New Drugs to Tackle Antimicrobial Resistance: Analysis of EU Policy Options

Priya Sharma, OHE[1]
Adrian Towse, OHE

Corresponding author:

[1]12 Whitehall, London, SW1A 2DY, Tel: 020 7747 1440, E-mail: psharma@ohe.org

Contents Page

Executive Summary

The Challenge

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 drugs. Recently, AMR has begun to command attention from European policy makers whose focus has moved towards addressing the lack of new drugs in the R&D pipeline of the pharmaceutical industry.

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

Our Contribution

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 by attempting to determine the size of the various incentives needed to make the net present value (NPV) for antibiotic development more competitive relative to other therapeutic classes.

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.

Push, Pull and Hybrid Incentives

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. Examples of push incentives discussed are product development partnerships (PDPs), tax credits, government funding of R&D, and funding and regulatory support for pre-competitive research consortia.

Pull incentives seek to mimic the market incentives that exist for commercially lucrative pharmaceutical products. Examples of pull incentives discussed in the paper are advanced market commitments (AMC), priority review vouchers (PRV) and fast track options (FTO), intellectual property (IP) extensions for antibiotics and transferable IP extensions.

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 antibiotic R&D. The consensus at the Stockholm conference was that a hybrid approach will be necessary. Examples of this include orphan drug and paediatric legislation, Project BioShield and the related CBRN countermeasures in the US, and the call option for antibiotics. Hybrid incentives combine both push and pull incentives and thus can, in theory, complement the advantages and disadvantages of both types of incentives.

Modelling the Impact

The baseline case for the development of an antibiotic was modelled using data from publically available, peer reviewed literature. Where possible, antibiotic specific data was used, otherwise antibiotic data was assumed to be similar to that of a new molecular entity (NME). 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 antibiotic R&D of $200 million or €153 million. At this level, investment in antibiotic 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 antibiotic R&D to that level.

The model only considers the impact and size needed of incentives implemented in Europe. We assume that the European market makes up 40% of the relevant global market of antibiotics, based on IMS data (IMS 2010). Sales and costs in other markets are not altered by any incentives modelled, although the global nature of the problem is discussed later in this paper.

The model was built in Excel and the NPV and internal rate of return (IRR) were calculated used using the Excel functions. The baseline NPV calculated for an antibiotic was -€31.50 million and the IRR was 10%, which goes some way to explaining the current lack of commercial investment.

Our Results and Recommendations

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

Incentive	Size of incentive (€)	New NPV (€)	New IRR
1 year AMC	980 million	153.89 million	17%
5 year AMC	1.38 billion (275 million per year)	156.52 million	16%
PRV	2.5 billion in 6 months	152.52 million	14%
6 month transferable IP extension	800 million	154.09 million	16%
2 years transferable IP extension	850 million (425 million per year)	155.92 million	16%
5 year transferable IP extension	1 billion (200 million per year)	158.85 million	16%
Market exclusivity	300% increase in antibiotic revenue in Europe	159.73 million	15%

In addition we found the effects of six month and two year (non-transferable) IP extensions for antibiotics on the NPV were minimal and the IRR remained at 10%. The FTO was modelled as direct funding of R&D and the results showed that direct funding at the earlier stages of R&D, i.e.

preclinical and Phase 1, have a significant impact on the NPV. For example, €34.62 million per year to fund preclinical development increased the NPV from -€31.50 million to €105.7 million. The FTO results highlight the value of push incentives, and a PDP of a similar size could be established. They further suggest that pull incentives alone will not address the fundamental lack of commercial attractiveness of the antibiotics market.

Our recommendation to policy makers is for a hybrid approach that includes both market-based methods and some push initiatives. It could be modelled on orphan disease legislation. A hybrid package around treating drugs for AMR in a similar manner to that by which orphan drugs are incentivized could be a successful, especially considering how successful orphan drug programmes have been in both Europe and the US. Our analysis indicates, however, that 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 account of the growing costs of AMR in any assessment of value.

We recognize, however, the problem of not wanting to encourage excessive uptake of new antibiotic products, thereby accelerating development of resistance. That suggests an important emphasis should be on the development of rapid point of care diagnostics, including companion diagnostics, to ensure drugs are only used on patients for which they are truly needed.

It also indicates that an alternative route be explored of an upfront payment for registration, rather than use, of a new antibiotic, in the form of an AMC, a PRV or a transferable IP extension. This could be combined with some pre-competitive collaboration and/or direct funding of R&D.

Adding the Global Dimension
The TransAtlantic Task Force established in 2009 provides an important opportunity to address regulatory issues, especially around clinical trial requirements and non-inferiority, and also 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 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. Incentives that may not be realistic for Europe alone, such as a PRV, could be put back on the table for discussion.

It is important to remember, however, that AMR is a global problem. The TransAtlantic Task Force provides an excellent starting point but more must be done within a global health framework. Other countries and other stakeholders, including the R&D-based 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 broader threat of resistance which goes beyond AMR.

Moving from talking to implementing
Most of the issues and possible incentives discussed in this paper are not new. Many stakeholders recognise the increasingly urgent need to move from discussion to action and the work of the Commission and the TransAtlantic Task Force provide important opportunities do so. Our recommendation to the Commission is therefore to establish a task force whose membership includes not only Member States, but also key players from the pharmaceutical industry, EMA, ECDC, academia etc. The task force will then be charged with working through these issues, as well as coming up with proposals for implementing incentives for antibiotic R&D. Lastly, but by no means

least, there has been no similar review to our knowledge of the problems for R&D in Europe into point of care diagnostics. Such a review is needed as a matter of urgency.

1. Introduction

1.1 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, so 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 largest cause of death in the European Union (EU) and all developed countries (WHO 2004, Projan 2003, Mossialos et al 2009).

AMR is, of course, only one part of the growing problem of drug resistance. It is, unfortunately, a natural and unavoidable consequence of treating infectious diseases with drugs (Beith 2008). As an increasing number of people have access to drugs to fight disease, resistance to lifesaving treatments for HIV/AIDS, Malaria, Tuberculosis and other infectious diseases has increased.

The focus of this paper is to move the discussion in Europe forward 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 do, however, seek to put the issues in Europe in the context of what is a global phenomenon. Consider the recently published study 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 (Kumarasamy et al 2010).

We note that the EU Commission has been tasked to come up with comprehensive proposals by the end of 2012. We hope that our paper will provide an input into this process which need not and should not take until the end of 2011.

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

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 antibiotics; (ii) the threat of bacterial resistance to patient safety; and, most recently, (iii) the need to stimulate R&D for novel antibiotics using appropriate incentives. To that end, the LSE was tasked to examine appropriate ways to stimulate the development of new antibiotics. Its findings and other material were discussed at a conference hosted by the Swedish Presidency in Stockholm in September 2009. 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, 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…"

A follow up conference is to be held in Uppsala in September 2010 to build upon the discussions held at the September 2009.

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 two bills, the Preservation of Antibiotics for Medical Treatment Act (PAMTA)[1] and the Strategies to Address Antimicrobial Resistance (STAAR) Act[2], that seek to address the non-therapeutic use of antibiotics in animal husbandry by attempting to limit or end the practice altogether, as the EU did in 2006, and improve monitoring and surveillance of antibiotic 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 antibiotics should be limited to therapeutic uses and that veterinarians should be involved in their administration (Harris 2010, FDA 2010). Finally, 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 antibiotics (HHS 2010).

The 10 by 20 Initiative and the TransAtlantic Task Force

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 antibiotics by 2020. IDSA believes that the antibiotic 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 antibiotic and diagnostic R&D (Gilbert et al 2010).

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[1] http://www.govtrack.us/congress/bill.xpd?bill=h111-1549&tab=summary

[2] http://www.govtrack.us/congress/bill.xpd?bill=h111-2400&tab=summary

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

2. Understanding the Problem

In order to move forward, however, we must first summarize the situation to date. To do so, 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 (Laxminiaryan and Malani 2007, Power 2006, Projan 2003, Payne et al 2007)

2.1 The global burden of antimicrobial resistance

The Center for Global Development (CGD) recently published a report on the global burden of drug resistance, with an emphasis on the developing world, and recommendations for major stakeholders on how to fight resistance (Nugent et al 2010), following an earlier report (Nugent et al 2008).

