

Policies and incentives for promoting innovation in antibiotic research

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AR; antibiotic resistance

NB: Contains hyperlinks for ease of navigation. Select CTRL + Click to follow links.

ABBREVIATIONS

ABS	Antibiotic stewardship
AMC	Advanced Market Commitment
BARDA	Biomedical Advanced Research and Development Authority
CA-MRSA	Community-acquired MRSA
CA	Community-acquired
CAP	Community-acquired pneumonia
CDC	US Centers for Disease Control and Prevention
CHMP	Committee for Human Medicinal Products at EMEA
CMS	Centers for Medicare and Medicaid Services
COA	Call Options for Antibiotics
cSSSI	Complicated skin and skin structure infections
DG	European commissions directorate general
DG SANCO	Directorate General for Health and Consumer Affairs
DNA	Deoxyribonucleic acid
DRSP	Drug resistant <i>Streptococcus pneumoniae</i>
EARSS	European Antimicrobial Resistance Surveillance System
EASAC	European Academics Scientific Advisory Council
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EDCTP	European and Developing Countries Clinical Trials Partnership
EFPIA	European Federation of Pharmaceutical Industries
EIB	European Investment Bank
EIF	European Investment Fund
EMBARC	European Consortium of Microbial Resource Centres
EMA	European Medicines Agency
ESAC	European Surveillance of Antimicrobial Consumption
ESKAPE	<i>Enterococcus faecium</i> , <i>Staphylococcus aureus</i> , <i>Klebsiella</i> and <i>Enterobacter species</i> , <i>Acinetobacter baumannii</i> , and <i>Pseudomonas aeruginosa</i> ,
EU	European Union
FDA	US Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
FIND	Foundation for Innovative New Diagnostics
FP7	European Union's 7 th framework programme
FRG	Functional Resistance Group
GAVI	Global Alliance for Vaccines and Immunization
GPL	General Public Licences
GSK	GlaxoSmithKline
HAP	Hospital-acquired pneumonia
HHS	US Department of Health and Human Services
HIV/AIDS	Human immunodeficiency virus / Acquired immunodeficiency syndrome

IDSA	Infectious Disease Society of America
IMI	Innovative Medicines Initiative
IP	Intellectual Property
MDR	Multidrug-resistant
MMV	Medicines for Malaria Venture
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MRSE	Methicillin resistant <i>Staphylococcus epidermidis</i>
NGO	Non-governmental organisation
NIAID	US National Institute of Allergy and Infectious Diseases
NIH	US National Institutes of Health
NCE	New Chemical Entity
NME	New Molecular Entity
NPV	Net present value
ODA	US Orphan Drug Act
OECD	Organisation for Economic Co-operation and Development
PCR	Polymerase chain reaction
PDP	Product Development Partnership
PhRMA	Pharmaceutical Research and Manufacturers of America
PIP	EU Paediatric Investigation Plan
PK/PD	Pharmacokinetics / Pharmacodynamics
POC	Point of care (diagnostics)
PDP	Product Development Partnerships
PRSP	Penicillin-resistant <i>Streptococcus pneumoniae</i>
PTK 0796	7-dimethylamino, 9-(2,2-dimethyl-propyl)-aminomethylcycline
QALY	Quality Adjusted Life Year
R&D	Research and Development
RDT	Rapid Diagnostic Test
RSFF	Risk sharing finance facility
SARS	Severe acute respiratory syndrome
SGC	Structural Genomics Consortium
SME	Small and medium enterprise
SPC	Supplementary Protection Certificate
STD	Sexually transmitted disease
TB	Tuberculosis
TDR	Special Programme for Research and Training in Tropical Diseases
USDEP	Ultra-Sensitive Diagnosis for Emerging Pathogens
VBP	Value-based pricing
VRE	Vancomycin-resistant <i>enterococci</i>
VICP	Vaccine Injury Compensation Program
WBCSD	World Business Council for sustainable Development
WHO	World Health Organization
WT	Wellcome Trust

GLOSSARYⁱ

Antibiotics

Antibiotics were originally natural products, made from either bacteria or fungi, which kill or inhibit the growth of bacteria which cause disease.

Antibiotic resistance

The ability of a bacterium to survive and even replicate during a course of treatment with a specific antibiotic. Failure to resolve an infection with the first course of antibiotic treatment may mean that the infection may spread, may become more severe and may be more difficult to treat with the next antibiotic that is tried.

Intrinsic resistance: natural resistance of bacteria to certain antibiotics.

Acquired resistance: normally susceptible bacteria have become resistant as a result of adaptation through genetic change.

Multidrug resistance: corresponds to resistance of a bacterium to multiple antibiotics.

Attrition rate

The number of antibacterial agents moving out of development over a specific period of time.

Antimicrobials

Medicinal products that kill or stop the growth of living micro-organisms and include **antibacterial agents** (more commonly referred to as **antibiotics**) which are active against bacterial infections). Antimicrobials are different from antibiotics in that they can be either natural or synthetic substances which kill or inhibit the growth of viruses, fungi and parasites in addition to bacteria.

Bacteria

Microorganisms that can be divided into categories according to several criteria. One way to classify bacteria is based on staining them using a method that divides most bacteria into two groups – **Gram-positive** and **Gram-negative** – according to the properties of their cell walls.

Call option: Option to buy an asset at a specified exercise price on or before a specified exercise date

ⁱ Sources: WHO; Merriam Webster's Medical Dictionary; Last JM. A Dictionary of Epidemiology; Mosby's Medical, Nursing; Allied Health Dictionary, 6th ed.; Courvalin, 2008; Joint Technical Report from ECDC and EMEA The bacterial challenge - time to react 2009; OECD glossary of statistical terms.

Clinical trial

A research activity that involves the administration of a test regimen to humans to evaluate its efficacy and safety.

Conjugation

Conjugation occurs when the cell surface of a donor and recipient bacteria come into contact to allow the transfer of circular DNA, called plasma which contains genes which code for resistance.

Data exclusivity

The period during which drug regulatory agencies are not permitted to accept licensing applications for follow-on drugs. A form of market protection distinct from, but related to, the patent system.

Deadweight welfare loss

A result of allocative inefficiency, when the equilibrium for a good or service is not Pareto optimal. Common causes include monopoly pricing, externalities, taxes or subsidies.

Drug (antibiotic) formulation

The composition of a dosage form, including the characteristics of its raw materials and the operations required to process it.

Examples are **oral formulation** (by mouth), **intravenous formulation** (by infusion into a vein).

Dual Non-Susceptibility

Bacteria that are resistant and thus not vulnerable to the therapeutic effects of two different classes of antibiotic drugs, minimizing the options for treatment of infection.

Efflux pump

The efflux pump is a channel that prevents the intracellular accumulation of antibiotic needed to kill the bacteria.

Externalities

Arise when an individual or companies behaviour has positive or negative effects on another person that is not directly involved in the transaction. Hence, prices do not reflect the full costs or benefits in production or consumption of a product or service.

Positive externality: results in under provision as the company does not obtain all of the benefits.

Negative externality: results in over-supply as the company does not account for the full external costs when producing the good.

First mover advantage

Market advantages gained by the first market entrant or occupant of a market segment.

Functional resistance groups

An antibiotic would belong to a particular functional resistance group (FRG) if the use of that antibiotic causes resistance to other antibiotics in the FRG but not resistance to antibiotics in other FRGs. Laximinarayan and Malini¹ proposed this concept because the current classification of antibiotics based on chemical classes is not in line with promoting the effectiveness of antibiotics. In particular, the use of a drug within one particular chemical class may not only lead to resistance to other drugs within that chemical class but may lead to resistance to drugs in other chemical classes.

Gram negative bacteria

Gram-positive and Gram-negative bacteria are differentiated according to the chemical and physical properties of their cell walls. Gram negative are more problematic than gram positive because they have an outer cell wall which makes them difficult to attack with antibiotics (Insight 2008). Gram-negative bacteria encompass strains such as *Escherichia coli*, *Helicobacter*, *Moraxella*, *Pseudomonas*, *Salmonella*, and *Shigella*.

Gram positive bacteria

Gram-positive bacteria encompass strains such as *Bacillus*, *Listeria*, *Staphylococcus*, *Streptococcus*, and *Enterococcus*.

Horizontal gene transfer

Most resistance is obtained by gene transfer from a resistant bacterium to a susceptible bacterium, through horizontal gene transfer.

Incentive

Any factor (financial or non-financial) that enables or motivates a particular course of action, or is a reason for preferring one choice over the alternatives.

Intellectual property protection

A type of legal monopoly whereby owners or inventors are granted certain exclusive rights in return for an invention with social value. Exclusive rights allow owners of IP to reap monopoly profits. These monopoly profits provide a financial incentive for the creation of IP, and pay associated R&D costs. In the case of pharmaceuticals IP protection is exerted through the patent system.

Methicillin-resistant *Staphylococcus aureus* (MRSA)

Hospital pathogen, but can also occur in healthy individuals in the community. More than 10% of bloodstream infections in hospitals are due to MRSA, MRSA patients have worse outcomes than methicillin-sensitive *Staphylococcus aureus*.

Multidrug-resistant (MDR) bacteria

Since bacteria can acquire resistance by both genetic mutation and by accepting genes coding for resistance from other bacteria, bacteria can become resistant to many different classes of antibiotic, resulting in the emergence of multidrug-resistant (MDR) bacteria.

Net present value (NPV)

A project's net contribution to wealth - present value minus initial investment.

New Chemical Entity

A drug that does not contain an active moiety previously submitted to, or approved by, a drug regulatory agency. Distinguishes originator drugs from generic drugs.

Nosocomial (hospital-acquired) infection

An infection occurring in a hospital or another healthcare facility, when the infection was not present or incubating at time of admission.

Orphan disease

US: A disease or condition affecting less than 200,000 people or affects more than 200,000 people but for “which there is no reasonable expectation that a developer could recover its R&D investment through sales revenue. EU: A life-threatening or chronically debilitating disease inflicting a maximum of 5 in 10,000 people

Open-source

A principle or broad range of tools to increase access to knowledge, information and tools as a method of generating innovation.

Pharmacokinetics/pharmacodynamics (PK/PD)

The study of the rate of drug action, particularly with respect to the variation of drug concentrations in tissues with time, and the absorption, metabolism and excretion of drugs and metabolites.

Prophylactic

Medication used to prevent disease. Reduces risk of postoperative infection, may be impossible to do many operations without prophylactic antibiotics.

Product development partnership

PDPs are a class of public-private partnership that focus on health product development. They are discrete organizations that largely (although not exclusively) coordinate the collaboration between public (funding) and private (expertise, assets) contributors.

Push incentive

Subsidies to help to fund research. By reducing the costs of inputs and advancing the state of basic science, push mechanisms aim to make drug development cheaper.

Pull incentive

Offer of a financial reward upon the delivery of a specified product.

Real option

The possibility to modify, postpone, expand or abandon a project.

Regulatory Review

A process performed by a regulatory agency i.e. FDA or EMEA, to confirm a health intervention is safe and efficacious for licensed (and therefore controlled) use within a population.

Reimbursement

The act of retrospective financial compensation for a cost incurred.

Selective Pressure

Influence of antibiotic on natural selection to promote one type of organism. Antibiotics kill susceptible bacteria and allow resistant bacteria to continue to multiply.

Strike price: Exercise price of an option

Systemic (or systemically administered) **antibiotics:** compounds administered parenterally (e.g. intravenously)

Transduction

Viruses can pass resistance between bacteria through a process known as transduction, when the resistant genes are contained in the head of the virus which can inject the resistant genes into bacteria that it subsequently attacks.

Transformation

Transformation is a process by which bacteria take up DNA from dead bacteria in close proximity and incorporate the new genetic material, which has advantageous genes such as resistance, into their own DNA.

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EXECUTIVE SUMMARY

Antibiotic resistance

According to the 2004 World Health Organization (WHO) report “Priority Medicines for Europe and the World”, infectious diseases rank as the highest total burden of disease worldwide as measured in disability-adjusted life years (DALYs)—31% of the total burden². In fact in 2004, infectious diseases were identified as the second leading cause of death in the world, placing them second in terms of global mortality rates with 2.47 deaths per 1000 (slightly behind cardiovascular disease, 2.63 deaths per 1000)². In 2004, infectious diseases accounted for more than a quarter of deaths at the global level (26.94%)². As regards bacterial infections in particular, pneumonia and diarrheal diseases alone kill approximately 3.8 million children under 5 each year³. Within the European Union (EU), it is estimated that 2 million patients every year acquire nosocomial infectionsⁱⁱ, such as methicillin-resistant *Staphylococcus aureus* (MRSA), and account for 175,000 deaths per year⁴.

Bacterial diseases are becoming increasingly virulent and resistant to currently available treatments. Resistance to antibiotics presents a major challenge in health care as resistant bacteria dramatically reduce the possibility of treating infectious diseases effectively and increase the risk of complications and death for patients with infections⁵. Resistance to entire antibiotic classes (e.g. β -lactams, quinolones, tetracyclines, glycopeptides and macrolides) is emerging rapidly and is prevalent at both the hospital and community level. Growth of resistance stems in part from over-prescription of antibiotics. There is a naive acceptance that infections encountered in hospital and especially in community practice are most effectively managed on the basis of clinical assessment⁶. As culture and sensitivity tests currently require 36–48 hours to provide results⁷ few infections are microbiologically confirmed sufficiently quickly to guide treatment decisions⁶. This presumptive treatment of patients means that viral infections are often misdiagnosed as bacterial infections, leading to inappropriately prescribed antibiotics. Risk aversion on the part of physicians (which is compounded by a mounting tendency for litigation in some countries) and ensuing over-prescription of antibiotics will continue to amplify the growth of resistance until physicians have more sophisticated and effective rapid diagnostic tests (RDTs) that are quick and easy-to-use at the point of care (POC).

Although specific recommendations for promoting research and development (R&D) for RDTs lie outside the scope of this report, it should be underlined that both supply and demand side measures should be assessed to better understand and support the development of RDTs at the POC to guide antibiotic treatment. From the supply side, inputs could take the form of targeted support for basic research and increasing access

ⁱⁱ Nosocomial infections result from treatment in a hospital but are not the patient’s primary condition.

to enabling technologies—although from an economic perspective there is little justification for incentives comprising large financial subsidies. From the demand side, a major review of incentives within the health system structure, financing and reimbursement arrangements, the legal framework (including liability issues), and clinical guidelines should take place. The aligning of incentive structures appears to hold the most promise in addressing both antibiotic resistance through more targeted and informed prescribing as well as in sending industry the sign that there is a significant demand for good diagnostic products for bacterial infections. Amongst the tools to help guide reforms, long-term cost-effectiveness analyses comparing the economic costs and benefits of presumptive treatment to the use of RDTs at the POC—given varying levels of pathogen resistance, varying diagnostic sensitivity and specificity, as well as varying price levels – should be performed.ⁱⁱⁱ Such an exercise would help determine the price up to which the public purchaser could consider the procurement of RDTs to be cost-effective.

Beyond the development and use of RDTs themselves, conservation of antibiotics will also require a re-alignment of incentive structures in primary care services and hospitals as well as within the overall financing structures to ensure that prescribers are not perversely driven to overuse antibiotics. Policies relating to performance measurement and spending should take a longer-term perspective in weighing the risks and benefits of overuse. Financing systems also need to support infection control and antibiotic surveillance (ABS) to discourage practices that increase the spread of resistance and wasteful prescribing. It is crucial that policy-makers design *coordinated* policies that encourage physicians to meet quality care standards with support from diagnostic tools, where needed, to determine the most appropriate treatment and use of antibiotics.

The antibiotics market

From an economic perspective⁹, antibiotic use is associated with one positive externality (the public health externality) and one negative externality (the antibiotic resistance externality)^{iv} that create failures in the market.

- Public health externality: when an individual uses an antibiotic as prescribed, the individual is typically cured of an infectious and contagious disease, which prevents him from spreading the disease to others.

ⁱⁱⁱ Similar analyses, which take into account varying levels of absolute and growth rates of pathogen resistance, varying levels of diagnostic accuracy, varying treatment and diagnostic price levels, as well as a long-term perspective have been carried out in the past for malaria 8. Shillcutt S. Cost-effectiveness of malaria diagnostic methods in sub-Saharan Africa in an era of combination therapy. *Bulletin of the World Health Organisation* 2008;**86**(2):81-160..

^{iv} An externality exists when one individual's or firm's behaviour, whether it is positive or negative, effects other individuals, and those effects are not taken account of in the market price. When there is a positive externality, there is insufficient use of a good or service because private agents do not receive all of the benefits of the good or service. The converse is true for a negative externality.

- Antibiotic resistance externality: when an individual uses an antibiotic, a small number of bacteria become resistant to the treatment. The externality is that the individual can transmit the resistant bacteria to other individuals who will eventually be unable to benefit from the use of the specific antibiotic to which the bacteria have become resistant.

Separate, yet related, to the externalities, are the characteristics of the market that render it relatively unprofitable from the perspective of developers. First, there is the existence of generic antibiotics on the market that are still (although to varying degrees) effective in treating the majority of infections faced by health services. Second, there is the emphasis by EU public health authorities on conserving the existing antibiotics that are intended for severe infection by using generics as first-line therapy wherever possible. This sends a message to industry that effective new antibiotics, when developed, will be dispensed infrequently and kept as last resort treatments even if rates of resistance to widely-used antibiotics are high. Third, the limited duration of antibiotic regimes, along with their fully curative nature (as opposed to just mitigating symptoms as in the case of chronic diseases) increases marketing costs (to keep the product salient in the minds of potential prescribers), and decreases expected returns on investment. Therefore, relative to other therapeutic areas, antibiotics do not appear profitable. One estimate suggests a risk-adjusted net present value (NPV) of 100 for antibiotics, compared to 300 for an anticancer drug, 720 for a neurological drug, and 1150 for a muscular-skeletal drug¹⁰. Fourth, as an antibiotic that develops resistance rapidly has a shorter clinical lifespan, it is argued that if a developer invests billions of dollars and takes significant time to develop a new antibiotic they may not reap the full benefits of their efforts¹⁰. The NPV for an antibiotic falls when resistance to a drug develops and spreads amongst the general population¹⁰. Fifth, with the lack of appropriate assessment within pricing and reimbursement agencies, the prioritisation and corresponding price paid by public purchasers may not reflect the relative effectiveness of antibiotics in reducing morbidity and mortality. For example, much higher prices are paid for some drugs—for example some cancer drugs or CNS-related drugs—that offer only a few weeks or months of additional life.

Incentives to promote research and development in antibiotics

The potential for an impending health crisis due to the lack of new antibiotics, along with the inherent externalities in the market and the likely cost-savings from improving treatment, provide ethical and economic justification for some intervention in the market by a public body. However, the design of the incentive—in terms of the timing and size of the prize, the organisational driver, and the target beneficiary—will determine its chances of success.

Traditionally, incentives to encourage R&D have fallen into two main types – push and pull methods. The direction of the incentive could perhaps be the biggest influence on

its chances of success. Push incentives focus on removing barriers to developer entry largely by affecting the marginal cost of funds to the developer for investments in R&D and tend to impact the earlier stages of the development process^{11 #270}. Examples include any subsidy made to a developer in the early stages of drug discovery or development such as grants or research-related tax breaks. These financial injections lower the cost of R&D for the developer by reducing the cost of necessary inputs. Push incentives may come from public as well as private sources such as venture capitalists or large philanthropic donors. In providing early funding, push mechanisms are particularly useful for attracting small and medium enterprises (SMEs) who often operate with less than 6 months cash on hand^{12v}. However, they are also fraught with several difficulties. For example, developers paid through push mechanisms often lack the motivation to move into the next, more applied, phases of production. There is also the danger for the eventual over-payment through push incentives to have a dampening effect on entrepreneurialism¹³. Push incentives also pose agency problems in that researchers are compelled to show their work in the best light possible, which may not accurately reflect the merits of the investment. The funder, therefore, bears most of the risk of product development funded through push mechanisms.

In contrast to push mechanisms, pull mechanisms involve the promise of financial reward only *after* a technology has been developed. Examples include simple monetary prizes, the promise of tax credits to match eventual product sales, intellectual property (IP) extensions, or specified advanced market commitments (AMCs). Pull incentives offer financial reward upon completion of technological advances in order to lure R&D investments in a desired direction. Also, as profits increase with decreasing development costs, they better align internal incentives to rectify inefficiencies. Finally, as pull mechanisms provide a reward only upon full product development and authorization, they provide researchers with the incentive to self-select the most promising products and thereby bypass many of the agency problems inherent in push mechanisms. However, if the incentive relies only on the promise of rewards (as opposed to a fully earmarked existing sum), pull mechanisms are at the mercy of the changing political and economic (and associated budgetary) tide. It has also been suggested that pull mechanisms may corrode existing non-financial incentives to collaborate and slow the overall search for solutions. Finally, as financial rewards in pull mechanisms are reaped only following product development, the financial risk involved in all stages of R&D falls on the developer. This unequal distribution of risk is perhaps the greatest limitation to these mechanisms.

The basic elements of push and pull mechanisms can also be combined to create hybrid mechanisms. Hybrid mechanisms may help overcome many of the problems faced by

^v In the US, BIO currently estimates that 120 companies, comprising 30 percent of all publicly-traded biotech companies are currently in this situation.

uniquely push or pull incentives by covering (at least partially) the developer's early R&D costs whilst also providing the profit lure to go through with full product development. Indeed, in a comparison of the ability of push, pull, and hybrid mechanisms to stimulate the development of effective treatments, the recent OECD report¹⁴ supports Hsu and Schwartz's conclusion that a hybrid mechanism would be the most viable¹⁵. Hybrid mechanisms may provide crucial impetus to overcome developer reticence at the different (and perhaps key) stages of product development: early stage push funding provides greater financial space to explore early discovery ideas without needing to understand their full potential, whilst the larger pull element entices them to undertake the latter phases of development, including expensive Phase III trials. The evolution between the respective incentive forces within a hybrid incentive (push to pull) is important in that developers have been understood to respond more to profit incentives at the later stages of the research process than at the earlier stages¹⁶. In combining push and pull incentives, hybrid mechanisms also spread risk between the funder and the developer.

The spreading of risk is especially important for antibiotics in that the development of an entirely new product (with a novel mechanism of action [MoA]) presents a significant technical challenge—and thus a high level of risk in going forward with development. Whilst new generations of existing antibiotics (product “follow-ons”) are useful in staving off resistance to certain drug classes in the short-term, longer-term solutions must focus on the development of antibiotics with these novel MoA. Faced with the option of investing in more lucrative markets such as chronic diseases, the idea of taking this risk is not appealing for many developers. Incentives should therefore allow for risk to be shared between the public or non-profit funder and the investing developer. Pull mechanisms alone place the risk on the developer while push mechanisms place the risk on the funder. A combination of both pull and push mechanisms will likely prove optimal.

The COA (Call Options for Antibiotics) model, developed by Brogan and Mossialos, functions as a hybrid push-mechanism, combines the principles of call options in equity markets with principles of an AMC. In the model a potential purchaser can buy a right (during drug development) to purchase a specified amount of the drug at a later date, for a specified price. If the drug never reaches the market, the purchaser only pays a premium equal to the cost of the initial “option” contract. A fair valuation of an option will make the current value of the premium equal to the expected future profit from holding the option. Thus, the purchaser is protected from the full risk associated with development, whilst the developing company is given an additional, earlier incentive to continue development. The greatest challenge is to persuade companies to invest in a market with low returns. Conventional thinking suggests that if it is possible to increase returns, at the very least giving the project a positive NPV that meets a predetermined threshold, then pharmaceutical companies are more likely to invest. Financiers,

economists and scientists would all be needed to determine if the options contract provided good value for money and was worth investing. Full disclosure of all test results (both from animal models and regulatory trials) would be necessary, in a manner similar to that required for licensing approval. Reluctance to disclose such proprietary information should be overcome by the desire to obtain preliminary funding – confidentiality would of course be essential. The group to evaluate the drugs could be an extension of the purchasing organisation. Finally, a key advantage of the model lies in the inherent disincentive it creates for over-marketing of the eventual product through the positive price gradient that is created through the development stages and after the defined number of options have been sold.

In addition to establishing a financing mechanism to drive R&D, further support to basic research is also needed. In the short term, addressing the decades-long exodus of specialist knowledge, skills and experience will be vital for the development of new antibiotics in future. Traditional tools, such as grants and fellowships can help attract new scientists to the field. However, in order to avoid losing existing knowledge that has strayed to other areas over the past decades, efforts should also be made to re-engage older researchers in the area of antibiotics. The EU seventh framework programme for research and technological development (FP7) funding could channel the necessary funding towards these efforts. Specifically, funding could be made available for basic research into resistance and potential targets (biomarker discovery), gene identification, platform technologies, clinical development. Support for open-access molecule libraries or open-access research more generally could also help remove crucial barriers to participation and collaboration. Efforts should be made to commit the necessary funds in advance, detaching them from annual budgetary negotiations that risk putting them at the mercy of political whims, the economic climate, and other perpetually changing forces.^{vi}

In the longer term, reimbursement and price re-structuring could also have a significant impact on the investment in R&D for antibiotics. However, within a European context, the success of this type of reform as an incentive would depend largely on the number of Member States adopting such an approach. A standardised European approach to assessment would make the prioritization of antibiotics more credible and in turn greatly contribute to the strength of such an incentive. These major policy changes will undoubtedly take time and, in this regard, reimbursement reforms should be perceived as a key approach for directing R&D investment towards long term needs rather than a solution to fill urgent treatment gaps. However, in the short term even minor price-restructuring within Member States could help pull vital investment in antibiotics.

^{vi} The 9 year budget commitment (for 2004–2013) apportioned in the in the US Project BioShield is an example of longer-term funding.

To the extent possible it will be important to foster further collaboration between large pharmaceutical companies and SMEs. Wherever possible, this support should aim to secure new SMEs to become involved but also ensure that any collaborative partnerships secure significant input from the pharmaceutical industry. The challenges mentioned may make potential collaborators out of groups that have been less interested in the past and the COA model may provide the mechanism through which this growth in collaboration becomes increasingly feasible. However, it is crucial that collaboration not lead to overly complex arrangements. For example, while close partnerships are very attractive in theory, complicated partnerships or intricate IP arrangements present the danger of repelling participants from any incentive scheme. This is especially true of the traditionally autonomous and financially self-sufficient large pharmaceutical companies. Indeed the PDPs for neglected diseases have demonstrated that negotiations over rights can be long and draining for developers accustomed to full autonomy and entirely IP-driven business models. Antibiotics—a therapeutic area with fewer potential reputation gains than neglected diseases—would be even less likely to compel large pharmaceutical companies to leave their intellectual property comfort zones and accept to share rights. It is also important that partnerships have significant industry input. Indeed the likely success of collaborative programmes such as the Innovative Medicines Initiative lie in securing consistent industry support and input. The COA model may offer the vehicle to encourage these partnerships, offering not only to capture significant industry input but also acceptable payment terms for funders. The COA model combines the financial investment incentives of an equity market and the clarity regarding minimum market size found in AMCs, with a “light touch” public-private collaboration (at least for fully developed products).

1.0 INTRODUCTION

Despite the abundance of safe, effective, and low-cost antibiotics since the mid-20th century, resistance to existing antibiotics has recently become widespread and created a global challenge to public health in the 21st century^{17,18}. Antibiotics are pharmaceutical compounds used to treat infections by killing or inhibiting growth of bacteria pathogens^{19,20}. Following the successes of early antibiotic therapies, such as penicillin, leaders in public health during the mid-20th century declared that the end of infectious diseases was approaching. However, infectious diseases currently remain the second-leading cause of death worldwide²¹. Antibiotic resistance—the evolution and spread of pathogenic strains not susceptible to antibiotic treatment—is widely acknowledged as the reason why infectious diseases continue to be a leading cause of death and disability worldwide.

The frequency and severity of antibiotic resistance is becoming evident worldwide. Previously, resistance was an isolated problem of hospitals and nursing homes. However, recently the proportion of community-acquired (CA) infections with bacteria resistant to antibiotics has increased^{22,23}. In 2006, the European Antimicrobial Resistance Surveillance System (EARSS) reported that pathogens resistant to the antibiotic penicillin occurred in up to 25-50 percent of isolates in France, Spain, and Romania, indicating that penicillin is becoming obsolete in these 3 European countries^{24,25}. Additionally, in 2006 the EARSS reported that Methicillin-resistant *Staphylococcus aureus* (MRSA) bacteria occurred in up to 25-50 percent of isolates in most of southern Europe, Ireland, and the United Kingdom^{24,25}. The recent rise of new strains of bacteria resistant to single and multiple classes of antibiotics has led to severe public health and economic consequences—higher treatment costs, longer duration of illness and hospital stays, increased risk of morbidity and mortality, and spread of disease^{26,27 28,29}.

Medical, public health, and scientific leaders and organizations worldwide recognize the severity of antibiotic resistance in both developed and developing countries. In an epidemiological report on communicable diseases in Europe, the European Centre for Disease Prevention and Control states that bacteria resistant to antibiotics is the most important disease threat in Europe^{30,31}. The United States (US) Centers for Disease Control and Prevention (CDC) state that antimicrobial resistance is currently one of the most pressing public health issues in the US^{32,33}. In a report on infectious diseases and antimicrobial resistance, the World Health Organization (WHO) recognizes that antibiotic resistance does not just present a challenge at the country-level but has also become a growing international problem^{34,35}. The rise of globalisation and subsequent increase in migration, trade, and travel means that no country can isolate itself from resistant bacteria^{5,36}. For example, in the US the majority of multi drug-resistant (MDR) typhoid cases originate in 6 developing countries^{34,35}. In response, governments have

taken a number of steps to reduce the spread of resistance. National and international surveillance and antibiotic stewardship (ABS) programmes have been developed to improve the appropriate use of antibiotics, including the surveillance of antibiotic consumption, monitoring of resistance patterns, and provision of advice to prescribers about which medicine to use ^{17,37}. However, without new antimicrobials, resistance will continue to spread and bacterial infections will become untreatable.

Currently, there is a lack of antibiotic research and development (R&D) and the industry pipeline has few late-stage candidates for drugs that can effectively combat the emergence and spread of drug-resistant bacterial strains ^{38,39}. Amongst the 15 largest pharmaceutical companies in 2004, only 1.6% of drugs in development were antibiotics, none of which were from novel classes nor addressed multi-resistant Gram negative infections ^{40,41}. Although non-profit entities, including the Wellcome Trust (WT) and the Bill & Melinda Gates Foundation, provide funding for biomedical research in the field of antibiotics, funding levels continue to be insufficient to stem the exodus of pharmaceutical research from this therapeutic area. With existing incentives for drug developers, development of new antibiotics is declining and current levels of innovation are inadequate ^{42,43}. Governments must take immediate action to strengthen incentives for antimicrobial R&D, basing their decisions on the best available evidence on probability of success in spurring adequate levels of investment and cooperation to achieving novel product development. This report aims to fill this information gap and stimulate more discussion and research in this area.

2.0 BACKGROUND ON ANTIBIOTICS

2.1 What Antibiotics Are

Antibiotics have revolutionized the treatment of infectious disease—turning life-threatening diseases into more manageable and treatable conditions. Antibiotics are used as chemotherapeutic agents in the treatment of various infectious diseases. In addition to treating CA infections, antibiotics have facilitated and improved the safety and outcomes of surgery and transplantation in hospitals and other health care settings^{6,44}. The use of such antimicrobial agents combined with global immunization programmes and improvements in sanitation, housing, and nutrition, has led to a significant fall in mortality from infectious diseases during the 20th century^{45,46}.

In general, an antibiotic is a compound or substance that either kills or inhibits the growth of a microorganism, such as bacteria, fungi, and protozoan. There are 3 major sources of origin for antibiotics—either naturally isolated, purely chemically synthesized, or semi-synthetically derived. In addition, antibiotics can be classified according to their effect on bacteria—antibiotics that kill the bacteria are classified as bactericidal whereas those that inhibit growth of bacteria are known as bacteriostatic. Lastly, antibiotics are defined according to their mechanism for targeting and identifying microorganisms — broad spectrum antibiotics are active against a wide range of microorganisms whereas narrow spectrum antibiotics target a specific group of microorganisms by interfering with the metabolic process specific to those particular organisms.

At the end of the 19th century and beginning of the early 20th century, scientists began the search for new antibacterial agents for the treatment of infectious diseases. In particular, the two groundbreaking discoveries occurred in the 1930s and 1940s that catalysed the microbial drug era—when Alexander Flemming and Selman Waksman discovered penicillin and streptomycin, respectively⁴⁷. In fact, microorganisms made a significant contribution to medicine and drug discovery over the past 80 years following these two discoveries^{48,49}. For example, of the 25 top-selling drugs reported in 1997, 42% were natural products or their derivatives and of these, 67% were antibiotics^{48,49}. Following the discovery, development, and successes of antibiotic therapies, the US Surgeon General William H. Stewart declared in the 1960s that infectious diseases had been defeated and “the war against pestilence [was] won”^{21,50}. However, the possibility of these “miracle drugs” successfully containing infectious diseases worldwide has recently been substantially undermined by the emergence of resistance to antibiotics.

2.2 Why Antibiotics Are Important

The world faces urgent and emerging infectious disease threats that can be mitigated and controlled by effective and appropriate antibiotic therapy. However, trends in prevalence, incidence, and global burden of disease indicate that we are far from conquering infectious diseases. More than one-third of the world's population is likely infected by bacterial pathogens^{51,52}. Despite the existence of antibiotic therapies, respiratory infections, tuberculosis (TB), and malaria continue to persist as major public health threats in the 21st century. For example, one-third of the world's population is currently infected with TB and almost 9 million people have active disease^{51,52}. According to the 2004 WHO report "Priority Medicines for Europe and the World", infectious diseases rank as the highest total burden of disease worldwide as measured in DALYs—31% of the total burden^{2,53}. In fact, infectious diseases were identified as the second leading cause of death in the world, placing second in terms of global mortality rates, 2.47 deaths per 1000 (slightly behind cardiovascular disease, 2.63 deaths per 1000)^{2,53}. In 2004, infectious diseases accounted for more than a quarter of deaths at the global level (26.94%)^{2,53}. Approximately 2 million fatalities occur per year from bacterial infections⁵². In particular, pneumonia and diarrheal diseases kill approximately 3.8 million children under 5 each year^{3,54}.

However, when considering just the European Union (EU), infectious diseases do not rank amongst the top 5 groups accounting for the majority of burden of disease^{2,53}. Infectious disease accounts for less than 7% of disease burden in the expanded EU^{2,53}. Although the disease burden of infectious diseases is significantly smaller in the EU than developing countries, resistant infections are increasingly posing enormous threats to health. In fact, resistant forms of infectious diseases common in developing countries are now becoming a public health challenge for developed countries, as demonstrated by recent concerns about possible outbreaks of extensively drug-resistant (XDR) TB^{55,56}. Common bacterial pathogens have become rapidly resistant to previously effective antimicrobial therapy, undermining antibiotics' ability to treat illness. The recent rise of new strains of bacteria resistant to single and multiple classes of antibiotics has led to severe public health and economic consequences—higher treatment costs, longer duration of illness and hospital stays, increased risk of morbidity and mortality, and spread of disease^{26,27 28,29}. In addition, mortality rates and the spread of community and hospital-acquired infections resistant to antibiotics have escalated in the past decade. A recent study from the US suggests that over 18,000 patients die each year in the US as a result of MRSA (57, 58). Despite the reduced therapeutic activity resulting from resistance, antibiotics still have an overwhelming therapeutic value and are necessary for treatment of many bacterial pathogens and infectious diseases. Therefore, continuous investment into the search for new agents and drugs with novel mechanisms of action (MoA) becomes necessary as resistance spreads and the global burden of infectious disease rises (note that estimates of the prevalence, mortality, morbidity,

costs, and burden of antibiotic resistance will be addressed in an upcoming detailed discussion of antibiotic resistance)

2.3 Externalities of Antibiotics and Antibiotic Resistance

The impact of antibiotic usage on population health can also be explained according to economic principles, particularly in terms of externalities^{1,9,57}. Following the Grossman model of health production, antibiotic treatment is a health care good consumed by an individual to produce health^{58,59}. A patient experiences private benefits from consumption of appropriate antibiotics, primarily in the form of improved health outcomes, reduced risk of mortality and morbidity, and shorter hospital stays. On the other hand, a patient incurs private costs from inappropriate antibiotic use—the bacteria in the patient’s system not killed by the antibiotic will make it difficult for the patient to overcome future infections^{9,57}. In addition to private benefits and costs, antibiotic consumption is associated with positive and negative externalities. An “externality” exists when an individual’s behaviour has positive or negative effects on another person that is not directly involved in the transaction. Consequently, prices do not reflect the full costs or benefits in production or consumption of a product or service. Therefore, when a good has a positive externality, the private company will not produce enough of the product or service since the company does not obtain all of the benefits. On the other hand, when a good has a negative externality, the private company will overproduce the good, as the company does not account for the external costs when producing the good.

It is important to assess the positive and negative externalities of antibiotic consumption and antibiotic resistance, respectively, whilst considering the policy responses and options to contain antibiotic resistance.^{vii} In the case of antibiotics, a positive or “public health” externality exists—appropriate antibiotic usage helps treat infections that otherwise could spread to the community^{61,62,9,57}. Therefore, the general public benefits when an individual consumes appropriately prescribed antibiotic therapy. According to economic theory, antibiotic developers will not produce enough antibiotics since the company does not obtain all of the benefits. In reality, discovery and development of new antibiotics has slowed dramatically over the past 25 years. Amongst the 15 largest pharmaceutical companies in 2004, only 1.6% of drugs in development were antibiotics^{40,41}. In addition, the industry pipeline has few late-stage candidates for antibiotics that can effectively combat the emergence and spread of drug-resistant bacterial strains^{38,39}.

^{vii} For further reference on the positive and negative externalities of antibiotic consumption, see the Coast et al. 1998 study in which the authors develop an extensive economic model to represent the positive and negative externalities of antibiotics. 60. Coast J. An Economic Perspective on Policy to Reduce Antimicrobial Resistance. *Social Science and Medicine* 1998;**46**(1):29-38.

Consequently, the pharmaceutical industry is not producing antibiotics at a socially optimal level.

In contrast, a negative externality is associated with inappropriate antibiotic usage and antibiotic resistance—the introduction of the antibiotic increases selection pressures for drug resistance in the environment since resistant bacteria can be transmitted to others, potentially reducing the effectiveness and benefits of the antibiotic medication to the public^{61,62}. Laxminarayan argues that suboptimal increases in resistance may be attributed to the fact that antibiotic effectiveness is a common property resource⁶³.^{viii} According to the “tragedy of commons” problem with antibiotic resistance, the consumer and the supplier of treatment rarely experience the direct effects of antibiotic resistance despite the fact that resistance negatively impacts the welfare of the public^{60,64}. In fact, private companies do not have an incentive to take into account the effect of their sales of antibiotics on future antibiotic effectiveness because of the cross-resistance across different antibiotics produced by various companies in the market⁶³. Consequently, the market price of antibiotics does not adequately reflect the true social cost of antibiotic resistance and thus there may be too many antibiotics sold to achieve a socially optimal level of consumption. It is important to note that as time progresses and resistance increases, the positive externality associated with reduced transmission may be reduced^{60,64}. Consequently, the negative externality associated with antibiotic resistance may diminish the public health benefits of antibiotic consumption. Laxminarayan and Brown argue that the current problem of antibiotic resistance is attributed to the fact that there is an absence of economic incentives for individuals to take into account the negative impact of their use of antibiotics on social welfare⁶⁵. Therefore, it may be necessary to address the “tragedy of commons” problem with respect to antibiotic resistance and thus create incentives for antibiotic developers to internalise the costs of resistance.

