DiMasi et al 2003	No

Paul et al costs were expressed in 2008 dollars and the DiMasi sales data used were expressed in 2000 dollars. As a result, we partially inflated the DiMasi sales data to 2008 dollars. Sales data were only inflated by 40% (the US market share) to account for the fact that pharmaceutical prices in other markets do not increase in line with inflation. All US dollar estimates were converted to Euros using a 0.737 exchange rate.

The effective patent life was assumed to be 12 years and the total product life length was 20 years following approval (Strongin et al 2002, DiMasi et al 2004). The assumed contribution rate, net of sales and marketing costs, taxes, and the cost of goods, was set at 50%, with each of the three components assumed to make up 16.7%. Global peak year sales, reached in year 9, were $419 million or €309 million (DiMasi et al 2004). Figure 7 plots the sales curve data used in the model.

[9] The "preclinical" phase includes the target to hit, hit to lead, lead optimization and preclinical phases. Probabilities of success were multiplied across all four phases to arrive at single number for the model.

Figure 7 Graph of sales data worldwide and for Europe



Our model includes both the cost of capital and the probabilities of success at each stage of the R&D process, hence the model risk adjusts for the non-diversifiable risk that investors consider when assessing a potential investment and for the diversifiable risk associated with conducting R&D, i.e. the likelihood of a particular company developing a successful drug in a particular area.

The baseline NPV calculated for an antibacterial was -€38.15 million and the internal rate of return (IRR) was 10%. This baseline NPV estimate is sensitive to the cost of capital used. A decrease from 11% to 10% increases the NPV from -€38.15 million to -€10 million while an increase to 12% decreases the baseline NPV estimate to -€60 million.

The purpose of the model was to determine the size and timing of the different incentives needed in Europe to increase the NPV of antibacterial R&D to $200 million or €147 million. This target NPV was chosen because it would make antibacterial development competitive, in terms of its NPV, relative to the other therapeutic classes listed in Table 1.

In order to ensure that what was being modelled was the impact of each of the incentives implemented in the European market only, 2009 IMS data was used to estimate the size of the European market for pharmaceuticals. This allowed global sales, as well as sales and marketing costs, and profit to be divided into two categories: Europe and the rest of the world. The European market share was calculated to be approximately 30% (IMS 2010).

However, because the purpose of these incentives is to stimulate the creation of novel antibacterials to address unmet need in Europe first, it may consume more than a 30% share of these newly developed antibacterials. To account for this, the model assumes that the European market makes up 40% of the total global market for the relevant antibacterials.

Using the probabilities of success listed above, and beginning with the assumption that R&D would be expected to result in the creation of one successful new antibacterial, we calculated the number of products needed to start at each phase of development. For example, if the probability of success at approval is 0.91, then 1.1 molecules are needed at the start of the approval phase. Working backwards, if the probability of success at Phase III is 0.786 then 1.1/0.786 molecules or approximately 1.4 molecules are needed at the start of Phase III. Similarly, if the probability of success at Phase II is 0.522 then 1.4/0.522 molecules or 2.7 molecules are needed to start at Phase II. Continuing in this manner, we calculated that 4.6 molecules are needed to start at Phase I (2.7/0.582) and 13 molecules (4.6/0.35) are needed at the preclinical phase.

Knowing the number of molecules needed to start at each phase we were then able to calculate the total cost of each phase of development by multiplying the number of molecules needed per phase by the corresponding cost per work in progress (molecule). The table below lists the total cost, in millions of Euros, for each phase of development.

Table 10 Total cost per phase of antibacterial R&D

Preclinical	Phase I	Phase II	Phase III	Approval
€179.27 million	€50.87 million	€78.96 million	€154.56 million	€32.40 million

The total cost before taking account of the opportunity cost of capital is €496m ($673m) in 2008 prices. After taking account of the cost of capital using the 11% rate the total cost of drug development is estimated at €1bn ($1.35m). This is consistent with the estimated range of $0.9m-$1.9m found by Mestre-Ferrandiz et al (2011).