According to these reports from CGD, the challenges faced in the developing countries include the following:

- 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 antibiotics 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 antibiotics. For example,

less than 40% of Shigella *flexneri* isolates are susceptible to cheap and safe antibiotics 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 (Nugent et al 2008)
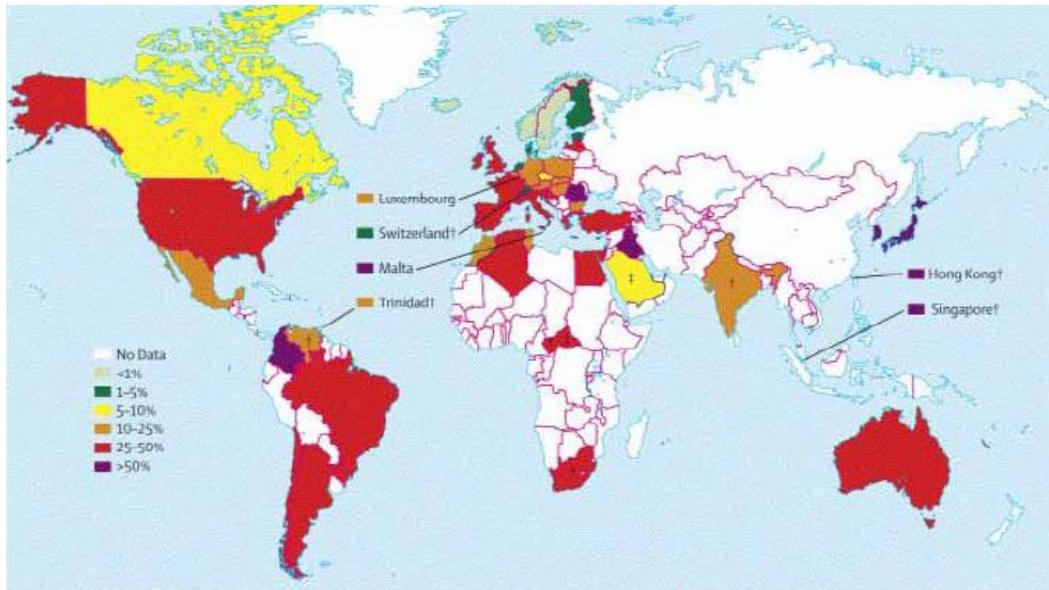
The clinical outcomes of AMR are increased morbidity and mortality. Several studies have shown that patients infected with a resistant strain of bacteria are likely to require longer hospitalization and are at increased risk of mortality. For example, the risk of mortality among patients infected with MRSA is double that of patients infected with non-resistant strains of *S aureus.*

There are other consequences. 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 AMR. 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 and generally paid for in full by the patient or by a country's government or donor on a patient's behalf. However, in countries with inadequate resources, not everyone who needs these drugs will be able to access them. The economic cost of AMR resistance in developing countries is not readily or easily measured and is complicated by the lack of available data.

The US has some of the highest rates of MRSA in the world. Approximately 60% of patients infected with *S aureus* in intensive care units in US hospitals cannot be treated with Methicillin. A study conducted in the US found that MRSA was responsible for 125,969 hospitalizations between 1999 and 2000. Compared to Europe in 2004, only Romania and Malta had higher rates of MRSA than the US that year. Similarly, Taiwan, South Korea and Japan had higher rates of MRSA than the US because of their high antibiotic 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 the medical and societal costs of ARM for a single hospital in Chicago. They estimated that the medical costs attributable to patients with AMR are between $18,588 and $29,069 per patient, excess length of stay due to infection was anywhere from 6.4 to 12.7 days, and that the overall societal costs for that one hospital were between $10.7 and $15 million.

Noskin et al (2007) estimate that, the total economic burden of a *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 estimates that the financial burden of AMR (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 (LOS) increases the likelihood of becoming infected with a resistant infection and the second is that infection then increases the overall LOS.

Many studies estimating the economic burden of resistance often only look at direct medical or hospital related costs and not from a societal perspective. As a result, many of the indirect costs such as productivity losses due to increased morbidity and mortality are not included. Similarly, many studies focus on the impact of AMR on a single hospital, country or region such as Europe, but it is a global problem with a shared economic burden that is not accounted for. As a result, the estimates provided in this section may well be a serious under-estimation of the true societal and global burden of AMR.

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 antibiotics, 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 resistant strains of bacteria led to 2.5 million extra hospital days: *Staphylococcus aureus, Escherichia coli, Enterococcus faecium, Streptococcus pneumoniae, Klebsiella pneumoniae, Pseudomonas aeruginosa* (Laxminarayan and Malani 2007).

The resulting extra hospital days and in-hospital costs were estimated to be over €900 million in 2007. Similarly, outpatient costs were estimated at €10 million and the productivity loss due to absence from work due to infection was calculated to be over €150 million per year.

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

Legend

▢ <1%	▢ 10.1-25%	▢ no data (including
▢ 1-5%	▢ 25.1-50%	countries which reported
▢ 5.1-10%	▢ >50%	less than 10 isolates)

↑ significant increasing trend

↓ significant decreasing trend
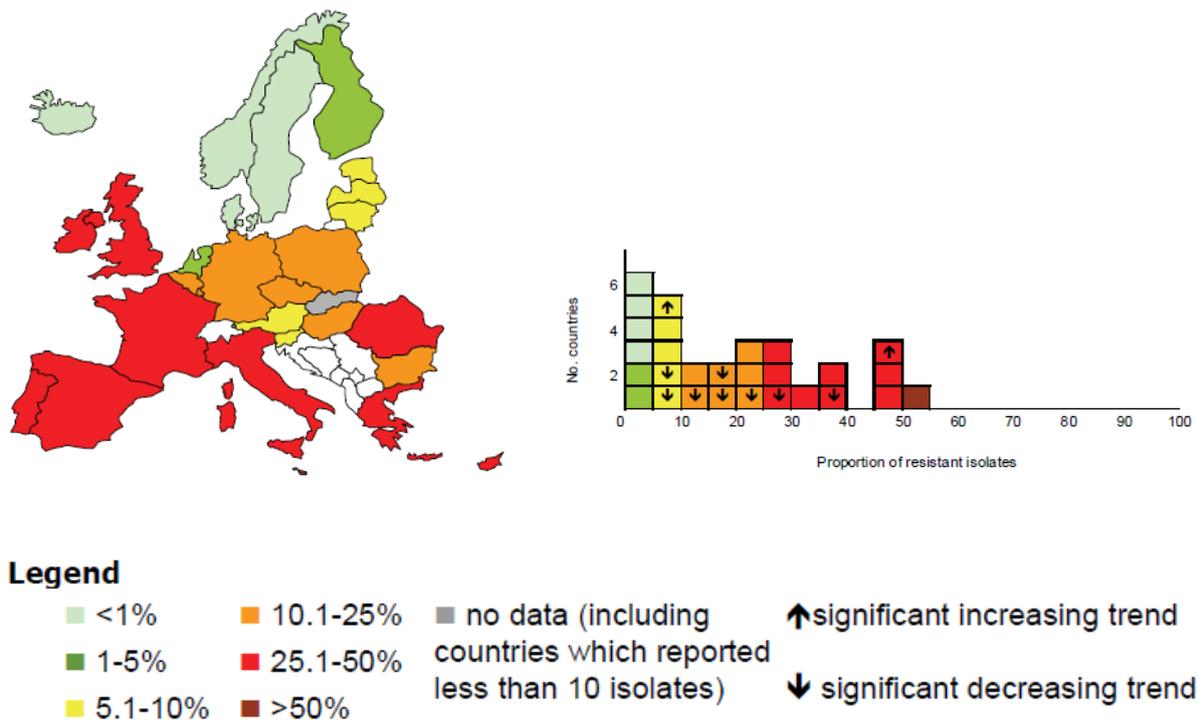
Productivity loss due to infection mortality was estimated to be approximately €450 million per year. The EMEA/ECDC (2009) calculated the total societal costs of infection due to AMR from selected resistant bacteria (see list above) to be €1.5 billion per year. Infections from the bacteria we list above were also responsible for approximately 25,000 patient deaths in 2007 in the EU, Iceland and Norway. Importantly, two-thirds of these deaths were due to Gram-negative bacteria[3].

2.3. The causes of antimicrobial resistance

Bacteria have developed resistance to almost every antibiotic 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 antibiotics and the approximate year of the first reported cases of resistance. The rate of bacterial resistance to new antibiotics is increasing rapidly.