In addition to the “tragedy of commons” problem associated with antibiotic resistance, resistance is inter-generational and thus likely to be incurred by future generations^{60,64}. Individuals and companies do not consider the impact of their current consumption on future stocks—that the use of antibiotics in the current period diminishes the effectiveness of antibiotics in the future periods. According to economic theory, consumers discount costs that occur in the future since they value a current dollar more than future dollar, when adjusting for inflation^{66,67}. Therefore, when the discount factor (the number which a future cash flow to be received is multiplied by to obtain the current present value) is low, society cares less about future resistance and thus the

^{viii} However, in his 2008 study, Saver notes how there is open debate whether antibiotics are truly analogous to common pool assets. Common goods can be renewed and replaced over time. On the other hand, the number of effective doses of an antibiotic may be finite and thus antibiotics could be characterized as an exhaustible resource. 62. Saver R. In Tepid Defense of Population Health: Physicians and Antibiotic Resistance. *American Journal of Law and Medicine* 2008;**34**:431-491.

social benefits of internalising the costs of resistance are relatively lower⁶³. In other words, if antibiotic resistance occurs in the future, the present cost of resistance would be less. Coast et al. notes how the time frame and the discount factor are both likely to impact whether reducing resistance will result in overall benefit for society^{60,64}. The authors explain that where time frames are long and discount rates are small, reducing resistance is likely to result in positive benefit to society. On the other hand, where time frames are short and/or discount rates large, there may be an overall cost to society if policies are aimed at reducing resistance.

When designing policies that internalize the costs of resistance and thus aim to reduce resistance, one must consider the fact that antibiotic resistance has an interregional nature—resistance can cross country borders and travel far distances^{60,64}. Coast notes that although 2 countries may provide the source, of and be the victims of resistance, the transfer and spread of resistance may be unequal^{60,64}. Additionally, Coast argues that policies aimed at reducing antibiotic usage within a particular country may not work in another country, given that local epidemiological factors impact the mechanisms of spread of antibiotic resistance^{60,64}. According to this logic, when local-level rather than global epidemiological factors are taken into consideration, policies combating resistance are more likely to result in positive benefit to society.

Lastly, the negative externality of antibiotic resistance is further exacerbated by the fact that an agency relationship exists between the physician and the patient. The less informed principal (patient) relies upon the fully informed agent (doctor) to act on his/her behalf and maximize his/her utility or welfare in the form of health. Therefore, physicians direct the course of therapy, such as prescribing of antibiotics. According to Reed et al., physicians face few incentives to withhold antibiotics from patients^{66,67}. Reed argues that physicians perceive the impact of each individual prescription on resistance to be so small that the potential cost of not prescribing the antibiotic outweighs the uncertain costs associated with resistance^{66,67}. Also, physicians frequently prescribe antibiotics when uncertain of diagnosis because of the high cost of liability in the case of treatment failure^{66,67}. Physicians do not consume the antibiotics that they prescribe and so they do not directly incur the costs associated with such inappropriate prescribing practices. Consequently, Saver suggests that to internalize costs appropriately, physicians should theoretically bear some of the resistance costs associated with antibiotic consumption or that the costs borne by patients and their physicians should be coordinated^{61,62}.

The positive “public health” and negative “antibiotic resistance” externalities associated with antibiotic consumption represent market failures since antibiotic developers, patients, physicians, and other consumers of antibiotics do not directly reap the full benefits of antibiotic consumption nor incur the full costs of resistance. Therefore, many experts recommend that policies that aim to curb the rapid spread of antibiotic

resistance need to create incentives that either internalise the costs of resistance or the benefits of antibiotic drug discovery and development.

3.0 BACKGROUND ON ANTIBIOTIC RESISTANCE

In order to understand why resistance to antibiotics presents such a threat to public health, it is necessary to understand how and why resistance develops and what can be done to curtail the ongoing spread.

3.1 What is Antibiotic Resistance?

Shortly after the introduction of antibiotics, resistance became a major challenge to treatment of infectious diseases. In 1928, Alexander Flemming first discovered antibiotics after isolating penicillin from the fungus *Penicillium notatum*⁶⁸.^{ix} Antibiotics were originally of natural origin, developed from bacteria or fungi^{48,49}.^x By 1940, the first antibiotic on the market called penicillin was developed and demand for the drug grew as antibiotics were seen as ‘miracle’ drugs for a rapid cure of illness. However, clinical cases of penicillin-resistant *Staphylococcus aureus* (*S. aureus*) infections were reported 3 years after the initial use of the drug and more than 60% of hospital *S. aureus* infections were resistant by the end of the first decade of widespread use of penicillin^{38,70}.

Antibiotic resistance, a complex process which results from the use and misuse of antibiotics, is a process by which bacteria change and develop properties that make the drugs used to treat them ineffective^{71,72}. When antibiotics are used, susceptible bacteria are killed, and bacteria which resist the drug survive and multiply, replacing the eradicated bacteria^{32,33}. This is an example of a selective pressure exerted by antibiotics, whereby resistant bacteria continue to grow and spread resistance^{73,74}.

There are various methods through which bacteria gain resistance. Some bacteria make an antibiotic ineffective before the drug can kill them, others rapidly pump the antibiotic out (antibiotic efflux), and some strains alter the drug attack site so that the antibiotic

^{ix} After the discovery of the fungus by Flemming, the development of the penicillin antibiotic was actually completed by Howard Walter Florey, Ernst Chain, and Norman Heatley.

^x Natural products continue to be important in the development of treatment of human diseases—of the 25 top-selling drugs reported in 1997, 42% were natural products or their derivatives and of these, 67% were antibiotics. 48. Demain A, Sanchez S. Microbial drug discovery: 80 years of progress. *The Journal of Antibiotics* 2009;**62**:5-16.. Antimicrobials are different from antibiotics in that they can be either natural or synthetic substances which kill or inhibit the growth of viruses, fungi and parasites in addition to bacteria 69. Canadian Institutes of Health Research (CIHR). Novel alternatives to antibiotic research initiative: Canadian Institutes of Health, 2007., whilst anti-infective is a term referring to antibacterials, antibiotics, antifungals, antiprotozoans and antivirals. However, many use the term “antibiotic” to refer to both natural and synthetic compounds which fight bacteria. 32. Centers for Disease Control and Prevention (CDC). If You Have a Cold or Flu, Antibiotics Won’t Work for You!: Centers for Disease Control and Prevention, 2008..

becomes ineffective^{32,33}. Resistance due to antibiotic efflux, is an increasing problem worldwide^{75,76}. The efflux pump is a channel that prevents the intracellular accumulation of antibiotic needed to kill the bacteria^{77,78}. Whilst some bacteria have a natural resistance to antibiotics, other bacteria can become resistant through genetic mutation or by acquiring resistance from another bacterium^{73,74}.

Genetic transfer of resistance occurs most often through conjugation, transformation, and transduction. Conjugation occurs when the cell surface of a resistant bacterium and recipient bacterium come into contact and transfer circular deoxyribonucleic acid (DNA) plasmids, which contains genes that code for resistance^{79 80-82}. Transformation occurs when bacteria take up DNA from dead bacteria in close proximity and incorporate the new genetic material, which has advantageous genes such as resistance, into their own DNA^{83,84}. Viruses can pass resistance between bacteria through a process known as transduction, when the resistant genes are contained in the head of the virus which can inject the resistant genes into bacteria that it subsequently attacks^{73,74}.

Since bacteria can acquire resistance by both genetic mutation and by accepting genes coding for resistance from other bacteria, bacteria can become resistant to multiple classes of antibiotics, resulting in MDR bacteria. Most resistance is obtained by gene transfer from a resistant bacterium to a susceptible bacterium through horizontal gene transfer^{19,20}. This type of spread can occur easily on the skin surface or in the gut, where bacteria mix with each other.

3.2 Severity of Antibiotic Resistance

Antibiotic resistance poses as a major challenge to local, national, and global public health. Resistant bacteria dramatically reduce the possibility of treating infectious diseases and infections effectively. In addition, antibiotic resistance increases the risks of complications, morbidity, and mortality for patients^{5,36}. In fact, infectious diseases are currently the third leading cause of death in the EU^{4,85}. The problem is further complicated and risks are escalated as resistance to entire antibiotic classes (e.g. β -lactams, quinolones, tetracyclines, glycopeptides and macrolides) is also emerging rapidly.

3.2.1 Antibiotic resistance trends in developed countries

Within Europe, antibiotic resistance is more prevalent in Southern than in Northern Europe^{19,20}. In particular, Scandinavia has the lowest and the Mediterranean countries have the highest prevalence of antibiotic resistance. Resistance may be higher in Southern countries due to differences in health systems, such as policies which allow antibiotics to be dispensed over the counter. Also, relative to Northern European countries, Southern, Mediterranean, and Eastern countries tend to have higher overall

usage of antibiotics (defined by daily doses/1000 inhabitants/day) ⁸⁶. Numerous studies confirm that increased antibiotic consumption is associated with the emergence of antibiotic resistance worldwide ⁸⁷.

Several national, continental, and international surveillance systems have been developed to track the spread of hospital- and CA antibiotic resistance, raise awareness of the problem, and stimulate governments to take action through policy interventions ⁸⁸. In the EU, the European Antimicrobial Resistance Surveillance System (EARSS) collects data on the prevalence and spread of major invasive bacteria relevant to antibiotic resistance throughout participating European countries ⁸⁸. In the US, the National Nosocomial Infections Surveillance (NNIS) System has collected nosocomial infection surveillance data of hospitals since the 1970s ⁸⁹. ^{xi} In addition to surveillance systems, a wealth of information on trends in resistance has been provided by studies conducted over the past several decades on particular pathogen isolates for hospital and CA infection cases. The following discussion provides an overview of the trends in resistance for particular pathogens that pose a challenge to public health.

Streptococcus pneumoniae

Streptococcus pneumoniae (*S. pneumoniae*) is a common cause of disease in Europe, particularly for young children, elderly people, and patients with compromised immune functions. Upper airway infections (e.g. sinusitis and otitis media), pneumonia, invasive blood stream infections, and meningitis are the most common clinical manifestation of this bacterium. Pneumonia, an acute respiratory infection, remains the number 1 killer disease worldwide ⁹⁰. Approximately 3 million people die of pneumococcal infections per year ⁸⁸. Thus, *S. pneumoniae* represents a significant bacterial pathogen that merits in depth surveillance and analysis of trends. ^{xii} The following discussion provides an overview of the data from the EARSS Annual Report of 2007 on the trends of *S. pneumoniae* resistance.

S. pneumoniae Resistance to Penicillin ⁸⁸

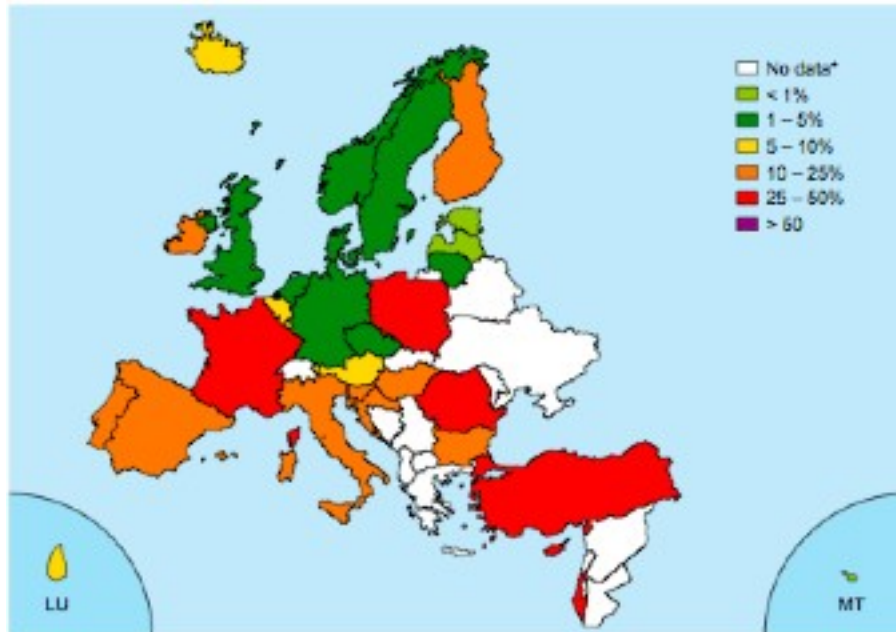
In 2007, 1,198 (10%) of the 11,606 *S. pneumoniae* isolates were non-susceptible for penicillin in 30 countries. However, penicillin non-susceptibility (PNSP) varies across Europe. In the majority of Northern European countries, PNSP levels were below 5% (except for Belgium 9%, Finland 13%, and Ireland 17%). On the other hand, PNSP was substantially higher in Southern and Eastern Europe and reached levels above 25% in Cyprus, France, Israel, Poland, Romania, and Turkey. In particular, the EARSS concluded that in 2007 the level of PNSP in Finland and Turkey was rising significantly and the proportion of fully resistant *S. pneumoniae* isolates was rising in Ireland, Slovenia, and Turkey. However, the EARSS also reported promising findings—the 3 countries with the

^{xi} Nosocomial infections result from treatment in a hospital but are not the patient's primary condition.

^{xii} For other bacterial pathogen resistance trends in Europe, please refer to the EARSS Annual Report (http://www.rivm.nl/earss/Images/EARSS%202007_FINAL_tcm61-55933.pdf).

highest levels of PNSP in 2006 (Spain, France, and Israel) demonstrated more than a 10% reduction of PNSP in 2007.

Figure 3.2.1 *Streptococcus Pneumoniae*. Proportion of Invasive Isolates Non-Susceptible to Penicillin in 2007. ⁸⁸

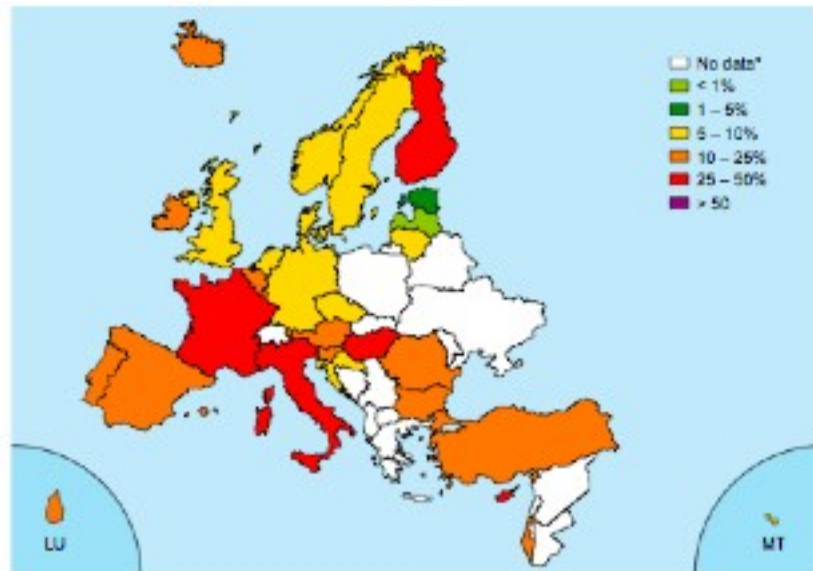


*These Countries Did Not Report Any Data or Reported Less than 10 Isolates.

S. pneumoniae Resistance to Erythromycin ⁸⁸

According to the EARSS Annual Report for 2007, 1,708 (16%) of the 11,014 *S. pneumoniae* isolates were non-susceptible to erythromycin. Reports of erythromycin non-susceptibility have risen since 2006. In 2006, 5 countries reported erythromycin non-susceptibility levels of less than or equal to 5%; however, in 2007, Estonia and Latvia were the only 2 countries reporting such low levels of non-susceptibility. In 2007, 8 countries had non-susceptibility proportions from 5–10% and 12 countries from 10–25%. The greatest proportions were reported in Cyprus, France, Finland, Hungary, and Italy, which all reached higher than 25% non-susceptibility levels. In particular, Finland demonstrated significant increases in erythromycin non-susceptibility—6% in 1999 vs. 26% in 2007. However, positive progress has also been made in Spain, France, the UK, Croatia, and Belgium as these countries experienced significant decreases in the proportion of isolates non-susceptible to erythromycin. In addition, in 2007 fewer countries reported very high levels of erythromycin non-susceptibility—in 2006, 6 countries reported over 30% erythromycin non-susceptibility in *S. pneumoniae* isolates, whereas in 2007 only 3 countries remained at this level—France, Hungary, and Italy.

Figure 3.2.2 *Streptococcus pneumoniae*: Proportion of Invasive Isolates Resistant to Erythromycin in 2007.⁸⁸

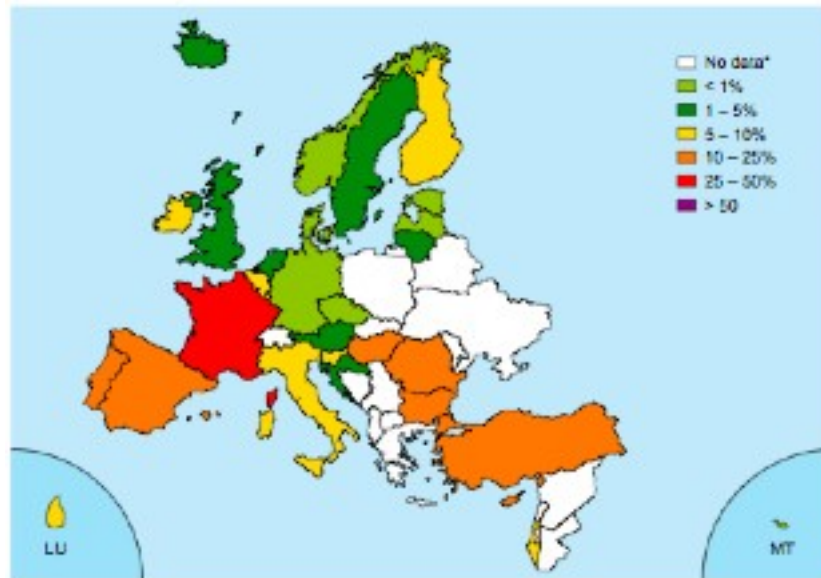


*These Countries Did Not Report Any Data or Reported Less than 10 Isolates.

S. pneumoniae Dual Non-Susceptibility to Penicillin and Erythromycin⁸⁸

In 2007, trends of dual non-susceptibility varied across Europe. Dual non-susceptibility remained below 5% for 13 countries and between 5–10% for 8 countries. However, high dual non-susceptibility levels of 10–20% were reported in 6 countries. In 2007, Cyprus and France reported the highest dual non-susceptibility levels, 20% and 29% respectively. The data highlights another worrisome trend—despite low relative numbers of dual non-susceptible isolates, 3 low-endemic countries (Norway, Germany, and the Netherlands) showed a continuously significant increasing trend of dual non-susceptible isolates. In addition, dual non-susceptibility levels have risen in Ireland, Finland, and Turkey. However, there are also signs of improvement in trends for some European countries with previously high dual non-susceptibility levels. In Belgium and Spain, dual non-susceptibility levels fell significantly—particularly in Spain where levels halved from 2001 to 2007.

Figure 3.2.3 *Streptococcus pneumoniae*: Proportion of Invasive Isolates with Dual Non-Susceptibility to Erythromycin and Penicillin in 2007.⁸⁸



*These Countries Did Not Report Any Data or Reported Less than 10 Isolates.

S. pneumoniae resistance is dynamic and thus surveillance systems like the EARSS are necessary to shed light on significant changes in resistance trends that may threaten public health. Although 5 countries (3 of which had the highest PNSP proportions in 2006) experienced significant decreases in PNSP levels, non-susceptibility is increasing in Finland and Turkey. In addition, despite the fact that several countries witnessed a drop in the prevalence of erythromycin non-susceptibility, an equal number of countries experienced a rise in non-susceptibility in 2007. Finally, dual non-susceptibility increased in the majority of European countries. However, Belgium and Spain are the exception, showing a decrease for dual as well as for PNSP and erythromycin non-susceptibility.

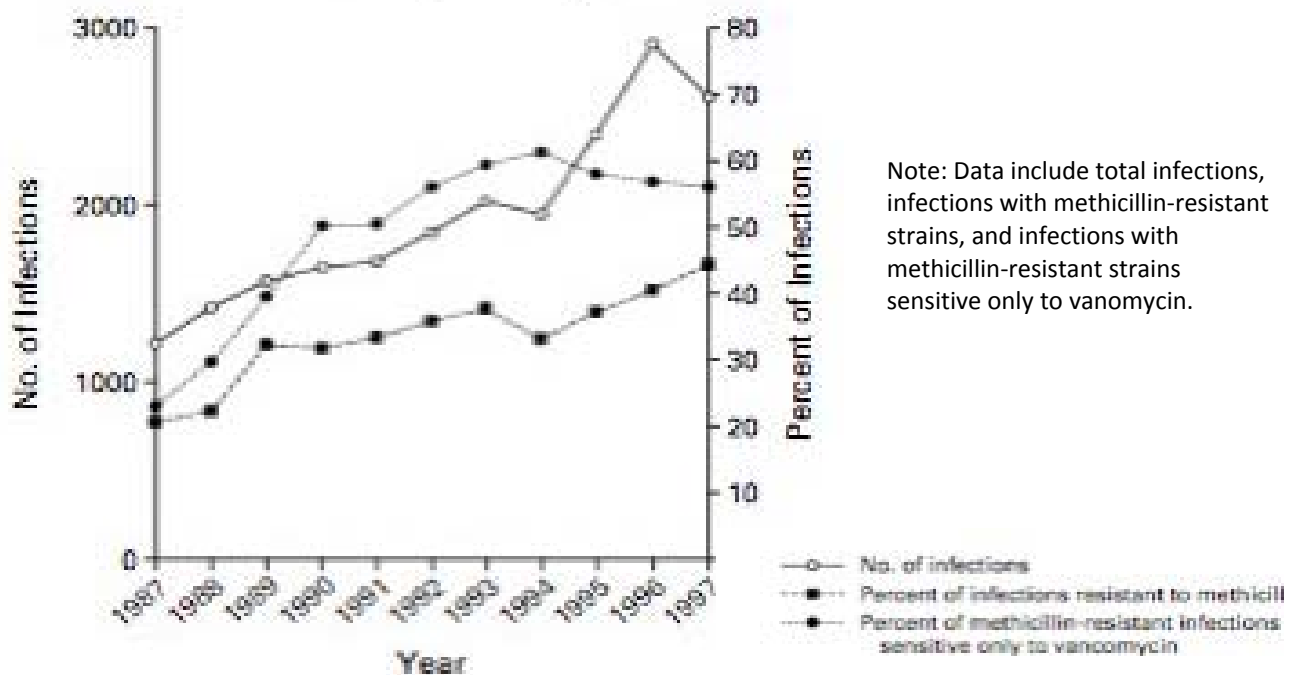
Staphylococcus aureus and Methicillin-resistant *S. aureus*

Infections caused by the *S. aureus* pathogen, particularly MRSA infections, are a major cause of illness and death worldwide. *S. aureus* is a leading cause of hospital-acquired infections and is increasingly becoming prevalent in CA infections as well. MRSA has rapidly spread in Europe—in 2006, methicillin-resistance occurred in up to 25-50% of isolates in most of southern Europe and Ireland and the United Kingdom (UK) (EARSS, 2007). In the US, MRSA is now the most commonly isolated antibiotic-resistant pathogen⁹¹. According to Klein et al., during the period between 1999 and 2005 in the US, the estimated number of *S. aureus*-related hospitalizations increased 62% (from 294,570 to 477,927) and the estimated number of MRSA-related hospitalisations more than doubled (from 127,036 to 278,203)⁹². Specifically, *S. aureus* manifests itself in numerous clinical outcomes—the pathogen is the primary cause of lower respiratory

tract infections and surgical site infections and the second leading cause of nosocomial bacteraemia, pneumonia, and cardiovascular infections⁹².

The pathogen is extremely difficult to treat and is associated with greater complications, mortality, and morbidity because of its evolving resistance to antibiotics. According to Lowy, by the late 1960s, more than 80% of community and hospital-acquired *S. aureus* isolates were resistant to penicillin⁹³. In particular, *S. aureus* isolates from intensive care units have rapidly become resistant to a greater number of antibacterial agents over the past several decades. Since 1970, the NNIS System has collected nosocomial infection surveillance data of hospitals in the US⁸⁹. In a report published in 2004, the NNIS System reported a continuing increase in antibacterial resistance in US hospitals⁸⁹. The data demonstrated that the proportion of *S. aureus* isolates that were resistant to methicillin, oxacillin, or nafcillin was nearly 60% in 2004. In addition, the NNIS System found that MRSA increased by 11% amongst nosocomial infections in intensive care unit (ICU) patients (calculated as the rate of 2003 compared with mean rate of resistance from the previous 5 years). Increased resistance means that fewer existing antibiotics can effectively treat such hospital-acquired infections. In the Figure 3.2.4 below, Lowy used data from the NNIS in the US to demonstrate the gap between the number of infections and the percent of infections sensitive and resistant to antibacterial agents⁹⁴.

Figure 3.2.4 *Staphylococcus aureus* infections in Intensive Care Units in the National Nosocomial Infections Surveillance System, 1987 through 1997.⁹⁴



As fewer antibiotics are sensitive to available antibiotics, morbidity and mortality due to MRSA have become an unfortunate reality for many patients. Studies have found that, with MRSA, the risk of mortality is double that of non-resistant strains of the bacteria⁹⁵. An estimated 2 million patients in US hospitals are infected with MRSA during hospital stays, accounting for 90,000 deaths, and in 70% of these mortality cases, resistant bacteria are the primary cause of death¹. Similarly, in the EU it is estimated that 2 million patients every year acquire nosocomial infections and account for 175,000 deaths per year^{4,85}.

Studies have also demonstrated a dramatic increase in the number of methicillin-resistant strains found in the community. Early studies of community-acquired MRSA (CA-MRSA) focused on particular patient groups, such as those with a history of injection drug use and other high-risk patients with serious illnesses, previous antibiotic therapy, or residence in a nursing home. However, Moreno et al. demonstrated that CA-MRSA was becoming present in patients with a general and non-high risk profile on admission to a US university hospital participating in the 21 month study⁹⁶. In addition to identifying that MRSA is spreading amongst the general population, Moreno et al. determined the frequency of CA-MRSA compared with nosocomial MRSA cases and found that 58% of MRSA cases were CA, 28.5% were nosocomial, and 13.5% were transfers⁹⁶.

3.2.2 Antibiotic resistance trends in developing countries

Whilst there are still high levels of resistance in developed countries, the most alarming levels of resistance are in developing countries^{19,20}. In developed countries a prescription is usually required for antibiotics, whilst in developing countries, antibiotics are often available over-the-counter, leading to self-medication and inappropriate use. A study found that in developing countries, rates of neonatal hospital acquired infections were 3–20 times higher than babies born in developed countries. And in low- and middle-income countries, 70% of nosocomial neonatal infections could not be treated by the WHO suggested regimen of ampicillin and gentamicin due to resistance^{97,98}. Resistance in developing countries often leads to death because of a lack of access to more affordable and effective antibiotics^{99,100}.

3.3 Clinical and Economic Impact of Resistance

The impact of antibiotic resistance can be assessed from the perspective of the hospital, a third-party payer, the patient, and society¹⁰¹. The majority of studies assess the impact of resistance from a hospital perspective as data regarding in-hospital morbidity, mortality, and the costs associated with resistance are relatively easy to retrieve¹⁰². Studies taking the patient perspective typically determine the short-term direct effect of resistance on the affected patient in terms of mortality and length of hospitalization. The indirect and long-term consequences of antibiotic-resistant infections on patients

should also be measured, however, such data is often difficult to gather. A few studies have assessed the impact of antibiotic resistance from the social perspective. Evidence collected so far suggests that antibiotic resistance leads to increased morbidity, mortality, and prolonged hospital stays and thus impose major financial outlays for health systems and patients. According to Cosgrove and Carmeli, the majority of published studies have shown an association between antibiotic resistance and adverse outcomes on the order of a 1.3–2-fold increase in mortality, morbidity, and cost for patients with resistant versus susceptible infections¹⁰². However, the full economic impact of antibiotic resistance is difficult to quantify due to differing perspectives as well as due to the numerous potential externalities to be considered. There is also a great deal of uncertainty surrounding the effect of current drug consumption on future resistance, and whether this ought to be included in cost estimates⁶³.

3.3.1 Clinical outcomes

Many studies conclude that greater mortality is associated with antibiotic-resistant infections, relative to antibiotic-susceptible infections. For example, Cosgrove et al. reported that the risk of mortality is doubled for patients with MRSA compared to patients with non-resistant strains of the bacteria⁹⁵. In a more recent and extensive report using meta-analysis of data from various studies with relevant mortality data published between 1980 and 2000, Cosgrove also determined that a significant increase in mortality was associated with MRSA bacteraemia, relative to methicillin-susceptible *S. aureus* (MSSA) bacteraemia (OR 1.93, P<0.001)²⁸. In another study evaluating patients with *S. aureus* surgical site infections, Engermann et al. determined that the presence of MRSA in a surgical wound increased the adjusted 90-day postoperative mortality risk by 3.4-fold compared with the presence of MSSA and by 11.4-fold compared with the absence of infection¹⁰³.

Various treatment-related factors are associated with the increased risk of morbidity, mortality, and length of hospital stay for patients with resistant infections. According to Cosgrove and Carmeli, antibiotic-resistant pathogens affect patient outcomes in 3 different ways¹⁰². First, the fitness of a bacterial pathogen may be altered by resistant genes, making the pathogen more or less virulent. Second, the presence of resistance in a bacterial pathogen can lead to a delay in the administration of appropriate antibiotic therapy. Third, the antibiotic therapies required to treat resistant pathogens may be toxic or inadequate¹⁰².

In terms of delay in administration of appropriate antibiotic therapy, patients with resistant infections are at risk of receiving delayed administration of effective antibiotic therapy. For example, approximately 43% of patients with MRSA did not receive appropriate therapy within 45 hours of onset of *S. aureus* compared with only 9.8% of patients with susceptible methicillin-resistant infection¹⁰⁴. Such a delay in adequate treatment is concerning as this increases the risk of poor clinical outcomes for patients.

Lodise et al. determined that when patients with nosocomial *S. aureus* bloodstream infections faced a delay in treatment exceeding 45 hours, their risk of mortality tripled¹⁰⁴. In addition to increased risk of mortality, Lodise et al. found that delayed treatment increased hospital length of stay for patients—the length of stay for patients with delayed treatment compared to those treated effectively within 45 hours of onset of nosocomial *S. aureus* bloodstream infections was 20.2 days versus 14.3 days, respectively¹⁰⁴. In addition to timing of treatment, antibiotic class, activity, and dosage also impact the clinical outcomes of patients infected with resistant bacteria. Cosgrove and Carmeli note that infections caused by antibiotic-resistant pathogens may require more toxic therapy that can lead to adverse outcomes¹⁰². For example, a study conducted by Levin et al. demonstrated that the use colistin for treatment of highly resistant *Pseudomonas* or *Acinetobacter* infections is associated with renal dysfunction¹⁰⁵. Other studies demonstrate that some antibiotic agents commonly used to treat resistant pathogens may in fact be less effective than other agents used to treat the susceptible strain of the infection. For example, research has demonstrated that vancomycin (which has become a cornerstone of therapy for serious methicillin-resistant infections) may in fact be inferior to antistaphylococcal β -lactams for treating infections with elevated bactericidal activity in terms of minimum inhibiting concentrations¹⁰⁶. Finally, in a more recent study, Cosgrove et al. propose another treatment related factor that may affect patient outcomes⁹⁵. They suggest that patients with severe cases of antibiotic resistant infection often require an increased frequency of surgical interventions to control infection²⁸. Therefore, early detection and diagnosis, timely treatment, and adequate dosage and class of antibiotic therapy are essential to improve clinical outcomes for patients with resistant bacterial infections.

3.3.2 Cost of resistance

In general, the total cost of resistance can be conceptualized as consisting of 3 components: 1) direct medical costs, which include longer length of hospital stay, increased costs within services, isolation and infection control measures, and increased frequency of surgical intervention and other complications; 2) organizational and infrastructure costs, which are associated with maintaining surveillance programmes and central reference laboratories; 3) and indirect costs, including lost earning potential stemming from morbidity and mortality amongst those with drug-resistant infections.

Numerous studies have been conducted to compare the morbidity, mortality, and costs associated with susceptible versus resistant bacteria in hospitals. In 1992, the US Office of Technology Assessment (OTA) conducted a study to estimate the hospital costs of antibiotic resistance resulting from hospital-acquired infections¹⁰⁷. The OTA estimated that the extra cost of hospitalizations resulting from antibiotic resistant infections was approximately \$1.3 billion (1992 US dollars). Canadian studies have also estimated direct costs associated with hospital care. According to Bryce and Kerschbaumer, drug resistant infections add approximately \$10,000 to \$20,000 to the cost of each hospital

stay in Canada, in terms of per diem room costs, case detection, prevention of cross-transmission and other indirect costs compared to drug susceptible infections¹⁰⁸. Birnbaum et al. estimated that such costs of each hospital stay accumulated to a national annual incremental cost between \$9 and \$14 million¹⁰⁹. It has also been estimated that if antibiotic resistance continues to rise at the current rate, the cost of antibiotic drug treatment in Canada could increase from \$695 million to over \$1.8 billion¹⁰⁹. In addition, many studies have sought to estimate costs associated with certain conditions. For example, the annual cost associated with antibiotic resistant ear infections is \$20 million in the US¹¹⁰, and in the UK, patients with drug-resistant urinary tract infections are 70% more expensive to treat at the GP level than those with drug-susceptible infections¹¹¹. In particular, many experts have estimated the direct medical costs associated with MRSA due to a growing public health concern regarding this pathogen. According to a study conducted by Engermann et al., patients with MRSA infection had mean attributable excess hospital charges of \$13,901 and \$41,274, compared to patients with MSSA infection and patients without infection, respectively¹⁰³.

However, there are contradictory conclusions from studies about the clinical and economic impact associated with susceptible versus resistant bacteria. Such differences may be explained by the fact that factors other than drug resistance may explain the association between resistant infection and higher mortality, morbidity, and costs. Methodology may vary, particularly in measuring the impact of resistance. These may include: controlling for length of stay; selection of the control group; adjustment for severity of illness; timing of the onset of infection; timing of the measurement of the severity of the underlying illness; defining mortality and morbidity; and the approaches used to measure costs associated of antibiotic resistance¹⁰². Howard et al. argue that a key factor underlying such differing results is patient severity of illness and how it is used to measure the affect hospital-acquired infections on patient outcomes¹¹². In addition, Lodise et al. note that certain medical and co-morbid conditions predispose patients to MRSA infection and that such clinical factors may independently contribute to adverse clinical outcomes⁹¹ leading to inherent selection bias in some studies. Finally, the varying treatment and prescribing practices across hospitals can influence study results¹¹². Despite these arguments, 2 meta-analyses studies that adjusted for severity of illness and co-morbid conditions demonstrated that the mortality rates were significantly higher for MRSA compared to methicillin-susceptible *S. aureus* infection and that the difference in mortality could not be solely explained by patient factors^{95 113}.

Many studies estimating the direct cost of resistance only consider the costs to the health sector, such as hospital length of stay, treatment, clinical complications, morbidity, and mortality. These may severely underestimate the true cost of resistance to patients and society. First, estimates of the direct cost of resistance on the health sector rarely consider the additional costs associated with physicians changing their

prescribing patterns to counter resistance. For example, according to Howard et al., studies that examine only the costs of treatment failure in patients with infections due to resistant pathogens may understate the burden of resistance because local susceptibility patterns may influence the physician's empirical treatment of patients with infections¹¹². Specifically, in areas where antibiotic resistance is prevalent, physicians fearing contagion may prescribe alternative drugs rather than the medication that in the absence of resistance would be preferred on the basis of cost, dosing schedule, or side effect profile¹¹². Howard et al. argue that the excess drug costs, inconvenience, and side effects experienced by patients when physicians switch empiric therapies should be included when measuring the burden of antibiotic resistance¹¹². Second, many studies do not incorporate a societal perspective when estimating the direct cost of resistance and thus do not consider the impact of resistance across all sectors of the economy. Smith et al. argue that the majority of cost estimates do not account for the impact of resistance on non-health sectors and economic indicators, such as national income, labour supply, and economic growth¹¹⁴. The authors use a computable general equilibrium model to take into account the economy-wide impact of antibiotic resistance.^{xiii} According to their model, the real gross domestic product (GDP) falls by between 0.4 and 1.6% (equivalent to a £3–11 billion loss in monetary terms in the UK). In addition, household income, government tax revenues, and total national savings fall by up to 0.3, 0.35, and 2%, respectively. The authors also estimate that consumers in the UK would be willing to pay about £8 billion to avoid the impact of MRSA. According to Smith et al., the model demonstrates that resistance affects not only the healthcare sector, but also the wider economy. Therefore, the costs and the social impact of resistance are severely underestimated and thus policies to contain resistance are frequently undervalued.

Phelps also attempts to account for the non-health sector externalities associated with antibiotic consumption as a consequence of resistance in the US¹¹⁵. In his calculation, Phelps considered the costs of prescribing more expensive drugs, costs of additional hospital days, and the costs of premature death. He estimated that the national cost of resistance ranged from \$100 million to \$35 billion (1989 dollars), depending on the rate

^{xiii} Smith et al. lay out an economic model to explain the impact of resistance on non-health sectors and the wider economy. They argue that increasing mortality and morbidity attributable to resistance amongst the population of working age will lead to a fall in the labour supply and labour productivity. Consequently, there would be a fall in national output since this is a direct function of the quantity (labour supply) and quality (productivity) of physical and human inputs. Such a decline in national output would translate into lower national income, national savings, welfare, and investment in capital, thus further diminishing the productive capacity of the economy. Therefore, the marginal cost of production to firms will rise, firms' profitability will fall, and thus unemployment will rise. Such effects lead to a reduction in overall social welfare. Smith et al. incorporate such impacts on the non-health sectors into their calculation of the costs associated with resistance. 114. Smith Rea. Assessing the macroeconomic impact of a healthcare problem: the application of computable general equilibrium analysis to antimicrobial resistance *Journal of Health Economics* 2005;24:1055-1075.

of resistance growth and probability of death following infection. Such a wide range of cost estimates demonstrates the difficulties of obtaining sufficient information to calculate the burden of resistance. In 2003, Elbasha modified this model to calculate the deadweight loss to society from resistance net of any benefit resulting from antibiotic treatment and reported an annual loss of between \$378 million and \$18.6 billion, with \$225 million attributed to amoxicillin use alone ¹¹⁶. In the EU, estimates of cost associated with antibiotic consumption in 2001 were €9 billion, with the costs associated with MRSA infections totalling €117 million ¹⁹. More comprehensive estimates of the social cost of antibiotic resistance are anticipated in the forthcoming Burden of Resistance and Disease in European Nations (BURDEN) project, commissioned by directorate general (DG) for Health and Consumer Affairs (DG SANCO).