In order to calculate the baseline NPV and establish the framework for modelling the different incentives, the total cost of each phase of R&D and approval, as well as the sales for Europe and the rest of the world were entered into an excel spreadsheet, with each cell representing a year in the development and product life cycle of the antibacterial. All costs were entered as negative values, while sales were positive. To calculate the revenue generated from sales, sales and marketing costs, the cost of goods, and taxes were deducted from the global sales data. The baseline NPV and IRR were then calculated using the cost and revenue numbers. The two figures below show how the R&D cost side, and the sales and revenue side of the model were set up.

Figure 8 R&D cost side of the model

	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0
	Preclinical					Phase I		Phase II		Phase III			Approval	
Probability of success														
Preclinical	0.35													
Phase I	0.582													
Phase II	0.522													
Phase III	0.786													
Approval	0.91													
Mean out of pocket costs	-2.48	-2.48	-2.48	-2.48	-2.48	-4.92	-7.37	-11.79	-11.79	-28.01	-44.22	-44.22	-19.65	-9.83
Sales (Global)														39.80
Sales (Europe)														15.92
Sales (Rest of World)														23.88
Cost of Goods														6.65
Sales and Marketing														6.65
Taxes														6.65
Cash inputs/Revenue	-32.60	-32.60	-32.60	-32.60	-32.60	-33.26	-33.92	-31.58	-31.58	-46.70	-61.82	-61.82	-21.60	9.06
NPV	-€38.15													
IRR	10%													
Cash Inputs/Revenue	-32.60	-32.60	-32.60	-32.60	-32.60	-33.26	-33.92	-31.58	-31.58	-46.70	-61.82	-61.82	-21.60	9.06
Incentive	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Incentive	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
New Cash Inputs/Revenue	-32.60	-32.60	-32.60	-32.60	-32.60	-33.26	-33.92	-31.58	-31.58	-46.70	-61.82	-61.82	-21.60	9.06
NPV	-€38.15													
IRR	10%													

Figure 9 Sales and revenue side of the model

	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
	Approval																			
Probability of success																				
Preclinical																				
Phase I																				
Phase II																				
Phase III																				
Approval																				
Mean out of pocket costs	-9.83																			
Sales (Global)	39.80	118.66	158.46	218.15	253.53	277.85	285.22	293.33	308.80	293.33	285.22	277.85	253.53	238.05	158.46	137.82	111.29	79.60	71.49	63.38
Sales (Europe)	15.92	47.46	80.00	87.26	101.41	111.14	114.09	117.33	123.52	117.33	114.09	111.14	101.41	95.22	63.38	55.13	44.51	31.84	28.60	25.35
Sales (Rest of World)	23.88	71.19	95.07	130.89	152.12	166.71	171.13	176.00	185.28	176.00	171.13	166.71	152.12	142.83	95.07	82.69	66.77	47.76	42.89	38.03
Cost of Goods	6.65	19.82	29.24	36.43	42.34	46.40	47.63	48.99	51.57	48.99	47.63	46.40	42.34	39.75	26.46	23.02	18.58	13.29	11.94	10.58
Sales and Marketing	6.65	19.82	29.24	36.43	42.34	46.40	47.63	48.99	51.57	48.99	47.63	46.40	42.34	39.75	26.46	23.02	18.58	13.29	11.94	10.58
Taxes	6.65	19.82	29.24	36.43	42.34	46.40	47.63	48.99	51.57	48.99	47.63	46.40	42.34	39.75	26.46	23.02	18.58	13.29	11.94	10.58
Cash inputs/Revenue	9.06	59.21	87.36	108.86	126.51	138.65	142.32	146.37	154.09	146.37	142.32	138.65	126.51	118.79	79.07	68.77	55.53	39.72	35.67	31.63
NPV																				
IRR																				
Cash Inputs/Revenue	9.06	59.21	87.36	108.86	126.51	138.65	142.32	146.37	154.09	146.37	142.32	138.65	126.51	118.79	79.07	68.77	55.53	39.72	35.67	31.63
Incentive	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Incentive	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
New Cash Inputs/Revenue	9.06	59.21	87.36	108.86	126.51	138.65	142.32	146.37	154.09	146.37	142.32	138.65	126.51	118.79	79.07	68.77	55.53	39.72	35.67	31.63
NPV																				
IRR																				

To model the different incentives and recalculate the new NPV and IRR a separate line was added to the spreadsheet, under the cash input/revenue line where the effect of each incentive could be simulated as described in section 3.3.