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[3] Gram-positive and Gram-negative are a way of classifying bacteria based on the chemical and physical properties of their cell wall. Gram-negative bacteria are more difficult to treat as they have an outer wall that makes them difficult to attack. Examples of gram-negative bacteria are *Pseudomonas, Salmonella* and *Shigella.* Examples of Gram-positive bacteria are *Bacillus, Staphycoccus* and *Streptococcus* (Mossialos et al 2009)

Figure 3 Timeline of the emergence of resistance (Mossialos et al 2009)
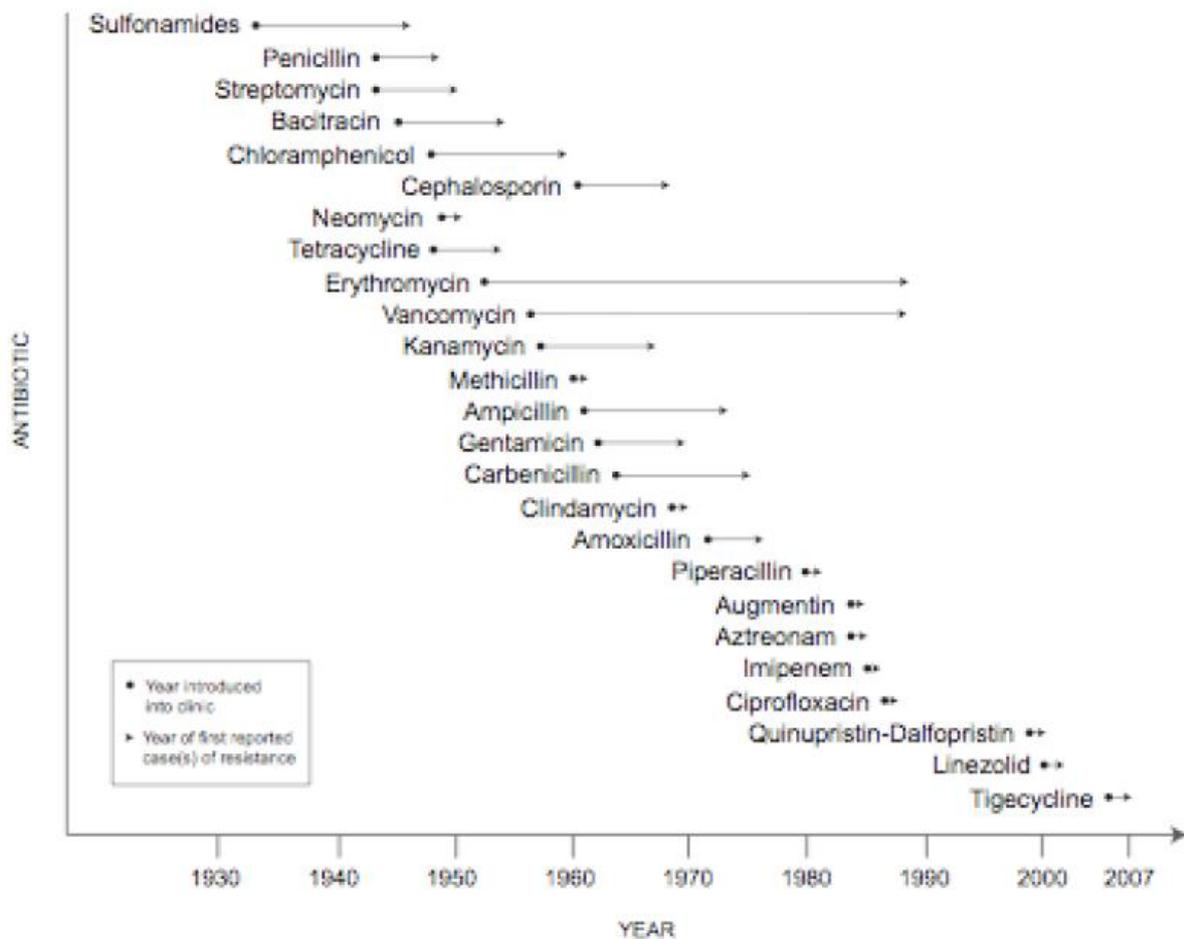
Bacterial resistance to antibiotics is a naturally occurring, evolutionary phenomenon. Yet resistance can be exacerbated in several ways.

Firstly, there is a well documented positive correlation between antibiotic use and the prevalence of resistance. Higher rates of resistance are seen in countries with higher antibiotic 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. There are two different aspects. One aspect is that physicians often prescribe antibiotics 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 found that approximately 55% of all the antibiotics prescribed in the US for upper respiratory infections were unnecessary (Taubes 2008). The second aspect is that physicians often prescribe broad spectrum antibiotics rather than more effective and targeted narrow spectrum antibiotics. There is a shared underlying reason for both aspects.

13

Figure 4 Correlation between penicillin use and prevalence of non-susceptible *S pneumoniae* (Albrich et al 2004)
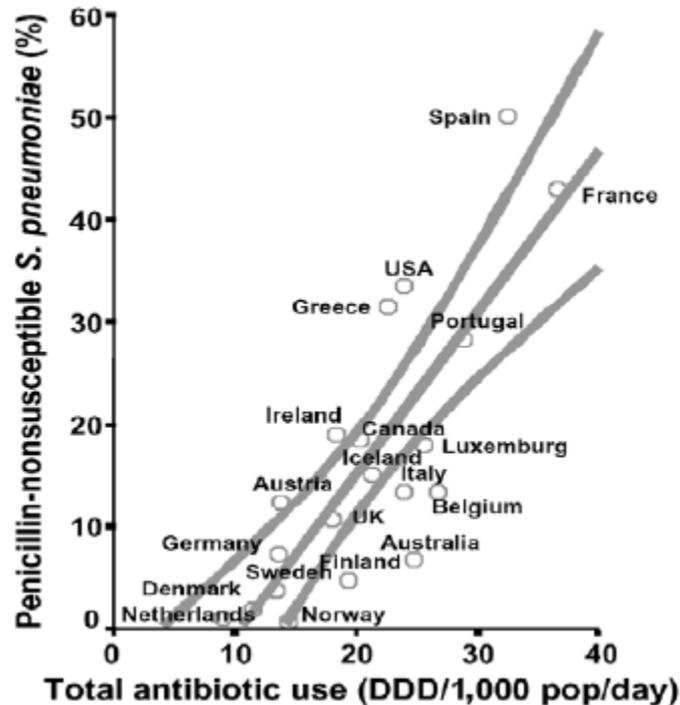
Rapid point of care (POC) diagnostics are not readily available to physicians to determine if the pathogen is viral or bacterial, and in the case of a bacterial infection, which bacterium is the culprit. The result is that most physicians faced with evidence of an infectious disease do not wait for test results that can often take days to come back, but err on the side of caution by prescribing broad spectrum antibiotics.

A third problem is patient non-adherence to the regime. This is a particular problem in developing countries where there are social and environmental factors that 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 antibiotics (Nugent et al 2008). It is a problem in developed countries also. Patients feel better and stop taking their medicine.

The fourth major problem is the misuse of antibiotics in farming and fishing. It has been estimated that approximately 70% of all antibiotics consumed in the US and 50% globally are given to livestock for non-therapeutic purposes (UCSUSA). 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 antibiotics from the quinolone class such as Ciprofloxacin. Quinolone antibiotics have been effectively used to treat infections in humans since the 1960s. However, when this class of antibiotics was approved for use in poultry husbandry in the 1990s, quinolone resistant strains of Campylobacter began to emerge (HSUS). The EU banned the use of antibiotics in farming in 2006 and the US is now taking steps to better regulate its use in farming. Legislation was introduced to Congress in 2009 with the hopes of banning the use of antibiotics in livestock production or at the very least better monitoring and regulating their use.

2.4. The current state of the pipeline of antibiotic development

Between the 1940s and the end of the 1970s pharmaceutical companies produced a steady flow of new antibiotics, 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 antibiotics and over 270 different drugs in clinical use. In the past three decades, however, only two new classes of antibiotics were discovered: oxazolidinones in 2000 and cyclic lipopeptides in 2003. Figure 5 tracks the timeline of the discovery of new classes of antibiotics.

More worryingly, in its technical report, the EMEA/ECDC (2009) identified only 15 systematically administered antibiotics with new mechanisms of action or targets that were under development in 2008, and that have the potential to meet the challenge of multi-drug resistance (MDR). Of these fifteen, eight had activity against Gram-negative bacteria, a positive finding given the fact that a several Gram-negative pathogens such as *Acinetobacter* 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 a number of mergers and acquisitions between companies. However, 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 antibiotics unit into a separate company called Basilea (Power 2006, Mossialos et al 2009). By 2005, Power (2006) estimates that the number of large pharmaceutical companies that had in-house R&D capacity for antibiotics had dropped to eight. IDSA estimates that currently only five major companies are actively involved in antibiotics R&D: GlaxoSmithKline (GSK), Novartis, Astra Zeneca, Merck and Pfizer.