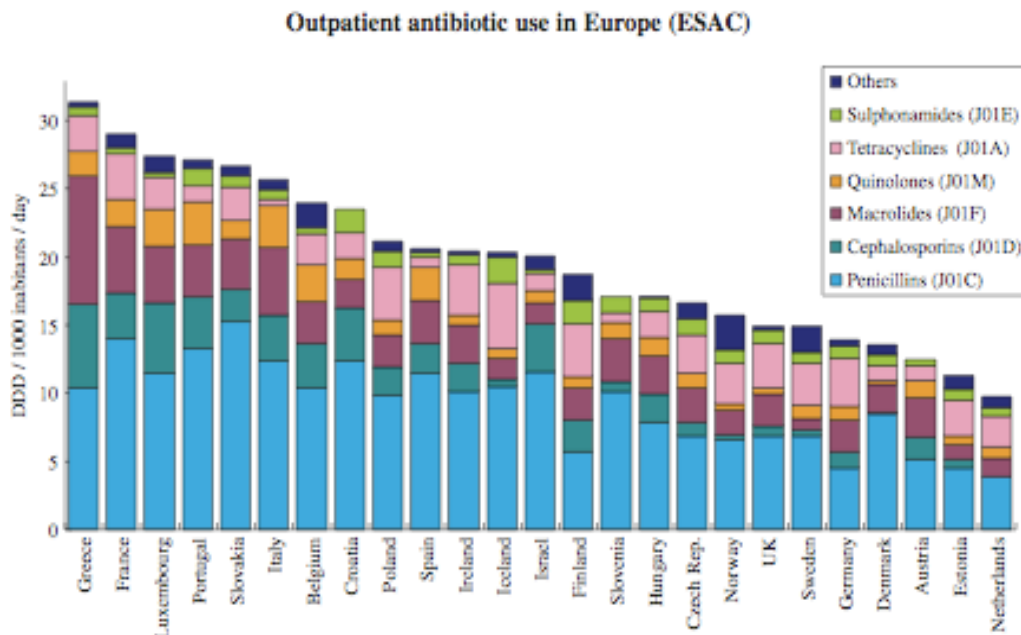
4.0 CAUSES OF ANTIBIOTIC RESISTANCE

The cause of the growth in antibiotic resistance is largely twofold: one reason is related to how antibiotics are used in practice and the other reason is related to insufficient investment into research for diagnostics and antibiotics.

4.1 Misuse of Antibiotics

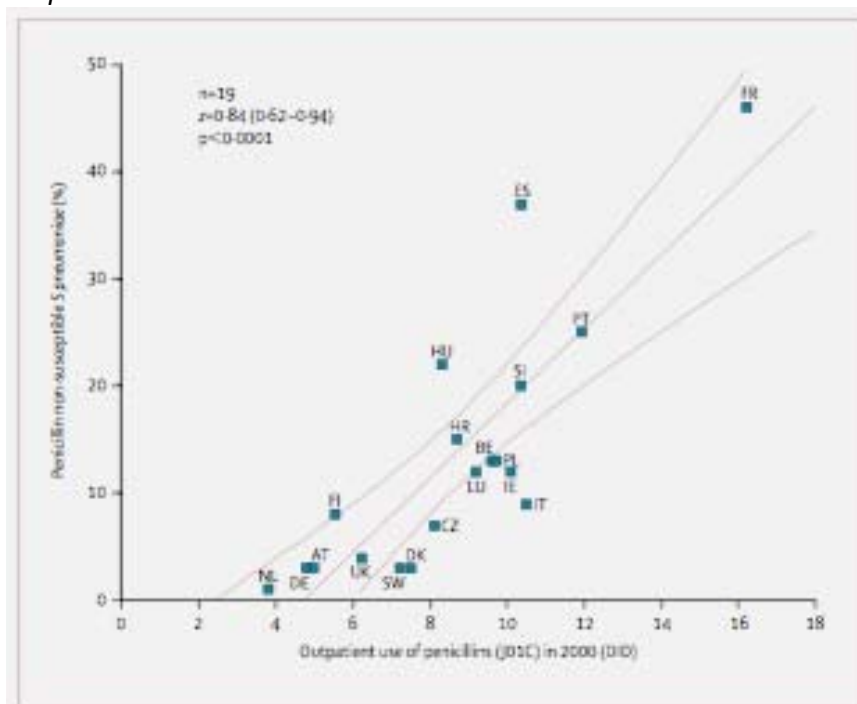
Antibiotic consumption and prescribing patterns vary within Europe, depending on the incidence of CA infections, cultural and social determinants, the pharmaceutical market, regulatory practices, public knowledge about antibiotics and resistance, and the health care system, structure and resources^{117#544}. The European Surveillance of Antimicrobial Consumption (ESAC) project is an international network of national surveillance systems that collects data on antibiotic consumption in ambulatory care and hospital settings from 34 European countries. Figure 4.1.1 provides a summary of data from the ESAC on total outpatient antibiotic use in 25 European countries in 2003^{117#544}. Compared to Northern European countries, Southern, Mediterranean, and Eastern countries tend to have greater seasonal variation in antibiotic usage (demonstrating inappropriate consumption of antibiotics during seasons with high rates of cold viruses) as well as higher overall usage (defined by daily doses/1000 inhabitants/day)^{118#537}. In addition to volume differences, there is also variation in the choice of therapy between European countries—Mediterranean countries tend to prescribe more broad-spectrum antibiotics^{119#543}.

Figure 4.1.1 Total Outpatient Antibiotic Use in 25 European Countries in 2003^{117#544}.



It is important to compare antibiotic consumption trends to rates of antibiotic resistance in order to determine whether or not policies encouraging reduction of antibiotic consumption can in fact slow the rapid spread of resistance. Numerous studies confirm that increased antibiotic consumption is associated with the emergence of antibiotic resistance worldwide^{87`#545}. For example, a study collecting data from the EARSS project, the telithromycin surveillance (PROTEKT) project, and the pan-European project demonstrated a positive correlation between resistance and antibiotic consumption^{120`#546}. Figure 4.1.2 below shows the study's conclusion that a positive correlation exists between penicillin use and prevalence of penicillin non-susceptible *S.pneumoniae*^{120`#546}. Thus, higher rates of resistance were observed in European countries with moderate to high antibiotic consumption.

Figure 4.1.2 Correlation between Penicillin Use and Prevalence of Penicillin Non-Susceptible *S. pneumoniae*.¹²¹



Key to Figure. AT: Austria; BE: Belgium; HR: Croatia; CZ: Czech Republic; DK: Denmark; FL: Finland; FR: France; DE: Germany; HU: Hungary; IE: Ireland; IT: Italy; LU: Luxembourg; NL: The Netherlands; PL: Poland; PT: Portugal; SL: Slovenia; ES: Spain; UK: England.

Inappropriate prescribing of antibiotics has facilitated the rapid spread of resistance. There are several actors in the health care system that may contribute to inappropriate prescribing—pharmaceutical companies who market their antibiotic to the general public, patients who insist on antibiotics, physicians who do not have time to wait for diagnostic culture test results or to explain why antibiotics are not necessary and thus prescribe them to save time, and physicians who are overly cautious^{122`#11}. For example,

studies have found that in developed countries physicians often over-prescribe antibiotics in an attempt to eliminate all risk¹²³. Pharmaceutical marketing often targets physician insecurity, encouraging harmful over-prescribing with broad-spectrum drugs¹²³. Such marketing practices are in many cases counter-productive as broad-spectrum antibiotics also kill the good bacteria that aid in natural function, and antibiotics are ineffective against viral infections¹⁰⁰. The problem is confounded by the fact that antibiotics are inexpensive to the patient through third-party coverage and inexpensive generics.

4.1.1 Physicians and healthcare providers

Antibiotic resistance poses as a challenge for health care providers (HCPs) for whom physicians are the predominant prescribers in general. To effectively treat infectious diseases and limit the emergence of antibiotic resistance and its spread, HCPs must change their evaluation, diagnosis, treatment, and prescribing methods.

Frequently, HCPs inappropriately diagnose and prescribe antibiotics for infections caused by viruses, such as the common cold. A 2001 study estimated that 55% of all antibiotics prescribed in the US for upper respiratory infections were unnecessary^{124`#541}. Rapid antigen-based diagnostic tests, such as for influenza and pharyngitis, can facilitate the evaluation process and help eliminate unnecessary prescribing of antibiotics^{68`#63}. However, lack of readily available and timely diagnostic testing contributes to cost- and time-related misuse of antibiotics. HCPs infrequently test for whether a patient has a viral or bacterial pathogen before prescribing antibiotics because rapid, real-time, reliable, point-of-care (POC) diagnostics are not always available and the cost of such advanced diagnostics can be prohibitive^{20,44,125}. Therefore, HCPs need improved and lower-cost diagnostic tools to facilitate diagnosis and thus reduce unnecessary prescribing of antibiotics.

In addition to ensuring accurate diagnosis, it is also important to improve prescribing practices once the HCP identifies that the infection requires antibiotics. HCPs frequently prescribe combination “broad-spectrum” antibiotics (that kill a wide variety of bacteria) when a single “narrow-spectrum” antibiotic (that kills specific bacteria) would treat the infection more accurately and effectively^{122`#11}. In theory, before initiating antibiotic therapy, HCPs should perform culture and sensitivity testing (C&S) to determine the most likely causative bacteria for a site of infection and thus use as narrow spectrum of an antibiotic as possible^{68`#63}. For example, the CDC currently recommends C&S of purulent wounds for routine infection management in patients^{68`#63}. However, most HCPs will not wait for a pathogen to be cultured when a patient is seriously ill. Consequently, in many cases, HCPs resort to broad-spectrum antibiotics. In addition to using C&S testing for determining the initial antibiotic therapy, a HCP should also take into account the patient’s risk for less common or resistant pathogens based on the individual’s medical and travel history^{68`#63}.

The length of antibiotic therapy is not usually based on clinical evidence and the majority of HCPs follow general recommendations that err on the side of caution. Few randomized controlled trials (RCTs) exist that establish how long antibiotic therapy should be prescribed for different infections. Of the few existing studies on the necessary length of therapy, the consensus appears to be that short-course therapy is just as effective as long-course therapy in treating bacterial infections^{124`#541}. However, this is still under debate and medical experts currently recommend that patients continue with the full course of antibiotics.

A final important factor to consider in relation to inappropriate prescribing is that HCPs respond to different incentives that often encourage excess antibiotic prescribing. An example of such an incentive is the Medicare quality improvement initiative that focuses on early antibiotic therapy for patients with lower respiratory tract infections (see box 4.1).

Box 4.1 Coordinating Prescribing Practices with Policies—Lessons from the Medicare Product Quality Research Initiative in the US

The Centers for Medicare & Medicaid Services (CMS) conducts the Medicare Product Quality Research Initiative programme of performance measurement to improve the quality of care for Medicare beneficiaries. The CMS programme uses clinical care pathways to achieve HCP compliance with recommended guidelines for quality care¹²⁶. The clinical pathways approach draws upon evidence-based recommendations for processes and provides assessable quality measures such as timelines. For patients with particular diseases or health conditions, hospital providers are expected to meet benchmarks for time intervals between emergency room arrivals to diagnostic and/or therapeutic procedures. In particular, the CMS records clinical pathways for Medicare patients admitted to hospitals presenting with lower respiratory tract infections. The CMS focuses on patients with lower respiratory tract infections because pneumonia accounts for a significant number of hospitalizations of Medicare beneficiaries—more than 60,000 fee-for-service Medicare hospitalizations yearly¹²⁷. Timing of antibiotic therapy for Medicare patients admitted to the hospital with lower respiratory tract infections has been an audited performance measure. The CMS focuses on this particular performance measure because timely administration of antibiotic agents to hospitalized Medicare patients with pneumonia is associated with improved survival. Reports demonstrate reduced mortality and improved health outcomes for Medicare patients and cost savings for hospitals when patients received antibiotics within 4 hours of presentation¹²⁷. Current CMS guidelines recommend that HCPs administer antibiotic treatment to patients with lower respiratory infections within 4 hours of admission to the hospital.

Hospitals and HCPs have increasing pressure to meet the CMS recommended guideline for antibiotic therapy since the performance measure is used as a basis for public reporting and pay-for-performance programmes. When the CMS sets benchmarks for the time interval for providers to administer antibiotics, providers and hospitals report and measure when antibiotics are prescribed. The CMS provides HCPs with the incentive to administer antibiotics as quickly as possible to meet the benchmark and thus there are no incentives to withhold antibiotics, even if inappropriate. However, existing diagnostic technology limits HCPs from having relevant evidence within the 4-hour time interval to determine whether a patient actually needs antibiotics. Conventional culture techniques require a couple of days before presence of a bacterial pathogen can be confirmed¹²⁶. Although new molecular techniques such as gene amplification take approximately 4 to 6 hours to quantify pathogenic organisms, such techniques are expensive and not suited for use in the hospital¹²⁶. Consequently, the CMS performance measure presents a challenge as providers do not have the tools to properly diagnose patients within the window of time to meet the target. The CMS target for timely antibiotic administration further complicates the process of diagnosis because HCPs are not penalized for inappropriate administration of antibiotics for viral upper respiratory tract diseases¹²⁶. Therefore, attempts to achieve a performance target of 100% for antibiotic administration may encourage inappropriate antibiotic usage¹²⁸. Consequently, many emergency departments initiate antibiotic therapy on Medicare patients who might present signs of respiratory infection without regard to the specific location or the causative agent of infection¹²⁶. Such behaviour is problematic since elderly patients with pneumonia present with atypical signs and symptoms¹²⁹. A recent study determined that Medicare patients with a hospital discharge diagnosis of pneumonia present in an atypical manner that could lead to a diagnostic uncertainty¹²⁹. Inappropriate diagnosis and antibiotic administration can lead to antibiotic resistance as well as divert limited resources from other patients actually in need of antibiotics¹²⁹.

The CMS example provides insight into the importance of embracing a whole system perspective and aligning incentives of various stakeholders when creating benchmarks for performance. Targets linked to pay-for-performance do encourage HCPs to follow particular evidence-based procedures that can lead to improved health outcomes. However, when the time interval for achieving a benchmark excludes the possibility of performing diagnostic exams, HCPs will not have the incentive to perform diagnostic exams on patients presenting with atypical signs and symptoms. In the case of antibiotics, HCPs have the incentive to engage in excessive antibiotic prescribing without proper diagnosis. Therefore, policy makers must design coordinated policies that encourage HCPs to meet quality care standards whilst also using discretion and diagnostic tools to determine the most appropriate treatment and use of scarce health care resources.

4.1.2 Livestock and agriculture

In addition to inappropriate prescribing and over-consumption of antibiotics, antibiotic use for growth promotion and treatment of infection in animal livestock contributes to the acceleration of antibiotic resistance. More than half of all antibiotics produced globally are used in animals^{63,85}. Despite the large quantity of antibiotics purchased for growth promotion in livestock, the value of this particular market is much smaller than the market for antibiotics used in humans because antibiotics purchased by humans are sold at a relatively higher price⁶³. For example, in 1992, Bayer's sales of human antibiotic Ciprofloxacin far exceeded sales of the animal-growth promoter antibiotic Baytril® (same class of antibiotics as Ciprofloxacin)—€ 2 billion compared to € 300 million respectively⁶³.

The livestock industry uses antibiotics predominately for two purposes—first, to improve feed efficiency and rate of weight gain, and second, for disease prevention and treatment⁶³. Animals are given antibiotics in low doses over a long period of time to promote growth, but this practice drives resistance through long-term exposure¹⁰⁰. However, antibiotics have only a minor effect on growth of animals. The EU banned their use for this purpose in 2006²⁰. The US still allows antibiotics in animals, but the Centers for Veterinary Medicine and the Food and Drug Administration (FDA) closely scrutinise animal antibiotic use¹³⁰. However, when there is an infectious outbreak, instead of singling out the infected animal, farmers commonly treat the entire flock, increasing the risk of antibiotic resistance.

4.2 The Role of Diagnostics in Antibiotic Resistance

The ability to identify targeted pathogens with rapid diagnostic tests (RDTs) could greatly improve the use of antibiotics as well as reduce the cost and time needed to conduct clinical trials¹³¹. Currently the most accurate and widespread identification of bacterial infections entails culture methods and biochemical assays within a laboratory setting which is slow, taking 36–48 hours to provide results¹³², although the availability of RDTs for certain bacteria are becoming more widespread (see Box 4.2). This deters doctors in both hospitals and general practice from waiting for results before treating patients or from sending tests to the laboratory at all. This often leads to viral infections being misdiagnosed as bacterial infections, leading to inappropriately prescribed antibiotics. Unnecessary use of broad-spectrum antibiotics is also widespread as the lack of appropriate RDTs hinders practitioners from determining the precise cause of the infection¹³². Risk aversion on the part of physicians and ensuing over-prescription of antibiotics will continue to amplify the growth of resistance until doctors have more sophisticated and effective diagnostics that are quick and easy-to-use at the POC and with easy maintenance.

In recent years some of the technical barriers to the development of RDTs have been lifted, for example with patents expiring on key platform technologies (such as those surrounding polymerase chain reaction [PCR]), to the point that academics no longer perceive significant technical barriers to their development. The persistent time-lag of RDTs reaching the market and their under-provision by the market suggest that a bottleneck exists somewhere in the market itself. It has been proposed that significant developer uncertainty surrounds the issue of whether the use of complementary diagnostic tests would increase or decrease the size of the corresponding antibiotic market share¹³³. Indeed the current absence of large pharmaceutical companies from the diagnostics market could suggest the presence of a perceived disincentive in developing RDTs to guide the use of their antibiotic products.

Demand side determinants, including the health system structure, health system incentives, health financing and reimbursement mechanisms, the legal framework, clinical guidelines and level of resistance, significantly impact RDT market demand¹³³. Systems that impose the cost of diagnosis and the cost of treatment for worsening infection on the same party should achieve proper alignment of incentives for fostering demand for diagnostics. Indeed this alignment should not be challenging in financing systems based on comprehensive private insurance, national health systems, or social insurance systems that cover primary care visits. However, decentralized budgeting and rationing policies may work against the incentives for proper diagnosis. For example, if physician budgets include RDTs but not the treatment of more acute infections deriving from inappropriate treatment (including treatment with ineffective antibiotics), they will be less inclined to use or to stress the need for RDT procurement. However, even in financing structures which would normally promote the use of RDTs, there seems to be a lack of foresight, with some industry representatives describing the lack of RDTs as simply due to the lack of perceived demand on the part of health services. Concerns surrounding eventual uptake and diffusion of a developed RDT were also cited by industry as serving as a barrier to development¹³⁴. Long-term cost-effectiveness analyses taking into account the prolonged misuse of antibiotics are urgently needed.

In addition to the health system, resistance adds to the difficulty of producing adequate RDTs. For even if the bacterial infection can be identified, the susceptibility of the pathogen to available antibiotics must also be known if the RDT is to guide treatment decisions. Short of running full susceptibility tests using multi-compound plates in the laboratory, an understanding detection of gene variant present could greatly improve the use of POC diagnostics.

In terms of current push funding for RDTs, the EU has the Seventh Framework Programme for research and technological development (FP7). Under the programme's third call for research, published in December 2008, a key priority was 'confronting the

increasing emergence and spread of antibiotic drug resistant pathogens in Europe'. One of the 3 translational research projects for antibiotic resistance is currently focussing on POC diagnostics. In addition, the 3 year, €4.2 million project to establish the European Consortium of Microbial Resource Centres (EMBARC) should also contribute to greater innovation in RDTs. Also, with funding from the European Commission (EC), the Ultra-Sensitive Diagnosis for Emerging Pathogens (USDEP) is a consortium that includes ApoH-Technologies, the Robert Koch Institute, the Institut de Recherches pour le Développement, and the Pontifica Universidad Catolica de Chile. The consortium is exploiting a single technology apolipoprotein H (ApoH), which may improve the detection threshold (sensitivity) for diagnosis of emerging pathogens, regardless of the molecular techniques used ¹³⁵.

Box 4.2 Current Status of Diagnostic Tests for Detection of MRSA

A recent review ^{136,291} looked at currently available RDTs for MRSA detection (nasal and blood specimens). This focused on amplification and probe-based assays, the former demonstrating how multiplexing (detection of more than one marker from a mixture) and rapid detection directly from positive blood cultures has become standard thanks to the advent of real-time PCR platforms and improvements in DNA-extractions methods.

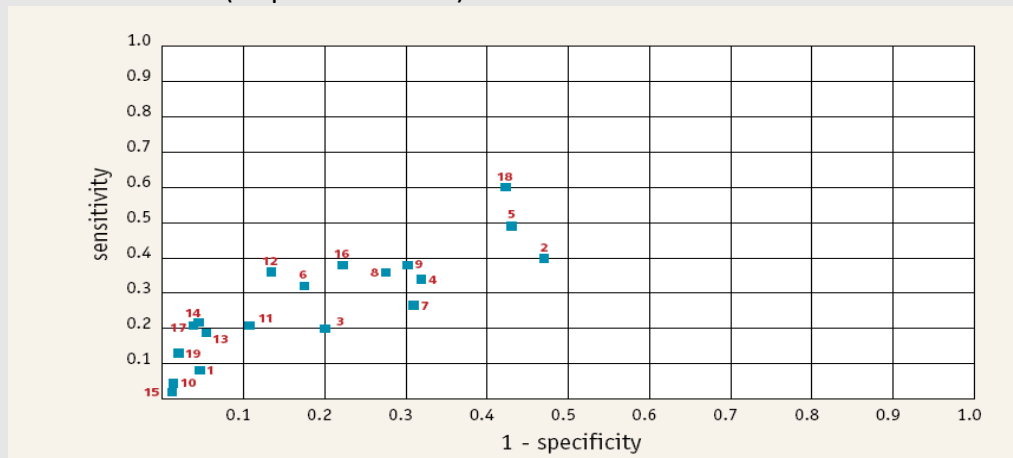
Table 4.2.1 Features and performance characteristics of commercial molecular assays for detection of MRSA. Adapted from Carroll 2008 ¹³⁶

	Test/Developer	Clinical Characteristics	Comments
	BacLite™ 3M, UK		Non-molecular assay
Molecular Assays	BDGeneOhm™ MRSA <i>BD GeneOhm</i> CA, USA	Sensitivity 88–96.1% Specificity 93.5–99% PPV 61.1–94% NPV 97–99.7% Targets: <i>SCCmec</i>	Amplifies some <i>mecA</i> -negative <i>S. aureus</i> ; does not amplify <i>SCCmec</i> type V; false-positive rate as high as 5%; inhibition as high as 0.7%–6%
	GeneExpert® <i>Cepheid, CA, USA</i>	Sensitivity 86.3–96.5% Specificity 90.4–94.9% PPV 80.5–90.4% NPV 96.6–99.6% Targets: <i>SCCmec</i>	No external peer-reviewed publications as of 2008 Likely to have similar issues as other assays that amplify targets in <i>SCCmec</i> insertion site
	HyplexStaphyloResist® <i>BAG Helathcare, Germany</i>	Sensitivity 91.5–97.6% Specificity 77.2–90% PPV 26.2–31.4% NPV 99.5–99.7% Targets: various (with hybridization)	No internal control and not available in US
	GenoQuick® <i>Hain Lifesciences, Germany</i>	Sensitivity 100% Specificity 99.4% PPV 96% NPV 100% Takes: 2hours 20 mins	No external peer-reviewed publications as of 2008

Non-amplified	PNA-FISH™ EVIGENE™ <i>AdvanDx, MA, USA</i>	Unlike PNA-FISH EVIGENE is able to distinguish MRSA from MSSA, both are rapid, simple, and has demonstrated an impact on patient outcomes	
Nucleic Acid Amplification	BDGeneOhm™ StaphSR Assay <i>BD GeneOhm CA, USA</i>	Sensitivity 100% Specificity 98.4% PPV 92.6% NPV 100% Targets: S.Aureas primers and probes; SCCmec target sequences	US FDA approval for positive blood cultures; FDA approval pending for nasal swabs, wounds; likely to have similar issues as other assays that amplify targets in SCCmec insertion site
	LightCycler® Staphylococcus Kit MGRADE <i>Roche Diagnostics, Switzerland</i>	Sensitivity & specificity 100% For CoNS: sensitivity 72%, specificity 92% Targets: ITS 16S-23S <i>mecA</i> gene for its ITS assay	Two separate non-FDA-cleared assay available for investigational use only; possible problem with mixed bloody cultures containing MSSA and MR CoNS

Their availability undoubtedly holds much promise not least as an effective tool for infection control programmes. Their more rapid turn-around times (2-4 hours as opposed to the 3 days' required by culture-based mechanisms), high negative predictive value of the assays and their ability to distinguish coagulase-negative staphylococci from MRSA and MSSA are significant developments. The consistently high sensitivities and specificities are in contrast to currently available TB diagnostics (see Figure 4.2.1, below) indicating the different technical challenges presented by different pathogens.

Figure 4.2.1 ROC Curve Based on Laboratory-based Evaluation of 19 Commercially Available RDTs for TB (all patients = 355).¹³⁷



The challenges that remain appear to be largely practical in nature. For example, laboratories must consider whether they have the resources to use these platforms as intended, for example, in real-time mode as opposed to daily batch testing. Also, clinical success in reducing the number of MRSA infections has thus far only been proven in the ICU^{136#291}. Their success in combating CA-MRSA has yet to be proven.

4.3 The Role of Vaccines in Antibiotic Resistance

Similar to antibiotics the pharmaceutical industry does not produce vaccines at a socially optimal level. The positive externalities of vaccines and antibiotics are in part related to the infectious nature of the diseases they target. Yet because vaccines can be administered preventatively as well as therapeutically (like antibiotics) the divergence between the private and social benefits become even greater^{138#1197}. Kremer and Snyder highlight that informational asymmetries are greater in the vaccines market than with drugs (predicting future demand is more challenging for a preventative product).¹³⁸ And also highlight how vaccine use may limit the size of its own market in the future¹³⁸. It is argued that this further reduces revenue and certainty relative to drugs, and likely reinforces the dogma that vaccines are necessarily, low-margin, single (or limited-use) products¹³⁹. However, vaccine development is reportedly both shorter (<10 years)^{140#1199} and less expensive than for drugs, with the most recent estimate^{141#1200} challenging previous estimates which placed vaccine development costs at approximately \$200 million^{142#1201}.

Despite the presence of these market failures which have contributed to years of underprovision (the vaccine market represents only 1.5% of pharmaceutical sales

^{143#1202}. Industry analysts have recently described vaccine R&D as a ‘high growth area’ increasing 26% between 1999 and 2003 ^{144#1203}. WHO has described some vaccine-pipelines as “crowded” ^{145#1204}, including for some of the most resistance-affected pathogens (see Appendix A). Whilst the reasons for this growth have not been systematically analysed, it is likely that increased availability of funding, increased regulatory certainty, improved supply infrastructures ^{139#1198}, technological advances and the focus on newer high-value products i.e. Prevenar™ (see Box 4.3) which offer the possibility of reduced reliance on high volume immunization schedules ^{144#1203}, have all contributed. With regards to funding specifically, the involvement of public and philanthropic donors (albeit largely for developing world vaccines) in combination with the introduction of market-related incentives such as the Vaccine Fund, AMCs and the International Financing Facility for immunizations ^{146#1205} have played a significant role and may in part explain the resurgence in private sector interest.

Vaccines offer the potential to reduce the demand for antibiotics and slow the spread of antibiotic resistance. For example, a US study of >37,000 children, heptavalent pneumococcal vaccine (PCV7) vaccination reduced first-line antibiotic prescriptions by 5.7% and second line by 13.3%. From the first dose to age 3.5 years PCV7 prevented 35 antibiotic prescriptions per 100 children vaccinated. Authors suggest that this translates into an overall reduction of 1.4 million antibiotic prescriptions annually in the US ¹⁴⁷. These findings were corroborated by a similar study in France that demonstrated a decrease in antibiotic treatment for AOM from 51.8% to 40.09% over two years ¹⁴⁸. Vaccines have varying ‘valences’ (an indication of how many serotypes [or antigens/bacterial strains] the vaccines are effective against), and the importance of including resistance-susceptible serotypes in newly developed vaccines is now widely acknowledged.

Examples from Europe

Interestingly two-thirds of global vaccine R&D is conducted by European companies and almost 90% of vaccine production takes place in Europe ^{149#1206}. A number of significant EU programmes such as the EC’s 36-month, €1.7 million novel vaccination strategies and vaccine formulations for epidemic and pandemic influenza control (NOVAFLU) and the 48-month, € 3.3 million efficacious vaccine formulation system for prophylactic control of influenza pandemics (PANFLUVAC), were launched in response to SARS (2002) and avian influenza (2003) threats. FP6 reportedly had 581 research groups from 52 countries participating in the ongoing EC supported vaccine research projects ^{146#1205}, with greater than 40% of the total EC contribution to basic vaccinology being attributed to 4 projects: including: MUVAPRED, Savin#MucoPath, MUNANOVAC and EPIVAC^{xiv}.

^{xiv} MUVAPRED; MUcosal VACCines for Poverty RElated Diseases, Savin MucoPath; project is developing vaccines for enteric and pulmonary infections, MUNANOVAC; Mucosal Nano Vaccine Candidate for HIV and EPIVAC; Epidemiology & Prevention of Vaccine-Preventable Disease.

Examples from the United States

Despite substantial and prolonged funding commitments and regulatory easing (less stringent data requirements under certain circumstances detailed in the BioShield legislation), the known pipelines for vaccines against biothreats remains relatively sparse although there has been a recent increase in public agencies seeking to commercialise avenues for their more successful projects^{150#1207}.

Box 4.3 Case study – Pneumococcal Conjugate Vaccine^{151#1208}

Conjugate vaccines such as Wyeth's heptavalent[†] pneumococcal vaccine (PCV7) Prevenar™, launched in 2000, have been shown to be effective in curtailing drug-resistant *S. pneumoniae* (DRSP):

- Decreased proportion of DRSP infections in immunised US children; from a peak of 45% in 2001 to 33% in 2002 i.e. Atlanta an incidence reduction of 85% between 1999 and 2002
- Lower incidence within the wider community due to herd-immunity effects. Evidence shows a risk-ratio reduction in toddler-to-infant transmission of 0.46–0.49
- PCV7 prevented 35 antibiotic prescriptions per 100 children vaccinated in a Californian study of 37,868 children (from first dose to 3.5 years). Suggesting 1.4 million antibiotic prescriptions could be prevented annually in the USA
- 77% decrease in invasive pneumococcal disease amongst children aged <5 years and a 39% decrease in hospital admissions for pneumonia amongst children aged <2 years^{152#1209}

Since its launch in 2000, PCV7 vaccine is already in widespread use globally and part of the National Immunisation Programme in 26 mature markets* (as of August 2008). It has been widely reported that the positive trends and impact of PCV on DRSP is eroded over time by increasing the proportion of DRSP (especially penicillin-intermediately resistant *S pneumoniae*) within non-vaccine serotypes.

[†]Wyeth's Prevenar 13 (13-valent) received its first regulatory approval in July 2009 and is currently undergoing FDA fast-track review.

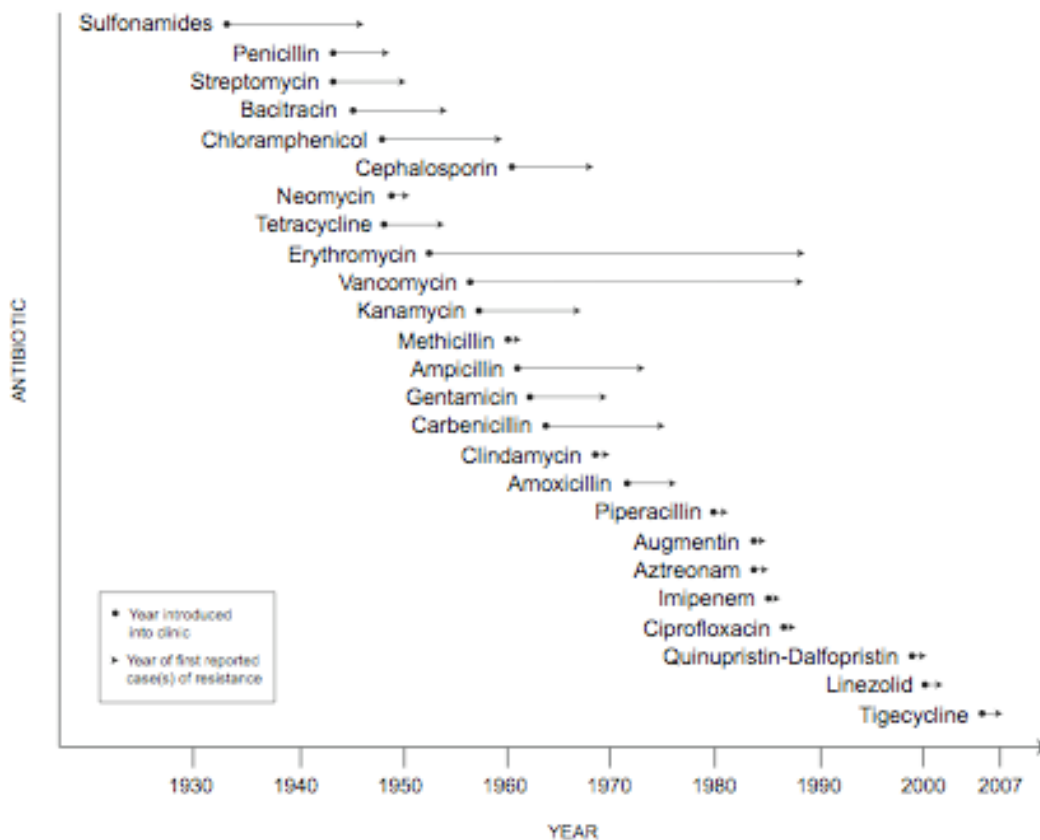
*In 2006, GAVI made funding available through 2015 for PCV introduction in the 72 countries with the lowest GNP per capita (<\$1,000 per capita) in 2003

4.4 Lack of New Antibiotics

In addition to the misuse of antibiotics and deficiencies of available diagnostic tools, the lack of sufficient development of new and novel classes of antibiotics challenges current

efforts to slow the rise of antibiotic resistance. Over the billion years of their existence, bacteria encountered a wide range of naturally occurring antibiotics and thus developed antibiotic resistance mechanisms to survive^{49,153#65}. Such survival mechanisms explain why bacteria have rapidly become resistant to most of the antibiotics developed over the past 50 years. In addition, bacteria have become resistant to multiple antibiotics, limiting the effectiveness of current treatment options for infectious diseases. In 2004, over 70% of pathogenic bacteria were estimated to be resistant to at least one of the currently available antibiotic drugs⁴⁹. Figure 4.4.1 below provides a timeline of antibiotics facing the problem of rapid emergence and spread of drug resistance^{38'#202,70}. Consequently, following the launch of an antibiotic agent, resistance in the targeted bacteria begins to develop^{154'#532,155}. New agents need to be consistently developed to keep pace with pathogenic bacteria acquiring resistance.

Figure 4.4.1 Timeline of the Rapid Rate of Resistance^{38'#202,70}.



Note: Dates are estimates.

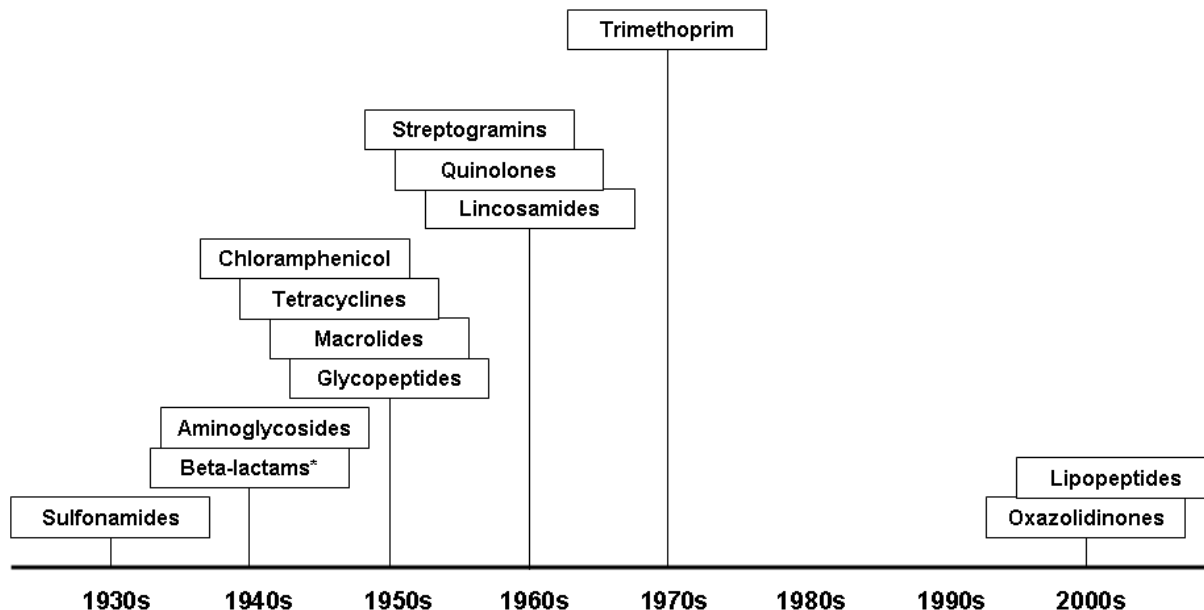
4.4.1 The antibiotic market

With sales of US \$79 billion per year, the anti-infectives market is the third largest pharmaceutical market globally after the central nervous system (CNS) and cardiovascular markets¹⁵⁶. The antibiotic market itself generates sales of US \$37 billion per year and accounts for 48% of anti-infectives and 5% of the global pharmaceutical market. In 1997, the antibiotics market was 10% of the global pharmaceutical market in sales values. Since then, this share has declined year on year as the growth in the antibiotics market was outpaced by the growth of the pharmaceutical market. Sales growth in the antibiotics market now stands at 1–2% annually versus 10% and 23% for anti-virals and vaccines, respectively^{156,157xv}.

The pharmaceutical industry provided sufficient production of new antibiotics from the 1940s until the late 1980s¹⁵⁴, several which were developed were of novel classes with new mechanisms to counter bacterial resistance to earlier agents. Figure 4.4.2 provides a timeline of the discovery of new classes of antibiotics. However, since the early 1990s antibiotic developers have launched a paucity of new antibiotic molecules that can address the problems caused by resistance. See Figure 4.4.3 for a visual representation of the significant drop in production of antibiotics over the past two decades.

Figure 4.4.2 Discovery of New Classes of Antibiotics

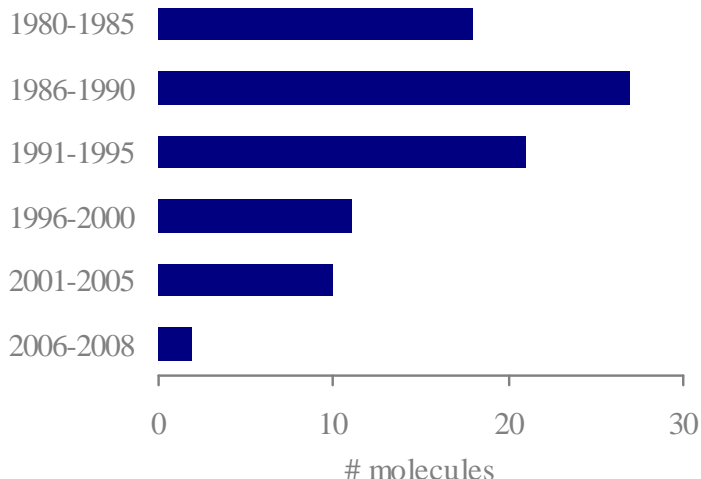
(Sources: Nordberg P et al, 2004, Levy SB, 2002, Singh MP, 2000)



^{xv} The growth of the antibiotic market peaked in 2003 at 11% from the previous year, due to the launch of Cubicin.