The void left by 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 gap without help. The majority of products currently under development by SMEs were licensed from the larger pharmaceutical companies who were downsizing their own antibiotics 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 antibiotics 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.

Figure 5 Timeline of new antibiotic class discovery (EMEA/ECDC 2009)
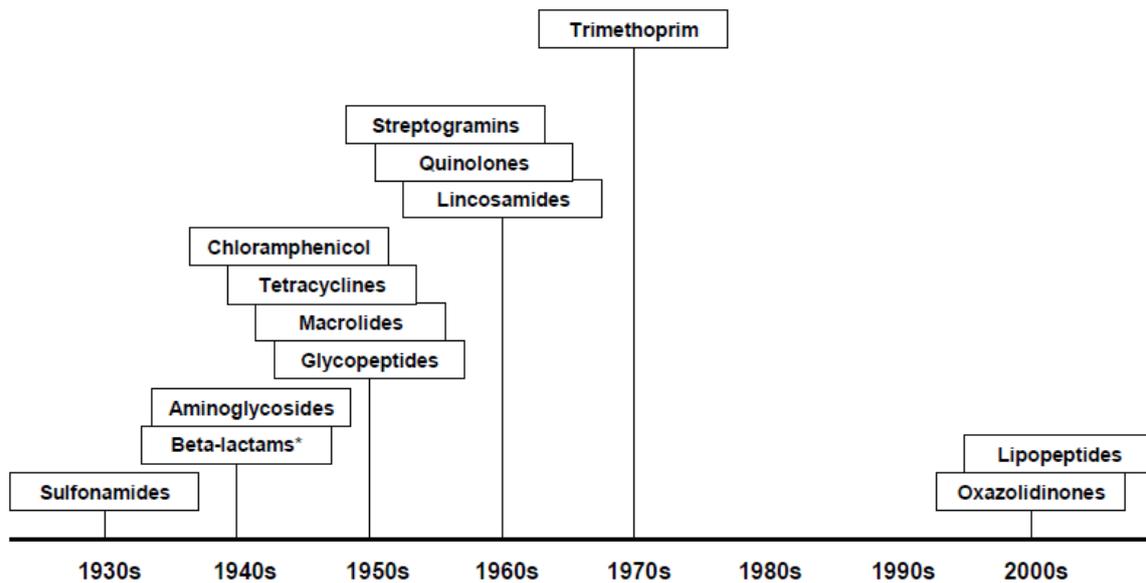
Of these 16, eight were found to have activity against Gram-positive pathogens and the other eight had activity against both Gram-positive and negative pathogens. Additionally they found several drug candidates in the early stages of development that had the potential to address the un-met need for Gram-negative pathogens, but they did not find any in the later development stages that solely targeted these pathogens. It is of course likely that many of these candidates will fail to make it to the market.

Boucher et al (2009) interviewed leaders in the field of anti-infective R&D at the following pharmaceutical companies: Abbott, AstraZeneca, Bayer, GSK, Lilly, Merck, Novartis, Ortho McNeil/Johnson & Johnson, Pfizer, Roche, Sanofi Aventis, Schering Plough and Wyeth. They found that between them the 13 companies that used to be leaders in the field of anti-infective drug discovery had only three new compounds (ceftobiprole, dalbavancin and PTK-0796) in the advanced stages of development.

These results of the EMEA/ECDC report (2009) confirm what Boucher et al (2009) observed in the US. The number of antibiotics 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 (i.e. administered intravenously) 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 incentivized to not only develop new antibiotics, but novel antibiotics that address the areas of unmet need. In order to address the problem one needs first to understand why it has happened.

2.5 The reasons for biopharmaceutical companies exiting antibiotics R&D

There are four major reasons why companies are exiting the market.

Low returns in the market

Although the market for antibiotics remains large there are a number of forces that exert downward pressure on market revenues leading to reduced commercial prospects for new antibiotics. The most important of these is the availability of generics. Two of the largest selling antibiotics (amoxicillin/clavulanate and ciprofloxacin) have generic counterparts. This type of competition keeps the prices for existing antibiotics low. The problem is compounded by the growing use of health technology assessment, 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, in reality it does not do so. Thus new antibiotics can expect to be priced below their true social value reducing the opportunity for companies to recoup their R&D investment.

Additionally, unlike chronic disease where treatment can last for months or even years, most antibiotics are used for short course therapy only. As a result, it is more profitable for pharmaceutical companies to invest in drug discovery for chronic diseases. In order to achieve a commercially attractive return on antibiotics, pharmaceutical companies would need to charge what payers may regard as unreasonably high prices in comparison to existing antibiotics. Because antibiotics are life-saving drugs, and therefore regarded as essential, they are subject to aggressive price control in many countries. 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 maximise their finite 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 relationship between the projected costs and revenues in terms of discounted cash flow. Table 1 shows the NPV of a number of different therapeutic classes, including antibiotics. From the Table below, it is clear that antibiotics are not particularly attractive relative to projects in other disease areas.

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

Therapeutic Class	Risk Adjusted NPV[4] x$1,000,000
Musculoskeletal	1,150
Neuroscience	720
Oncology	300
Vaccines	160
Injectable Antibiotic (Gram-positive)	100

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

Scientific difficulties surrounding antibiotic development

The main challenge to antibiotic 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. It was hoped that the complete sequencing of a bacterial genome would result in an abundance of targets, however, that has not happened. For example, GSK's success rate for antibiotic high throughput screening (HTS) was four to fivefold lower than for targets for other therapy areas (Payne et al 2007). The authors reviewed the available literature between 1996 and 2004 and found that whilst over 125 antibiotic 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 antibiotic discovery has shifted back to tried and tested approaches. Pharmaceutical companies are generating 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 antibiotic, but the underlying mechanism of action and therefore the path of resistance is unchanged and thus resistance continues to build.

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. A target based approach to drug discovery seems ill suited to antibacterials. For example, when attempting to find a broad spectrum antibiotic, what is really 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. So, while the target based approach has been productive in other therapeutic classes, such as HIV/AIDS, it has been less so for antibiotics.

The regulatory environment

Regulatory agencies such as the FDA in the US or the EMA in Europe can have a direct impact on antibiotic 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 antibiotic R&D.

In 2001 both the FDA and the EMA changed the requirements for clinical trials involving antibiotics. In clinical trials, new antibiotics are required to show non-inferiority compared to a currently registered antibiotic. Prior to 2001, regulatory agencies used a sliding scale to determine non-inferiority with the lower limit of the 95% confidence interval (or 97.5% confidence interval for a single-tailed test) for the new drug being less than 10-20% lower in efficacy than the reference drug. This is the delta value. The delta value used depended upon the anticipated cure rate and the number of evaluable patients expected for a particular indication. For antibiotics, the delta value was usually 15%.

The FDA had two particular concerns with this approach. Firstly, it believed that as a result of this sliding scale approach successively less effective comparators were being selected and this was leading to a presumed equivalence of what were in reality statistically and clinically in-equivalent products. This was 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. 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 trials 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 antibiotic and (b) substantially delayed the point of entry into the market. Recruiting a larger number of patients for clinical trials for rare indications would have been difficult, taking time 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 antibiotic from $100 million to $35 million. The effects of the proposed changes were dramatic. A number of pharmaceutical companies put their antibiotics programs on hold and at least two companies withdrew from the market entirely. As a result of these unintended consequences, the FDA held a meeting with the Pharmaceuticals Research and Manufacturers of America (PhRMA) and 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 avoided a potential crisis, but there were some lasting effects, including the delayed development of a number of new products. The exit of Eli Lilly and Bristol-Meyers Squibb from the field of antibiotics occurred around this time. A lot of uncertainty remains around the requirements for clinical evaluation.

Restrictions on antibiotic use
A number of polices have been implemented to curb the use of antibiotics. 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 antibiotics, were put into effect including the distribution of booklets, television and radio spots, and a website. The campaign was successful at decreasing the rates of antibiotic consumption: total sales decreased by 11.7% and 9.6% respectively during the 2000-2001 and 2001-2002 December-March campaign periods.