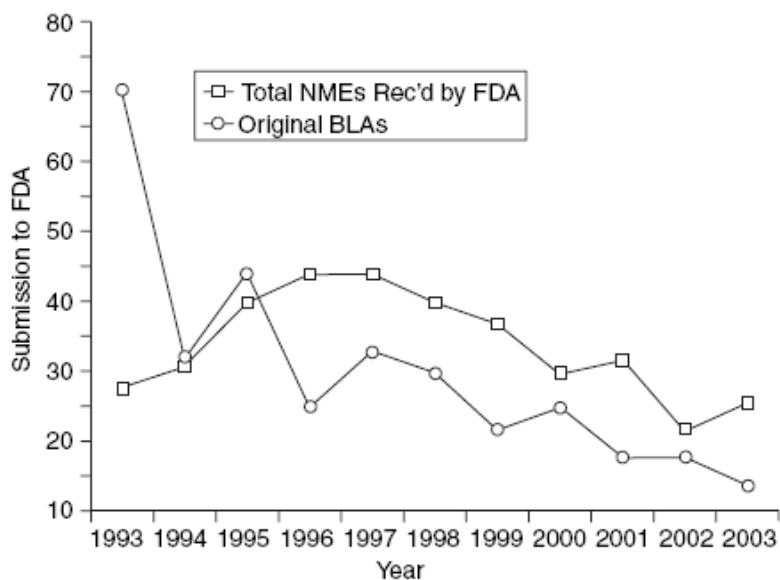
Penicillins were the first beta-lactams. Other frequently used agents of the beta-lactam class include cephalosporins and carbapenems, developed in the 1960s and 1980s respectively.

Figure 4.4.3 Number of Antibiotic Molecules Launched Since 1980 IMS Health LifeCycleTM 157



However, it should be noted that this trend is not specific to the antibiotics market. There has been a decline in activity across all therapeutic classes. This can be seen in Figure 4.4.4 which highlights the decreasing submissions to the FDA across all therapeutic classes

Fig. 4.4.4 Ten Year Trend in Drug and Biological New Molecular Entity Submissions to the FDA¹⁵⁸.



Over the past 3 decades, the number of large pharmaceutical companies funding and maintaining internal capacity for R&D of antibacterial therapies has dramatically declined. Many experts argue that such a decline in antibacterial drug discovery and development can be explained by the fact that pharmaceutical companies have decided to shift R&D resources away from antibacterial drug discovery programmes to more profitable therapeutic areas (e.g. musculoskeletal and CNS drugs)^{159,160}. Powers states that the current situation is a result of downsizing of antibiotic R&D programmes during the 1970s and 1980s¹⁰. In addition, Chopra notes that mergers and take-overs of pharmaceutical companies during the past decade have led to loss of research groups with expertise in antibiotic drug discovery¹⁶¹. Despite the rise of MRSA and VRE epidemics in the early 1990s, Pray points out that the resurgence of pharmaceutical companies returning to the field of antibiotic R&D was only temporary³⁹. By 1991, approximately 50% of large pharmaceutical companies altogether cut or reduced funding for infectious disease research programmes¹⁶². By 2005, only 8 pharmaceutical companies maintained in-house R&D capacity for antibiotics¹⁰. In the past decade, major pharmaceutical companies: Aventis, Eli Lilly, and Bristol-Myers Squibb altogether discontinued R&D efforts in the field of antibiotics¹⁰. On the other hand, in 2000, Roche spun its anti-infectives R&D unit into a separate company called Basilea¹⁶³. A handful of pharmaceutical companies including GlaxoSmithKline (GSK), Pfizer, and Johnson & Johnson continue to fund antibacterial research. Although Wyeth^{xvi} discontinued its anti-infective discovery programme, the company continues to fund the development of a few promising anti-infective drugs. In addition to funding antibacterial research, GSK has been developing potential novel treatments with the work of its Infectious Diseases Centre of Excellence for Drug Discovery. In fact, Payne and Gwynn argue that GSK has developed more potential novel treatments in the past 4 years than in the previous 20 years due to the complete DNA sequencing of a bacterial genome¹⁶⁴. However, according to Taubes, GSK's sequencing and evaluation of 300 "canonical" bacterial genes, thought as essential to the viability of bacteria, has fallen short of expectations¹²⁴. GSK spent 7 years and more than \$70 million evaluating these genes to only find 5 leads—four to fivefold lower than for other therapeutic areas¹²⁴. Consequently, none of GSK's antibacterial products have yet made it to market, as demonstrated in Table 4.4.1 below.

In addition to large pharmaceutical companies, biotechnology companies and smaller pharmaceutical companies—collectively and henceforth known as small to medium enterprises (SMEs)—have stepped in to fill some of the void in antibiotic development. Chopra et al argue that smaller companies are engaging in antibiotic R&D, particularly for the development of agents for health-care-associated infections, because the commercial returns are attractive and favourable for SMEs¹⁶¹. As highlighted by Box 6.4.1, a number of the molecules are being developed or have been developed by small

^{xvi} Wyeth was bought out by Pfizer in early 2009.

pharmaceutical companies, sometimes alone or in partnership with other companies. This shift is likely because large pharmaceutical companies require annual sales of US \$500–800 million to recoup R&D costs, whereas SMEs need substantially lower annual sales to recoup investments (perhaps US \$100–\$200 million per year)¹⁶⁵. It has been suggested that SMEs and other research bodies (like universities) are more interested in innovative research as opposed to ‘blockbuster’ research. However, Chopra et al point out that most of the products currently being developed by SMEs were originally in-licensed from larger companies who were down-sizing their commitment to antibiotic discovery¹⁶¹. Therefore, SMEs’ focus efforts on developing and bringing to market previously discovered molecules (e.g. by large developers) rather than discovering new targets in-house. For example, Cubist acquired the rights to Daptomycin from Eli Lilly in 1997 and obtained marketing authorisation from the FDA in 2003¹⁶⁵. Chopra et al. note that SMEs endure high costs when taking a new drug to market and thus have limited financial resources left to invest in new drug discovery efforts or basic research programmes¹⁶¹. In fact, no SME has been able to sustain itself on internal research and discovery programmes¹⁶⁶. In addition, according to Projan, many SMEs face other significant financial pressures and barriers to entry¹⁵⁹. SMEs often lack the financial stability to enter into the antibiotics market, which is associated with substantial uncertainty concerning return on investment. Biotechnology investment in the field began falling in the late 1990s due to funding problems¹⁶⁶. Therefore, small companies have often relied on investors and government funding for drug development. For example, the Biotechnology Industry Organization reported in November 2008 that almost 100 publicly traded biotechnology companies were facing less than 6 months of cash flow¹⁶⁷, making them financially unstable and vulnerable to economic downturns. In fact, such barriers to entry are apparent when considering the fact that large pharmaceutical companies have been primarily responsible for new antibiotic development—between 1980 and 2003, 93% of new agents were developed by large pharmaceutical companies rather than SMEs¹⁶⁸. Table 4.4.1 provides a list of the pharmaceutical and biotechnology companies that have launched antibiotics since 2000. The table demonstrates the significance of SMEs involvement in developing antibiotics.

Table 4.4.1 Antibiotic Launches Since 2000 IMS Health LifeCycle™ 157 157

Brand	Ingredient	Class code	Launch year	Country	Company
Zyvox	linezolid	J1X	2000	USA	Pfizer
Ketek	telithromycin	J1F	2001	Germany	Aventis
Invanz	ertapenem	J1P	2002	USA	Merck & Co.
Omegacin	biapenem	J1P	2002	Japan	Meiji Seika
Q-Roxin	balofloxacin	J1G	2002	South Korea	Choong Wae
Pazucross	pazufloxacin	J1G	2002	Japan	Mitsubishi Pharma
Sword	prulifloxacin	J1G	2002	Japan	Meiji Seika
Factive	gemifloxacin	J1G	2003	South Korea	LG Chemical
Cubicin	daptomycin	J1X	2003	USA	Cubist Pharma
Tygacil	tigecycline	J1X	2005	USA	Wyeth
Finibax	doripenem	J1P	2005	Japan	Shionogi
Geninax	garenoxacin	J1G	2007	Japan	Taisho: Toyama Kagaku
Gracevit	sitafloxacin	J1G	2008	Japan	Daiichi Sankyo

Despite funding and development efforts made by large pharmaceutical companies and SMEs, the discovery and production of new antibacterial agents has slowed dramatically over the past 25 years. In 2004, the Infectious Diseases Society of America (IDSA) conducted an analysis of pipelines of 15 major pharmaceutical companies and 7 biotech companies and published findings in the report “Bad Bugs, No Drugs”¹⁶⁹. The authors found that the pharmaceutical companies and biotech companies had only 4 antibiotics in Phase II or III clinical development, compared with 67 drugs for cancer, 34 for metabolic/endocrine disorders, 33 for inflammation/pain, and 32 for pulmonary diseases. In a recently updated report published in 2009, the IDSA concluded that the number of antibacterials in phase II or III of clinical development remains minimal 4 years following the previous study¹⁷⁰. Interviews with leaders of anti-infective development at Abbott, AstraZeneca, Bayer, GSK, Lilly, Merck, Novartis, Ortho McNeil/Johnson&Johnson, Pfizer, Roche, Sanofi Aventis, Schering Plough, and Wyeth revealed that only 3 new compounds were in advanced clinical development (1. ceftobiprole, 2. dalbavancin, and 3. PTK-0796). The study concluded that there are currently no antibiotics in advanced development that have activity against either purely Gram-negative bacteria or against other bacteria already resistant to all currently available antibiotics. Another recent study by European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency (EMA) and European Centre for Disease Prevention and Control (ECDC) reveals the small number of antibacterials in

development. In 2009, the ECDC and the EMEA published a Joint Technical Report that provides current evidence of the lack of antibacterial drug development to tackle MDR¹⁵⁴. The results of the ECDC and the EMEA Joint Technical Report indicate that there is a general lack of agents that act on new targets or possess new mechanisms of action. See Box 4.4 below for a summary of the conclusions of the report.

Box 4.4 The Bacterial Challenge—Time to React¹⁵⁴

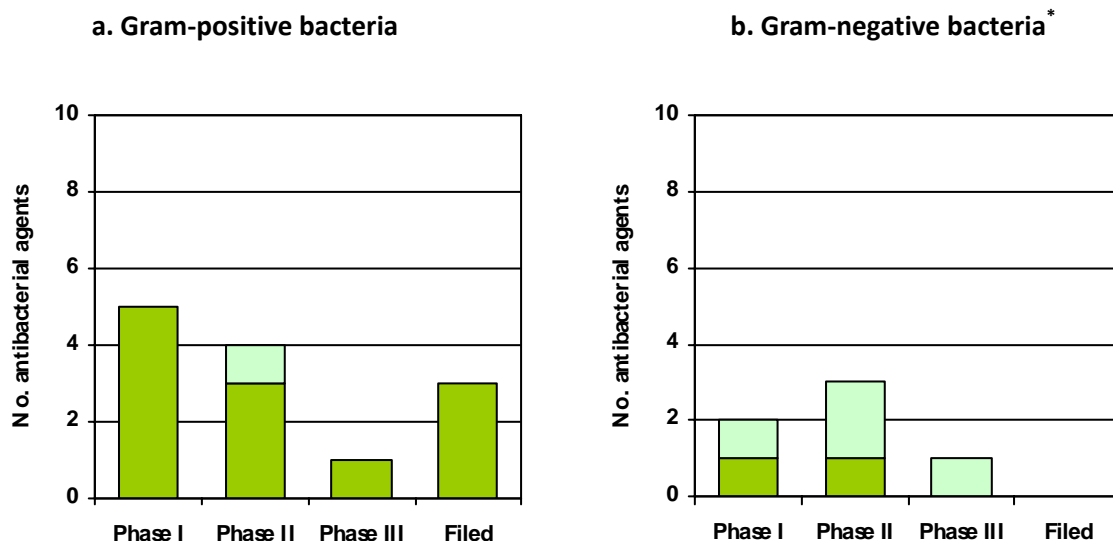
Main findings from the EMEA and ECDC Joint Technical Report “The Bacterial Challenge—Time to React”.

The ECDC –EMEA study assessed the current state of the antibacterial drug development pipeline by collecting data from the two commercial databases Adis Insight R&D and Pharmaprojects on antibacterial agents in clinical development. The main results from this analysis were as follows:

There is a gap between the burden of infections due to multidrug-resistant bacteria and the development of new antibiotics to tackle the problem.

- Resistance to antibiotics is high among Gram-positive and Gram-negative bacteria that cause serious infections in humans and reaches 25% or more in several EU Member States.
- Resistance is increasing in the EU among certain Gram-negative bacteria such as recently observed for *Escherichia coli*.
- Each year, about 25 000 patients die in the EU from an infection with the selected multidrug-resistant bacteria.
- Infections due to these selected multidrug-resistant bacteria in the EU result in extra healthcare costs and productivity losses of at least EUR 1.5 billion each year.
- Fifteen systemically administered antibacterial agents with a new mechanism of action or directed against a new bacterial target were identified as being under development with a potential to meet the challenge of multidrug resistance. Most of these were in early phases of development and were primarily developed against bacteria for which treatment options are already available.
- There is a particular lack of new agents with new targets or mechanisms of action against multidrug-resistant Gram-negative bacteria. Two such agents with new or possibly new targets and documented activity were identified, both in early phases of development.
- A European and global strategy to address this gap is urgently needed.

Figure 4.4.5 New systemic antibacterial agents with a new target or new mechanism of action and *in vitro* activity based on actual data (dark colour bars) or assumed *in vitro* activity based on class properties or mechanisms of action (light colour bars) against the selected bacteria (best-case scenario), by phase of development (n=15).¹⁵⁴#532 Data made available courtesy of the EMEA



Note: In vitro activity based on actual data is depicted at the bottom of each column in darker colour. Assumed in vitro activity based on class properties or mechanisms of action (where applicable) is depicted in a lighter colour at the top of each column.

** Two carbapenems have been omitted from Figure 4.4.52b since they are no more active than earlier carbapenems against Gram-negative bacteria. The relative novelty of these agents was based on a better profile of activity against antibiotic-resistant Gram-positive bacteria and are therefore included in Figure 4.4.5a.*

The growth in antibiotic resistance has led to an increasing need for discovery of novel classes of antibiotics for both community and hospital-acquired bacterial infections. In addition to the general lack of antibiotics coming to market, Charles and Grayson highlight another issue in the antibiotic market—it is crowded with “me-too” antibiotics, drugs from the same class developed by competing companies¹⁶⁸. Although the discovery of new drugs is essential to curb the spread of resistance, Chopra et al. warn against the development of me-too analogues of existing antibiotics¹⁶¹. They argue that the development of me-too drugs is counter-productive because pre-existing resistance mechanisms may evolve rapidly to confer resistance to the derivative antibiotic. According to Chopra et al., pharmaceutical companies and SMEs need to select

molecular strategies that minimize the potential for future selection of resistance to new agents. However, pharmaceutical companies have focused discovery efforts on modifying or combining existing antibacterial compounds as opposed to discovering novel classes of antibiotics. Only 2 new classes of antibiotics have been introduced over the past 30 years, the oxazolidinones in 2000 and the cyclic lipopeptides in 2003. All other antibiotic agents that have launched^{xvii} in the past decade are derivatives of old classes with limited therapeutic value due to growing resistance. In fact, Charles and Grayson demonstrate how several of the antibiotics classified as “new” were actually discovered in the 1980s¹⁶⁸. Poor initial results and issues with toxicity forced many pharmaceutical companies to cease development of antibacterial agents¹⁶⁸. For example, the antibiotic daptomycin, which was shelved in the early 1990s due to toxicity, is currently being reassessed at a lower dose¹⁶⁸. According to Monnet, ketolides and glycylicyclines, which are sometimes put forward as novel classes, originate from existing classes¹⁶⁵. In addition, Monnet notes that the majority of “new” molecules that have been introduced since 1980 are part of the 2 antibiotic classes cephalosporines and fluoroquinolones (See Table 4.4.2. below)¹⁶⁵. However, these 2 classes are far from novel—they were originally discovered between the 1940s and 1960s. Consequently, few novel antibiotics have come to market in the past decade. Table 4.4.2 below provides a visual representation of the number of antibiotic molecules launched since 1980 by class and decade.

Table 4.4.2 Number of Antibiotic Molecules Launched Since 1980 by Class and Decade

Antibiotic class	1980–1989	1990–1999	2000–2009
Aminoglycosides	2	1	0
Carbapenems	0	3	3
Cephalosporines	18	12	0
Fluoroquinolones	5	11	6
Macrolides	6	4	1
Monobactam	2	0	0
Penicillins	6	1	0
Others	1	3	3

Source: IMS Health LifeCycleTM 157

Currently, there is a lack of novel antibiotics in late stages of the pharmaceutical pipeline because of a sustained focus on non-novel antibiotics. In a study from 2005, Barrett found that of 600 drugs in clinical development, approximately 12 were novel antibiotics, and of these, only about 3 were novel scaffolds¹⁶⁶. Table 4.4.3 provides information on late-stage antibiotics according to whether the drug is in Phase III clinical trials, pre-registration with the FDA (i.e. a New Drug Application [NDA] has been submitted), registration with the FDA (i.e. the drug has been approved), and marketed

^{xvii} Received marketing approval from a regulatory agency.

(i.e. the drug is available with a prescription). Since there have been a number of recent FDA rejections, these are also indicated in Table 4.4.3. The majority of the antibiotics listed in Table 4.4.3. come from existing classes of antibiotics. Fidaxomicin is the only antibiotic that is a first in its class, although tigecycline is part of a new class of drugs that are similar to tetracyclines. Importantly, the table only lists antibiotics that are marketed or in late-stages; there are a number of other promising biotechnology treatments for infectious diseases. Opebacan (manufactured by XOMA), for instance, is a modified recombinant fragment of a bactericidal, permeability-increasing protein that is currently undergoing Phase III clinical trials for treatment of meningococcal disease. It has received an orphan drug designation from both the FDA and EMEA.

Table 4.4.3 New* Antibiotics Recently Marketed, in Late-Stage Clinical Development, or Rejected by the FDA.

Drug name ¹	Company ²	Class	Status in the US
Ceftaroline	Forest Laboratories (Takeda)	Cephalosporin	Phase III
Ceftobiprole	Basilia and Johnson & Johnson	Cephalosporin	Not approved, conducting additional audit work
Cethromycin	Advanced Life Sciences (Abbott)	Ketolide	Pre-registration
Dalbavancin	Pfizer (Toyama)	Glycopeptide	Phase III
Doripenem	Johnson and Johnson (Shionogi) ³	Carbapenem	Marketed
Faropenem	Replidyne (Daiichi Asubio Pharma)	Carbapenem	Rejected
Fidaxomicin	Optimer	Macrocyclic	Phase III
Garenoxacin	Schering-Plough	Quinolone	Marketed
Iclaprim	Arpida (Roche)	Diaminopyridine	Rejected
Oritavancin	Targanta	Glycopeptide	Rejected
Prulifloxacin	Optimer (Nippon Shinyaku) ⁴	Quinolone	Phase III
Ramoplanin	Oscient and Pfizer	Glycolipo-depsipeptide	Phase III
Telavancin	Theravance and Astellas	Glycopeptide	Pre-registration
Tigecycline	Wyeth	Glycylcyclines	Marketed

¹Sitafloxacin is available for use in Japan but not outside of Japan. Tebipenem is currently undergoing clinical trials in Japan.

²If the antibiotic is licensed from another company, the company that holds the license is listed in parentheses

³Outside of Japan, Johnson & Johnson markets doripenem, but Shionogi markets the drug in Japan.

⁴Nippon Shinyaku has licensed prulifloxacin to different companies; in Japan Meiji Seika received approval in 2002, in Europe Angelini received approval in 2004, and in China Lee's Pharmaceutical Holdings has just concluded a license agreement with Nippon Shinyaku.

* New here is not meant to signify novel
Source: IMS Health LifeCycle™

4.4.2 Areas of unmet need

Given the lack of sufficient R&D for infectious diseases and emerging levels of resistance, an important exercise is to lay out major areas of unmet need. Importantly, there is disagreement within the literature over what areas constitute the greatest unmet need and this section aims to summarise the main themes from the literature. The need for new treatments can be broken down by whether bacteria are gram-positive or gram-negative and by biofilm resistance. According to Barrett and Barrett the re-emergence of Gram-negative pathogens and MRSA rank among the top problem pathogens among hospital settings¹⁷¹. Rice recently dubbed *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Enterobacter species* as the “ESKAPE” pathogens to highlight the fact that they currently cause the majority of US hospital infections and effectively “escape” the effects of antibacterial drugs^{172,173}. Although there are existing effective treatment options available for most common infections, many experts argue that the most significant needs are for drugs to treat emerging strains of MRSA and resistant Gram-negative bacterial infections¹⁷⁴.

Gram-positive bacteria

Agents from several antibiotic classes are available to treat Gram-positive bacteria, but emerging resistance to existing antibiotics has led to the development of new antibiotics to treat MRSA and vancomycin-resistant *Enterococcus faecium* (VCE), including daptomycin, linezolid, quinupristin-dalfopristin, and tigecycline¹⁷³. However, these available treatments have important limitations, particularly none are proven to work better than vancomycin against MRSA and linezolid and quinupristin-dalfopristin have some toxic side-effects¹⁷⁵. Other Gram-positive pathogens with unmet need are *Staphylococcus epidermidis*, VCE, *Enterococcus faecalis*, and mycobacteria. In the past 5 years only 4 agents have been approved that have clinical activity against these bacteria: daptomycin, gemifloxacin, telithromycin, and tigecycline¹⁷⁶.

In addition, the emergence of CAinfections that are resistant to existing antibiotic therapies raises concern. The virulence of the newly identified MRSA strains, including CA-MRSA, is another area where unmet need now lies¹⁷⁷. MRSA is an increasingly common pathogen in all forms of pneumonia¹⁷⁸ and studies indicate that there are indications of possible outbreak of widespread CA-MRSA infections¹⁷⁹. This trend is already visible in the US where CA-MRSA infections are the leading cause of identifiable skin and soft tissue infections in emergency rooms¹⁷⁵. Despite the fact that treatments are available or in the pipeline (cephalosporin, glycylicycline, dalbavancin, linezolid, and quinupristin–dalfopristin) to treat CA-MRSA infections, MDR strains are beginning to emerge¹⁷⁵. In addition, there is uncertainty surrounding best clinical practices for

treatment of CA-MRSA. In particular, there is a consensus that additional studies are needed to define the optimal antibiotic choices for the treatment of MRSA pneumonia¹⁷⁸.

Gram-negative bacteria

Gram negatives have a long history of taxonomic changes, moving from one family to another¹⁸⁰, and they express a variety of modifying enzymes that reduce the activity of antibiotic once they have entered the cell. Breaching the Gram negative cell wall is also a challenge for scientists. Therapies for Gram-negative organisms are associated with lower rates of successful bacteriological and clinical outcomes, together with increased toxicity, likely contributing to the lack of sufficient R&D in this area¹⁸¹. Gram-negative organisms, including *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia* are frequently MDR and are considered to be the primary cause of infections in immunocompromised patients, especially patients in intensive care units.

Antibiotics that are in the pipeline for the treatment of serious Gram-negative bacterial infections include ceftarolin, ceftobiprole, and the cephalosporins. Also, tigecycline has the potential to treat some multi-drug resistant Gram-negative organisms. Other potential compounds include doripenem and faropenem¹⁸², and antibiotic peptides and efflux pump inhibitors are two new classes of agents under development. Polymyxins are old antibiotics traditionally considered to be toxic, but which are being used because of their activity against resistant Gram-negative organisms.

Biofilms^{xviii}

Another problematic form of resistance is the formation of biofilms, which are discussed further in section 4.5.4. Development of antibiotic agents that have activity against biofilm bacteria with proven efficacy in treating infections without device removal would be a major advance in antibiotic therapy¹⁷³.

The evolution of resistance

Whilst newer antibiotics generally show low susceptibility to resistance initially, the fact that most antibiotics are either natural products or derived from natural products, indicates that resistance is inevitable for all antibiotics¹⁸³. Knowledge of how multiple efflux pumps remove antibiotics across the cell surface indicates that some infections, like *P. aeruginosa*, which has a multitude of efflux pumps, will always develop resistance to antibiotics. Novel treatments will always be necessary in these situations, and researchers need to aim for individual new molecular entities (NMEs), not necessarily new antibiotic classes, that have no cross-resistance with existing antibiotics.

^{xviii} Biofilms are a slimy layer formed when bacteria colonize foreign material, such as intravascular or urinary catheters, orthopaedic devices, and other implantable materials.

The usability of existing treatments

The availability of highly active, once-daily intravenous (IV) antibiotics like ceftriaxone and potent, broad-spectrum oral agents like fluoroquinolones provided many opportunities for early discharge of patients for whom prolonged antibiotic administration was required. However, there are concerns that the dosing schedules of some other antibiotic agents are incompatible with administration outside of hospital and inconvenient for community treatments, thereby requiring prolonged hospitalisations and increasing the risk for further infection. This indicates an unmet need for developing newer oral agents that can be administered in the community setting and IV agents with better dosing schedule.

Safety issues of 3 drugs that led to withdrawal from some markets also indicate the need for better antibiotics. Temafloxacin was withdrawn from sale in the US shortly after its approval in 1992 because of serious adverse reactions resulting in 3 deaths¹⁸⁴, whilst trovafloxacin was withdrawn from the market in 1996 due to the risk of hepatotoxicity. Grepafloxacin was withdrawn in the US owing to its side effect of lengthening the QT interval on the electrocardiogram, leading to cardiac events and sudden death¹⁸⁵.

Multi-resistant pathogens

Although most pathogens are susceptible to at least 1 antibiotic, pathogens are increasingly resistant to multiple antibiotics¹⁸³. In particular, Boucher et al. argue that MDR Gram-negative bacteria constitutes a major challenge for the future¹⁷². However, despite this concern, the ECDC and the EMEA report demonstrates that there is a lack of systemically-administered agents with activity against Gram-negative bacteria displaying new MoA¹⁵⁴. Payne et al. note that the troubling situation is further exacerbated by the fact that there are high attrition rates for antibacterial agents in early stages of clinical development¹⁶⁴.

It is important to determine whether the pharmaceutical and biotech industries are developing antibacterial agents that respond to unmet needs previously described. Table 4.4.4 from the ECDC and the EMEA report summarizes new systemic antibacterial agents by degree of novelty, phase of clinical development, new target or new MoA, and route of administration¹⁵⁴. The table helps demonstrate whether new antibacterial agents fill an unmet need. According to the table, the majority of the investigational agents identified by the searches were directed against the same target and had the same MoA as at least 1 licensed agent¹⁵⁴.

Table 4.4.4 New systemic antibacterial agents with new target or new mechanism of action and in vitro activity based on actual data or assumed based on known class properties or mechanisms of action against the selected bacteria (n=15, as of 14 March 2008) ¹⁵⁴. Data made available courtesy of the EMEA

Name of agent	Mechanism of action (MoA)	Degree of novelty	Route of administration *
WAP 8294A2	Membrane integrity antagonist	New MoA	IV, Top
PZ-601	Cell wall synthesis inhibitor	New target	IV
ME 1036	Cell wall synthesis inhibitor	New target	IV
NXL 101	DNA gyrase inhibitors / DNA topoisomerase inhibitor	New MoA	IV, PO
Friulimicin B	Cell wall synthesis inhibitor	New MoA	IV
Oritavancin	Cell wall synthesis inhibitor Membrane integrity antagonist	New target	IV, PO
Telavancin	Cell wall synthesis inhibitor Membrane integrity antagonist	New target	IV
Ceftobiprole medocaril	Cell wall synthesis inhibitor	New target	IV
Ceftaroline fosamil	Cell wall synthesis inhibitor	New target	IV
Tomopenem	Cell wall synthesis inhibitor	New target	IV
hLF1-11	Chelating agent / immunomodulation	New MoA	IV, PO
Lactoferrin	Chelating agent / immunomodulation	New MoA	IV, PO
Talactoferrin-alfa [†]	Chelating agent / immunomodulation	New MoA	PO, Top
Opebacan [†]	Membrane permeability enhancer/immunomodulation	New MoA	IV
NXL104/ceftazidime	Beta-lactamase inhibitor + cell-wall synthesis inhibitor	New target	IV

* Information on routes of administration is uncertain in early drug development.

[†] Agents with only assumed in vitro activity.

According to Barrett and Barrett, although hundreds of antibiotics are on the market, these represent derivatives of only a small handful of structural classes ¹⁷¹. In particular,

although many of the new candidate compounds close to launch attempt to fill unmet medical need, none are likely to solve the problem of the need for a new broad-spectrum antibiotic that fights MDR pathogens¹⁷¹. Barrett and Barrett propose that there need to be novel ways to identify new bacterial targets for the discovery of novel inhibitors and additional useful classes for pharmaceutical intervention¹⁷¹. They support the expansion of the field of microbial genomics, which is the use of bioinformatics to catalogue the entire metabolic mechanisms of microbes and identify all essential functions¹⁷¹. Unless scientists focus their efforts on identifying novel bacterial targets against emerging resistant pathogens, antibiotic developers will continue to develop antibacterial agents that do not respond to unmet needs.

4.5 Why There is a Lack of New Antibiotics

There are numerous factors that explain the decline in interest by large pharmaceutical companies in R&D of new antibiotic therapies.

4.5.1. Antibiotic restrictions deter pharmaceutical investment in R&D

A “vicious cycle” persists that puts pharmaceutical R&D in conflict with public health policy recommendations¹⁰. To slow the rapid spread of antibiotic resistance, policymakers and organisations worldwide have been funding and operating campaigns that teach providers and patients about the issue of antibiotic resistance and appropriate consumption behaviour. Several countries are adopting regulations, public campaigns, and policies that encourage appropriate use of antibiotics and target various stakeholders within healthcare systems—patients, HCPs, health insurance companies, pharmacists, and pharmaceutical companies. National education campaigns to encourage the general public about appropriate antibiotic use have been conducted in Australia, Belgium, France, and the UK⁸⁶. For example, the government in Belgium has generated public awareness through antibiotic consumption and patient education materials, using booklets, leaflets, television and radio advertising and a website¹⁰. Belgium implemented policies aimed at changing physicians’ prescribing practices—family practitioners receive feedback on their prescribing habits¹⁰. Evaluations of the nationwide campaign in Belgium conclude that the country appears to have been successful in reducing high rates of antibiotic consumption—total antibiotic sales decreased 11.7% and 9.6% (in defined daily doses) during the 2000–2001 and 2001–2002 December–March periods during the campaign¹⁸⁶. In addition to reducing consumption, data from Japan, Finland, Hungary, and Iceland suggests that national policies promoting the restriction of antibiotic usage can result in decreased levels of drug-resistant bacterial infections³⁹. Although the US has not yet implemented a nationwide educational campaign, the US CDC has funded campaigns in 28 states and is

expanding the GetSmart^{xix} programme incrementally⁸⁶. Studies demonstrate educational campaigns in the US have contributed to a recent decline in oral antibiotic prescription rates for children in the US¹⁸⁷. However, despite encouraging prescription rate declines, survey data from a recent national study in the US showed that misunderstanding about the appropriate use of antibiotics continues to exist amongst the general population—44% of individuals surveyed who used an antibiotic within the past year reported skipping doses and 45% of individuals surveyed who used an antibiotic within the last year believed that antibiotics can effectively treat viruses¹⁸⁷. Recently, the FDA has taken a step to warn patients about over-consumption of antibiotics by issuing a regulation that requires antibiotics through labelling.

Many industry experts argue that public health measures limiting the use of antibiotics act as disincentives for pharmaceutical companies to invest in antibiotic R&D^{10 21 9}. This problem is often called the supply-side externality of antibiotics—policies which encourage more prudent use of antibiotics decrease pharmaceutical profits, stifle innovation and investment, reduce development of antibiotics, and thus leave the public dependent on existing antibiotics that may not be very effective⁹. Such a situation creates conflict between the 2 necessary means of controlling resistance—restricting use of antibiotics and developing new antibiotics.

4.5.2 Challenges in the antibiotics market—the Net Present Value

The cost of bringing a new product to market is another major barrier to the development of new antibiotic drugs to combat resistance. In 2001, the Tufts Center for Drug Development estimated the average cost to develop a new prescription drug to be US \$802 million¹⁸⁸. According to this estimate, it is of little surprise that economic considerations are cited as the most common reason for terminating drug development¹⁰.

Pharmaceutical companies must make difficult economic trade-offs given their large yet finite financial resources. The net present value (NPV) is a key parameter used to decide within which competing therapeutic area to invest capital for discovery and development of novel therapies¹⁵⁹. Pharmaceutical companies calculate the NPV to evaluate an investment decision, compare investment strategies, and determine the viability of specific products within the market¹⁰. In general, the NPV provides an estimate of the projected costs and potential returns of a development programme, according to current values and in terms of cash flow¹⁰. In more technical terms, the NPV is the expected value of a given project after projecting expenses and revenues into the future and discounting for the potential investment value of financial resources spent on the project¹⁵⁹. In addition, when calculating the NPV, companies incorporate

^{xix} Further information can be found at: <http://www.cdc.gov/getsmart/>

risk assessment and adjustment to model the combined risks at different points in the development process and evaluate the likelihood of obtaining regulatory approval ¹⁰. Table 4.5.1 below is an example of risk-adjusted NPVs calculated for various project therapeutic classes in 2003 ¹⁵⁹. Projan and Power argue that the NPV of antibiotics is lower than the NPV of other pharmaceutical treatments. According to such NPV estimates, Projan argues that antibacterial agents are not an attractive therapeutic investment.

Table 4.5.1 Risk-Adjusted NPV x \$1,000,000 for Project Therapeutic Classes ¹⁵⁹.

Project therapeutic class	Risk adjusted NPV x \$1,000,000
Musculo skeletal	1,150
CNS	720
Oncology	300
Vaccines	160
Injectible antibiotic (Gm+)	100
AS-psoriasis	60
Liver transplant	20
Oral contraceptive	10

In the case of antibiotics, Power argues that policy restrictions and resistance both negatively impact the NPV. According to Power, policies encouraging minimal use of antibiotics (such as labelling antibiotics with warnings against their use) reduce the cash flow and thus the potential profit of a pharmaceutical company investing capital in antibiotic R&D ¹⁰. Power contends that increased regulatory measures also increase development costs, limit the number of indications or diseases for which a drug can be recommended as standard treatment, and thus reduce chances to obtain a satisfactory return on investment ¹⁰. Figure 4.5.2 provides a graphical representation of the relationship between the NPV, antibiotic restrictions, and increased regulatory hurdles. In addition, Power demonstrates how resistance can have a negative effect on the NPV. Antibacterial agents that develop resistance rapidly have a shorter clinical lifespan and are only useful for a few years ¹⁰. Therefore, according to Power, a pharmaceutical company that invests billions of dollars and takes over a decade to develop a new antibiotic may not reap the full benefits of such efforts. Consequently, Power states that the NPV for an antibiotic falls when resistance to a drug develops and spreads amongst the general population. Figure 4.5.2 provides a graphical representation of this relationship between NPV (in terms of turnover) and resistance.

Figure 4.5.1 The Impact of Antibiotic Restrictions and the Regulatory Environment on the NPV ¹⁰

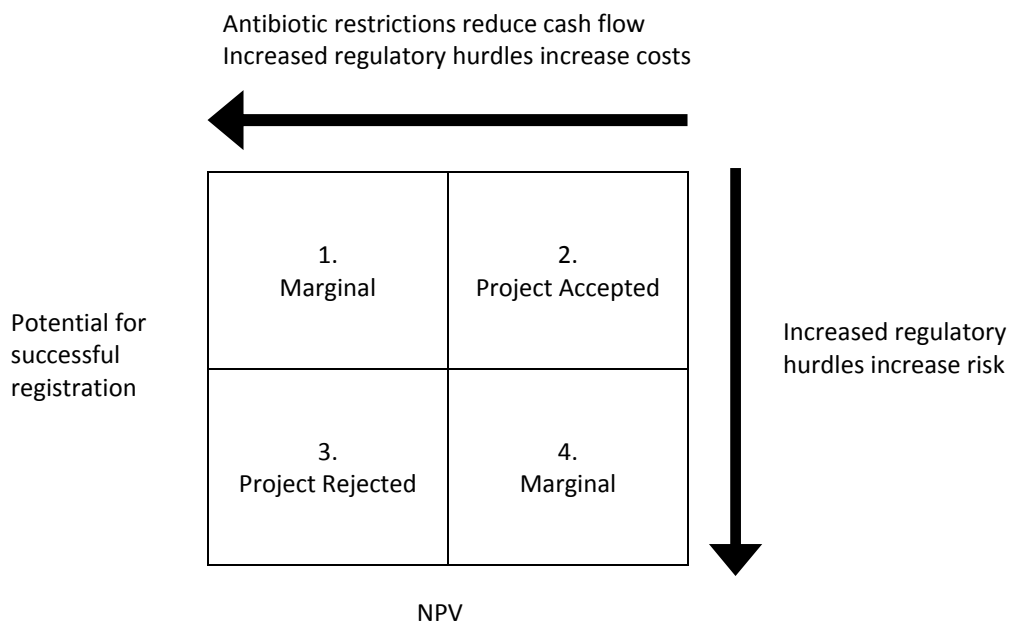
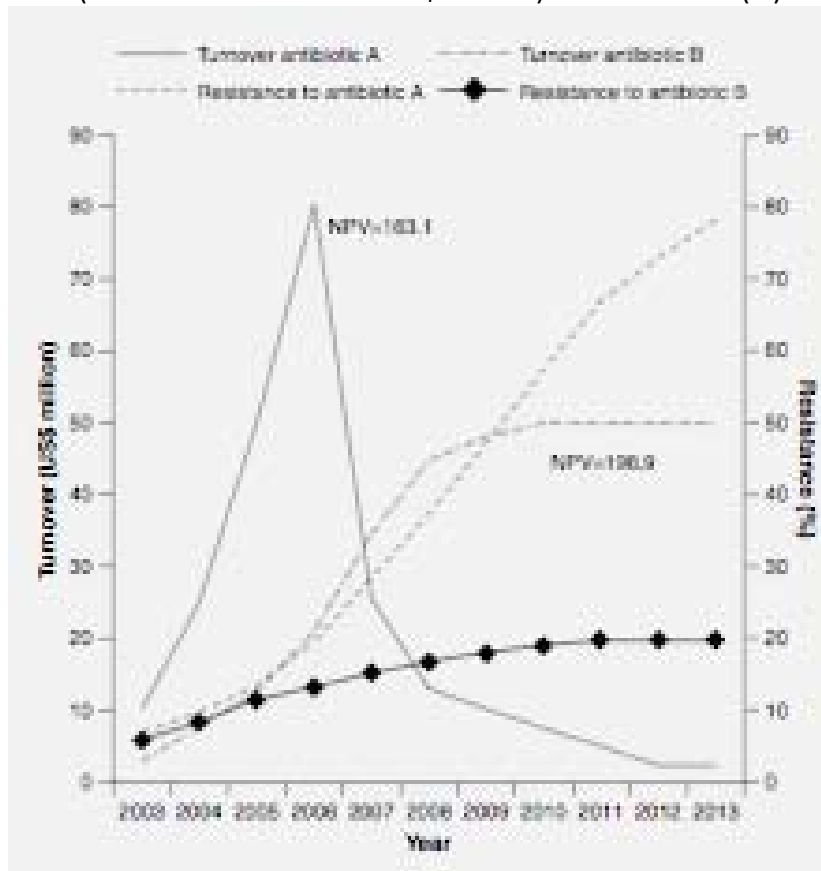


Figure 4.5.2 NPV (in terms of turnover in US\$ million) vs. Resistance (%) ¹⁰.