This, however, also highlights a tension between two aims of antibiotic management. One the one hand, policy makers want to restrict the use of antibiotics to prevent the spread of resistance, while on the other, they are trying to promote the development of novel antibiotics to combat resistance. The result is what Power (2006) describes as a vicious cycle. Market restrictions stifle innovation

decreasing the number of antibiotics being developed. As a result, health care systems become more dependent on existing antibiotics 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 antibiotic restrictions. Source: Power 2006
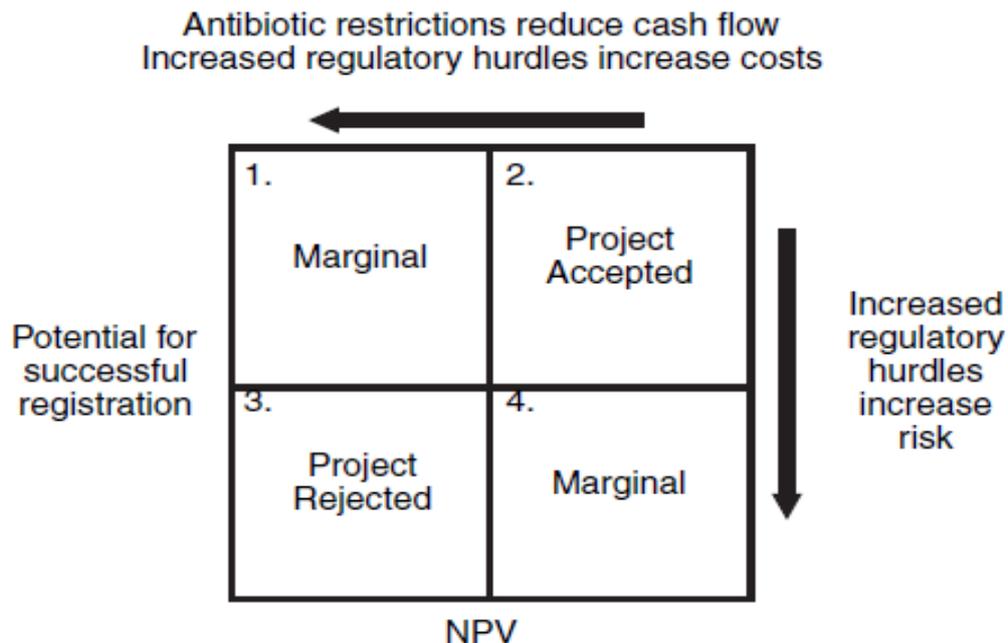

Figure 6 taken from Power (2006) shows the relationship between the NPV and the impact of both regulatory factors and use restrictions on the likelihood of a company proceeding with a project. Restrictions on the use of antibiotics decrease the potential for profit while increased regulatory hurdles increase development costs and decrease the chance of successful registration, pushing a project from "accepted" to "marginal". Of course, an antibiotic to which resistance will develop quickly will have a shorter clinical life compared to one for which resistance is slower to develop. In theory an innovation could benefit from restrictions on use that slow the spread of AMR in a particular time period if overall long term sales were much higher. This would depend on the extra length of life, the length of the patent, the price of the drug, and the likelihood of competitive entry eroding that price or market share. If, as seems plausible, the build up of resistance is largely a function of the cumulative volume of use of an antibiotic, 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 treatments for infectious diseases (Philpson 2000). However, they note that limiting use of antibiotics to slow down the build up of AMR discourages R&D into new antibiotics 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

antibiotics "even though such limits are the appropriate policy in the absence of technological change." (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 policy must tackle both. In other words, restricting use of existing antibiotics makes sense as we don't know how many new antibiotics we will get, and when a new antibiotic appears it will be subject in turn to restrictions, because we don't know when the next one will come along. Another strong policy lever is therefore required to stimulate R&D, as use restrictions reduce R&D incentives.

3. Modelling Potential Solutions

3.1 Disincentives and market failure in other markets
Many of the disincentives that pharmaceutical companies face in the market for antibiotics are not unique. Similar market failures and 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 benefits of drugs for paediatric use. The policies enacted or put forth in an attempt to correct for these market failures will be discussed in the next section as possible solutions for antibiotics. We initially set out the similarity of the challenges.

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. One measure of the magnitude of the health disparity between rich and poor countries is the difference in average life span. In rich countries it is 77 years, while in poor countries it is 52 years (Widdus 2001). There are a number of the reasons why large pharmaceutical companies find markets for neglected diseases unattractive and some are the same as those discussed for antibiotics. These markets have low returns as the people who need the drugs the most 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 neglected disease programmes (Wheeler and Berkley 2001, Hecht 2009).

Orphan drugs
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 in the US, 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 in the EU. The main problem with orphan diseases is the low number of potential patients. 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). A similar problem is observed with antibiotics. New antibiotics tend to be reserved to maintain their effectiveness against resistant pathogens. This reduces their use and the potential to earn a viable return on the R&D investment.

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 and low profit market, a view they similarly hold for the market for antibiotics.

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. Children have been termed "therapeutic orphans". 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 program would have to be undertaken later, after the drug has a licence for adults; and (ii) the market is too small to justify such an investment (Boots 2007, Grieve et al 2005). In this case, pharmaceutical companies need to be incentivized to perform additional paediatric studies.

3.2. Solutions to address market failures

A number of solutions have been proposed to correct the types of market failure identified above. Many, if not all, have also been proposed as solutions to the antibiotics problem, discussed in great detail in the literature and put forward as solutions at the conference in Stockholm last year. To date, however, there has been no attempt to our knowledge to narrow this list down, prioritizing them in terms of their impact or of the size needed to incentivize companies to undertake additional antibiotics 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, and the implications of the results are discussed as well. The ultimate objective of this paper is to help move the AMR discussion forward by presenting a realistic and feasible short list of incentives. The incentives discussed in this paper are already part of a shortened list. They 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 antibiotics problem. They are:

- advance market commitments (AMCs);
- priority review vouchers (PRVs) and the fast track option (FTO) variation of the PRV;
- patent extensions;
- transferable patent extensions;
- product development partnerships (PDPs),
- tax incentives, direct funding of R&D, funding and regulatory support for pre-competitive research consortia'
- the call option for antibiotics (COA);
- orphan drug legislation;

- Project BioShield and related CBRN counter-measures.

The incentives can be broken down into two categories: push and pull. 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. The push incentives discussed here are direct funding of R&D, tax incentives, product-development partnerships (PDPs) and funding and regulatory support for pre-competitive research consortia. Pull incentives seek to mimic the market incentives that exist for commercially lucrative pharmaceutical products. Pull incentives included in this paper are advanced market commitments (AMCs), patent extensions, transferable patent extensions, and fast track and priority review vouchers.

Push incentives can be attractive to SMEs because they typically have limited resources and funding for R&D. However, they have a number of disadvantages. For example, they are subject to principal-agency problems, specifically information asymmetry 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 lack the motivation to continue development once they have reached the end of the push funding, particularly if they have exaggerated its likely scientific prospects in order to get the funding. 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 successful products. The information asymmetry does not give rise to a moral hazard problem. Because developers only receive a reward after a product has been developed, they have a strong incentive to be realistic about their prospects. 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 wasteful investments in research lines that are not likely to yield a viable product. 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 this particular instance, a pull incentive can begin to suffer from the same problems as a push incentive.

Additional challenges in organising a pull incentive 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 nominal and real cash than push rewards in order to reward investors for the risk of failure; (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 and partly about the likelihood and ability of the funder(s) to honour the commitment (Grabowski et al 2008).

There is growing recognition that neither push nor pull incentives alone may be able to cost-effectively stimulate antibiotic 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 uncertainty (what are the chances of getting to a drug candidate that meets likely success criteria?). Either may be able to address development uncertainty (given a drug candidate that meets likely success criteria, what are the chances of getting it successfully licensed for marketing?) The consensus coming out of the conference in Stockholm was that a hybrid approach will be necessary to stimulate and foster R&D for antibiotics. Examples of hybrid approaches include orphan drug and paediatric legislation, Project BioShield and the related CBRN counter-measures in the US, and the call option for antibiotics. These combine both push and pull incentives and thus can in theory complement the advantages and disadvantages of both types of incentive. Perhaps most importantly, however, they spread the risk between the developer and funder.

3.3 Modelling the NPV of antibiotic development

To date, there has been no attempt to determine the size of the various incentives needed to make the NPV for antibiotic 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, for example, what an AMC for antibiotics 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, i.e. provide policy makers and industry leaders with a short list of incentives that should be considered realistic and feasible to implement.

The baseline case for the development of an antibiotic[5] was modelled using data from publically available, peer reviewed literature. Where possible, antibiotic specific data was used, otherwise antibiotic data was assumed to be similar to that of a new molecular entity (NME). Table 2 provides a list of the references used for the baseline case variables, the variables, and indicates if they were antibiotic specific or not.