Other conditions unique to the antibiotics market result in lower NPV and thus fewer revenues for pharmaceutical companies.

First, the majority of antibiotics treating infectious diseases and bacterial pathogens are administered to patients for short courses of therapy. On the contrary, patients suffering from chronic conditions take medications for prolonged periods and thus therapies treating chronic conditions are often more profitable than antibiotics. The NPV of antibiotics is significantly lower than for drugs treating chronic conditions—according to Power, the NPV is approximately 100 for an antibiotic, 300 for an anticancer drug, 720 for a neurological drug, and 1150 for a muscular-skeletal drug¹⁰. Thus, such estimates demonstrate that the profitability of antibiotics is limited. Currently, the most profitable antibiotic, Pfizer's Zithromax, has sales of approximately \$2 billion per year, much less than drugs taken for chronic conditions and much less than drugs taken for chronic conditions, such as Lipitor with revenues of about \$9 billion per year⁹. Therefore, according to Projan and Power, pharmaceutical companies that use NPV estimates to rank drug development priorities, will rank antibiotic drugs as a lower priority than therapies for chronic conditions^{10,159}. Therefore, pharmaceutical companies are shifting their focus to R&D of drugs for chronic conditions rather than infectious diseases.

Another relevant factor that reduces the possibility of a high return on investment in new antibacterial agents is that generic pharmaceutical manufacturers dominate the antibiotics market. Two of the largest selling and most widely used antibiotics are generic forms—amoxicillin/clavulanate (Augmentin) and ciprofloxacin (Cipro)¹⁵⁹. According to Power, pharmaceutical companies have difficulty competing against generic manufacturers because generic manufacturers do not bear the risks of drug development. This allows them to set drug prices extremely low compared to pharmaceutical companies and thereby gain a large share of the market¹⁰.

Patent expiry acts as another development-related challenge for pharmaceutical companies seeking to maximize revenues. When a patent expires, Power argues that the pharmaceutical company faces uncertainty concerning future revenue streams¹⁰. In addition, Chopra notes that the patent life on a pharmaceutical product is often insufficient to recover the investment and offset the risks associated with the long time required for developing antibacterial agents¹⁶¹.

The numerous challenges unique to the antibiotics market have significantly reduced the market revenues for pharmaceutical companies investing in this therapeutic area. Most antibiotics generate only US \$200–\$300 million in revenues annually, whilst the costs of bringing any drug to market are currently estimated to be US \$400–\$800 million per approved agent¹⁸⁹. According to Projan's research, the actual market shares of

recently launched antibiotics that were developed to target resistance, notably linezolid and quinipristin-dalfopristin, have not captured as much of the market as originally hoped ¹⁵⁹. Projan argues that small market shares have encouraged pharmaceutical companies to shift R&D resources away from antibacterial drug discovery to more profitable therapeutic areas within which to invest R&D resources (e.g. musculoskeletal and CNS drugs) ^{159,160}.

However, opposing arguments also exist. Pray argues that global antibiotic sales are quite significant and several antibiotics have reached blockbuster status ³⁹. For example, according to Pray, sales of GSK's Augmentin totalled approximately \$1 billion in 2007. Despite the fact that there is money to be made in the antibiotics market, Pray does acknowledge the fact that the financial risk associated with becoming involved in antibiotic R&D acts as a disincentive to becoming or staying involved in the antibiotics market. Although branded antibiotics have achieved blockbuster status, many pharmaceutical companies are not willing to bear the economic risk. However, one could also argue that the profitability of other competing therapeutic areas will decrease due to impending patent expiry. Despite the profitability of blockbuster drugs, the development landscape is changing such that companies may soon have lower revenues because of approaching patent expiry dates, as demonstrated in Table 4.5.2. Therefore, the lack of foreseeable profits in chronic condition drug development may stimulate pharmaceutical companies to view investment in R&D for antibiotics as more valuable when estimated by NPV calculations.

Table 4.5.2 List of Top 13 Oral Drugs – 11 of Which Will Reach Patent Expiry by 2012. List compiled from various sources.

No.	Product	Company	US patent Expiration	2007 US Revenues (billions)
1	Lipitor	Pfizer	Mar-2010	\$8.1
2	Nexium	AstraZeneca	May-2014	\$5.5
3	Plavix	Bristol-Myers Squibb	May-2012	\$3.9
4	Vytorin/Zetia	Merck/Schering	Apr-2017	\$3.7
5	Seroquel	AstraZeneca	Sep-2011	\$3.5
6	Singulair	Merck	Aug-2012	\$3.4
7	Prevacid	TAP	May-2009	\$3.4
8	Actos	Takeda	Jan-2011	\$2.9
9	Effexor XR	Wyeth	Jun-2010	\$2.9
10	Lexapro	Forest	Mar-2012	\$2.6
11	Risperdal	Johnson & Johnson	Jun-2008	\$2.6
12	Protonix	Wyeth	Jan-2011	\$2.5
13	Zyprexa	Eli Lilly	Oct-2011	\$2.4

4.5.3. The regulatory environment

The regulatory environment is another factor acting as a barrier to R&D of antibiotic agents. Trends in drug approval by the FDA demonstrate that there have recently been significantly fewer approvals—the period from 1996 to 2001 had significantly more approvals (523 approvals) than the period from 2002 to 2007 (450 approvals)¹⁹⁰. In addition, there has been a sharp decline in approval of NMEs since 2004—just 18 NMEs were approved by the FDA in 2007¹⁹⁰. Consequently, pharmaceutical companies are reluctant to invest effort and resources in developing NMEs. The FDA has experienced a dramatic fall in applications for NMEs—in 1995 the FDA received approximately 40 applications and by 2003 this had fallen to approximately 25¹⁰.

Regulatory requirements for proving efficacy and safety of NMEs have led to greater uncertainty and risk in the market authorisation process for antibiotics over the past 8 years. A major area of uncertainty has been in relation to non-inferiority, particularly requirements for demonstrating relative efficacy within tighter statistical parameters¹⁵⁹. Stricter statistical parameters and approval requirements have had the unintentional effect of substantially increasing costs for pharmaceutical companies and thus eliminating incentives to invest R&D in antibiotics¹⁰. Additionally, the drug approval process has been further complicated for antibiotics as regulatory agencies are less prepared to accept adverse side effects with antibiotics than with other classes of therapeutic agents¹⁶¹. Also, the lack of clinical trial guidelines from regulatory agencies regarding the type of clinical trial (e.g. placebo-controlled vs. non-inferiority clinical trials) and acceptable evidence to demonstrate safety and efficacy of new antibiotics diminishes incentives to invest in antibiotic discovery and development²¹. Given the significant debate surrounding non-inferiority versus superiority and the divergent regulations of the FDA and EMEA, there is significant uncertainty for the industry, greatly contributing to disincentives for antibiotic R&D¹⁹¹. Section 6.3 goes into further detail about the various regulatory requirements and the impact that such regulations have on drug development.

The difficulties in conducting antibiotic clinical trials are another reason why developers are reluctant to invest in R&D. Amongst the major challenges faced, there is the difficulty in recruiting a sufficient number of patients with the appropriate indications, a lack of RDTs to identify and recruit appropriate patients, and a high degree of regulatory scrutiny.

4.5.4 Scientific difficulties of antibiotic development

The scientific difficulties of antibiotic development have no doubt influenced the insufficient investment in R&D for infectious diseases. One of the key challenges that scientists face is finding a lead compound, a substance that can act as an antibacterial agent¹⁹². Lead compounds then need to be screened and refined to see whether they can be candidate drugs. It has been estimated that it requires, on average, 20 candidate

drugs to yield 1 marketable drug. There are different routes that scientists can take to discover lead compounds, including screening natural sources for antibacterial properties; screening synthetic compounds against isolated cellular targets; or employing novel methods of modifying older molecular targets¹⁹². As developing antibiotics from natural sources was felt to be inefficient and time consuming, many pharmaceutical companies have recently switched to methods involving combinatorial chemistry and target-based genomic approaches^{xx}. However, it has been suggested that these new approaches have turned out to be costly and inefficient and have not yet resulted in any new antibiotic discoveries^{160,164}. The fact that screening lead products has not led to many candidate drugs may be due to the bias within synthetic chemical screening libraries toward molecules for mammalian targets and not bacterial targets¹⁹².

Scientists are increasingly recognising that part of these scientific difficulties are due to the fact that bacteria have 'intrinsic' means of resistance¹⁶⁴, where biofilms and efflux pumps are two of the most important contributors.^{xxi} The problem with bacterial resistance in biofilms appears to be some change in the bacterial characteristics that make them less susceptible to antibiotics, and there appear to be multiple resistance mechanisms that work simultaneously¹⁹³. Other properties of biofilms mean that antibiotics are unlikely to be able to effectively target all cells in the biofilm. Efflux pumps, which decrease the intracellular concentration of antibiotics, are also important contributors to resistance

Part of the scientific difficulty in developing antibiotics is a lack of good data on chemical compounds. The classic screening of compound libraries in the search for new antibiotics was not producing results, resulting in pharmaceutical companies developing 'me-too drugs' instead of novel therapies¹⁹⁴. This pushed many companies to funnel resources into more cutting edge technologies such as genomics, combinatorial chemistry and rapid throughput screening¹⁶⁰. Whilst these technologies have identified new targets, this has not yet resulted in marketable drugs. Aside from the recent development of 2 narrow-spectrum antibiotics (linezolid and daptomycin), there have been no new structural classes of antibiotics since 1963¹⁹⁵.

^{xx} Target-based genomic approaches involve comparing the genome sequences of different pathogenic species to determine the genes that most of the species have in common 192. Royal Society. Innovative mechanisms for tackling antibacterial resistance: Royal Society,, 2008.

5.0 HEALTH SYSTEM RESPONSES TO ANTIBIOTIC RESISTANCE

Numerous national and international organisations have addressed the antibiotic resistance problem using a variety of mechanisms. Most developed countries have national-level policies addressing antibiotic resistance. Some of the focus has been at the health system level, where institutions have been created to collect and monitor data, inform stakeholders, and change health practices. More recently, measures to stimulate R&D in infectious diseases have arisen, although most of these measures have focused on neglected diseases and bioterrorism and not antibiotic resistance. This section outlines a selection of these responses to antibiotic resistance within the EU and the US and very briefly describes their perceived level success to date.

Surveillance and antibiotic surveillance (ABS) are 2 major tools health systems have developed to reduce antibiotic use, and Europe and the US have taken a number of actions on these fronts, albeit to varying degrees. As resistance typically varies regionally and even between local administrative zones, there is a need to have both national and local surveillance systems established. The use of surveillance systems is an attempt to achieve a number of goals, including; the understanding and prediction of antibiotic resistance, the detection of new resistance mechanisms, monitoring and understanding the impact of changes in antibiotic prescribing, public health guidelines infection control, identifying outbreaks of resistant pathogens, and educating health care stakeholders and the public about antibiotic resistance, *inter alia*^{196,197}. Crucially, findings from surveillance help alarm us to burgeoning emergencies in which our existing lines of antibiotics become impotent vis-à-vis the bacteria in our environment.

The parameters and definitions of ABS vary across countries and within the literature. However, in general, ABS is a continuous effort to optimise the use of antibiotics within health care institutions to improve patient outcomes, achieve cost-effective treatment, and reduce antibiotic resistance, particularly within hospitals (200, 201). ABS programmes can encompass a number of different interventions, some of which include education and guidelines, formularies and restricted prescribing, review and feedback for providers, information technology to assist in decisions, and antibiotic cycling^{xxii}. Overall, proper ABS entails the selection of an appropriate drug, optimisation of the dose and duration, and minimisation of toxicity and conditions for selection of resistant pathogens¹⁹⁸. Box 5.1. provides a brief summary of the literature on antibiotic use policies.

^{xxii} Antimicrobial cycling entails a scheduled rotation of the antimicrobials used within the inpatient setting and also within specific units of the hospital e.g. ICU.

Box 5.1 The literature on policies to guide appropriate antibiotic use

This box provides a brief overview of the literature highlighting the variable effectiveness of interventions to decrease inappropriate and overall antibiotic prescribing. Comprehensive, systematic reviews of prescribing interventions point to the limited evidence previously available to decision-makers. The most common interventions target non-financial incentives and are generally categorised as “persuasive” (i.e. facilitating change in prescribing behaviour) or “restrictive” (i.e. forced change) initiatives. Gaps in the literature still remain.

Simple, persuasive interventions

Concerning the use of low-cost interventions such as the use of audit and feedback or printed educational material, there is a small, although often statistically significant, reduction in overall prescribing^{199,200}. Educational outreach visits by ‘academic’ detailers (from government or third-party payer organisations) also demonstrate a small but consistent reduction in prescribing, but the long-term effects are unknown²⁰¹.

The use of best-practice or consensus-driven guidelines to improve antibiotic prescribing can be a successful intervention²⁰², but guidelines can be difficult to implement at the individual clinician level. One option is to use clinical decision support systems (CDSSs), which may reduce time spent in hospital and the potential of acquiring a nosocomial infection through reduced medication errors and optimised drug dosages^{203,204}. However, CDSSs must be implemented properly and need to be available at the point of decision-making and provide specific directives and/or advice to be most effective²⁰⁴. Importantly, CDSSs may not address the root cause of inappropriate antibiotic prescribing, as it returns when the intervention is removed²⁰³.

Simple, restrictive interventions

In comparison with persuasive interventions, restrictive interventions have demonstrated a more statistically significant reduction in inappropriate antibiotic prescribing²⁰⁵. Interventions targeting formularies to limit the use of certain drugs for specific diagnoses are effective at influencing prescribing behaviour upon successful implementation²⁰⁶. For certain viral conditions (e.g. upper respiratory tract infections), delayed prescribing has also been shown to be highly effective¹⁹⁹, although a systematic review by Spurling *et al.*²⁰⁷ outlines the limited capacity of delayed prescribing.

Complex, multifaceted interventions

Comprehensive, multifaceted interventions appear to be the most effective mechanism for addressing antibiotic resistance and inappropriate antibiotic use^{199,208}. Effective interventions incorporate both financial and non-financial interventions and coordinate multidisciplinary experts (e.g. infectious disease specialists, clinical microbiologists,

pharmacists, administration). The programmes may also be combined with rigorous hospital-based infection control programmes to address both prescribing practices and the emergence of nosocomial infection. Dellit et al find evidence to support the financial viability of effective multifaceted ABS schemes, and drawing on data from recent studies, they highlight the ability of such programmes to reduce antibiotic prescribing by 22–36% in the US. The literature documenting the cost-effectiveness of such interventions is small but growing ²⁰⁸.

Examples from Europe

In 1998 the EARSS was founded to coordinate the monitoring of antibiotic resistance in Europe, whilst the ESAC, established in 2001, monitors the consumption of antibiotics ²⁰⁹. The objectives of EARSS were to standardise laboratory practices, improve data reliability and validity, and foster the creation of national networks for the collection and testing of samples for antibiotic resistance. EARSS is now the largest and most comprehensive surveillance system in the world, including more than 800 microbiological laboratories that cover over 1300 hospitals in 31 countries ²⁰⁹. EARSS collects information on the following pathogens: *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Escherichia coli*, *Enterococcus faecium/faecalis*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. Meanwhile, ESAC is an annual, longitudinal database of antibiotic use covering 33 countries. There are still a number of challenges to gathering ESAC data as collection is delineated according to ambulatory, inpatient, and nursing home care, and different methodologies apply to each. For instance, countries often have dispense data but not actual consumption data and electronic health systems are still not widespread or well supported in all countries ²⁰⁹. However, the ESAC project is actively working to improve data collection and develop quality indicators for antibiotic use.

Several countries have comprehensive pre-existing ABS programmes, including Belgium and Austria ²¹⁰. In 2006, with the support of 9 member states^{xxiii}, the EC established “ABS International – Implementing antibiotic strategies for appropriate use of antibiotics in hospitals in member states of the EU”. The 2-year, EU-financed project implemented ABS tools such as the development of antibiotic lists and quality indicators for antibiotic use, mechanisms to analyze consumption data, and the training of national experts and national ABS trainers.

Table 51.1 highlights the degree to which several northern European countries, namely, Denmark, Finland, the Netherlands, Norway, and Sweden, have implemented successful interventions to address antibiotic resistance. Whilst other factors, such as lower bed occupancy rates cannot be discounted, the impact of sustained, aggressive policies to

^{xxiii} Austria, Belgium, the Czech Republic, Germany, Hungary, Italy, Poland, Slovenia and Slovakia

combat antibiotic resistance is striking in two particular cases: Sweden and the Netherlands ^{211,212}. The Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA) integrates research, policy formation, and implementation and engages multiple relevant stakeholders ²¹³. STRAMA has access to annual, regional data on the antibiotic susceptibility of 6 bacterial species, whilst the Swedish Reference Group of Antibiotics methodology subcommittee (SRGA-M) has been effective in standardising the microbiological laboratories. Apoteket AB, Sweden's state-owned wholesale pharmaceutical supplier, also provides comprehensive data on outpatient antibiotic sales in Sweden. This highly coordinated effort, which now includes stringent hospital-based infection control policies, represents one of the most effective strategies in the EU ²¹³.

Table 5.1.1 Susceptibility (S)/Resistance(R) results for *S. aureus* isolates in a selection of European countries, 2007 ^{25#842}

Country	Number		Total N	Percentage	
	S	R		S	R
Austria (AT)	1364	139	1503	90.8	9.2
Belgium (BE)	656	199	855	76.7	23.3
Bulgaria (BG)	105	16	121	86.8	13.2
Switzerland (CH)	740	104	844	87.7	12.3
Denmark (DK)	1304	11	1315	99.2	0.8
Estonia (EE)	188	18	206	91.3	8.7
Spain (ES)	1224	418	1642	74.5	25.5
Finland (FI)	801	13	814	98.4	1.6
France (FR)	3154	1096	4250	74.2	25.8
Croatia (HR)	234	141	375	62.4	37.6
Luxembourg (LU)	83	22	105	79.0	21.0
Malta (MT)	50	55	105	47.6	52.4
The Netherlands (NL)	1449	20	1469	98.6	1.4
Norway (NO)	789	1	790	99.9	0.1
Sweden (SE)	2151	11	2162	99.5	0.5
Slovenia (SI)	387	35	422	91.7	8.3

In the Netherlands the Dutch Working Party on Antibiotic Policy (Stichting Werkgroep Antibiotica Beleid, SWAB) coordinates efforts against antibiotic resistance, including the national surveillance system. Since 2002 the Netherlands has employed restrictive antibiotic prescribing practices and a rigorous 'search and destroy' policy in hospitals. Patients admitted to hospital are assessed for potential risk (4 risk groups) of MRSA infection, with rigorous screening/monitoring, sanitation and isolation protocol implemented depending on the patient's risk assessment. The prevalence of MRSA is now below 1% ^{212,214}.

The Netherlands has also adopted a notable mentorship role within the EU. The 36-month EUREGIO (Evaluation of Cross-Border Regions in the EU) MRSA-net

Twente/Münsterland project created a highly integrated regional network for the control, monitoring, and epidemiological standardisation of infectious disease protocol for MRSA along a section of the Dutch/German border. The scheme incorporated regional and national governments, academic institutions, hospitals, microbiological laboratories, public health offices, professional associations, nursing homes and patient transportation services²¹⁵. The transfer of knowledge and effective practices through the EUREGIO MRSA-net Twente/Münsterland project could serve as a model for other regions characterized by stark dichotomies in prevalence or expertise.

In Europe there is also an increasing interest in financial incentives to change behaviour, such as pay-for-performance schemes²¹⁶. Within the 2008–2009 National Health Service contract for acute services in England, financial penalties were incorporated for failing to meet nosocomial infection targets, and the Department of Health has set a target of reducing *Clostridium difficile* infections by 30% by 2011. The primary care trusts will administer the scheme with penalties, capped at 2% of income, levied on hospital trusts, which do not achieve the yearly target reductions²¹⁷.

Examples from the United States

There are a broad range of surveillance systems that collect data on antibiotic resistance in the US, although this information is not available in a single place. States have the ultimate decision when it comes to collecting data related to antibiotic resistance and the associated economic and health costs. The CDC has no authority to require states to collect data.

Thus far, the US federal government has not been heavily involved in studying ABS. However, organisations such as the IDSA, have become actively involved in providing guidelines for ABS²⁰⁸. Not surprisingly, the availability and quality of ABS programmes within the US varies widely. Echoing the results of previous studies²¹⁸, a survey conducted from 2001 to 2003 within top academic hospitals in the US found that most hospitals had not implemented such programmes, largely due to uncertainties surrounding the application of the programmes to their specific institutions as well as the financial difficulties in obtaining the resources and trained personnel to run the programmes²¹⁹.

In US hospitals the reimbursement and accountability structure of treatment expenses may also hinder infectious disease control. Third-party coverage of expenses arising from antibiotic resistance reduces incentives for hospitals to control infections. In response to this problem, the US Deficit Reduction Act, which became operational in October 2008, shifts a significant portion of the financial burden of treating nosocomial infections to hospitals. Under the new legislation, Medicare will no longer reimburse hospital-acquired infections that arise following (surgical site infections) bariatric surgery, selected orthopaedic surgeries, selected elective procedures, in addition to

catheter-associated urinary tract infections and vascular catheter-associated bloodstream infections^{220,221}.

As there is currently no federal strategy to tackle antibiotic resistance in the US, research on transmission, prevention, clinical therapy, and product development is fragmented. In 1999 an interagency Antimicrobial Resistance Task Force was established by Congress to coordinate federal efforts, however, with little authority and funding, it was unable to implement the Public Health Action Plan to Combat Antibiotic Resistance by the time its authorisation had expired in 2006.

In 2007 a key proposal to consolidate efforts was put forth by Senators Brown and Hatch in the form the Strategies to Address Antimicrobial Resistance (STAAR) Act (S.2313). The Act proposed establishing Surveillance and Research Networks (ARSRN) across the country to work in collaboration with the CDC, the NIH and other federal agencies to actively bring together experts in surveillance, prevention, and research. Sites were intended as a 'clinical research network,' similar to those used by NIH to study other priority disease areas and would include isolate collection capacity.

The STAAR Act proposed enhancing the authority of the Task Force to review data, make recommendations, and integrate efforts in the Public Health Action Plan. It also proposed establishing an Office of Antimicrobial Resistance in the Department of Health & Human Services to coordinate inter-agencies efforts and act as a central repository for data on the amount of antibiotics used in humans and animals in the US, including an Advisory Board to help learn from international experts. Whilst the Act did not pass upon first introduction, on May 13, 2009 it was reintroduced by Representative Matheson and—at the time of writing—its inclusion was being considered as part of the upcoming healthcare reforms.

6.0 ANALYSIS OF OPPORTUNITIES AND INCENTIVES TO STIMULATE R&D FOR ANTIBIOTICS

This section organizes proposed incentives to stimulate antibacterial R&D into 4 categories: push mechanisms, pull mechanisms, regulatory mechanisms, and hybrid push-pull mechanisms. Each incentive may entail changes in the health system, the regulatory infrastructure, or require government assistance. The section is also punctuated with a number of case-studies that explore some of the current experimental models or practical experience in more depth. Many of the proposed incentives have been used by governments and other public sector bodies to stimulate R&D for neglected and orphan diseases. The lessons are particularly relevant for antibiotics, as neglected diseases and orphan diseases also face economic disincentives for R&D that, without intervention, create a gap between social need and the actual provision. The advantages and disadvantages of each proposed incentive are provided, along with evidence regarding practical implementation when available. Applicability to antibiotics and implications for smaller developers are also discussed. The length of discussion regarding each of the individual incentives is largely a function of the amount of relevant literature identified. In a few cases (those serving as a basis for key recommendations) the length of discussion is also a reflection of the incentive's perceived relative merits.

6.1. Push Incentives

Push incentives focus on removing barriers to developer entry largely by affecting the marginal cost of funds to the developer for investments in R&D and tend to impact the earlier stages of the development process^{11`#270}. This section considers examples of push incentives implemented at an institutional level targeting structural changes such as opening-up research and stimulating human resources, as well as more fiscal approaches targeting individual companies or developers such as direct public funding and tax relief mechanisms.

6.1.1 *Increasing access to research*

Recent years have seen a movement towards increasing access to research. Industries such as the computer software industry have demonstrated innovative and subsequent commercial success using more collaborative models. Awareness of their success, combined with a growing recognition of the collaboratively limiting nature of the patent system, have lead to a growing interest in the use of “open-source” models within biomedical sciences.

The breadth of application of the open-source principle (increasing access to research) varies from ‘opening-up’ scientific databases and compound libraries, through to the

creation of comprehensive, decentralised, virtual communities where all potential contributors, from scientists to members of the public, can pursue challenges, review others' contributions, download computerised tools, publish their findings and consult others through on-line forums^{222' #271, 223' #272}. A fundamental characteristic of these ventures is the use of general or public-domain licensing as the mechanism to manage IP protection. Important examples include: General Public Licences (GPL) in which any follow-on innovators must share any improvements they make; the Creative Commons Attribution License, which permits anyone to use the information for any purpose as long as correct attribution is given and licenses (for developing world products) allow commercialisation outside of this context; and the Creative Commons License in which a developer waives all rights to their work^{223' #272}.

Munos^{222' #271} argues that similar processes have been positively contributing to medical innovations for a long-time and cites the example of crucial idea sharing amongst physicians in establishing novel uses of existing drugs (off-label prescribing). Initially inspired by the Bioinformatics sector, a number of product development partnerships (PDPs) – for whom an open-source approach is one element of their 'virtual pharma' model – have increased in the past decade. The Structural Genomics Consortium (SGC; Box 6.1.1), the Human Genome project, the Single Nucleotide Polymorphism Consortium, and Collaborative Drug Discovery (for TB research) are high-profile examples of such collaborations. More recently, many formalised web-based initiatives have also been expanding and gathering momentum in the fields of publishing (public library of science [PLOS] an open access, peer-reviewed library), clinical trials (WHO International Clinical Trials Registry Platform [ICTRP], European Clinical Trials Database [EudraCT]), and specific diseases (e.g. the cancer Biomedical Informatics Grid® (caBIG®) or group of diseases i.e. neglected diseases (e.g. Open Source Drug Discovery [OSDD])). The newest initiative 'Initiative for Open Innovation' (IOI) is broader in its scope hoping to create a 'comprehensive global cyberinfrastructure that does not recognise differences within and between sector, discipline, jurisdiction or language'. It hopes to provide a means to explore the boundaries of open innovation to create, test, validate and support new modes of collaborative problem solving made possible through the transparency of its system.

It is widely acknowledged that communication promotes the advancement of science. This fact has been expanded upon by De Bresson who suggests that the 'weak' links that characterise open-source approaches lend themselves more to innovation than to other more formalised networks that tend to reinforce existing orthodoxies^{224' #273}. This finding is corroborated by evidence highlighting that innovation spikes when diverse minds interact frequently in an unstructured manner^{225' #274}. Additionally, it has been argued that open access approaches overcome some of the market distortions created by the patent system, such as the absence of natural collaboration between amongst commonly driven stakeholders (e.g. different pharmaceutical companies, governments,

academia etc), which results in less innovation overall ²²⁶. Other more tangible benefits of this approach include the reduction of duplicated research and the possibility for collaborative approaches to exist alongside more traditional competitive models ^{222#743}. It may also lead to rapid accumulation and application of knowledge, faster technology diffusion. As regards pharmaceuticals specifically, the advantages of this approach are likely to be greatest during the knowledge-based phase of development, which in drug development occurs early in the life-cycle i.e. identification of targets, understanding metabolic networks, designing clinical trials or computerised disease models ^{222'#271}.

However, it has also been suggested that—relative to the software industry—the application of open source approaches in biomedical research is less successful. High costs, high failure rates, tighter regulation and a more burdensome IP regimens render pharmaceutical industry quite different from the software industry ^{222'#271}. The most challenging obstacle to overcome would likely be the proprietary culture that currently exists in pharmaceuticals. However, even these can be overcome.

Examples from the US

The US recently passed a progressive bill aimed at increasing access to publicly-funded research. The 2009 Federal Research Public Access Act (FRPAA) would require that manuscripts of journal articles stemming from grants made by US government agencies to be openly available openly on the internet within 6 months of publication. This legislation was first introduced to the Senate in May 2006 by Senators John Cornyn and Joe Lieberman and was re-introduced by the same sponsors in June 2009.

Application to treatments for priority bacterial diseases

The expansion of open-source approaches to stimulate innovation for antibiotics holds promise. However, few of the requisite tools and knowledge are as yet in the public domain. Compounded by the strong proprietary nature history in the field which has been further reinforced by recent high profits, the impact of these approaches may be limited in the short-term. However, the questioning of the patent system along with know sharing technologies, coupled with a changing development landscape more generally, would suggest that open source approaches will provide important contributions to product development quite soon.

Application to SMEs

Given the lower revenue thresholds faced by SMEs, along with the potentially greater gains in working collaboratively due to their limited size, it would appear that open-source approaches to drug discovery have much to offer SMEs.

Box 6.1.1 The Structural Genomics Consortium

The SGC is a PDP with the goal of determining the 3 dimensional structures of proteins related to medicines and placing them without restriction in the public domain. It was funded by 11 public and private entities including: Vinnova Swedish Agency for Innovation, Swedish Foundation for Strategic Research, and the Knut and Alice Wallenberg Foundation, the , the Canadian Institute of Health Research, Canadian Foundation for Innovation, Genome Canada, Ontario Genomics Institute, Ontario Ministry of Research and Innovation, Novartis, Merck, GSK (SGC UofT)). The SGC has US \$120 million in total funding, including a \$20 million investment from the pharmaceutical industry²²⁶. The SGC investigates proteins selected by academic and participating industrial researchers and all investigation results are promptly made publicly available on free databases. No one is given prior access or rights to data or progress information, even funding partners (SGC).

6.1.2 Scientific personnel

A result of long-term insufficient antibiotic R&D is a lack of personnel with the appropriate scientific experience¹⁶³. Anecdotal evidence from interviews with independent scientists and pharmaceutical companies indicates that more scientific personnel with knowledge in infectious diseases are sorely needed. The lack of experienced scientists stems from a number of causes. At one time it was thought that science had conquered infectious diseases, and the leaders of many pharmaceutical companies began their careers when this was a widespread belief²²⁷. The resulting decline in R&D for infectious diseases has led to an entire generation of researchers experienced in antibiotics being forced to switch research areas.

In an attempt to partially counter this “brain drain”, fellowship programmes have been established in the EU and US. High profile examples include those offered under the EC’s 7th Framework Programme for Research and Technological Development (FP7) ‘people’ specific programme which evolved from its predecessor the Human capital and Mobility programme. This is entirely dedicated to human resources in research, and has an overall budget of more than €4,7 billion over a 7 year period until 2013, which represents a 50% average annual increase over FP6. In 2006, nearly €9, 478 million was distributed to health through ‘Marie Curie Actions’. These developed from Marie Curie Fellowships to encompass all stages of a scientist’s career path. Professional societies such as the European Society of Clinical Microbiology and Infectious Diseases, European Society for Paediatric Infectious Diseases and the International Diseases Society of America (IDSA) which offers joint awards with the Education and Research Foundation (ERF) and the National Foundation for Infectious Diseases (NFID) are a significant

contributor to training and development. Private foundations also contribute with examples such as the UK's Medical Research Council (MRC) and WT (see Box 6.1.2, below).

Post doctoral fellowships and increased grant funding are two prominent means, with proven success, of attracting newer scientists. As new researchers have much less knowledge and experience in working with infectious diseases, and their overall contributions may be less than if older researchers were also recruited back into the field. Thus, any strategy must be enough to bring in both new and experienced researchers. Munoz proposes that open-source approaches potentially offer a flexible and therefore attractive way of bringing more experienced (even retired) scientists to reengage with the field in coordination, shepherding or facilitating roles^{222' #271}.

Box 6.1.2 The Wellcome Trust (WT)

As the UK's largest largest donor, the WT spends approximately £600 million annually on biomedical research with diversified investment assets of £13.1 billion²²⁸. This makes it one of the world's largest medical research charitable foundations. For many years the trust has been a ardent supporter of research addressing antibiotic resistance (see 4.26.7) at all stages of the product development cycle. The WT funds projects that both 'Advance knowledge' through basic science (biomarker discovery, gene identification [Sanger Institute]), scientific careers (PhDs, post docs, fellowships etc), and 'Use knowledge' within drug discovery (project and programme funding)²²⁹, see section 6.4.

For 2008 the Trust provided £525 million in funding (an increase of 27% on 2007) in the form of 1,131 grants (2,999 applications)²²⁸. £450 million has been committed each year of its current 5 year strategic planning cycle (2005-2010)²²⁹.^{xxiv} The majority of the WT's funding is for basic science, with approximately 5% in 2008 earmarked for technology transfer (TT) (see Box 6.4.2)²²⁸. Within the funding of basic science, the WT places a strong emphasis on supporting scientists and clinicians at the early stages of their careers. In 2008 it provided approximately £58million in fellowships. Commitments have been made to increase the budget to implement a more systematic approach for monitoring progress and increase international projects²²⁹.^{xxv}

6.1.3 Direct funding of research

National level funding of research has a long history, especially through public research institutions. For example, the UK channels its research expenditures through two main routes: the Medical Research Council (MRC) and the National Institute for Health Research (NIHR). The US channels most of its funding through a number of agencies

^{xxiv} These are reviewed annually to reflect investment performance.

^{xxv} Currently approximately 90% of funding is for UK-based projects.

such as NIAID, NIH, HHS, CDC, BARDA etc. In many countries the not-for-profit sector also plays a pivotal role in directly funding or subsidising research (see Box 6.1.2), in some cases as part of PDPs.

Examples from Europe

The FP7 is the EU's main funding mechanism for research, and the programme runs from 2007 to 2013. The focus of the FP7 is on increasing Europe's growth and competitiveness, with the 4 main areas of funding:

- **Cooperation**, which entails cooperative research between nations in 10 thematic areas (one of which is health);
- **Ideas**, which focuses on riskier research and does not define specific research areas;
- **People**, which supports European researchers through training, career development, and mobility; and
- **Capacity**, which aims to improve research capacities within Europe.

FP7 has a budget of €6 billion for cooperative Health research, corresponding to an annual average of approximately €900million. In relation to antibiotic resistance, the 7th Framework project included a call for research into major infectious diseases that pose a threat to public health. Under this theme, there were calls for global collaborative research into preventing antibiotic resistance, research on how specific antibiotic products influence resistance in humans, and research on diagnostic tests for identifying specific pathogens and identifying antibiotic susceptibility to resistance.

One recently announced FP7 project is EMBARC, a collaboration between 10 research centres in 7 countries which aims to synchronise how the research centres preserve and identify samples. The project will also explore alternative approaches for identifying and classifying organisms. EMBARC has currently received 3 years of funding from the EC for €4.2 million, but the consortium will explore ways of gaining private funding beyond the original 3 years²³⁰.

An additional example of the use of 7th framework funding is the Innovative Medicines Initiative (IMI), a product development partnership (PDP) (see Box 6.1.3 below).

Box 6.1.3 The Innovative Medicines Initiative (IMI)

In 2007 The EC and European Federation of Pharmaceutical Industries (EFPIA) launched IMI to explore new patient centric approaches, methods and enabling technologies addressing key bottlenecks of drug development. IMI projects are designed as an independent entity bringing together industry and academic experts specifically to tackle safety and efficacy bottlenecks in the drug development process. These precompetitive projects focus on improving the ability to predict the safety and efficacy profile of a development compound in patients. Better predictability would allow for candidate compounds with lower probability of success to be discontinued earlier, thereby saving time and creating savings for companies and public funders. Resources could then be concentrated on the more promising compounds.

The IMI structure consists of a Governing Board which directs operations and oversees implementation of the Strategic Research Agenda developed jointly by industry and other stakeholders, e.g. academia. At the time of writing the Board was made up of 5 representatives from industry; 5 representatives from the EU (3 from DG Research, 2 from DG Enterprise and 1 from DG SANCO); an Executive Director who manages operations supporting implementation of the Strategic Research Agenda; and a Scientific Committee with an advisory role, composed of 15 members from academia, patient groups, industry and regulators.

IMI funds pre-competitive collaborative projects by way of a multi-staged call process. With input from other stakeholders, the EFPIA participants select issues (surrounding the predictability of safety and efficacy) on which they would like to collaborate and provide the specific scientific project outline. The IMI administration then publishes the selected Calls accessible for all potential partners from academia, SMEs, and other non-EFPIA groups (incl. public authorities, patient groups, non-EFPIA companies). Interested groups together submit an Expression of Interest (Eoi) to the IMI Joint Undertaking (IMI-JU) and a scientific panel consisting of leading scientists from academia and industry who together make their selection. The original EFPIA participants and this selected group jointly develop the Full Project Proposal for approval by the IMI administration. EU funding is only allocated to academic group / SMEs/ patient groups. Participating EFPIA companies match the level of EU funding through in kind donation of resources for projects (staff, laboratory facilities, materials, clinical research, etc.).

The budget for the initiative for 2008-2013 is €2 billion, half of which comes from the 28 (current) EFPIA company participants and half from the EC through the FP7.

Participation in IMI-funded projects is intended to appeal to SMEs by giving them the opportunity to validate their know-how, product prototypes and offerings in

collaboration with large pharmaceutical companies. It is argued that this collaboration will help them attract more venture capital. The initiative is also intended to appeal to academics by offering the opportunity to work with large companies with better infrastructure capabilities, government, and patient groups, as well as provide them the chance to apply their ideas in basic research to a patient centric drug development process. Finally, for large pharmaceutical companies, IMI is expected to provide crucial tools for making the development process more efficient--and thus less costly—as well provide them with early involvement with government to harmonize standards for the development process.

It is argued the potential success of IMI derives from its focus on “pre-competitive” technology, which increases the chances for close collaboration and sharing of knowledge. Also, as an industry-driven initiative--the IMI is expected to receive full industry buy-in. However, the research location requirements will entirely preclude participation by EFPIA members with anti-infectives arms based in the US. In addition, the industry lead may present drawbacks. Namely, its chosen areas of work may be more likely to derive from pure financial interest rather than reflect the most pressing therapeutic needs.

With regards to their intellectual property, IMI’s stated mission is to ensure that the learning from their projects are widely available on “fair and reasonable terms” (not open source) -- initially to the project participants and to the wider community at the end of a project. IMI has just completed the first Call process, which received approximately 150 applications. Fifteen full projects have now been accepted. These projects and their expected outcomes are outlined in Appendix C. A second Call for EOIs is expected in the autumn of 2009, possibly also including calls in the area of infectious diseases. At the time of writing the details of this Call had not been released.