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[5] The antibiotic specific data used for the model is for a broad spectrum antibiotic, however, the policy makers are most likely to be interested in Gram-negative antibiotics. It is unclear how this might affect the model and any of its results. Our view is that costs may be similar, but revenues may be lower.

Table 2 References used for the baseline model

Variables		Reference	Antibiotic Specific
Phase lengths (years)	Preclinical: 5.5	Paul et al 2010	No
	Phase 1: 1.5		
	Phase 2: 2.5		
	Phase 3: 2.5		
	Approval: 1		
Cost per Work In Progress (millions €)	Preclinical: 14.11	Paul et al 2010	No
	Phase 1: 11.44		
	Phase 2: 30.51		
	Phase 3: 114.41		
	Approval 30.51		
Probability of Success (preclinical[6])	0.35	Paul et al 2010	No
Probabilities of success (Phase I-approval)	Phase 1: 0.582	DiMasi et al 2010	Yes
	Phase 2: 0.522		
	Phase 3: 0.786		
	Approval: 1		
Sales figures and product life length		DiMasi et al 2004	Yes
Discount Rate	11%	DiMasi et al 2003	No

The assumed contribution rate, net of sales and marketing costs and the cost of goods, was set at 50% and each of the three components made up 16.7%. Global peak year sales (reached in year 9) were $389 million or €297 million (DiMasi et al 2004). Figure 7 plots the sales curve data used in the model.

All US dollar cost estimates were converted to Euros using a 0.7627 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).

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[6] 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
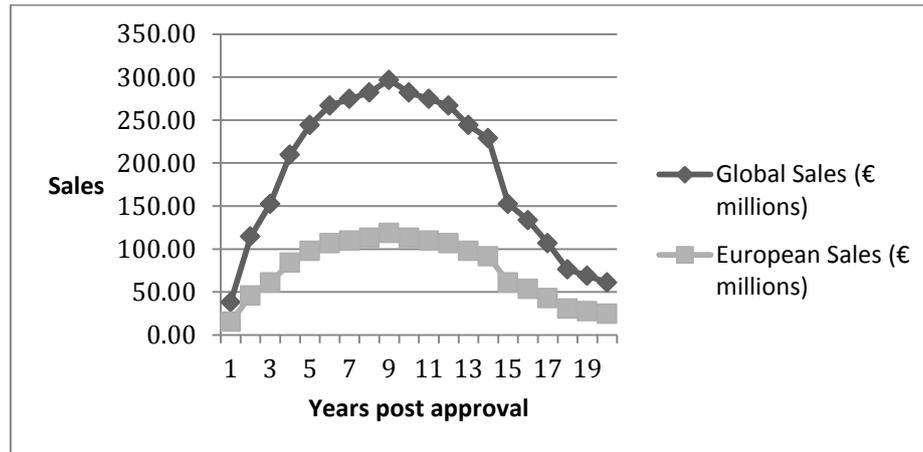
All the variables were entered into a model built in Excel, with each cell representing a year. To accommodate half years in the product development timeline it was assumed that the first six months of the year were spent on preclinical R&D for example, while the remaining six months were spent conducting Phase 1 R&D. One half of the spreadsheet included the costs of the various stages of development per year, while the other half included global sales data as well as sales data for Europe and the rest of the world (see below). The cost of goods, sales and marketing costs, and taxes were subtracted from the sales figures to calculate the total revenue earned per year. A separate line was added to accommodate the various inputs required to model the incentives. The NPV and internal rate of return (IRR) were calculated using the Excel functions.

The baseline NPV calculated for an antibiotic was -€31.5 million and the internal rate of return (IRR) was 10%, i.e below the cost of capital used to discount the cash flows.

The purpose of the model was to determine the size and timing of the different incentives discussed below needed in Europe to increase the NPV of antibiotic R&D to $200 million or €153 million. This target NPV was chosen because it would make antibiotic development competitive, in terms of its NPV and IRR, 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 incentives implemented in the European market only, 2009 IMS data was used to estimate the size of the European market for pharmaceuticals thus allowing global sales data, as well as sales and marketing costs, and revenue to be divided into two categories: Europe and the rest of the global market. 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 antibiotics to address unmet need in Europe first, it may consume more than a 30% share of these newly developed antibiotics. To account for this the model assumes that the European market makes up 40% of the relevant part of the global market for antibiotics.

Advanced Market Commitments (AMCs)
An AMC is a commitment by a government or a private/international organization 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 (Batson 2005, Brendt and Hurvitz 2005) 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 a developed world market for drugs. 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%.

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 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, close 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 appealing in that it would be easy 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. Alternatively, it could discourage participation as there is no incentive to continue R&D if a rival company is close to completion or has successfully developed a drug or vaccine. Most importantly, however, is the fact that a winner takes all approach is ill-suited to the process of drug development. The scientific process rarely results in the first product being clinically more effective or safer for all patients than all others products that follow. Rather, there typically will be a number of related products each with different risks and benefits. If a superior product was subsequently developed and the AMC was already pre-committed to provide a clinically inferior product then a major ethical problem would appear (Berndt and Hurvitz 2005).

The "multiple winners" approach better encourages competition but would be much more complex to administer. The size of the reward each company receives is smaller, thus decreasing the strength

of the R&D incentive and potentially acting as a disincentive from participating. If developers' feel they will not be rewarded enough, they may stop R&D before a product is successfully developed.

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 difficult to combine with a multiple winners approach (Berndt and Hurvitz 2005).

Determining the size and price of the AMC are the most difficult and critical task. 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 an AMC of $3.1 billion based on the sales revenues of successful products.

It is important that an effective price is chosen. If the price is too high, it could result in an inefficient 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 high 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 well 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).

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). 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 antibiotics 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. 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.

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 to the AMC. Exceptions could be made, however, if countries with the highest burden are unable to pay their proportionate share. Some of those 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 antibiotics meet the criteria outlined by the AMC, dispute resolution and distribution of the new antibiotic(s).

Modelling Results for the AMC

Two versions of an AMC were modelled. The first was 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 antibiotic was available for sale in the rest of the world, European sales revenue was set to zero for the duration of the AMC. Sales and marketing costs were also reduced for the length of the AMC. Once the AMC expired, as with AMCs for neglected diseases, the developer agrees to sell the new antibiotic in Europe at cost. Thus once the AMC for the antibiotic expired, it followed the sales curve for antibiotics set by DiMasi et al (2004) but sales revenues in Europe were decreased by 50% to reflect the lower price.

The second AMC modelled was 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 revenue was 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 sale revenue in Europe reduced by 50%. The results of the modelling exercise for the one and five year AMCs are shown in Table 4.

Table 3 Results for AMCs

	Size of AMC (€)	Baseline NPV (€)	New NPV (€)	Baseline IRR	New IRR
1 year AMC	980 million	-31.5 million	153.89 million	10%	17%
5 year AMC	1.38 billion (275 million per year)	-31.5 million	156.52 million	10%	16%

The CGD AMC Working Group estimated the size of an effective AMC to be $3 billion or approximately €2.3 billion. The results of the modelling exercise, however, suggest that the size of the incentive can be smaller than this, primarily because there is substantial sales revenue from non-European markets, notably the US. However, several different forms of AMR may need to be targeted requiring multiple AMCs.

Priority Review Vouchers and the Fast Track Option

The priority review voucher (PRV) is an incentive for R&D for neglected diseases, 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. 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 (Ridley et al 2006). FDA "priority review" is normally only for drugs that tackle a life-threatening condition. In order to use it, the voucher holder must notify the FDA 365 days in advance of filing the new drug application (NDA) (Grabowski et al 2008).

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 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.

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

If there was an equivalent to a PRV in the EU that allowed a drug to be launched six months earlier, the result of this is that (a) there is a time benefit as take up begins six months earlier, and (b) it spends an additional six months on the market before it goes off patent. This latter, and most important, effect is modelled by attributing six months of revenue from a blockbuster drug before it goes off patent to the antibiotic revenue stream, i.e. there is a lump sum cash input in year 12 which represents additional on-patent revenue generated by the blockbuster drug as a result of entering the market six months earlier.

PRVs are market specific, i.e. a PRV granted by the EMA for a drug has no bearing on how quickly that drug enters other markets, the estimate of the revenue needed from a PRV to increase the NPV to €153 million must come from a drug in the European market.