Examples from the United States

In the US, the NIH is part of the Department of Health and Human Services (HHS) and is the main agency responsible for conducting and supporting medical research. The main NIH body responsible for infectious diseases is the National Institute of Allergy and Infectious Diseases (NIAID), which conducts and funds basic and applied research in infectious and other diseases and currently provides over US \$700 million in annual funding for antibiotic research²³¹. Examples of projects funded by NIAID have included research on potential targets for new anti-infectives, development of efflux pump inhibitors, research on the structure and physiology of biofilms, and reduction of the toxicity in antibiotics. NIAID has also funded translational research to help researchers advance from basic research to an approved product in the area of vaccines and rapid diagnostics. Another interesting development is the engagement of NIAID in product development partnerships (PDPs). For instance, NIAID helped establish the Lilly Not-for-

Profit Partnership for TB Early Phase Discovery in 2007 and has collaborated with the Medicines for Malaria Venture (MMV).

However, up until the passage of the 2009 American Recovery and Reinvestment Act, which increased the NIH budget by 34% for two years ²³², funding was a problem for the NIH. Between 2004 and 2008, the NIH faced flat budgets, budget cuts, or minor budget increases. As reported by some interviewees and the literature, only a fraction of NIH extramural grants receive funding. For instance, a 2007 paper reported that only 18% of NIH extramural grants received funding, and the average age of first-time grant winners was over 40 ²³³.

Box 6.1.4 Project BioShield

In July 2004 the US implemented the Project BioShield Act, which gave the HHS the authority to expedite research, develop, and purchase priority countermeasures for chemical, biological, radiological, and nuclear threats from terrorists ²³⁴. In 2004 the government allocated US \$5.6 billion in funding for a 10-year period ²³⁵. The HHS agencies involved in BioShield

Include the following:

- The NIH, the FDA, and the Agency for Healthcare Research and Quality (AHRQ) that together manage all R&D-related issues; and
- The CDC and the Office of Emergency Preparedness that handle preparedness-related issues.

In December 2006 the Pandemic and All-Hazards Preparedness Act (PAHPA) clarified which drugs, biologics, and medical devices were considered national security priorities under Project BioShield ²³⁴. For infectious diseases, PAHPA indicates that the BioShield programme can be used to stimulate research or acquire treatments for an infectious disease only if the countermeasure is also a national security countermeasure. To facilitate R&D of countermeasures to security threats, PAHPA created the Biomedical Advanced R&D Authority (BARDA).

In relation to incentives for infectious disease R&D, NIAID and BARDA are the main agencies that provide basic research and funding for pre-clinical and clinical development of treatments. The NIAID, is heavily involved in biodefense research, particularly in funding basic research and early stages of clinical development. Most recently, the NIAID awarded Achaoden, a biotechnology company, funding of up to US \$26.6 million over 5 years to develop countermeasures to gram-negative bacteria such as *Yersinia pestis* (causes bubonic plague) and *Francisella tularensis* (causes tularemia) ²³⁶.

Whilst NIAID helps fund early stage development, BARDA focuses on mid- to late-stage product development. BARDA's portfolio includes projects on broad-spectrum antibiotics^{xxvi}, vaccines^{xxvii}, and RDTs. In 2006 BARDA was given a two-year US \$1.07 billion budget to facilitate R&D of countermeasures, and subsequent appropriations have been made on an annual basis²³⁴.

When partnering with companies to take bioterrorism countermeasures further through the development process, BARDA offers milestone-based payments. If determined essential for the success of the contract, BARDA is authorised to pay up to 50% of the contract amount for milestone achievement. A separate clause from the original BioShield Act also allows BARDA to authorise up to 10% of the contract in advance to the company, but the company must refund the advance payment if the product cannot be delivered to the national stockpile programme.

The fact that BARDA is funded on an annual basis as opposed to having a longer-term fund (as the procurement function of BioShield) creates difficulties for long-term planning. In particular, when the US Congress delayed passing the 2009 budget, BARDA was forced to operate under the previous year's budget and could not initiate new projects until a new budget was passed.

General considerations for future application

Government efforts to fund large-scale R&D projects have a mixed record of success, with failures such as the Carter administration's synthetic fuel programme and the Clinch River Breeder Reactor cited²³⁷. There is a question of whether the government is best suited to judging the viability of research programmes. There is the inevitable information asymmetry between the decision maker and the researcher, with the research groups having the incentive to present their research in the most positive light. Moreover, decision makers have an incentive to present funded projects in the best possible light to increase their available budget²³⁷. However, these problems are also inherent in other funding mechanisms like PDPs, and even within private companies themselves.

One of the most significant pitfalls of government-funded research is the connection with politics. For instance, government funding is often set on an annual basis and is

^{xxvi} BARDA is concerned with developing antibiotics that can be used to address a range of terrorist threats as opposed to a "one bug, one drug" solution.

¹⁹ Because the intent is to stockpile vaccines for an emergency, BARDA is most interested in single-dose, stable vaccines that do not need to be frozen. BARDA has also encouraged companies to develop methods of administration that are easier in the event of an emergency, for instance nasal administration or patches.

thus dependent on the individuals in power, the economic climate, and other perpetually changing factors. Providing longer-term funding for instance, the 9 year period 2004–2013 as apportioned in the in the US Project BioShield, is one possibility of creating more stability for government-funded research. Another result of the connection between politics and government funding is that politicians may set the research agenda, which may have little connection to areas of unmet need, or more connection with the issues affecting their constituents.

Many of the problems with government funding are, however, more limited with smaller programmes. In the case of antibiotics, targeted, small-scale financing could be made available, such as for basic research into antibiotic resistance and potential targets (biomarker discovery), gene identification, platform technologies, clinical development, and scientific careers (PhD's, postdoctoral research fellowships etc) as we saw in section 6.1.2.

6.1.4 Tax Incentives

Tax incentives for R&D typically take 3 forms: 1) tax credits; 2) tax allowances; and 3) tax deferrals. The first of these is increasingly and overwhelmingly the predominant form. Although all tax incentives have the same result of raising the NPV of prospective research projects^{238#1210}, they can be applied in different ways. Tax incentives tend to be applied to a developer's current (personnel and material) expenditures or to a company's capital (equipment and facilities) expenditures.

Tax credits and allowances are similar in that they apply to current expenditures, reducing the after-tax cost of R&D and a company is limited on their annual claim. However there are two important distinctions—credits are a specified deduction (percentage) against final tax liability whereas a tax allowance enables companies to deduct more from their taxable income than they actually spend on R&D. Additionally, the former is independent of corporate income tax rate. Frequently, tax credits and allowances are designed to include a deferral characteristic, which greatly increase their appeal to SMEs. Tax allowances and credits also have a temporal element—allowances can be used to offset future tax and credits can be carried forward to offset tax in future years. The level of tax credit and allowances vary between countries. Although the level of tax credit varies, all countries all allow companies to deduct up to this percentage of qualifying income expenditure on R&D activities when calculating their profit for tax purposes in the year they are incurred^{239#1211}. The range of tax allowances extends from 13.5% in Belgium to 150% in the UK

With regards capital expenditures, some countries allow an immediate and full write-off against a business's taxable profits (Canada, Denmark, Ireland, Spain and the UK), whereas other countries require taxable profits (or a proportion) to be depreciated over

their economic life. In the UK this is possible by allowing companies to put the cost of capital instead of depreciation (not taxable) in the commercial accounts^{240#1212}. Through these examples we see that tax designs enable tax payments to be deferred and made more or less appealing to SMEs. However, it is also possible for tax incentives to be bought, sold, or invested²⁴¹.

Amongst these 3 forms, the variation in incentive designs is considerable. For example, some may be more accurately classified as a pull incentive such as tax credits for marketing expenses, which function as an award for reaching the market. Some tax credits can be difficult to distinguish from direct funding or subsidies (see previous section), especially where SMEs receive a 'refund' for the excess tax credit even when their tax bill is initially too small to benefit. This is the case for the 50% tax credit under the US ODA, which – for many SMEs – means it functions effectively as a research subsidy. In addition to being directed at the specific 'gap' of concern, tax credits can be directed at basic research, assets, or applied R&D. In particular, they can target companies that are likely to produce the greatest social return for the lost government tax revenue. They are often designed with small companies in mind and frequently target at collaborative research (such as PDPs)^{238#1210}. The design is also dependent on the structure and national tax framework in which it applies, which is why there is so much variation and so little comparison across and between OECD and EU countries^{238#1210}. For example Sweden and Finland demonstrate high private R&D expenditures in the absence of substantial direct and indirect funding which is accounted for largely by structural considerations such as their focus on highly skilled, human capital-intense production. Their business tax rates (28% and 29% respectively) are amongst the lowest in the OECD area^{238#1210}.

Examples from Europe

In 2008, the French government undertook a major reform of its tax system to maintain and promote R&D and make France an attractive country for innovation, which had been suffering from the 'brain drain' and absence of competitiveness^{242#1213}. The French Finance Act for 2008 includes a reduced rate of corporation tax arising from income resulting from IP. Basic and applied research activities are also eligible for preferential tax treatment:

- depreciation of assets dedicated to R&D projects (including patents acquired);
- costs of employees with the appropriate technical skills (including social charges) dedicated to R&D projects;
- operating expenses dedicated to R&D assessed at 75% of the former amount;
- subcontracted research activities (even within the EU);
- certain type of expenses related to compliance with regulatory standards

Examples from the US

In addition to the ODA, in 2007 Senator Charles Schumer introduced S.2351 into the Senate and Representative Edolphus Towns introduced H.R.4200 into the House of Representatives to create a 50% R&D tax credit for companies developing treatments for qualified infectious diseases. The tax credit was non-deferrable, meaning that the company could not retain the tax credit until it was profitable. Eligible products would have included drugs and biologics, vaccines, and diagnostic tests. The criteria for which products would qualify were broad and would have included areas like HIV/AIDS. The bill never came up for debate and thus was never passed.

General considerations for future application

In addition to the advantage of reducing the effective costs of R&D investments, a suggested benefit of tax incentives is that the industry remains in control of R&D while profits continue to be market-driven rather than government-decreed. This suggests that tax incentives result in fewer market distortions than more direct government funding and will incur fewer transactional costs. Although concerns are frequently raised regarding the efficiency of these incentives, and the difficulties linking changes in R&D activity to fiscal measures, it is now widely acknowledged that tax incentives are thought to increase private expenditure to a level equal or just below the level of the lost tax revenue (negative price elasticity)^{243#265 238#1210}. In the context of neglected diseases and vaccines, tax incentives have been particularly important for encouraging basic research, which is below the socially optimal level and thus cannot be supported solely by pull mechanisms. As discussed in Section 2.0, due to similar constraints, push mechanisms like tax incentives are also likely to be beneficial in the antibiotic market in restoring R&D closer to socially optimal levels.

However, there are several criticisms of tax incentives, particularly in relation to their effect on government expenditure and innovation. Tax credits for R&D expenditure increase government expenditures substantially. Between April 2000 and April 2006 around 22,000 claims for R&D tax credits (for all eligible sectors) were made in the UK costing the UK treasury almost £1.8 billion^{239#1211}. One proposal to relieve the government of such expenditures is that marginal cost pricing should be provided by developers in return for substantial tax relief^{244#1214}. In the case of public purchasing of pharmaceuticals this would mitigate concerns of governments 'paying twice' for innovation. Despite the large government expense, tax incentives do not guarantee the development of an innovative product. To get around this problem, the government could instead provide tax credits for marketing expenses or combine tax incentives with pull mechanisms^{18,243}. The latter is more favourable to governments in the context of antibiotics as reducing the costs of post-launch activities, such as sales and marketing will run counter to resistance-control efforts. Tax incentives also require additional costs to monitor companies employing creative accounting to maximise their claim²⁴⁵, which may negate the transactional costs savings. Additionally, tax incentives tend to be less

transparent than more direct funding mechanisms. Whilst there are many mechanisms in place to increase their appeal to SMEs, tax incentives can be argued to still favour those companies with taxable profits, and favour near-term rather than longer-term – more exploratory – projects and investments. Finally, in designing tax incentives EU competition laws and WTO protectionism rules need to be borne in mind.

Application to antibiotics

If tax incentives are to be expanded to promote R&D for antibiotics, they must target the earlier R&D phases – encouraging product development – and not be linked to marketing to ensure maintenance of product efficacy. The French case presents some examples of how tax incentives could be designed and targeted to antibiotic development. For example, options include a tax incentive on platform technology patents, more widespread tax relief for specialist anti-infective personnel, expenses related to the compliance of regulatory standards (i.e. charges associated with fast-track schemes), or clinical trials.

Application to SMEs

The ability of tax incentives to attract SMEs to innovate is under debate. Yin argues that by leaving revenue margins as opposed to cost margins unaffected, a flat-rate tax credit will be ineffective at stimulating innovation in markets with small revenue potential²⁴³. Thus, small companies with limited taxable profits will not be responsive to this incentive. However, tax incentives are increasingly being designed specifically for SMEs, some providing more generous relief to SMEs than to larger companies^{238#1210}. For example, the enabling of developers to be ‘refunded’ a tax credit despite their limited profits is a significant tax relief. Credit deferrals are also an important mechanism to increase their appeal to SMEs, particularly if this is made possible long in advance (for example 10 years under the Canadian system). Importantly, the benefit to SMEs of these schemes are that they receive the benefit at the point of expenditure, as opposed to retrospectively (like other schemes) satisfying their immediate need for funding. Even tax incentives on capital expenditures have proven to become more appealing to SMEs, with both 100% write-downs and accelerated depreciation schemes increasing their appeal. Some argue that tax incentives aimed at SMEs are unlikely to have significant effect on aggregate investment spending, but may encourage innovative expenditures at the margin^{238#1210}. Others argue that SMEs have lower uptake of these schemes and are less likely than larger companies to take full advantage^{238#1210}. However, if the tax incentive could be sold on the open market, SMEs might find this option more useful, although there is no precedent for this type of transaction. Another argument is that tax credits could be provided to form capital from investors and retained earnings^{xxviii 169#30}.

^{xxviii} Retained earnings refer to the proportion of net income that is reinvested in the company rather than given out as dividends.

6.2. Financial ‘Pull’ Incentives

Pull incentives offer financial reward upon completion of technological advances in order to lure R&D investments in a desired direction. They gained favour in the 1950s and 1960s with proponents arguing that demand not only drives the rate and direction of innovation but crucially directs companies in rectifying inefficiencies^{246#748}. This section explores prizes, advance market commitments and mechanisms within the existing patent system to influence innovation from the demand side of the market.

6.2.1 Monetary prizes

Prize systems featured strongly throughout the 19th and 20th centuries as the predominant mechanism to stimulate innovative solutions to society’s challenges, especially in the aeronautical and space industries. As far back as 1802 Edward Jenner was awarded the prize of £10,000 and 5 years later a further £20,000 from the British parliament for the discovery and development of the first vaccine – against smallpox²⁴⁷. The 1990’s saw a renewed interest in prizes as a mechanism to stimulate innovation in the life sciences. In 2001, at a World Business Council for sustainable Development (WBCSD) meeting, a global discussion was initiated regarding possible new business models for drug development²⁴⁸. This led to the premise of the ‘Medical Innovation Prize Fund Act’ (HR 417), a US congressional bill, passed in 2005, under representative Bernard Sanders²⁴⁹ proposing a country-wide implementation with developers being directly rewarded on the basis of a drug’s incremental therapeutic benefit to consumers, through a Medical Innovation Prize Fund created from 0.5% of US GDP. At the same time the WHO was being lobbied to consider proposals for a New Global Medical R&D Treaty²⁵⁰ part of which suggested a global fund (as a way of funding a prize system) in which every country should share the costs of drug development. So far no ‘large’ fund has been created in order to support a prize proposal on the scale of these earlier discussions. However a number of prizes have been announced in recent years largely including the 1994 Rockefeller prize for sexually transmitted disease (STD) diagnostics, the 1996 CASP prize for predicting protein structure, the 2006 X-Prize Foundation prizes for genomics; the 2006 X-Prize Foundation prizes for genomics in addition to their forthcoming prize for a TB diagnostic (see Box 6.2.1). These larger prize schemes complement the smaller <\$1 million prizes offered by InnoCentive a web-based registry for scientific innovation prizes founded by Eli Lilly in 2001 and with 80 prizes awarded to date.

Monetary prizes can take a number of different forms, including those that enable the manufacturer to retain the patent, those that require the manufacturer to forego the patent, elective systems such as the optional reward scheme, milestone monetary prizes

and best entry tournaments, amongst others. Each of these incentives is discussed below.

Box 6.2.1 Example of a prize used for a diagnostic test, X PRIZE Foundation

X PRIZE is a financial award given to the first team to achieve a specific goal set by the foundation.^{xxix} In 2008, the X PRIZE Foundation received a planning grant from the Bill and Melinda Gates Foundation to apply the prize concept to the development of an effective point-of-care TB diagnostic targeted for use in the developing world.

Whilst still in the design phase, provisional prize features include:

- A prize fund of between \$20–30 million will be accumulated from philanthropic donors. No formal metric was used to determine this value, although the literature was consulted and interviews performed to establish approximate development costs. These were then risk adjusted.
- The prize will be awarded within a time frame of 5–7 years
- The prize fund will likely to be split amongst multiple winners determined by ranking teams according to their final performance against weighted pre-determined criteria and at the discretion of an independent panel made of stakeholders representing a range of expertise including clinicians, patients, public health administrators, entrepreneurs, and scientists. Additional ‘bonus’ prizes are also under consideration for achieving other specifications such as applicability in HIV patients and in drug susceptibility testing.
- Any IP arising from the prize will remain with the winner as – at the time of writing – no specific licensing terms were likely to be specified.
- An additional and interesting design feature that separates it from previous prizes is an ‘enforced’ collaboration requirement. Incorporated partly out of acknowledgement that an individualistic, non-competitive approach will be unlikely to succeed and partly to help teams overcome practical, barriers they may face (regulatory hurdles, access to specimen banks, manufacturing expertise, etc). Teams will be ‘guided’ through the process with the foundation providing expert advice and even paying for certain important development elements (laboratory evaluations and clinical studies) in return for participation at a number of summits aimed at information-sharing and fostering collaboration.

Assuming sponsorship can be secured to make the prize a reality, the major challenges likely to remain are: determining a product specification that balances what is both achievable and sufficiently useful (innovative), balancing developer certainty (in terms of fixing the prize fund, product, specification and competition terms) with necessary

^{xxix} The 2004 Ansari X-PRIZE was granted for development in commercial lunar travel.

flexibility – a downfall of the 1994 Rockefeller Foundation Prize for an STD diagnostic²⁵¹, ensuring the prize is effectively targeted and is successfully adopted by the market.

Monetary prize – winner foregoes patent

As an alternative to exclusive patent rights, governments could reward innovation with large monetary prizes linked to the impact of the innovation^{xxx 252}. This would be a compulsory scheme, and the company would agree to forego its patent rights to the product^{xxxi}. The intuition behind monetary prizes that require the manufacturer to forego patent rights for the award-winning lies in their potential to reduce the deadweight welfare losses associated with monopoly pricing²⁵³ arising from the patent system. Love and Hubbard²⁴⁹ estimate that to stimulate \$1 of R&D, consumers must spend \$8-9, whilst the private sector's contribution to R&D was less than 9% (around US \$51 billion) of global pharmaceutical sales in 2005.

In addition to reducing deadweight welfare losses associated with the patent system, there are several additional advantages arising from the use of monetary prizes to decouple the reward from the innovation. Prizes may be particularly useful in areas that are not financially attractive for companies but provide a social benefit²⁴⁹, and only researchers that have produced successful products get rewarded (i.e. prizes do not subsidise unsuccessful research). Without granting companies monopoly power over pricing, prizes allow the donor to determine the value of the research incentive²⁵⁴.

Prize systems pose challenges in terms of the timing and how to reward follow-on innovators and potential duplication of efforts. The Sanders bill address the issue in suggesting that the prize payments for a new product reflect the incremental value of the improvements and the degree to which the new product built on or benefited from the innovation of the original product--with the original innovator continuing to receive payments even if their market share fell to zero²⁴⁹. There is also the issue of timing the payoffs, as it is difficult to calculate the long-term benefits of a newly introduced drug. To counter this uncertainty, some suggest staggering prize payouts over time²⁴⁹.

^{xxx} For instance, there have been proposals for the awards to be made according to the improvement in Quality Adjusted Life Years (QALYs).

^{xxxi} Another possibility is to make the scheme voluntary and allow the company to choose between a monetary prize and a patent. This is discussed below as the “optional reward system”.

Box 6.2.2 *Ex-ante* award calculation

Incentives in which the magnitude of rewards are estimated *ex ante* (e.g. monetary prizes, AMCs) pose significant challenges due to the difficulty in determining the appropriate size of reward to attract investment whilst not overpaying. In choosing the appropriate level of reward, the donor effectively chooses the social value of the innovation, thereby replacing the market itself. The deadweight welfare loss under a patent system will only be mitigated fully if the value is calculated optimally. However this is difficult when this may only become apparent *ex post*²⁵³. One argument is that a monetary prize must be larger than a subsidy, as competing companies still bear the risk of failure under this incentive¹. Assuming that the monetary prize would only apply to treatments for priority bacterial diseases, the reward would still need to compete with drugs that have higher NPVs, and thus the outlay for the reward would be larger than the outlay under a system like funding for basic and some clinical research. Kremer has argued the value should be the private value times a fixed mark-up at roughly the difference between the social and private value of the invention²⁵⁵. Other mechanisms have been proposed for how to determine social value in the absence of the market mechanism, these include Kremer's auction system to determine the private value²⁵⁵ and Hopenhayn's²⁵⁶ mandatory buyout approach which recognises the value of incremental or follow-on innovation through a system in which the innovator pays a prearranged buyout amount to the owner of the prior state-of-the-art innovation. The new innovators may choose from a menu of buyout fees to be paid to him by an innovation that wishes to supplant him, with a greater buyout fee requiring a greater up-front payment made to the planner. An additional consideration when determining the prize value is if the company receives other funding for product development, for instance through tax incentives, then the prize could be smaller in magnitude.

Hubbard, Love and Hollis propose the fund's value is fixed for reasons of budget predictability²⁴⁹. Most proposals also suggest the judging of the winner and distribution of the prize funds be proportional to the relative innovation or benefits, however the metric (usually Quality Adjusted Life Year [QALYs]) for assessing this also presents some challenges in practice and with the prize fixed there will be extensive pressure to ensure the method for valuing the inventions is fair and efficient. One suggestion is that a prize of US \$3 billion be awarded to the first effective treatment for a high-priority pathogen²⁵⁷, although the discussion has not been taken further.

Application to treatments for priority bacterial diseases

With regards to antibiotics, the pull mechanism inherent in prizes may offer a number of important advantages. The effect of this is, of course, dependent on the appropriate calculation of the prize (see Box 6.2.2 for discussion). Also, the separation of sales from

the recouping of R&D costs helps preclude the over-marketing and subsequent over-consumption of the final product.

Application to SMEs

The forgoing of patent rights has generally not been part of the business model of the existing large pharmaceutical companies. In this sense, smaller companies may be more likely to take part in this less orthodox approach. However, monetary prizes in general will only be attractive to SMEs if they already benefit from early stage funding in the form of venture capital or other forms of push funding. Certain business models will make some SMEs more attracted to prizes than others. For example, those for whom the strategy is to bring one product to market rather than develop a further portfolio of drugs will be particularly interested. It should also be noted that, given the lower revenue requirements for smaller companies, smaller sized awards could be used.

Monetary prize – winner keeps patent

Because creating a fund sufficient to purchase the patent rights from a manufacturer may be difficult in practice, particularly for governments faced with annual budgets, another form of monetary prize is to offer a smaller reward to the first company to market, allowing the company to retain patent rights. To combat resistance, the prize could include requirements that the company agree to marketing restrictions, as previously suggested by IDSA.

Again, the advantage of this design lies in its ability to pull innovation forward if the prize amount is appropriately calculated. The main disadvantage of the design is that consumers not only subsidise the monetary prize^{xxxii}, they are forced to pay monopoly prices for the drug.

Optional reward system

Shavell²⁵⁴ has suggested an optional reward system in which the developer is free to choose between a monetary reward and a patent. This would give the developer more time to assess the value of their product within a more up-to-date economic and competitive environment and make their choice of reward accordingly. In this regard, the option reward system reduces the amount of risk faced by the developer, passing it to the funder.

Abramowicz²⁵⁸ suggests that a developer will choose the prize over the patent if they believe the government is offering too much. One could also argue that a developer may be willing to take a lower payout under the optional reward system if it perceives the

^{xxxii} A system could be devised whereby a company reimburses the government for some or all assistance it received in researching and developing the product if it receives a monetary prize. However, the prize would likely need to be even larger as there are already insufficient incentives for companies to develop antibiotics even though government funding of basic research exists.

utility associated with the certainty of payout outweighs the utility associated with a higher but more uncertain payout. Furthermore, due to asymmetry of information, the developer may know that a new drug will have a shorter-than expected length of effectiveness, and thus the government reward will be too high. This is particularly relevant to the uncertainty surrounding the growth of antibiotic resistance and presents a major drawback for the optional rewards proposal. As both patents and prizes do not occur in isolation Davis suggests further research is necessary to determine how the two interact²⁵³.

Milestone monetary prize

Under this incentive scheme, researchers are rewarded for reaching certain milestones within the product development process, for instance, rewards for completing Phase I and Phase II trials. This provides similar advantage to other pull mechanisms except it represents a lower risk to developers in that they can earn rewards incrementally. Another advantage of a milestone monetary prize is that a greater number of researchers may be encouraged to participate, since, as conceived, the winner does not take all. Smaller companies would also be more attracted to this scheme as they receive reimbursement for development costs sooner, making it easier to attract venture capitalists to put up funding for later stages of development.

A disadvantage is that the funding body would be rewarding both successful and unsuccessful research. That is, a product might make it through Phase I and receive an award for reaching that milestone, but it may fail during Phase II trials. However, a significant proportion of molecules fail during Phase I, so setting the first milestone for successful Phase I trials eliminates part of this weakness. Also, as the most expensive stage of clinical trials occurs with Phase III testing, providing a large milestone payment after Phase II would help SMEs find the additional funds to conduct Phase III trials.

Best-entry tournament

Related to monetary prizes is the best-entry research tournament in which a sponsor provides a reward to the company that has progressed the furthest in research by a specified date²⁴⁵. This system has been used to select architects for construction projects but has not yet been applied to drug development. This model relies on a pull mechanism and single reward to promote competition amongst developers. In not specifying the required development stage to be achieved, the proposal may attract risk-averse developers. The ability to create competition will, of course, depend largely on the number of developers with promising molecules in sight as well as the level of collusion amongst them. The main advantage of this incentive design lies in its ability to attract developers who believe they have a chance of winning—those with existing molecules that have been previously set aside. Whilst these molecules may be useful for developing follow-on products, they may be less likely to develop into promising novel products. However, this needs to be investigated further. A major disadvantage

of this proposal lies in the fact that donors would commit to paying the reward even if overall progress were not significant and the product were to never make it to market.

6.2.2 Advanced market commitments

An Advanced Purchase Commitments (APCs), also and henceforth known as an Advanced Market Commitments (AMCs), is an agreement by a third party or parties (donors), typically a government or international agency, to subsidise the purchase of a pharmaceutical product at a pre-agreed price and volume^{241,259,260}. There are a number of different variations of AMCs, the two most common being the “winner takes all” and the “multiple winners” approaches.

Initially endorsed by the UK government in 2004 for promoting R&D for a malaria vaccine, and largely based on the model proposed by Kremer, the AMC concept received support in from the G8 in 2005²⁶¹. However, it wasn't until 2007 that the proposal was made a reality by the GAVI Alliance when they received US \$1.5 billion in pledges from 5 countries (Canada, Italy, Norway, Russia, and the United Kingdom) and the Bill & Melinda Gates Foundation for an AMC for vaccines to target pneumococcal pneumonia²⁶². The AMC is currently a pilot programme, aiming to stimulate late stage development and manufacturing of suitable vaccines at affordable prices. A price of \$3.50 has been committed for low income countries compared to \$70 per dose elsewhere. GAVI will spend \$ 1.3 billion through 2015, with implementing countries also providing a small co-payment²⁶³. However the model has been criticised by a number of non-governmental organisations (NGOs)^{264,265} as being a poor use of donor funds not only because of the existence of developed world demand, but also because two candidate vaccines were already nearing regulatory approval when the AMC was announced in 2005. Hence this AMC did not stimulate the development of a vaccine that otherwise would not be developed, it served more as a procurement contract to encourage companies to meet demand in poor countries at subsidised prices²⁶⁴. The costs associated with this – in terms of additional pharmaceutical profits – have been estimated to be around \$600 million²⁶⁵.

AMCs – winner takes all

The key advantage of an AMC is that, by specifying the volume (number of doses) to be purchased and their price, the AMC reduces the risk to the developer and potentially increases the size of the market. Consistent with most pull mechanisms, AMCs reward successful outputs with predetermined characteristics rather than rewarding inputs into research that may not succeed²⁶⁶. In doing so, AMCs explicitly link payment to product quality²⁶⁷. Additionally, the developer is free to pursue whichever R&D approach or mechanism it feels maximises its chance of success. Finally, it has been suggested that AMCs combine the incentives of patents and monetary prizes but eliminate the price

distortions associated with patents because the profit maximising developer does not set the final price^{237,255}.

To prevent an AMC remaining unfilled indefinitely, clauses and provisions within AMC contracts allow the sponsor to exit if the product is not delivered within a specified amount of time (a sunset clause) or if changes to the disease environment negate the need for the product (a force majeure clause). To prevent abuse by either the third party payer or the pharmaceutical company, ultimate authority lies with the independent regulatory body²⁶⁷. To overcome uncertainty over the commitment, all proposals now make an AMC legally enforceable by contract law, providing the credibility necessary to influence investment behaviour²⁶⁷ and reassure all parties (especially developers) that commitment won't be reneged upon. In addition to having the price guarantee, co-payment and volume commitments are all legally committed and binding from the outset and overseen by an independent body, such as an adjudication committee²⁶⁷.

Despite these systems, concerns regarding the public funder's ability to fulfil its commitments remain. This is especially a concern with respect to the developing world where infrastructural weaknesses impact ability to procure and deliver in practice. In all contexts the political cycle is rarely longer (<5 years) than the proposed duration of such a commitment (10–15 years) providing further uncertainty. Additionally, recent reports of the US government reneging on its commitments to purchase flu vaccine²⁶⁷ will likely exacerbate these concerns. These issues of credibility have prompted calls for private foundations to act as sponsors²⁶⁷ and further mechanisms to provide assurance, such as combining future purchase commitments with enhanced purchases of existing and frequently underused products²⁶⁶, as has successfully been demonstrated by GAVI in cooperation with the Gates foundation^{xxxiii}.

Although there has not yet been a solution to the free-rider issue that arises when other markets benefit from products developed under an AMC, the higher prices and price distortions paid by parties outside of the contract or contracted parties may significantly mitigate this. A global fund, such as that proposed to counter free-riding of the products of prize funds²⁵⁰, could possibly be applied to AMCs. For those parties within the contract, the most common proposal has been a two-tiered pricing structure²⁶⁷. According to this structure, a high (guaranteed) price is paid for the first treatments,

^{xxxiii} Under GAVI's strategy for new and underused vaccines, an estimated additional 213 million children were reached between 2000 and 2008, primarily with vaccines for hepatitis B, Haemophilus influenzae B (Hib) and yellow fever. Support was provided in the form of 5-year grants with the expectation that countries would increase their national contribution, leading to eventual financial sustainability. This immunization programme is widely perceived as a successful model for effectively purchasing vaccines. 266. Webber D, Kremmer M. Stimulating industrial research and development for neglected infectious diseases: economic perspectives. *Bulletin of the World Health Organization* 2001;**79**(8).

enabling a more rapid recovery of their investment and with greater certainty. This high price is combined with an additional commitment to supply further treatments at a lower price (base price) close to the marginal cost of production. Barder states that this transfers a proportion of the risk from the companies to the sponsors, since the NPV of the revenues to the company is much more stable than it would be under a single price charged over a longer time period²⁶⁷. However, Barder does acknowledge that getting purchasers (or funders in the case of developing countries) to make a finite commitment to pay the risk-adjusted costs of R&D and acknowledge it is a cost-effective use of scarce resources will not be easy.

Support for AMCs has recently emerged among key stakeholders within governments and the pharmaceutical industry. Concerns over political feasibility have been abated since the UK government and the G8 have both advocated for AMCs. In addition, the theoretical and practical simplicity of implementation of AMCs has helped garner support for their use. For example, in an analysis of requirements for implementing the malaria AMC, it was concluded that no additional legislative approval was deemed necessary before entering a legally binding commitment²⁶⁷. Although several countries have recently committed funds and political support remains strong due to the simplicity of AMCs, no product has yet been produced through an AMC and thus no country has actually distributed payments for product development. For example, the UK's Department for International Development (DFID) has indicated that any AMC expenditure would not be recorded in the UK national accounts until the government is actually buying vaccines. In addition to the government advocating for AMCs, industry is also supporting the use of AMCs. Light suggests that this is due to their voluntary nature and the idea of industry retaining control over the IP²⁶⁸. Despite this growing government and industry support and administrative feasibility it is, as yet, unclear whether this support will be eroded by public resistance to large public financial sums being directed to what is seen as a highly lucrative industry.

There remains some debate as to whether the competition created by AMCs will stifle rather than foster collaboration, duplicate funding and 'crowd-out' other incentives²⁶⁸. Their current use in conjunction with other initiatives (for example push incentives also supporting malaria and pneumococcal vaccine development) will inform this debate and determine if AMCs may serve as a complementary tool.

However, difficulties remain in determining the appropriate contract terms and level of reward that brings the right product to market, thus providing sufficient developer incentives without leading to overpayment. It is challenging for the executive committee to accurately determine *ex ante* the appropriate contract terms and price and volume commitment without knowing the costs of production, advances in science, and regulatory changes in advance. This information is difficult for manufacturers themselves and hence will lead to difficulties in them assessing whether the AMC is

worthwhile. The cost-effectiveness of the scheme may be reduced if any of these factors are calculated inaccurately.

Additionally, under an AMC, the product must receive approval from the regulatory agency before the purchase agreement can be fulfilled, and thus an AMC may be considered a variation of a monetary prize (although more complex in nature). This means that AMCs do not eliminate risk for the developer entirely because only successful products are rewarded^{269,270}. One alternative is the multiple winners approach discussed earlier (Section 6.2.1); however, an alternative solution proposed by Barder suggests that due to the impossibility of anticipating all contingencies and writing them into the product specification, a minimum threshold quantity should not be specified in the contracts. Therefore, if a superior product becomes available and also qualifies for the price guarantee, the recipient countries would be able to choose which products they wanted to use. This more closely mimics an actual market and ensuring subsequent developers are rewarded, proportional to the product value determined by the market. However, it also removes some of the market certainty to draw developers. Application of an AMC in a developed market may enable better demand forecasting as a mechanism to alleviate some of this problem. Pricing structure and the terms dictating how a developer is able to exploit its monopoly protection will also impact developer reward and hence risk.

Application to treatments for priority bacterial disease

Like monetary prizes, an AMC is a one-time payoff as opposed to an ongoing stimulus for R&D. Therefore, an AMC might address the immediate need for a replenished antibiotic pipeline. However, it does not address the continual need for novel products to combat resistance. To combat this problem one could put out calls for research to receive AMCs every few years, however, this is an expensive proposition. Also, given the potentially high cost of an AMC, the reward would have to be conditional on developing truly novel products. In the case of multiple winners, the products would also have to display properties (namely mechanisms of action) that are distinct from one another.

Another relevant question related to antibiotics and AMCs concerns the determination of the purchase volume given changes in the epidemiological environment. One option is that the government could commit to purchasing a certain amount and simply stockpile the product if too much is purchased.

Box 6.2.3 Stockpiling

Although historically antibiotic stockpiling at both the national and supranational level may have been minimal, managed at the level of each facility, and largely uncoordinated at any higher levels i.e. regional, national, supranational, this trend is set to change in response to the recent bioterror and pandemic threats²⁷¹. In Europe this will likely take

place within the programme of cooperation on preparedness and response to biological and chemical agent attacks (BICHAT).

Acceptance of a product for a national or European stockpile presents a potentially lucrative opportunity for developers. However, to qualify for stockpiling, antibiotics will likely have to be formulated for simple consumption to ensure they can be disseminated widely to the public in the case of an emergency. Indeed, anecdotal evidence from the US suggests that antibiotics in their originally marketed parenteral formulations are generally not considered for stockpiling. This may have substantial cost implications for developers and must be taken into account in calculating incentive rewards aimed at producing products for stockpiling.

Application to SMEs

Existing AMCs seem to have predominantly targeted large pharmaceutical companies¹⁶. It has been suggested that the modelling undertaken thus far has largely assumed price levels for blockbuster products, rather than relatively successful products (in this case vaccines)^{268 #228}. They have also not included design features, such as milestone payments, which would increase their appeal for SMEs^{268 #228}. Despite the targeting of large companies, numerous academics (16, 270, 275) as well as the large companies themselves (through IFPMA) have suggested that AMCs may be most relevant ‘in areas where most needs can be met through adaptive research [incremental innovation]’²⁷². This runs counter to the assertion by the CGD²⁶⁷ that AMCs will serve as a ‘long, deep pull back to basic research’ that might lead to the development of truly novel products. One possible explanation for the IFPMA stance (from 2005) may be that AMCs under discussion did sufficiently lower the risks associated with undertaking innovative research.

Again, without some form of venture capital or early stage push funding, smaller companies are unlikely to be able to benefit from AMCs. Designs to attract smaller companies would need to shift some of the reward forwards to meet their need for early stage funding. In this sense, more hybrid pull-push incentives may be needed if participation by SMEs is desired.

AMCs – multiple winners approach

The multiple winners approach arose as an attempt to mitigate developer risk arising from the ‘winner takes all’ approach, where subsequent developers faced the risk of receiving no reward or return on their investment. This design could also mitigate purchaser unease arising from the fact that under a ‘winner takes all’ design, purchasers would be obliged to reward only the first developer even if subsequent drugs were superior. Other advantages of opening the guaranteed market to multiple products would be to stimulate greater competition and potentially downward price pressure.

Additionally, this could contribute to the product reaching more people by increasing the continuity of supply²⁶⁹.

Under the “multiple winners” approach, more than one company can receive a proportion of the AMC. Some authors suggest that the first several products meeting the specification, through independent means even if not necessarily superior, would be eligible for the price guarantee, provided they represent an improvement on existing products – for example for certain target populations or conditions²⁶⁹. A variation of this is to reward all those achieving the minimum specification. Apportioning the AMC based on clinical superiority has been discussed in the context of prize funds (see Section 6.2.1)

There are also several disadvantages inherent in this approach. Both the smaller overall reward and the increased risk if payouts are not predetermined for each developer, would serve to diminish the incentive strength. Additionally, if manufacturers feel they will not be rewarded adequately for their efforts, many could discontinue R&D. Multiple winners also adds administrative complexity and would likely dilute the reputation gains that may add appeal for developers.

6.2.3 Intellectual-property mechanisms

IP protection effectively grants monopoly status to products for a given period of time to allow developers to recoup high R&D costs and make a profit. This section explores incentives that use altered IP protection arrangements to promote the development of antibiotics.

Patent Pools

A patent pool is a financing mechanism that enables the collective acquisition and management of IP for use by third parties for a fee. Patent holders from the public or private sector may contribute patents to the pool. Subsequently, a developer wanting to use the patent to develop a new product can seek a license from the pool against the payment of royalties to produce the medicines. This reduces transaction costs and barriers to market entry resulting from IP protection. The pool design, specifically the geographic area of license coverage, will determine the level of competition. The wider the area, the larger the demand, the more producers maybe be expected to compete which would drive down prices. Conversely as the patent-holders retain the right to license the patents outside of the patent pool, the smaller the pool, the lower the demand, so there will be fewer competitors and beneficiaries to the scheme.