The results of model indicate that a drug needs to generate approximately €2.5 billion in revenue in the last six months of its patent if it were to meet the criteria of achieving an NPV of €152.52 million and the new IRR is 14%.

However, it is important to take into account the other effect of a PRV, which is shifting the sales curve forward so that companies begin to earn revenue sooner. Using IMS sales data for 2009 for Lipitor, the top selling drug worldwide which earned $2.9 billion or €2.2 billion in Europe, we can roughly estimate the value of shifting the sales curve forward had Lipitor been priority reviewed (IMS 2010). If we assume that peak year sales (in this case assumed to be €2.2 billion) were reached in year 5 and continued for 7 years thereafter, using an 11% discount rate, the value of shifting the

sales curve forward is approximately €1.7 billion. This could offset some of the €2.5 billion needed to increase the NPV to €153 million and thus make a PRV an attractive incentive to large pharmaceutical companies who have potential blockbusters in their portfolio and to smaller companies who can sell a PRV to a larger company.

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) it is, however, an R&D funding mechanism, rather than an incentive, for neglected disease R&D. Companies are allowed to purchase an FTO for a drug of their choice and the funds raised as a result are used to support neglected disease R&D. Like the PRV, the FTO is also tradable to other companies. To optimize the prices of FTOs, a limited number (one or two vouchers each year) could be sold via an auction. However, an FTO could operate as a pull mechanism in the same way as a PRV. A company bringing an antibiotic 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 conditions such as diabetes and obesity.

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, respectively and that the total development time was almost 3 years shorter for fast track 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

FTOs can function as a pull incentive or as a push incentive. For our modelling we assume that a company invests into antibiotic R&D a proportion of the revenue it could generate by selling or using a FTO. For modelling purposes we assume that the company invests 50% of the expected FTO returns to boost its own R&D program for antibiotics. We illustrate using the money at different stages of development from preclinical through to approval and for each phase, the money is assumed to be distributed equally across the entire length of the phase.

Moran (2005) estimated that if Eli Lilly had been able to fast track Prozac® they would have earned, in potential returns $500 million after-tax (€381.35 million) or $761 million after-tax (€580.41 million), depending upon the stage of development that the fast tracking could have taken place. These two estimates were used to determine the impact of an FTO on the NPV for antibiotic R&D if only 50% of these expected returns were invested in antibiotic R&D. The first scenario assumes that €190.7 million were reinvested (50% of €381.35 million) and the second assumes that €290.2 million were reinvested (50% of €580.41 million). The results are presented in Tables 7 and 8, respectively.

Because FTOs are market specific, i.e. an FTO for a drug in Europe does not apply to the US, any revenue generated from fast tracking that is then reinvested in antibiotic R&D comes solely from the European market.

Table 4 Results for an FTO with €190.7 million reinvestment

Development phase	Length of phase(years)	Size of incentive/year (€)	Baseline NPV (€)	New NPV (€)		New IRR
Preclinical	5.5	34.62 million	-31.5 million	105.70 million	10%	21%
Phase I	1.5	127.13 million	-31.5 million	63.71 million	10%	14%
Phase II	2.5	76.28 million	-31.5 million	44.85 million	10%	13%
Phase III	2.5	76.28 million	-31.5 million	27.93 million	10%	12%
Approval	1.5	127.13 million	-31.5 million	15.98 million	10%	12%

Table 5 Results for an FTO with €290.2 million reinvestment

Development phase	Length of phase (years)	Size of incentive/year (€)	Baseline NPV (€)	New NPV (€)	Baseline IRR	New IRR
Preclinical	5.5	52.76 million	-31.5 million	177.60 million	10%	Could not be calculated
Phase I	1.5	193.5 million	-31.5 million	113.42 million	10%	17%
Phase II	2.5	116.08 million	-31.5 million	84.69 million	10%	15%
Phase III	2.5	116.08 million	-31.5 million	58.95 million	10%	13%
Approval	1.5	193.5 million	-31.5 million	40.77 million	10%	12%

The results of the model for FTOs show the impact of funding early stage research. In both cases funding the preclinical stage and phase I had more of an impact on the NPV than any funding of the later stages. This is primarily due to the effect of discounting. Similarly, the size of the incentives needed to increase the NPV to a competitive level is 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.

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. In the US, priority review would result in an 8 month time gain compared to standard review. An FTO, however, could potentially yield 1-2.5 years saved (Moran 2005).

The scope of the FTO is wider than that of a PRV. PRVs are available to drugs that would normally not qualify for priority review as defined by the FDA and Moran (2005) estimates that this represents 75% of all new drugs approved in the US. On the hand, an FTO is available to all drugs that would not normally qualify for fast tracking which is approximately 90% of all new drugs in the US and includes drugs that qualify for standard or priority review. As a result, FTOs would result in more drugs reaching the market sooner compared to a PRV (Moran 2005). A resulting disadvantage applicable to both PRVs and FTOs is that health systems will be required to purchase these drugs earlier, and this imposes an additional cost burden to the health care system. (Moran et al 2005). One assumes, however, that health care systems will only use drugs that bring value (in terms of patient and other benefits) relative to price.

Critics of fast tracking and priority review fear that rapid review comes at the expense of safety. Philipson et al (2005), however, find that the net effect was a gain to 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).

The FDA already has priority review and fast-track programs in place. Implementing these programs in the EU may not make as much sense. For example, granting priority review through the EMA approval process is less useful than granting priority review through the FDA approval process as EMA approval times are already shorter and the drug must also be approved for pricing and reimbursement purposes at the member state level. A more relevant incentive might be to grant companies who have developed an antibiotic that targets unmet need an accelerated review through Member States pricing and reimbursement process for another drug in its portfolio. As with the PRV in the US, companies would have to pay a user fee to ensure adequate resources are available for the accelerated regulatory review[7].

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[7] We understand that a forthcoming article by Ridley and Sanchez in the September 11, 2010 issue of the Lancet develops and discusses a European version of a PRV.

Intellectual Property Rights (IPR) play an important role in stimulating R&D and driving innovation. As a result, a number of proposed incentives are related to IPR.

Intellectual Property (IP) extensions

Because companies apply for patents early on in the drug development process, the effective patent life 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), 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 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 of 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 past 10 years of effective patent life were in the last five years that were 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 2 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 had 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 3 years of exclusivity for the approval of a new indication for an already approved antibiotic and five years for the approval of previously unapproved older antibiotic (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 additional six months is given even if there is no demonstrated benefit in

children. The reward is provided in exchange 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 which is being sought.

- The Orphan Drug Act (ODA) (discussed below).

Modelling IP extensions

Two 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, and a two year extension that is available to companies who file a PIP on an orphan drug. 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 NPVs increase and was it enough of an increase to make the NPV for antibiotics R&D competitive.

An IP extension delays competition from generics and follow-on drugs, 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. Sales during the period of extended exclusivity are assumed to be the same as sales in the last year of the patent, year 12. For the six month IP extension, sales in year 13 are equivalent to half a year sales from year 12 plus half a year of sales from year 13. For a two year IP extension, the sales for years 13 and 14 are the same as in year 12.

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 5 presents the model results for IP extensions.

Table 6 Results for IP extensions

	Baseline NPV (€)	New NPV (€)	Baseline IRR	New IRR	Size of effect on NPV (€)
6 month IP extension	-31.5 million	-31.35 million	10%	10%	0.15 million
2 year IP extension	-31.5 million	-30.75 million	10%	10%	0.6 million

IP extensions seem to be ineffective at increasing the NPV to a competitive level. Neither the six month nor the two year IP extension succeeded at making antibiotic R&D a worthwhile investment. This is primarily due to the effect of discounting and the timing of the incentive, i.e. towards the end of the product life.

Outterson et al (2007) argued against IP extensions in part because antibiotics 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 antibiotic R&D. They believe that the prospect of antibiotic 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 any decision as to *where* R&D should take place in order to best generate replacement revenues. Our modelling suggest patent extensions for antibiotics will not provide a strong incentive for antibiotic 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 antibiotic 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 transferable IP extensions believe that it provides pharmaceutical companies with a significant incentive to invest in antibiotic R&D, irrespective of their size. For large pharmaceutical companies, the prospect of extending patents on a lucrative drug is very appealing as the returns 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 until patent expiry in 2010, a six month extension would be worth $3.1 billion to Pfizer. For smaller companies without their own blockbuster drug, selling the IP extension to a larger company can be profitable for them as well.

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 antibiotics. 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 antimicrobial research. They believe that transferable IP extensions will cost between $8.7-$11.9 billion per newly developed antibiotic. This far exceeds the current estimate by DiMasi et al (2003) of $800 million required to develop an NME.