Historical experience with patent pools exists in the fields of agriculture, electronics and information technology. Within healthcare they have largely been discussed when IP barriers are the cause of access or scale-up problems, such as in the developing world with newer HIV medicines or in the developed world in responses to the SARS outbreak.

As regards the former, in July 2008 UNITAID launched a pool – funded through a tax on airline tickets – with the aim to scale-up access to newer antiretroviral medicines (ARVs) for HIV treatment in developing countries and encourage the development of adapted formulations²⁷³. A cost-benefit analysis of the pool, initiated by James Love and completed by UNITAID, estimated that, when looking at only developing countries, it would take only a 1% impact on generic competition before it would pay for itself. This excluded other benefits such as increased competition, development of better manufacturing processes, new fixed dose combinations²⁷⁴. A broader proposal for an Essential Medical Inventions Licensing Agency (EMILA) is still under review. The most recent was announced by GSK in March 2009²⁷⁵ and is a separate patent pool to address neglected tropical diseases (NTDs) more broadly (the 16 diseases defined by the WHO) was announced by GSK in March 2009²⁷⁵. Whilst in its infancy and not currently including other institutions or organisations, it has made available the IP of approximately 80 patent families. GSK has declared the patents they are actively pursuing and are accepting applications for licences in areas and indications that they themselves are not pursuing. If an application is successful, GSK has committed to providing licenses for the development of medicines for the treatment of NTDs in low income countries (LICs) on favourable terms albeit with geographical and therapeutic area restrictions^{xxxiv}. Additionally GSK have indicated willingness to consider, on a case-by-case basis, licensing pooled IP for use outside LICs under two arrangements. The first of these is the possibility of allowing a third party to sell into an LIC on a royalty basis or for GSK themselves to take a licence (one-off fee or royalties) in order for them to sell the products into developed countries themselves^{275xxxv}. Finally, the World Health Organisation convened a panel in 2005 to look into the feasibility of a patent pool to ensure rapid access to vaccines or medicines in case of a SARS outbreak. Initial support – including that of the relevant patent holders – seemed favourable and the patents are currently under review by two US law firms. However, it remains unclear if this proposal will come to fruition.

Within patent pools, efficiency gains are made through the collective management structure which centralises, simplifies and streamlines the administrative, legal and bureaucratic processes of obtaining and managing licenses from a multitude of patent holders. This is true for both simple but especially where 'blocking' patents (patents frequently belonging to a patent cluster or thicket) exist. The use of patent clustering as an anticompetitive tool was highlighted by the EU's recent competition enquiry into the pharmaceutical industry. The possibility of a 'one-stop-shop' versus multiple individual agreements reduces costs and market entry barriers to potential new developers or manufacturers²⁷⁷. Further cost-savings may be achieved through the reduction of

^{xxxiv} At the time of writing details of these restrictions were unavailable

^{xxxv} Alnylam is the first company to add its patents to the patent filings GSK provided to populate the pool²⁷⁶. GSK RP. Alnylam joins GSK in donating intellectual property to patent pool for neglected tropical diseases. 2009..

litigation costs for patent infringements. Also, perhaps more importantly, pools increase access to IP as developers and manufacturers no longer need to wait out the patent term, which can allow for faster downstream innovation, technology transfer and scale-up if and when necessary²⁷⁷.

Application treatments for priority bacterial diseases

Patent pools have largely been discussed in the context of ensuring rapid access to existing technology and enabling incremental progress through 'follow-on' technology as opposed to their ability to stimulate brand new innovation. In the antibiotic market, where incremental innovation is unlikely to be a long-term solution, one could argue that such an arrangement may not bring the necessary innovation to produce truly novel products. Another consideration which may limit the applicability of a patent pool for antibiotics arises when we consider whether royalties would be perceived as sufficient compensation for relinquishing IP rights, especially if the patented technology has any chance of contributing to the development of a novel product.

Application to SMEs

Theoretically any developer could benefit from patent pool arrangements if they were well placed to carry forward subsequent development of a product. Generally, however, smaller companies stand to gain more from such arrangements in that the traditionally high costs associated with obtaining access to existing IP would be eliminated. However, this will not negate the obvious advantage of larger companies having the capital necessary to explore many molecules by undertaking extensive exercises of trial and error.

Patent buyout

A patent buyout takes place when a fund is used to purchase the IP of a new product and secure it in the public domain. Buyouts can be used as components of prize mechanisms or AMCs or simple product purchases by a public body. By eliminating monopoly power over pricing, buyouts allow the donor to determine the value of the research incentive. Also, as the patent no longer belongs to the developer, others may improve upon the existing product for commercial purposes during the patent life if licenses are granted by the eventual patent owner (in this the public body). If licenses are not granted, this would limit the possibilities for follow-on innovation. As with prizes and AMCs, the main disadvantage of buyouts relates to the calculation of the optimal buyout price.

Extended intellectual property protection

The argument behind extended IP protection lies in the fact that obtaining market authorization is usually a long process that reduces the effective life of a patent. Proponents suggest that profits that a company would obtain from selling its product during the effective patent life of a product may not be sufficient to justify the costs of

R&D, particularly in the case of products with a high cost of R&D and/or lower revenue potential. Extended IP protection is thus argued to be a necessary requirement to increase revenues to a sufficient level to assure the recouping of R&D costs and acceptable levels of profit.

Examples from Europe

Within Europe drugs can qualify for increased IP protection under 3 programmes: Supplementary Protection Certificates (SPCs), orphan drug legislation, and paediatric drug legislation

In 1993 regulation regarding SPCs came into existence across the EU^{xxxvi} 278. The SPC allows the manufacturer to gain additional protection for time lost in regulatory reviews. It is a separate right from the patent that comes into effect only once the patent expires and provides protection for a specific active ingredient that has received marketing authorization. In the case of numerous patents on a product, patent holders must select one “basic” patent and file an application in each Member State issuing the patent and from which an SPC is sought²⁷⁹ #278. The duration of protection is calculated from the time between patent filing and market authorization. This figure is then reduced by 5 years and subject to a maximum of 5 years, whilst the total marketing exclusivity that the product enjoys cannot exceed 15 years^{xxxvii}. No more than one SPC may be granted per patent holder, however, two different patent holders may receive SPCs for the same product as long as applications are filed before the first SPC is granted. SPCs differ from patent-term extensions in the US in that more than one SPC can be granted on a “basic” patent if the products have a different active ingredient and separate marketing authorization. SPC protection extends to the particular use of the product that was the subject of the marketing authorisation as well as to any other use of the product authorised before the expiry of the basic patent, even if authorisations were secured by third parties²⁷⁹ #278. The further protection brought by SPCs have been found to significantly increase sales revenues from high-selling drugs. For example, French points out that 80% of Prozac sales in Europe over the last 10 years of effective patent protection were achieved in the 5 years covered by the SPC²⁷⁹ #278.

The EMEA’s Committee for Orphan Medicinal Products defines an orphan product as a significantly beneficial product that prevents, treats, or diagnoses a life-threatening or chronically debilitating disease inflicting a maximum of 5 in 10,000 people. Since April 2000 drugs eligible for orphan drug designation are entitled to 10 year data exclusivity and other incentives like access to the EMEA’s centralised approval procedure, fee reductions for regulatory procedures, and free scientific advice²⁸⁰. Although not standardized, orphan drugs also receive tax incentives from the Member State level.

^{xxxvi} Although, the regulation did not come into force in Austria, Finland, Norway, and Sweden until 1994.

^{xxxvii} The total marketing exclusivity period can be extended to a maximum of 15.5 years for products demonstrating the paediatric provisions.

Lessons from the US, however, suggest that the primary attraction of this type of legislation for the pharmaceutical industry is the market exclusivity component²⁴⁵. The outline of EU and US legislation is included in Table 6.2.1^{281#778}.

Table 6.2.1 Comparison of US and EU Orphan Drug Legislation and Processes (adapted from Rinaldi 2005^{281#778})

		US	EU
Administrative body		FDA/OOPD	EMA/COMP
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
Incentives	Market exclusivity	7	10*
	Data exclusivity	5 yrs (NCE); 3 yrs (non-NCE)	10 (+1) yrs NCEs
	Funding	Grants for clinical research (pharma and academia eligible)	Framework programmes for research plus 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 years)
No. of designated orphan drugs (as of April 2005)		1,449†	269†
No. of orphan drug marketing authorizations (as of April 2005)		269†	20†
2004 market value		\$27 billion≠	0.7%–1% national budgets (predicted to reach 6%–8% of total budgets by 2010)**

* Can be reduced to 6 years if at the end of the 5th year the criteria outlined in article 3 (i.e. if a product is sufficiently profitable to no longer justify exclusivity) are no longer met ; †as of April 2005; ≠ Visiongain report; ** de Verax, Alciméd

Sources: STOA, 1999; Stolk et al., 2005; Orphanet, www.orpha.net; EU Community Register of Orphan Medicinal Products, pharmacos.eudra.org/F2; US Office of Orphan Products Development, www.fda.gov/orphan.

Due to differences in legislation, facility and speed of access to orphan drugs is not the same across 15 European countries. The EMA publishes a table^{xxxviii} comparing member state legislation across the union and using a number of criteria to rank the legislation from slow (Belgium, UK) or complex (Denmark, Finland) through to rapid (France) or easy (Germany, Sweden).

^{xxxviii} Available from: http://ec.europa.eu/health/ph_threats/non_com/docs/EMA_chart_en.pdf

In 2007 the EU enacted paediatric drug legislation, which requires companies applying for marketing approval of a new drug to produce a Paediatric Investigation Plan (PIP). The PIP, components of which can be deferrable, includes information on the timing and proposed means of testing the quality, safety, and efficacy of the product in a paediatric population²⁸². Manufacturers can obtain exemptions in certain situations, however there are incentives to comply. For newly approved products, the SPC can be extended by 6 months if the company files a PIP. Orphan drugs potentially gain an additional 2 years. Drugs exclusively for paediatric use or [all-age] paediatric formulations that were launched before the legislation came into effect can also receive the Paediatric Use Marketing Authorisation (PUMA), which grants up to 10 years of market exclusivity. Although these drugs must not already have patent protection or be covered by an SPC.

Examples from the United States

In line with some of the programmes for extended IP protection available in Europe, antibiotics can qualify for increased IP protection under 4 programmes: the Hatch-Waxman Act, the FDA Administration Modernization Act, the QI Program Supplemental Funding Act and the ODA.

The 1984 Drug Price Competition and Patent Term Restoration Act, commonly known as the Hatch-Waxman Act, specified that certain drugs could qualify for patent term extensions equal to half of the time spent in clinical testing plus all of the time spent in the marketing application process²⁸³. The extension may not exceed 5 years, and patent protection cannot exceed 14 years after approval of the product. Importantly, as the Hatch-Waxman Act explicitly excluded antibiotics from extended IP protection, the 1997 FDA Modernization Act (FDAMA) extended the patent extension provisions to antibiotic products not submitted in an application prior to 1997. Most recently, in 2008 the US Congress enacted the QI Program Supplemental Funding Act, providing 3 years of exclusivity for the approval of a new indication for an already approved older antibacterial drug and 5 years of market exclusivity for the approval of a previously unapproved older antibacterial drug¹⁷².

In 1982 the ODA, which was an amendment to the Federal Food, Drug, and Cosmetic Act, passed. Under the Act, an orphan disease is one that affects fewer than 200,000 people in the US or a drug that the FDA determines will not be profitable for at least 7 years after marketing approval²⁸⁴. Orphan designated products are eligible for 7 years of market exclusivity, grants, tax credits, accelerated review, protocol assistance and waivers of certain fees (see table 6.2.1).

The Pediatric Exclusivity Provision^{xxxix}, enacted as part of the 1997 FDAMA, grants 6 months of additional market exclusivity to manufacturers that successfully perform studies in children as specified by the FDA²⁸⁵. A number of antibiotic products have benefited from this exclusivity provision including ciprofloxacin and ertapenem.

General considerations for future application

Extended IP protection allows companies to charge higher prices for drugs over a longer period of time and restrict generic competition. Both health systems and patients pay higher prices, leading to a diversion of resources from other priorities and potential barriers to access for patients. Generic companies also lose as they must forego profits that could be made by entering the market at the time of the normally scheduled patent expiry. Not surprisingly, under orphan drug legislation, many drugs for rare and neglected disorders have been very lucrative. For instance, 5 of the top 10 best selling biotechnology drugs worldwide in 2001 were originally approved as orphan drugs²⁸⁶, and the first generation of AIDS treatment was a profitable orphan drug²⁸⁷.

However, it is also suggested that extended IP protection is an inefficient mechanism for stimulating R&D. Outterson et al²⁵⁹ calculate that approximately 17.5% of revenue from extended IP protection would be funnelled back into R&D, yielding approximately US \$910 million in additional R&D globally per year. A significantly larger proportion of the returns from extended IP protection, approximately US \$4.29 billion per year, would be spent on other corporate expenses and profits. Moreover, even if there were a binding commitment to compel firms benefiting from this scheme to channel the profits into R&D for infectious diseases, some suggest that the scheme would only lead to the production of one new antibiotic drug per year²⁵⁹. Currently, no such commitment exists within orphan drug and paediatric legislation in either the EU or the US.

Application treatments for priority bacterial diseases

Much of the discussion of extending IP protection for antibiotics surrounds their ability to inhibit the emergence of resistance. This is explored in some detail in Boxes 6.2.4 and 6.2.5. It is unclear whether the social loss associated with monopoly pricing is outweighed by the gains from reduced consumption. Additionally, some argue that the social cost of extended IP protection fails to counter the benefits that new antibiotics create through treating MDR bacteria²⁸⁸. Kades²⁸⁹ also claims that the benefit of a longer useful life outweighs the cost. Outterson et al²⁵⁹, however, argue that extended

^{xxxix} The provision applies to drug and biological products approved under section 505 with patent life remaining on listed patents or for which exclusivity remains under the Drug Price Competition and Patent Term Restoration Act (Pub. L. 98-417) or the Orphan Drug Act (Pub. L. 97-414).

protection could postpone the development of new drugs, thereby accelerating the resistance problem, as a developer has no incentive to develop a follow-on drug until the patent is nearing expiration.^{xl}

Application to SMEs

Extended IP protection is certainly attractive to developers who can afford to support basic and clinical research. However, many SMEs are unlikely to be in this position. Again, without some early funding, SMEs are unlikely to benefit much from purely pull mechanisms such as extensions to IP protection.

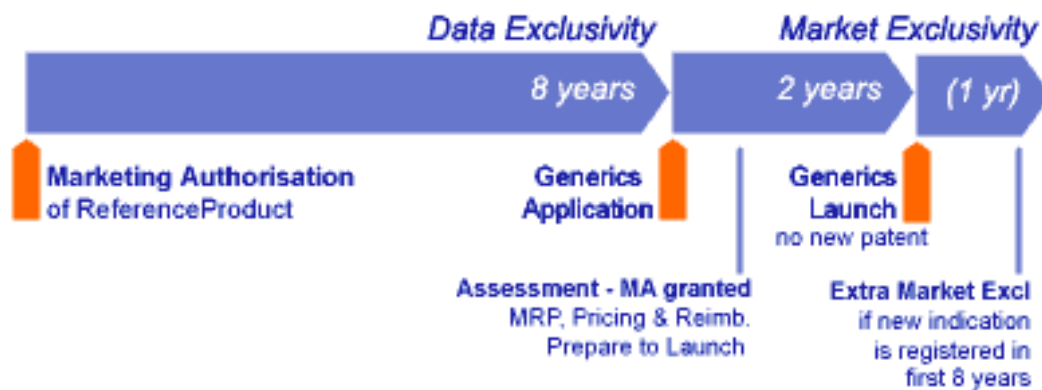
Extensions of data exclusivity

Data exclusivity is an expression of trade-secrets (undisclosed information) and hence distinct from the patent system which determines market exclusivity. The latter determines when a generic equivalent can be placed on the market and the former when a regulatory agency can begin to review applications from generic competitors. Both are calculated from the point the initiator product was authorised. The difference usually extends market exclusivity by 1 to 3 years beyond the data exclusivity period whilst registration and marketing occurs. Data exclusivity was introduced in Europe in 1987 to compensate for insufficient product patent protection in some countries^{290#1215}.

In 2004 as part of the new EU pharmaceutical legislation aimed at harmonising processes across member states⁴, data exclusivity was extended and the 8+2(+1) model adopted (see Figure 6.2.1 below) applying to all new chemical entities. The new model allows for 8 years of data exclusivity from the date of initial authorization in the Community, during which time regulatory authorities are not permitted to accept any abbreviated NDAs from generic manufacturers, plus 2 years of market exclusivity and an additional year (+1), if an existing product is switching status or applying for a new indication^{290#1215}. In the US the equivalent period, since 1997, is 5 years if the application is for a NCE or 3 years of data exclusivity for a non-NCE.⁴ However a large number of EU countries still work to the former 6 year exclusivity for example Austria, Denmark, Ireland, Spain, Norway and the 12 new member states.

^{xl} As discussed above, there are a number of advantages to having later generation antibiotics 10. Power E. Impact of antibiotic restrictions: the pharmaceutical perspective. *Clinical Microbiology and Infection* 2006;**12**(Suppl 5):25-34..

Figure 6.2.1 EMEA 8+2(+1) arrangements in the EU ^{290#1215}.



The duration of data exclusivity is important because it allows for an unchallenged period on the market, even for products protected by weak patents (e.g. patents granted on the basis of formulation). Theoretically the market incentive of data exclusivity is less restrictive than patents, because it does not legally restrict other companies from generating their own registration data, but the time and expense for generic companies to generate pharmaceutical registration data and compile their submission dossier means that, in reality, data exclusivity provisions act as a significant market barrier. For most drugs, the period of data exclusivity appears shorter than the market exclusivity offered under patent protection (around 20 years, but up to 25 in presence of an SPC or PTR) however there are a number of situations in which this may not be the case. For example, this is not the case if the development period of a drug is particularly long, for drugs that do not benefit from full patent protection, or biogenerics (generic versions of biosimilars). This is corroborated by an IMS Health Report suggesting that 'very few high-selling drugs gain further marketing monopoly from data exclusivity provisions....only those without SPCs or those taking an exceptionally long time to complete the process gained significantly' ^{291#1216}. Conversely, generic companies perceive data exclusivity as an extension – or additional layer – of monopoly protection keeping their products off the market ^{292#1217} across the board, with others arguing that given orphan drug provisions, data exclusivity is duplicative and unnecessary ^{293#1218}.

Application treatments for priority bacterial diseases

As regulators cannot accept applications from competitors during the data exclusivity period, these mechanisms can substantially postpone the entry of competitors. As such, the application of data exclusivity extensions to antibiotics raises similar issues as patent term extensions although they are likely to receive even more fierce opposition from the generics industry.

Box 6.2.4 Using the intellectual property mechanism to inhibit the development of resistance

Inhibiting the development of resistance

Many argue that the main benefit of extended IP protection is a potential reduction in antibiotic resistance²⁹⁴. Whilst the restriction of generic competition is a criticism of extended IP protection, reduced generic competition may actually be a benefit when it comes to antibacterial resistance^{xli}. Specifically, generic competition lowers prices, which can accelerate consumption and resistance. It is argued that by stretching out the duration of IP protection, the government is essentially delaying the growth in resistance that may occur when IP protection are exhausted.

However, it argued that extending IP protection would, on the contrary, increase the growth rate of resistance by deterring the production of follow-on products and inhibiting (postponing investments) innovation²⁵⁹. Outtersen additionally argues that longer patent periods are financially inefficient (as so little of the increased revenue will be used to fund further antibiotic R&D) and patents' time-limited nature creates an incentive to sell over the socially optimal level ('patent holder waste') making them counter-productive to conservation strategies.

The current patent system itself could be contributing to the growth of resistance. It is argued that resistance might accelerate a few years before the exhaustion of IP protection, as companies have an incentive to maximise sales before generic competition enters, otherwise known as 'patent holder waste'^{1,259}. Linezolid, for which the FDA issued a warning letter to the manufacturer over its overzealous marketing of the antibiotic, is an example that the authors cite of patent holder waste. Spellberg⁵⁰, however, argues that pharmaceutical companies typically front load the marketing of a drug soon after market authorisation. Additional literature refutes the patent holder waste theory as brand advertising has been found to start declining two years before patent expiration²⁹⁵.

If several patents within the same antibiotic class are held by different companies, the tragedy of the commons may emerge^{259,294}. Individual companies cannot control the sales of antibiotics by other companies, and therefore all companies aggressively market the drug and accelerate the development of resistance. If the number of patent holders of cross-resistant drugs is small, companies could privately coordinate to regulate total sales (similar to the Organization of the Petroleum Exporting Countries, OPEC), but current collusion laws bar companies from coordinating in this manner. Laws prohibiting anti-competitive behaviour would need to be changed. However, the question of what

^{xli} Evidence of this assertion is lacking, though, and there is a clear need for research on the relationship between generic competition and antimicrobial resistance.

to do when one of the drugs within the class were off patent would remain. The potential solutions to this dilemma are to implement broad patents for Functional Resistance Groups^{xliii} (See Box 6.2.5).

Box 6.2.5 Broadening intellectual property protection

Another variation of patent extension incentives is to apply patents over Functional Resistance Groups (FRGs)^{xliii} rather than by chemical classes, in order to reduce resistance arising from competition between drugs under different patents for the same condition¹. An antibiotic would belong to a particular functional resistance group (FRG) if the use of that antibiotic causes resistance to other antibiotics in the FRG but not resistance to antibiotics in other FRGs. Laximinarayan and Malini proposed this concept because the current classification of antibiotics based on chemical classes is not in line with promoting the effectiveness of antibiotics¹. In particular, the use of a drug within one particular chemical class may not only lead to resistance to other drugs within that chemical class but may also lead to resistance to drugs in other chemical classes.

The advantages of this system would be that the owner of a patent for a FRG would have the incentive to manage its drugs and slow the development of resistance^{38,65}. The theory is that broad patents will stop companies from competing for the same pool of effectiveness within a FRG and provide an incentive for companies without a patent for a FRG to develop new antibiotics outside of the patented classes⁶⁵. Whilst this system would further raise drug prices and increase social costs, the benefits of conserving antibiotic effectiveness may outweigh the social costs of oligopoly power⁶³.

However, a number of practical challenges present themselves against this proposal. As multiple patents and off-patent products would already exist within FRGs, significant research would be needed to understand how to divide, amalgamate, and compensate within this type of system. Also, with regards to defining FRGs, the classification would likely need to be dynamic as resistance develops. However, perhaps most challenging (see section 6.3) is the requirement for not only a relaxation of anti-trust laws to allow companies to collude in this way but also consideration of a *sui generis* right which may be necessary given that many classes of antibiotics have off-patent drugs or patents owned by different companies. Another disadvantage is that developers would have no incentive to research drugs in other FRGs where patents already exist¹, which may hinder the development of follow-on antibiotics.

²⁹ The EU is currently in discussion to reduce this to 6 years

Wildcard patent extensions

Under wildcard patent extensions, also known as transferable IP protection, a company that successfully develops a new antibiotic is granted a patent extension for another drug that is approaching patent expiration in its portfolio. Suggested lengths of the patent extension range from 6 months to 2 years in the US ¹⁹¹ and to up to 5 years in the EU ^{296 297} or proportional to therapeutic benefit.

The main advantage of the scheme is that it would present a significant reward for large companies with lucrative products to protect or for small companies who could sell the extension to them. In some ways wildcard patent extensions demonstrate advantages over extended IP protection in that the scheme does not exacerbate the ‘tragedy of the anticommons’ in the antibiotics market itself ²⁹⁸.

However the main disadvantage of the scheme is the significant social costs of a wildcard patent extension. The estimated cost of allowing wildcard patents for just 10 drugs exceeds US \$40 billion. This estimate does not include the cost of other economic incentives for developing a new product, such as government grants supporting research or tax credits. If included, drug development costs could be US \$8.7–\$11.9 billion per delivered drug, greatly exceeding the current industry estimate of US \$400–\$800 million per new molecule ¹⁸⁹. The estimate also does not include the possibility of a company stacking multiple patent extensions onto one blockbuster drug ²⁵⁹.

Another major criticism is that wildcard extensions transfer the cost of developing a new drug for one disease onto patients with another disease, raising concerns about equity and transparency ^{245,259}. The ethical implications of this cost-shifting between unrelated patient-groups and concerns over the resulting bad publicity are the main reason why the EFPIA and the Pharmaceutical Research and Manufacturers of America (PhRMA) no longer advocate incentives based on wildcard extensions.

The anti-competitive nature of the scheme further hinders its applicability. Wildcard patent extensions delay generic entry in a particularly inequitable manner. In the market within which the patent extension is applied generic companies awaiting patent expiry would suddenly be blocked from entry. The generic company must then wait additional time before entering the market. If frequent, this creates a risk of generally disincentivising generic companies to invest in demonstrating bioequivalence until the brand-name patent has expired, i.e. when there is certainty that the patent cannot be extended. This would lead to slow entry of generics into any market in which wildcard patent extensions might be applied—the most lucrative markets. These are exactly the markets society desires more competition, not less. The additional time lag also provides the patent owner further time not only to develop follow-on products to capture market share, but also to spin off “friendly” generics to nullify any exclusivity granted to their first competitors.

There are currently no wildcard schemes in operation for pharmaceuticals in either the EU or the US. The most recently proposed scheme was the US Biodefense and Pandemic Vaccine and Drug Development Act of 2005, also known as the Bioshield II programme, which was intended to stimulate countermeasures to biological weapons. In this case the exclusivity provision attracted such vehement opposition by the generic industry, it had to be removed before the Act was signed into law^{xliv}.

Application to treatments for priority bacterial diseases

Spellberg et al.²⁹⁹ estimated the costs of the wildcard patent extension compared to the savings derived from a new antibiotic drug to treat multi-drug-resistant *Pseudomonas aeruginosa*. The authors found that a wildcard patent extension applied to one new antibiotic would cost US \$7.7 billion over the first 2 years and US \$3.9 billion over the following 18 years. The most conservative estimates indicate that even if the new antibiotic only reduced the annual cost of *P. aeruginosa* infections by 50%, the wildcard patent extension would be cost neutral by 10 years after the approval of the new antibiotic and would save society US \$4.6 billion by 20 years after approval. They conclude that the patent extension is an economically viable incentive for antibiotic R&D and will result in cost savings to society over time if applied in an appropriate manner.

To contain the social costs, Spellberg et al. also argue that the wildcard extension could include a profit compromise whereby there is a cap on the amount of profit that the benefiting company can earn.³⁰⁰ An alternative suggestion by IDSA proposed a stipulation that 10–20% of the profits gained from the patent extension on the lucrative drug be targeted toward R&D for antibiotics.¹⁶⁹ These proposals deserve attention, however, the risks of over-compensation, inequity, and significant market distortion would likely prevail.

Application to SMEs

Unless the wildcard design includes a provision allowing a developer to sell its wildcard patent extension, SMEs will have little to gain from this scheme. Specifically, the developers most attracted to the scheme will be those with lucrative drugs approaching patent expiration.²⁴¹ Furthermore, a large developer that is otherwise uninterested in antibiotic R&D might decide to purchase a small developer dedicated to developing antibiotics just to procure a wildcard patent extension for a lucrative drug in its portfolio.²⁴¹

^{xliv} See Laxminarayan for further details. An initial block on sales of wildcards lead to the eventual quashing of even the non-tradable wildcard extension proposal. 63. Laxminarayan R. How broad should the scope of antibiotic patents be? *American Journal of Agricultural Economics* 2002;**84**(5):1287-1292.

Whilst making the patent extension transferable across companies would make it more attractive to SMEs who could sell it on to companies with blockbuster drugs, the incentive could significantly distort the eventual market to which it is applied. As such, there is a trade-off between luring SMEs to the scheme and minimizing the distortionary nature of the wildcard.

6.3 Regulatory mechanisms

Given the risky nature of the drug discovery and development process and the significant expense involved, one option to stimulate R&D is to improve the regulatory process for developers willing to take on the challenge. A number of stakeholders in the antibiotic field argue that regulatory processes are prohibitive and need streamlining to foster innovation.¹⁶⁰ Changes could involve accelerating the development process through the adoption of less onerous requirements and faster market authorisation as well as post-authorisation benefits such as reduced liability measures. This section will explore some of these proposals.

6.3.1 Clinical trials

Clinical trial requirements

Most clinical trials for antibiotics involve the comparison of the test drug against an active control, which is generally another antibiotic that has been approved by the regulatory agency for that indication. In most cases trials undertaken have been non-inferiority trials. These trials have several inherent weaknesses: no internal demonstration of assay sensitivity, no single conservative analysis approach, lack of protection from bias by blinding, and difficulty in specifying the non-inferiority margin.^{301#220} The latter is a margin represented by a 'delta' value and used to determine whether there is a clinically-acceptable difference between the test drug and active control.³⁰² The size of the delta has created much controversy within the area of pharmaceuticals and has led to numerous changes in regulation over time.

Under a sliding-scale approach, the acceptable delta value is contingent upon the anticipated number of patients that could be evaluated for that condition and the expected cure rates¹⁰. In the past, requirements for most antibiotics included a the delta value of 15%. However, the FDA's major concern with the sliding-scale approach was a fear of 'bio-creep', whereby slightly inferior products could be approved sequentially over time given that drugs with lower efficacy rates could use wider deltas, the result being that approved products could be merely equivalent to a placebo³⁰².

The stricter approval requirements had the unintentional effect of substantially increasing costs for pharmaceutical companies. In particular, decreasing the delta from 15% to 10% meant that pharmaceutical companies had to more than double the

number of patients enrolled in clinical trials. Consequently, the new statistical parameters doubled the costs of running clinical trials, inflated the overall expense of developing a new antibiotic, and thus eliminated incentives to invest R&D in antibiotics^{303 10}. It has been estimated that under the FDA and EMEA statistical guidelines, the NPV for a novel Gram-positive antibacterial would reduce from 100 to 35¹⁰. This change in the delta value is credited with causing the withdrawal of antibiotic research programmes from Bristol-Myers Squibb and Eli Lilly and with delaying the development of tigecycline¹⁰. Faced with this industry response, the FDA dropped the across-the-board 10% delta requirement and moved to a case-based approach, where the indication, projected efficacy, and comparators are taken into account¹⁰. The EMEA's 2004 Note for Guidance mentions that the choice of delta should be carefully considered for each individual trial and requires applicants to justify its choice taking into account the anticipated efficacy of the reference treatment in the indication under study. It is however mentioned that in many instances the delta is likely to be 10%

Superiority trials are needed to show that a new drug is indeed better than those on the market or at the very least better than a placebo. They do not have the same weaknesses of the non-inferiority trials³⁰¹ and normally they require fewer patients, which can lead to lower costs. However, these trials may also be more difficult to conduct and can only be undertaken for mild-to-moderate (generally self-resolving) infections when they involve the use of a placebo arm.^{xlv} Superiority trials are needed to show that a new drug is indeed better than those on the market or at the very least better than a placebo. They do not have the weaknesses of the non-inferiority trials³⁰¹ and they require fewer patients, which can lead to lower costs. However, these trials are also more difficult to conduct and can only be undertaken for mild-to-moderate (generally self-resolving) infections due to their use of a placebo arm. There is significant debate about the acceptability of superiority trials, particularly as regards to the ethics of not providing treatment for the control group^{191,304xlv}. In the case of antibiotics specifically, some argue that the superiority trials do not take into account the fact that an antibiotic that currently fails to demonstrate superiority to the standard therapy may actually in the future be an effective therapy when resistance develops to the standard antibiotic¹⁵⁹. Consequently, superiority trials may not factor in the importance of projected efficacy for antibiotics. Despite the debate, the FDA has started calling for clinical trials with superiority design for certain indications, specifically acute bacterial sinusitis, otitis media, and the exacerbation of chronic bronchitis²⁸⁸. It has also recently issued guidance about community-acquired pneumonia (CAP) and when superiority trials are appropriate. The main impetus for this regulatory shift appears to be concerns over whether the antibiotic is better than placebo (no treatment) for mild

^{xlv} In the case of trials for severe infection they use an active arm.

^{xlvi} It is important to note that the debate does not centre around the use of superiority trials for mild infections, but there is debate around the need for superiority trials for some strains of infections like CAP.

infections^{xlvii}, particularly given the possibility that treatment of mild infections with antibiotics may accelerate resistance. EMEA still requires non-inferiority trials with a licensed control for the approval of new antibiotics. However for infections like otitis media and other mild-to-moderate (generally self-resolving) infections the current guidance prescribes superiority trial (against placebo) as being "desirable". Following a recent report by the EMEA/CHMP^{xlviii} (Committee for Medicinal Products for Human Use) a re-consideration of the strict adherence to non-inferiority trials with a defined delta for evidence of efficacy is recommended. The issue is currently under consideration.

Additionally, the drug approval process has been further complicated for antibiotics since the FDA is less prepared to accept adverse side effects with antibiotics than with other classes of therapeutic agents¹⁶¹. For example, the FDA delayed approval of Ketek, an antibiotic made by Aventis, for 3 years as a result of adverse effects associated with Trovan and Raxar. Rubin argues that the cost of delays in approval of Ketek, \$518 million, is about 100 times higher than the \$6 million upper-bound estimate of the expected benefit from any increase in expected safety because of the longer, more careful approval process⁹. Therefore, according to Rubin, the FDA's additional testing for antibiotics is not economically rational with respect to improving patient welfare⁹. Instead, Rubin suggests that a more cost-effective alternative would be to approve the drug in the normal manner and allocate additional resources for Phase IV analysis⁹.

Pharmaceutical companies may hesitate to initiate new clinical trials for antibiotics because guidelines for clinical trials in this therapeutic area remain unclear. In response to such uncertainty, the Infectious Disease Society of America (IDSA) has pushed heavily for clinical trial guidance from the FDA and has put forth recommendations for the FDA to "accelerate the publication of updated guidelines for antibiotic clinical trials to provide needed clarity, and revisit existing guidelines as appropriate to ensure their relevance"¹⁶⁹. In addition, the EMEA has made a concerted effort since it began publishing on the issue in 1996³⁰⁵#281. Such pressure has acted as a stimulus for the FDA to publish clinical trial guidelines²¹. Whilst the FDA did not issue clinical trial guidance for antibiotics for many years, since the autumn of 2006, the FDA has held a number of workshops and issued guidance on conditions like bacterial sinusitis, acute bacterial otitis, and CAP, amongst others. However, at the time of writing, significant frustration was felt by industry with respect to the clarity, consistency, and timing of guidance. Since 2001, the FDA has stated that guidelines in 5 areas would be published and the paucity of newly published guidelines further exacerbates regulatory uncertainty²¹. Without a very clear picture of regulatory requirements ahead of trials and throughout

^{xlvii} Some patients may spontaneously improve, regardless of whether or not they took an antibiotic.

^{xlviii} Report can be found at <http://www.emea.europa.eu/pdfs/human/itf/12731807en.pdf>

(trials can often last beyond 10 years), it is unlikely that developers will be compelled to engage.

The lag in publishing guidance for indications is likely due to insufficient resources being devoted to the area. In the case of the FDA it was made worse by the severe lack of personnel in recent years (following controversy over safety of an accepted drug). The EMEA and FDA may require greater funding and staff to sufficiently expand guidance.

Tools for proving safety and efficacy

The traditional tools used to assess product safety and efficacy, such as animal models or in vitro screening, have not changed in many years, and are known to be imperfect predictors of responses in humans. Along with the high cost of trials, scientists are therefore looking for better methods to predict the effect of drugs. Pharmacometric analyses refers to the increasingly sophisticated ability to model an agent's pharmacokinetic (PK) or pharmacodynamic (PD) properties and their effect on disease progression³⁰⁶. Provisional trial data are inputted into a model to determine optimal dosing based on risk-benefit assessment and are then extrapolated to assess the safety and efficacy findings to the wider patient population. This 'in silico' or computer-based technology is argued to have revolutionised the product development process in other industries such as the automotive and aeronautical industries, which are now developed and tested largely using computer-based systems³⁰⁷.

However, so far the discussion around the expanding role of pharmacometrics in regulatory applications has largely focused around situations or circumstances where demonstrating safety and efficacy within populations can be problematic: i) special populations (such as children) ii) rare pathogens or those with reduced susceptibility iii) specific types of infection. A recent study by the FDA³⁰⁶ looking at approvals over a 4-year period across 3 therapeutic areas indicated that pharmacometrics data was used when reviewing a new drug application (NDA) in 17% of cases (42 out of 244). These data were retrospectively deemed 'pivotal' in 54% of the cases and supportive in 46%. Of the 14 reviews that were pivotal to approval-related decisions, 5 identified the need for additional trials, whereas 6 reduced the burden of conducting additional trials

In Europe this prospective estimation of safety and efficacy has recently gained wider acknowledgement from regulatory agencies given a mounting body of supporting evidence³⁰⁸. The FDA notes that some commentators believe the extensive use of such technologies could reduce drug development costs by 50% and generally favours the concept of model-based drug development, using pharmaco-statistical methods³⁰⁷. One US trial quantified potential savings as '3 years of drug development time and 1 clinical trial'³⁰⁶ (when seeking early regulatory support). They also suggest "the time and money needed to perform the pharmacometric analysis is negligible compared with the costs of unsuccessful trials"³⁰⁶. The EMEA maintains a broad stance that PK/PD analysis is

recommended where appropriate and acknowledges its role in potentially reducing the number of Phase I/II studies necessary. However, the EMEA currently issues no definitive guidance of when PK/PD approaches may be used to supplant formal clinical investigation, proceeding on a case-by-case basis. The EMEA currently does not support its use in significantly reducing the scope and content of Phase III programmes³⁰⁸.

Application to treatments for priority bacterial diseases

On the surface, clinical trials for antibiotics appear to be less complex than for other conditions due to the fact most patients with bacterial infections typically recover within a few days or weeks of receiving treatment, thereby providing clear therapeutic endpoints. Research on animal models is also generally easier for antibiotics as the animals can be easily infected with the pathogens for study. Nonetheless, there remains a lack of clarity with regards to whether clinical trials for antibiotics cost more or less than clinical trials for other conditions. Some suggest the total costs of these trials to be US \$500–\$800 million³⁰⁹, which is similar to the US \$400–\$800 million⁴⁰ estimate for drugs generally. Other literature suggests that the cost of clinical trials is particularly high for hospital-based infections, at around US \$50,000 per patient¹⁶³. Phase III costs alone have been estimated to run up to US \$500 million¹⁶³ and for antibiotics can be 60% higher than the average of all drug classes⁹.

Whilst the exact cost is unknown, one certainty is that if developers seek indications of severe infection, trials must include a significant number of cases with resistant pathogens. In comparison with products in many other clinical areas, one broad-spectrum antibiotic can target multiple diseases (e.g. *S. Aereus*, pneumonia, skin and soft tissue infection, etc.)¹⁶⁹. In the past, multi-indication trials were permitted. However, now pharmaceutical companies must run clinical trials for each indication for which they intend to market their product, which significantly increases the cost of trials. As patient recruitment for trials occurs prior to the revealing of the nature of the pathogen and it is impossible to predict when resistance will occur, these trials are difficult and expensive. This problem is further compounded by the difficulty in identifying the pathogen quickly due to a lack of advanced POC diagnostics as well as the requirement that clinical trials be performed on antibiotic-naïve patients¹⁷³. In the IDSA report¹⁶⁹, authors describe one company's difficulty in trying to develop an antibiotic to treat VRE to illustrate the patient recruitment problem. Using patient entry criteria that were developed in conjunction with the FDA, the company was only able to enrol 3 patients over two years of the study. During a second study, the company was only able to enrol 45 patients over 18 months. This is despite the fact that there are at least 26,000 hospital-acquired cases of VCE every year in the US¹⁶⁹.