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, they assume a two year extension. However, the period of IP 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 ¾ 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 raising 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 antibiotic R&D under a transferable IP extension program. 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.

<u>Modelling Results for Transferable IP extensions</u>

The transferable IP extension was modelled as if it was applied to a blockbuster drug coming off patent just as the antibiotic was being launched. Any revenue generated by the extension is attributed to the first few years the antibiotic is on the market. Three different lengths of extension were modelled to determine the approximate amount of revenue 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 revenue 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 (€)	Baseline IRR	New IRR
6 month transferable IP extension	800 million	€3.2 billion	-31.5 million	154.09 million	10%	16%
2 year transferable IP extension	850 million (425 million per year)	€850 million	-31.5 million	155.92 million	10%	16%
5 year transferable IP extension	1 billion (200 million per year)	€400 million	-31.5 million	158.85 million	10%	16%

Despite being contentious, transferable IP extensions could be a very effective and feasible incentive for antibiotic R&D. As with PRVs, a six month transferable IP extension is likely to be an

unrealistically low incentive because no drug currently on the market earns enough in Europe to fill the gap in revenue. 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 antibiotic 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 extension appealing over this period. These extensions would also appeal to SMEs as they would be able to sell them to a number of larger companies who already have blockbuster drugs on the market.

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. Most push incentives are discretionary. 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 not include some 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.

In the discretionary area, 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 of 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 Medicine 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 and academia, as well as the public and private sector-including 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 portfolio of projects, rather than donors funding specific projects. This enables the PDP to be held accountable for the outcomes 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 to impress donors. However, in the longer term it will be expected to deliver.

The two main advantages of PDPs are that they reduce the risk associated with R&D by spreading risk across a range of products or a portfolio 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 is a simpler push mechanism. In both the EU and the US there is a long history of government funding of scientific research. In the US, the 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 funding mechanism is the FP7, which has a programme dedicated to addressing the problem of AMR (Mossialos et al 2009). However, there is a question as to whether or not the government is best suited for determining the viability of a project or projects beyond basic and the 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 as consortium this 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 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 results for an FTO highlight the value of push incentives. We can reinterpret the results in Table 4 and Table 5 as indicating the potential value of a PDP with (respectively) €190.7m and €290.2m to invest. If the money was put into early stage projects then it could be expected to achieve an approved new antibiotic. The results suggest that any early stage funding or support would go a long way towards impacting the NPV for antibiotic R&D and should be included in any proposals for stimulating antibiotic 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 due 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 product 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 because either their patient population exceeded 200,000, as happened with HIV/AIDS, or 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 this regulation could have a dampening effect on the strength of the incentive, especially 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 extend this program to cover antibiotics. Target pathogens should be identified and any resulting antibiotics would be granted orphan drug status and subject to the same push and pull incentives as the other drugs. 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 would vary from country to country. For example, France fast tracks pricing and usage decisions about orphan drugs but England and Wales does not, applying the same critiera 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 developers of an orphan drug. This is modelled here as an increase in European revenue. Specifically, of interest is the percentage increase in European revenue needed to increase the NPV to €153 million. To determine this, the revenue line was separated into two according to market share: Europe (40%) and the rest of the world (60%).

Sales and revenue in the rest of the world are unaffected by this period of exclusivity. A further assumption is that the volume of antibiotics sold has not changed. Rather than looking at increased sales in Europe, the purpose is to model an increase in price as a result of market exclusivity.

The results of the model indicate that revenue in Europe must increase 4.2 times or by over 300% in order to make the antibiotic R&D competitive. Doing so increases the NPV to €159.73 million and the new IRR = 15%. 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 antibiotic" scheme.

Project BioShield and CBRN legislation in the USA

We can contrast the success of orphan drug legislation with that of CBRN countermeasures in the USA. Following the anthrax attacks in the United States 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 Department of Homeland Security (DHS) and the HHS, as well as heads of other federal agencies determine that there is a CBRN threat. The Secretary of the 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 in particular, 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). Similar to orphan drug legislation, Project BioShield contains a mix of push and pull incentives.

Project BioShield has come under criticism for a variety of reasons. Firstly, critics argue that the sizes of 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. 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. Project BioShield does not offer any 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 2006-07).

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 anthrax vaccine.

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)

In their report, Mossialos et al (2009) describe a COA-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 (COV) model first proposed by Brogan and Mossialos (2006) in which a potential purchaser buys the rights, 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 has only lost the premium, i.e. the price of the option paid to 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 get 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. An appropriately priced premium could spur a development race and 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.

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. Similarly, 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 antibiotic R&D

The results of the model only tell us half the story. We need to look at the cost of the programs relative to the gains that could result from investing in programs to stimulate the creation of new antibiotics in Europe. For example, the EMEA/ECDC report (2009) estimated that AMR to selected bacteria resulted in approximately 25,000 deaths in 2007. However, it only valued these lives on the basis of the productivity impact on the economy of losing the output from workers dying early.

If each life is given a value based on the value of a Quality Adjusted Life Year (QALY) or the value of a statistical life, then values closer to €1 million per death may be more appropriate. The total cost of these deaths could be equivalent to €25 billion. Suppose that €1.3 billion was spent on an AMC for an antibiotic. Further suppose that this antibiotic was able to reduce the number of deaths by 10% or 2,500 per year. The result would be a savings of €2.5 billion per annum, compared to a one off cost of €1.3 billion. A 10% reduction in deaths also results in additional savings elsewhere such as decreased in-and out-patient hospital costs and increased worker productivity. Investing in incentives for stimulating antibiotic R&D is likely to bring about not only enormous health gains, but also significant cost savings. However, more work is required to understand the true economic and health burden and the potential impact on this burden of new drugs.

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 EU 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.

Our recommendations are as follows:

- Our preference is for a hybrid policy based around treating drugs for AMR in a similar way to Orphan Drugs. It 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. Although push measures and regulatory advice and review will be an important part of such a package, the critical element, as with orphan drugs, will be the market power that such a measure would bring. 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 account of the growing costs of AMR in any assessment of value.
- Such a hybrid would encourage companies to seek sales volume. Use of point of care diagnostics and recognition of the importance of tight controls on use as part of any premium pricing arrangement may be ways to avoid any adverse consequences. An important emphasis should therefore be on the development of rapid point of care diagnostics to ensure that drugs are only used on patients for which they will be effective.
- We do not think a European PDP for antibiotic drugs is a sensible option at the present time. PDPs have worked extremely well in generating pipelines in the absence of commercial incentives. It is better for Europe to invest in generating the commercial incentives for drug R&D. A PDP for diagnostics may make more sense given that it is likely to be much harder to increase commercial incentives in this area.
- An upfront payment for registration (rather than for volume of use) in the form of an AMC "prize" or a PRV or a transferable IP extension would make sense as an alternative to an

Orphan Drug type hybrid. All three incentives would reward the launch of an effective drug rather than actual volumes of use. A PRV and a Transferable IP are similar but a PRV might be more acceptable as it would ensure earlier access to drugs. 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 antibiotics, and the need for companies to generate attractive returns in their R&D investments. A major obstacle however is that they are expensive, requiring a large pot of central EU funding or as a diffused burden on EU Member States health systems.

- An area worth further research is how many lives would be saved by bringing new antibiotics to the market. Policy makers and all stakeholders need a better sense of what the pay-off would be for investing in antibiotic R&D. If this was known, it might help to put the cost of potential incentives into perspective.

- The TransAtlantic Task Force dialogue between the US and Europe is very important. 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 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 the Task Force 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 in different 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.

- The TransAtlantic Task Force 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 antibiotics 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.

The Commission will have to decide whether the EU can afford to wait until the end of 2011 or whether it should act now. A related decision will be whether or not the Commission decides to take action on its own or wait until the US is ready to move forward as well. When and if the Commission decides to move forward there are two significant obstacles it will have to overcome. Firstly, it will have to address scepticism from Member States that it is not qualified to tackle this problem and secondly, it will have to consider that there is little funding currently available for the market based incentives proposed in this paper. Our recommendation to the Commission is therefore to establish a task force whose membership includes not only Member States, but also key players from the pharmaceutical industry, EMA, ECDC, academia etc. The task force will then be charged with working

through these issues, as well as coming up with proposals for implementing incentives for antibiotic R&D. Lastly, but by no means least, there has been no similar review to our knowledge of the problems for R&D in Europe into point of care diagnostics. Such a review is needed as a matter of urgency.

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