According to some experts the characteristics of bacteria and antibiotics particularly lend themselves to PK/PD modelling. For example the ease with which pathogens can be

isolated and the relative ease with which potency, potential doses and schedules (most likely to slow the development of resistance) can be determined potentially facilitate a greater dependence on these tools relative to other therapeutic areas³¹⁰. However, others believe that their use in helping to understand antibacterial activity is insufficient to predict patient response to treatment³⁰⁸. Overall, current evidence appears to lean towards the suggestion that the quantity and robustness of data provided by these models is currently insufficient to support expansion of their application, especially in replacing human trials. However, the determination of appropriateness is far beyond the scope of this report. The inclusion of these models in this report should simply be taken as a reflection of the extensive amount of interest in this area. Serious investigation of these tools within the context of lightening the regulatory burden are currently taking place elsewhere.

6.3.2 Accelerated regulatory review

Fast track programmes, priority review, as well as vouchers to transfer the two, are incentive mechanisms which reduce the length of regulatory review to bring forward the recouping of investments and increase first mover advantages. Under fast track approval, the regulator helps eligible drugs receive marketing approval more quickly through close guidance. Priority review, which can be done separately or as part of the fast track, reduces the amount of the time it takes for drug registration. Depending on the design of the scheme, the privilege can be applied to the product for which the R&D incentive is sought or else the privilege can be transferred to another drug in the same developer's portfolio. In the case of vouchers for fast track or priority review the privilege is transferrable to other products and to other developers³¹¹#24,312'#104. An additional feature of the voucher is that --if the awarding one voucher has proven insufficient to stimulate innovation--the regulatory body may award multiple vouchers simultaneously to boost the strength of the incentive³¹².

Examples from Europe

The EMEA accelerated review procedures aim to provide a regulatory decision within 150 days of submission. There are, in addition, two procedures namely 'conditional approval' (functionally equivalent to the FDA's 'accelerated approvals') introduced in 2006 and approval for 'exceptional circumstances' introduced in 2004.

Table 6.3.1 Differences between EMEA accelerated review mechanisms

Conditional Marketing Authorisation	Marketing Authorisation under Exceptional Circumstances
Demonstrate positive benefit-risk balance, based on scientific data, pending confirmation	Comprehensive data cannot be provided (specific reasons foreseen in the legislation)
Authorisation valid for one year, on a renewable basis	Reviewed annually to reassess the risk-benefit balance, in an annual re-assessment procedure

Once the pending studies are provided, it can become a "normal" marketing authorisation	Will normally not lead to the completion of a full dossier and become a "normal" marketing authorisation
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EMA experience with accelerated approval procedures is more limited compared with the FDA, with only 7 conditional approvals and 17 exceptional circumstance approvals since each programme's inception (see Table 6.3.2 below) ^{313#1222}.

Table 6.3.2 Products with conditional and exceptional circumstance EMA approvals to date ^{313#1222}.

	Outcome Year				
Opinion	2004	2005	2006	2007	2008
Normal	26 (89.7)	20 (87)	33 (84.6)	38 (82.6)	42 (91.3)
Exceptional	3 (10.3) a	3 (13) b	3 (6.7) c	5 (10.8) d	3 (6.5) g
Conditional	NA	NA	3 (7.6) e	3 (6.5) f	1 (2.2) h
Total Positive	29 (100)	23 (100)	39 (100)	46 (100)	46 (100)

A 'conditional approval' may be granted for medicines that satisfy an unmet medical need (needs for which no treatment is readily available), and when the CHMP believes the data suggest that product benefits outweigh its risks but is incomplete. The company is given obligations to fulfil, namely the conducting of further studies. Unlike under the FDA system, EMA conditional approval is renewed on a yearly basis until all obligations have been fulfilled. Two drugs received conditional approvals in 2008. One of these, Tyverb, received confirmation of the 2007 positive opinion (which had reservations regarding safety). It has yet to receive full approval.

EMA exceptional circumstances approval is normally granted when the applicant is unable to provide comprehensive data on the efficacy and safety of the medicine for certain reasons. This is usually due to the rarity of the condition, limited scientific knowledge in the area concerned, or ethical considerations involved in the collection of such data. As for conditional approvals, exceptional circumstances approval requires the applicant to subsequently demonstrate the safety of the product and apply for approval on a yearly basis. In 2008 the EMA granted 3 products exceptional circumstances approval, two of which (Pandemrix and Celvaplan) were approved by consensus for prophylaxis of influenza under pandemic situations ^{313#1222}.

Whilst the FDA and EMA programmes are similar in that both retain the option to take the drug off the market if clinical benefit or subsequent trials are not completed, the EMA maintains the additionally option of imposing financial penalties if postmarketing studies are not delivered as agreed. The EMA also generally faces fewer accusations regarding lack of transparency as it publishes both its positive and negative opinions.

Examples from the United States

The FDA has had a fast track mechanism in place since 1993. Evidence from the fast track programmes indicates this is a successful in reducing overall drug development time by up to 3 years with this comprising a 2–2.5 year cut in clinical development time and a 1 year cut in regulatory review time³¹¹. Recently the FDA has extended eligibility of the scheme to non-life threatening diseases. It has been suggested that these extensions may dilute the effectiveness of this system unless resources are similarly scaled-up.

The FDA has had a priority review mechanism in place since 1992 through which it aims to cut the average review time from 10 months to 6 months³¹⁴. In 2007 as part of the FDA Amendments Acts, the FDA implemented a priority review scheme for neglected diseases^{315`#221}. This legislation affects some infectious diseases occurring primarily in developing countries where there is significant unmet need, for instance, TB, dengue fever, and cholera. CoArtem, an antimalarial drug developed by Novartis that has been available outside of the US was the first drug to receive a priority review voucher^{315`#221}.

General considerations for future application

Some argue that providing priority review compromises the safety of regulatory review³¹⁶. However, the study often cited as evidence of this does not necessarily show that increased speed of approval reduces safety. The authors point out that it was the existence of a deadline in their model that led to this result, not accelerated review times³¹⁷. Other studies do not support the contention that accelerated review compromises safety^{312,318}. However, regardless of the actual safety risks, the safety issue may still arise as a argument within the political arena. Some suggest that improving the current system of post-marketing surveillance could provide more evidence on the safety questions and alleviate safety concerns³¹². Others propose that increasing staffing and relying less on deadlines could result in the same degree of review efficiency without increasing the risk. Design considerations include payment of a supplemental fee – passed along to the developer – to cover the additional resources needed to speed up review and prevent review compromise of other waiting products (as in the current FDA model).

In contrast, it has been suggested by others that this process results in a net public health gain. Philipson et al³¹⁹ found that between 1979 and 2002, the net gain to consumers from faster approval of drugs was 180,000-310,000 life years, compared to only 56,000 life years lost as a result of fast track approval and lower safety. The authors also found that fast-track approval and regulation increased the return on investment by US \$11 billion--\$13 billion³¹⁹

Whilst the transferability to lucrative markets is a key strength of the voucher incentive and makes the incentive appealing even to small companies, it also imposes distortions

in the market to which it is ultimately applied by causing other companies to discontinue development of their drugs in that class³¹¹. It is also argued that the selling of the voucher to developers with blockbuster products creates a lack of transparency³¹⁶.

When not transferrable to other drugs, accelerated regulatory review processes provide faster access to the desired innovative drugs without delaying access to cheaper generic drugs. However, this design may be of limited financial value to the developer unless other mechanisms are in place to achieve a high price for the product upon entry. When accelerated privilege is transferrable to other products it will likely be applied to a blockbuster drug. Whilst the scope of the vouchers have been criticised for being 'too narrow,' designed to focus on innovation (the active ingredient must not have been previously approved) hence omitting drugs with only incremental benefits, this has been undermined by the lack of restriction on the voucher's eventual application. For example, Novartis was awarded a voucher^{xlix} with an estimated worth of >\$100 million for a drug that has been available in other markets for over 10 years (prior to voucher issuance) mitigating the focus on innovation³²⁰.

Application to treatments for priority bacterial diseases

Antibiotics for serious infection in principle already qualify for accelerated regulatory assessment in both the US and Europe if they fulfil certain criteria common to all applications for accelerated assessment. The persisting lack of new antibiotics being produced^{154'532} suggests that these incentives offer insufficient benefits to attract the necessary R&D. The possibility of using vouchers is a relatively new (and yet to be adopted in Europe) and clearly would increase the strength of the incentive.

Application to SMEs

As SMEs typically face an immediate need for cash to fund R&D, accelerated review mechanisms, which provide a chance of (albeit faster) payoff in the future, are likely to be less attractive to smaller companies than larger companies. A smaller company could try to use the future possibility of a voucher as a bargaining chip with a venture capital firm or a large pharmaceutical company seeking to purchase a company's drug pipeline³¹⁵, but it is unclear whether the mere goal of attaining a voucher would be sufficient to attract venture capitalists or large pharmaceutical companies.

^{xlix} On April 8, 2009, the FDA announced it had awarded Novartis a one-time priority review voucher (PRV) to use towards a future new drug application. The PRV was awarded to Coartem (artemether and lumefantrine) a malaria treatment.

6.3.3 Pricing & reimbursement

Reimbursement and pricing present an important opportunity to influence the antibiotics market. Optimal reimbursement and pricing policies aim, on the one hand, to depress economic rents to avert exploitation of the purchaser and, on the other hand, to offer sufficient reward for innovation to ensure future investments in research. In Europe pharmaceutical prices are regulated in several ways, including: the direct means of reference pricing, formulary pricing, capping or item-by-item price negotiation, as well as indirectly through rate-of return regulation^{321' #282}. However chosen, levels of reimbursement for products are a result of negotiation between the developer and the purchaser who respectively act as monopolist (the developer with the innovative product) and monopsonist (the purchaser who is often a regulatory body)^{321' #282}.

In theory, if it is the case that pharmaceutical developers achieve increasing returns to scale and scope such that average cost decreases with increasing levels of output (and thus average cost exceeds marginal cost of production), incentives to promote R&D can allow some monopoly profit to be retained by the developer by offering a price that is higher than average cost^{321' #282}. However, with the inability of the regulator to observe R&D costs, in practice the process of finding the appropriate price is difficult.

Kesselheim and Outterson^{316' #283} as well as others^l have proposed a system of reimbursement for antimicrobials based on their social value. The system would entail modelling the health impact of new antibiotics and then allowing manufacturers to price according to the results. For instance, if the new antibiotic were to reduce the number of inpatient stays, then the price could be higher to account for savings to the system (see box 6.3.1).

Despite its many merits, social-value based reimbursement would, in practice, present numerous challenges. Notably, decisions surrounding the measurement of social value of a product is contentious – although even an imperfect metric such as the QALY^{li} would likely suffice for such calculations in the short term. Limited pricing reform to better reflect therapeutic value may be possible in the short-to-medium term or while a more holistic, social-value based system is under development. The (fulfilled) promise of a higher prices would in itself go far in luring developers to antibiotics. Also in contrast to patent-term extensions, reimbursement incentives have would allow developers to recoup R&D costs early on and reduce the amount of risk faced by developers.

^l Authorities in countries such as the United Kingdom have considered similar proposals (for all pharmaceuticals, not just antimicrobials) to price drugs according to societal value.

^{li} The QALY design is currently under revision.

Reimbursement and pricing reform should indeed be explored further with respect to the particular financing arrangements in each European Member State. However, the success of these reforms in luring developers to invest R&D for antibiotics is likely to be much greater within a standardized European system that can credibly offer a given price for a product with stipulated characteristics on a large scale.

Application to antibiotics

As antibiotics for severe infection are life-saving products they would stand to attain high prices under a reimbursement system basing price on therapeutic or social value. Indeed they would likely be amongst the most rewarded. In addition, as opposed to patent-term extensions, reimbursement incentives have the ability to influence other stakeholders such as doctors and patients. It is argued that the higher prices that could be attained in a value-based reimbursement system could reduce prescription and consumption antibiotics to more appropriate levels and thereby help conserve them for future use^{322`#294}. Also, as suggests the ACE system (See Box 6.3.1) reimbursement incentives could be used to reward infection control measures and ABS as well.

Application to SMEs

As with other demand-side measures, this proposal would not provide the crucial early stage funding that many SMEs need to survive. However, the assurance that higher prices will eventually be paid for the developed product is likely to increase the chances for SMEs to attract venture capital to fund early stages of development.

Box 6.3.1 Antibiotic Conservation and Effectiveness (ACE) Programme Proposal^{323`#695}.

The debate surrounding antibiotic resistance is complicated by the fact that the two pillars of control – conservation of existing antibiotics and production of new antibiotics – interact dynamically, with the former shrinking the market to stimulate the latter. Experts argue that an optimal incentive structure would need to do both, thus aligning incentives closer with public health goals. The ACE proposal is a cluster of integrated solutions to systematically address the antibiotic resistance issue and considers these dynamic complexities with the key objective of creating and maintaining better markets for continual antibiotic effectiveness. At its core lie 3 proposals which require no changes to the existing drug approval and IP protection systems:

1. **New antibiotics rewarded** based on meeting public health and conservation goals through tying market exclusivity provisions to the continuing effectiveness of the drug. It is argued this would internalise the negative externalities of consumption, although it would also provide a relatively modest incentive on its own. In practice, the regulatory agency would set targets, such as that morbidity from the agent remains below a set percentage.
2. **Antibiotic reimbursement mechanisms** based on value-based purchasing, to support usage patterns more aligned with their intrinsic value and thus rational

development of new drugs. In practice, companies would price their drugs freely, based on the health impact of their new product and reimburse ABS and infection control activities similarly.

- 3. Limited waivers of anti-trust law**, to enable coordination of market activities where cross-resistance may result. Specifically, the authors propose that for identified drug-bug pairings (where cross-resistance is a problem) the regulatory agency, in coordination with the antitrust agencies, would issue certificates or waivers authorising limited joint coordination of conservation activities that would not result in prosecution. Both US and EU competition agencies have indicated provisional openness to such a suggestion.

The authors pre-empt opposition or challenges to their proposal and counter these through the following arguments: the pharmaceutical industry will be a sufficient target (and the most powerful and upstream target) to make responsible for utilisation of its agents; that an expensive effective antibiotic is preferable to a cheap, ineffective one; the federal health board created as part of the American Recovery and Reinvestment Act of 2009 will make health impact modelling possible; collusion and gaming are limited by waiver specificity. Additionally, supplementary cash prizes are proposed if the incentives are ineffective. Lastly, a patent buy-out is suggested as an alternative to the reimbursement mechanism.

6.3.4 Liability protection

Pharmaceutical industry representatives previously interviewed by the IDSA were found to consider liability limitations a strong incentive to develop new antibiotics¹⁶⁹. This type of liability protection has been applied to childhood vaccines in the US under the Vaccine Injury Compensation Program (VICP). Ratified by Congress in 1986 the VICP is funded by an excise tax imposed on vaccine doses, and intends to protect medical doctors and vaccine manufacturers from liability in cases of injuries caused by vaccines. The law was enacted to address the vaccine supply shortages which resulted from the exodus of manufacturers following numerous court cases in the 1970s and early 1980s.

In Europe, Pharmaceutical manufacturers have a duty to properly test their products before releasing them onto the market, using the criteria established by EU legislation (Directives 65/65/EEC, 93/41/EEC, 2001/83/EC). In order to harmonise the laws of Member States concerning liability for defective products and ensure a high level of consumer protection, the EC invoked Directive 85/374/EEC on the "approximation of the laws, regulations and administrative provisions of the Member States concerning liability for defective products" in 1985. Additionally there is increasing EU legislation covering the conduct and patients involved in clinical trials. For example the 2001 Clinical Trials Directive (2001/20/EC) and the most recent Good Clinical Practice

Directive (2005/28/EC). These state that trials may be undertaken only if "provision has been made for insurance or indemnity to cover the liability of the investigator and sponsor"³²⁴. Additionally, VICP-type legislation was part of the EU influenza pandemic preparedness recommendations put forward by DG SANCO's Health Threat Unit (C/3) formed in 2003 to bring together the former Unit on Communicable, Rare and Emerging Diseases, and the Task Force on Bioterrorism Programme of Community Action in the field of Bioterrorism.

The IDSA recommends that liability limitations be extended to antibiotics that treat targeted pathogens. Limited liability has been recommended by others for areas of high unmet need including pandemics and paediatric indications³²⁵. The Bioshield II (S. 975) legislation ratified in December 2005, was at least in part a response to the failings of Bioshield I (S. 666) to ensure sufficient liability protection for industry³²⁶. Congress passed part of the Bioshield II - the liability protections and no-fault compensation scheme – in the form of the Public Readiness and Emergency Preparedness Act (PREP) this was an attempt to internalise the positive externalities associated with the development of possible bioterrorism and pandemic countermeasures and to address the markets lopsided risk-benefit ratio of developing biodefense medicines³²⁶. The primary effects of PREP legislation hinge on liability protections for drug companies (in effect shifting them to federal government), under provisions intended to remove financial risk barriers for any new vaccines that need to be rushed to market in case of an emergency. In the context of Bioshield II Mayer's concerns around the legislation include: inadequate compensation for affected individuals, insufficient deterrence of negligent tortfeasors and the impact of precedent setting on normal medicinal product liability [186].

Application to treatments for priority bacterial diseases

If liability limitations were to be reserved for only the more severe and previously untreatable indications, their application to antibiotics could potentially be justified. Indeed if the product were a last resort treatment less opposition would exist. However, given the public outcry regarding safety concerns with products authorized and subsequently removed from the market, it should be expected that proposals on liability limitations will face potentially significant public, and hence political, opposition.

6.3.5 Anti-trust laws

As mentioned briefly in the context of extending IP protection, the inability of one firm to control the sales of antibiotics by other companies creates a 'tragedy of commons'^{259,294} resulting in aggressive marketing of the drug, thereby accelerating the development and spread of resistance (including cross-resistance). In response to this problem a proposal has been made to relax anti-trust laws to allow a company to sell the rights to its product to another pharmaceutical company with a competing antibiotic, and thereby create monopolies over groups of similar products. Patents for

Functional Resistance Groups rather than individual drugs could then be created (FRG, see Boxes 6.2.4 and 6.2.5. This would give developers the incentive to manage sales and consumption patterns (and hence resistance) more closely to the socially optimal level^{38,65}.

However, it is not clear how off-patent products would be handled. This proposal appears to assume that the number of patent holders of cross-resistant drugs is small. This may not be the case. If the number of patent holders was large it is unclear if, and how, this mechanism may breakdown, what practical challenges may arise and what monitoring and oversight would be required. The main disadvantage to this proposal is that it would require a change in current anti-trust laws which prohibit this anti-competitive behaviour. It would also be politically challenging to implement, given its potential to set precedent, and risks providing further monopoly profits to pharmaceutical companies.

6.3.5 *Sui generis* rights

A *sui generis* rights allow the holder of the original patent to produce the antibiotic in perpetuity, effectively eliminating the development of generics for off-patent drugs¹. They are argued to be a potentially powerful tool to control the development of resistance are needed given that many classes of antibiotics have off-patent drugs and patents are owned by different companies. (The implementation of *sui generis* rights maybe a necessary requirement if FRGs see Boxes 6.2.4 and 6.2.5)

Under proposed *sui generis* arrangements it is unclear who would receive rights for off-patent antibiotics. One proposed solution is to hold an auction for the rights over certain classes of antibiotics¹. While the ability to market products in perpetuity would draw much interest from developers, the implications for the wider patent system could be significant. It should therefore be seen as an extreme measure.

6.4 'Hybrid' incentive models

There is growing acknowledgement that neither push nor pull mechanisms alone are sufficient to stimulate innovation. The successes seen with most PDP models as well as the orphan drug model (which offers tax pushes along with market exclusivity pulls) designed to address the undersupply of drugs for neglected disease and orphan diseases respectively may provide the seeds of evidence to support this theory. This section explores existing hybrid mechanisms and puts forward a new one for consideration.

6.4.1 Product development partnerships

Product development partnerships (PDPs) are voluntary collaborations between state and non-state organisations to drive the development of drugs that might not ordinarily make it to market (275, 314, 330)^{lii}. Participants in PDPs can include the pharmaceutical or biotechnology industry, the government, non-profit organisations, academia, and other public organisations. There is some debate surrounding the definition and parameters of these partnerships³²⁷, although this debate is beyond the scope of this report.

The classic PDP model is a partnership between a publicly funded organisation and a private pharmaceutical company with both contributing resources²⁹⁷. The private pharmaceutical company provides industry expertise, and the public organisation obtains the majority of funding for the project. Funding is principally via grants from philanthropic organisations, such as the Bill and Melinda Gates Foundation the Rockefeller Foundation, and the Wellcome Trust. Pharmaceutical companies have not as been significant contributors as originally hoped, although there are notable exceptions. For instance, by 2007 the Global Fund had received US \$150 million from the Gates Foundation and US \$2 million from the industry³²⁸. Government funding has also been less than expected. As of April 2005 governments were responsible for less than 20% of total funding for PDPs²⁹⁷. Importantly, the majority of funding for PDPs comes from the Gates Foundation, and there are concerns surrounding the sustainability of many PDPs if this funding source were to end³²⁸.

Depending on how selective researchers are in defining PDPs, estimates of the number of existing PDPs range from 23 to 100³²⁸. One estimate of PDP activities suggests a total spending of at least US \$500 million thus far³²⁹. Within the health arena, the primary focus of PDPs has been on neglected diseases such as malaria and leishmaniasis, with efforts toward producing vaccines, microbicides, and diagnostics³³⁰. The Malaria Vaccine Initiative (MVI) and the International AIDS Vaccine Initiative (IAVI) are two

^{lii} PDPs that focus on improving access to medicines and PDPs that deal with global coordination and financing mechanisms are also prominent, but given the focus of this report on innovation, only PDPs that deal with the development of drugs and vaccines are considered.

prominent examples. Although most PDPs are less than 10 years old, this approach to stimulating innovation already has examples of success. Between 1975 and 1999, a number of pharmaceutical companies were exiting the field of neglected diseases, leading to only 13 new drugs being developed for neglected diseases during this period. As of September 2005, nearly three-quarters of all neglected disease R&D (47 projects) were being conducted by PDPs working with small and multi-national pharmaceutical companies²⁹⁷.

Box 6.4.1 Examples of promising drugs developed through PDPs

Artemether. In 1989 Chinese researchers presented their results on artemisinin derivatives at the CHEMAL special meeting in Beijing³³¹. CHEMAL was the steering committee that funded research on malaria chemotherapy for the Special Programme for Research and Training in Tropical Diseases (TDR). As the artemisinin derivatives were not protected by a patent, the product was not attractive to the pharmaceutical industry. CHEMAL therefore undertook initial R&D studies. The organisation then entered into partnerships with Kunming Pharmaceutical Factory and the pharmaceutical company Rhone-Poulenc Rorer (now Sanofi-Aventis) to develop the injectable artemether for severe malaria. Artemether obtained marketing authorisation in France in 1996 and elsewhere thereafter.

Artemotil. Artemotil is also an injectable artemisinin derivative for the treatment of severe malaria³³¹. The drug which was developed by TDR in collaboration with a Dutch company called Artecef and the Walter Reed Army Institute of Research. It received marketing authorisation in 2000.

Miltefosine. Miltefosine (Impavido) is an antiprotozoal drug originally tested for treatment of cutaneous-cancer patients, although research in the late 1980s indicated that the drug could be a potential treatment for leishmaniasis (also known as black fever)³³². TDR moved the molecule through the initial stages of testing and then formed a partnership with the Indian government and a German developer Zentaris to develop the drug. Miltefosine is currently available in a number of countries³³³ and is under investigation as a potential treatment for HIV infections³³⁴.

Moxifloxacin. Moxifloxacin (Avalox or Avalex) is a synthetic fluoroquinolone that was developed by Bayer. Prior to its approval for treatment of TB, moxifloxacin was available for treatment of other conditions like upper respiratory infections and skin and skin structure infections. In 2005 Bayer and the Global Alliance for TB Drug Development (GATB) entered into a partnership to test and develop the drug for treatment of TB³³⁵. Bayer donated moxifloxacin for use within the clinical trials and covered the cost of regulatory filings, whilst GATB coordinated and funded the clinical trials with additional

funding from the CDC, the FDA Orphan Products Development Center, the European and Developing Countries Clinical Trials Partnership (EDCTP), and the British Medical Research Council. Avalox is currently awaiting regulatory approval for TB treatment.

Paromomycin. The company Farmitalia donated the holding license of paromomycin to the WHO in the 1990s. Paromomycin is an antibiotic that was originally developed for oral use against gut pathogens but, in this case, was being tested as an injectable to treat visceral leishmaniasis³³⁶. Farmitalia believed the drug was unlikely to be profitable because of the expense of clinical trials of the socio-economy of the target market³³⁷. The WHO began running Phase I and II trials and the Institute for One World Health completed the clinical trials. The drug successfully made it through market authorisation.

These partnerships can be appealing to industry in that they provide a direct reduction in the costs and risks of innovation. PDPs exploit the comparative advantage of all participants and allow the developer to choose the timing and level of partnership with the public organisations. Specifically, the developer can focus on the less costly discovery phase of new chemical entities and partner with a PDP during the more expensive drug development and/or clinical trial stages³¹¹. The public sector then bears most of the risk, offsetting much of the developer's opportunity costs³³⁸. The developer must agree to take a reduction in eventual profits under this model. It has been suggested that ,even if a developer abandons further R&D for a product due to the financial and logistical challenges of development, a PDP may work with another company or organisation to complete the process³¹¹. Paromomycin (see Boxes 6.4.1 and 6.4.3) is a successful example of a PDP taking over a product license from another PDP and bringing the product through development.

Box 6.4.2 Wellcome Trust: Technology Transfer Division

WT's technology transfer division spent a total of £44.7 million in 2008 and £30.2 million of that total was spent on grants provided through its 3 programmes: 1) seeding drug discovery (compound discovery and/or lead optimisation); 2) translational awards; and 3) strategic translation awards (the latter distinguishable by the much larger involvement of the WT). The technology transfer division comprises less than 5% of total WT funding (see Box 6.1.2 in section 6.1). It covers all therapeutic areas in a variety of fields. The division's activities vary from shared risk endeavours (see SCG Box 6.1.1 also in section 6.1) to its core activities which more closely resemble a PDP.

While the division is a recent development, 6 (non-drug) products have already been successfully launched since the departments' inception in 2003³³⁹. Additionally,

antibiotic-related support for technology transfer has totalled £75 million for 39 projects³³⁹, with key examples of the WT's translational support for antibiotic resistance detailed below:

- **Achaogen Inc**^{340`#285} In May 2008, the company received a £4.1 million award for three years to develop novel, broad-spectrum aminoglycosides with superior efficacy and improved safety as therapies to treat MDR Gram-negative bacterial infections (e.g. *enterobacteriaceae*) and MRSA. The company obtained follow-on funding of US \$27 million from the US NIAID
- **Novacta Biosystems Limited**^{341`#286} In 2004, the company received an award of £3.9 million for two years. The award was to discover and develop a type B lantibiotic (lanthionine-containing antibiotics), including analogues of mersacidin and the development of a new one for the *C. difficile* infection
- **Prolysis**^{342`#287} In October 2006, the company was awarded £3.5 million for less than 3 years. The research involved progressing a novel antibacterial chemical series that specifically inhibits Staphylococcal cell division through a chemical optimisation programme, preclinical development, and into Phase 1 clinical trials. The company also received a LINK grant in applied genomics from the Biotechnology and Biological Sciences Research Council and the Department for Innovation, Universities and Skills (formerly the Department of Trade and Industry).
- **GSK Infectious Diseases Centre of Excellence for Drug Discovery (ID CEDD)**^{343`#288} In April 2007 the WT awarded GSK a £4 million grant for 3 years to help support a new class of Gram-negative antibacterials to combat drug-resistant infections which commonly cause HAP and septic shock. This is GSK's eighth centre of excellence and will act as an independent business entity. The WT stepped in when an in-licensing drive resulted in a greater number of projects than GSK was able to support, and this was not seen as sufficiently lucrative for the level of resource required. The WT will receive a financial consideration on any commercial product resulting from the collaboration with GSK. However, since the initial grant, follow-on funding and procurements have been secured:
 - *September 2007*: US \$41 million for 5 years from the Defence Threat Reduction Agency (DTRA) to develop antibacterial compounds for Gram negative biothreat agents{GSK, ##289
 - *June 2008*: Mpex Pharmaceuticals provided GSK access to their novel efflux pump inhibitors (EPI), shown pre-clinically to overcome efflux-based resistance to multiple classes of antibiotics in both in-vitro and in-vivo studies. Mpex will receive a US \$8.5 million upfront payment, US \$6.5 million in equity financing, and US \$200 to US \$250 million for each product candidate from GSK. Additionally, Mpex will receive tiered royalties, dependent on sales achieved{GSK, ##290}.

One of the key lessons learnt from existing PDPs is that with multiple partners -- each with its own agenda and strengths and weaknesses -- functioning management are essential. Buse and Harmer³²⁸ indicate that, whilst the quality of management can differ vastly between PDPs, there are key areas across most PDPs where practices could be improved^{liii}: The governance structures of many PDP have substantial room for improvement, particularly in regards to laying out partners' roles and responsibilities, performance monitoring, overseeing corporate partner selection and managing conflicts of interest, and providing a transparent decision making processes³²⁸. Also, when performance monitoring is not prioritized, there is little accountability of not only the respective partners, but the PDP itself. Transparency amongst many of the PDPs is also thought to be an issue, especially with regards to their choice of research areas.

A common theme in the literature and amongst interviewees is that the procedures governing partner selection are problematic. In a review of 18 partnerships, Buse³⁴⁴ found that only 4 of the partnerships practiced any screening of partners. The rationale seemed to be that the very act of corporate participation was a sufficient predictor of good corporate behaviour. Moreover, a number of stakeholders have expressed concern that the process for vetting applications from developers for involvement in the PDP is difficult. In particular, the pharmaceutical applicant knows far more about the likelihood of success of the product and may be prone to over emphasising its potential. With different partners offering different expertise, inputs, levels of funding, and levels of competence, this requires long and costly due diligence to determine the safest partner. This has been propped as a significant barrier to collaboration²⁹⁷.

Box 6.4.3 Institute of OneWorld Health

With its staff of approximately 30 experienced pharmaceutical scientists, the Institute for OneWorld Health (iOWH) aims to challenge the assumption that pharmaceutical R&D is too expensive to create new medicines exclusively for the developing world. It is focused on 4 therapeutic areas of great unmet medical need and follows a largely standard PDP model combining open-source approaches in the early stages with outsourcing in the latter stages²²². However, it maintains a flexible approach to be able to tailor to the specific requirements of the therapeutic area and demands of the partners.

The work of iOWH on visceral leishmaniasis and malaria involve existing compounds with the former having resulted in a new formulation -- and its first drug approval -- and the latter having resulted in an innovative manufacturing strategy. The VL work involved signing a collective licensing agreement with the WHO TDR to develop an injectable

^{liii} As the Buse and Harmer (2007) paper covers all PDPs, not just R&D PDPs, not all of their lessons are discussed in this report. For a more complete explanation of the lessons, please see their paper.

formulation after it was unable to find a sponsor for a large-scale trial. Now included on the WHO's EML, paramyocin IV was given orphan drug status by the FDA in 2005 and is currently manufactured in India and made available at cost. The iOWH work on malaria treatment has resulted in a new low-cost technology platform to assist with artemisinin scale-up and supply issues. The innovative enabling knowledge was licensed 'royalty-free' from academia to a biotechnology company who optimised the strain, purified and developed the scalable process. Sanofi-Aventis eventually became involved to assist with the an industrial manufacturing process with each stage being coordinated and facilitated by iOWH.

iOWH's has also been successful in gaining access to Roche's compound libraries for diarrheal diseases. A biotechnology company has now been recruited to perform high-throughput screening of more than 780,000 molecules to select up to 40 new anti-secretor drug leads which will undergo pre-clinical studies at the Centre for Health and Population Research in Bangladesh (ICDDR,B). Also, following receipt of an exploratory grant from the Gates Foundation is exploring drug candidates against soil-transmitted helminth infections. So far their efforts have lead to two products in early phases of development: one post-screening and the other nearing the end of pre-clinical studies.

Larger, or umbrella, PDPs have the ability to simultaneously adopt numerous projects dealing with the same health condition. While pharmaceutical companies themselves generally avoid concentrating resources on single indications to avoid creating competing products, it has been suggested that the diminished concerns for profit allows for focussing down on single indications, thereby reaping economies of scale with regards to knowledge, ideas, across projects³³⁶. An example from the neglected disease arena is the MMV, which built up a portfolio of 10 pre-clinical and clinical and 11 discovery stage projects within the first 5 years³³⁶. MMV successfully took novel synthetic peroxides from basic research to clinical trials in only 4 years.

Application to treatments for priority bacterial diseases

A clear benefit of PDPs with regards to antibiotics lies in the potential for reducing antibiotic resistance as the relegation of profit leads to weaker marketing pressures which in turn allow health systems to more easily restrict the prescribing of products. However, a key challenge for PDPs lies in their ability to negotiate an acceptable return for the private sector partner. As has been seen with PDPs for neglected diseases, the necessary balance between improving public health and allowing profit maximisation for developers can be difficult to attain^{338,345}. Partnership arrangements for drugs developed for both developing and developed country markets are particularly difficult to negotiate³⁴⁶ especially surrounding IP protection and pricing¹⁸. A proposed solution is to separate the various stages of antibiotic development and licensing¹⁸. Specifically, a not-for-profit foundation could be created for development stages up through Phase II trials. Products could then be licensed to commercial companies for sale in the

industrialised market, whilst sales in the developing world would remain on a not-for-profit basis, as in the CoArtem case mentioned above. Aiello et al.³⁴⁵ also recommend combining PDPs with other incentives such as market exclusivity, patent extensions, tax incentives or fast-track approval to alleviate this tension between the public and private sector and further incentivize developers.

Application to SMEs

PDPs are likely to appeal to SMEs given the early stage funding that can be accessed. Another advantage is that SMEs may have the scientific expertise but lack the necessary regulatory and marketing expertise, and a partner within the PDP can contribute to these stages of development. Thus, PDPs can provide SMEs with the necessary funding, technical support, and help with market entry^{297,311}.

6.4.2 Call Options for Antibiotics (COA) model

As discussed in previous sections, incentives to encourage research for neglected drugs have fallen into two main types – push and pull methods. Each of these mechanisms is not without its shortcomings, the details of which will be discussed in the following pages. Much of the research in this area stems from the field of neglected drugs/vaccine development and it is instructive to consider, in some detail, two recent proposals that have garnered attention. The first is the creation of an advanced market commitment for vaccines, developed by Levine, Kremer & Albright³⁴⁷ at the Center for Global Development (CGD) and the second is the Call Options for Vaccines (COV) method, proposed by Brogan & Mossialos³⁴⁸. This section will focus primarily on the development and implementation of the latter as it applies to the field of antibiotic R&D, as well as suggestions for the combination of both the COV and advanced market commitment to further enhance R&D stimulation. Here we aim to demonstrate that an initial investment in exchange for a discounted future price could give the proper incentives to make neglected antibiotic research attractive and profitable.

The COV mechanism has been described previously by Brogan and Mossialos, however, it is worth briefly reviewing the principles of this model to inform future discussion. The COV model proposes a new incentive mechanism combining both push and pull methods, based loosely on the principles of call options in equity markets. In a typical call option, an investor can purchase the right to buy a share of stock at a later date for a fixed price. The idea behind an option is that an investor can pay a premium now for the potential to profit later. However, the ability to profit later is not guaranteed, thus risk is involved in the payment of the premium. The seller of the call option also undertakes some risk, since any potential profit will come at the seller's expense. However, it is quite probable that an initial investment in exchange for a discounted future price could give the proper incentives to make antibiotic research attractive and profitable.

Incentives

The necessity for innovative proposals to stimulate R&D stems directly from the inherent misalignment of corporate and public health incentives in certain drug categories. While much work has focused on the difficulties of stimulating R&D for vaccine development of certain diseases (TB, malaria, AIDS), much of this applies as well to antibiotics. The common thread is that the sufferers of these diseases make up a disproportionate share of the world's poor. Therefore, funding is often limited with which to pay high prices for drugs or vaccines that may ease the burden of disease. This makes it difficult for corporations to justify undertaking R&D in such projects that do not provide a reasonable assurance of a profit. Bacterial infections affect both rich and poor countries, but in disproportionate shares, and in a non-uniform manner. Virulent strains of bacteria may be susceptible to one form of antibiotic in one region, but develop a resistance to the same antibiotic in a different region. This often has to do with utilization and availability, but utilization patterns are only one of many factors that contribute to economic viability of antibiotic R&D. Other factors, more systemic to health care systems have been discussed elsewhere in this report, however the common thread between antibiotics and vaccines is that market forces in the rich world cannot effectively subsidize development in these areas, as it can in more profitable drug classes (such as cholesterol, diabetes and certain cancer drugs). Thus, the stage is set for alternative forms of funding to contribute to this important work.

Purchase Commitments and Advanced Market Commitments

There are a number of design issues which must be considered when developing purchase commitments. To begin with, the commitment will not be effective unless the sponsor stays committed. Governments might change funding priorities after several years²⁶⁶. Similarly, countries might attempt to avoid adherence to patents or to the terms of the commitment. Also, an advance purchase commitment requires advance specification of the vaccine or drug which will qualify for purchase. The targeted pharmaceutical might work differently in certain populations, or provide risk / benefit ratios acceptable in a severely stricken country that might be unacceptable in more developed nations³⁴⁹. Regulatory approval could be used as the overriding qualification for purchase, but will not necessarily determine efficacy requirements. Finally, the value of the purchase commitment must be large enough to stimulate development, but still smaller than its social value (the maximum gain from the total benefit of the antibiotic for society).

The approach by the CGD guarantees a certain price, subsidized by sponsors of the advanced market commitment, for a specified number of units of a qualifying vaccine. The decision to purchase a newly developed vaccine is undertaken by individual countries or purchasers, who contribute a small copayment, with the difference between the guaranteed price and the copayment made up by the AMC sponsors. This

commitment holds for a set number of vaccines, the number of which is determined by the initial guaranteed price, such that the entire market commitment of the sponsor is \$3 billion. For instance, an international sponsor may commit to a market price of \$15 per dose for a malaria vaccine. A developing nation might be able to pay \$1 per dose, with the balance made up by the sponsor of the AMC. The first 200 million units will be guaranteed to fetch such an artificially high price, with any additional units sold at a reduced price directly to the purchasers. While the price is guaranteed for any vaccine, the quantity is not, as countries are not obligated to purchase developed vaccines. This price (but not quantity) guarantee removes the need to explicitly specify the conditions of an acceptable vaccine, but still maintains a credible commitment to purchase. This mechanism underscores the implicit assumption that the key to successful development is to translate social benefits into corporate profits, as the next section explains. Pull mechanisms hinge on the decision of companies to undertake R&D projects, given an expected future cash flow. To understand these decisions, it is worth reviewing the basics of corporate finance and project valuation.

Investment Decisions and Project Valuation

The valuation of biotechnology and pharmaceutical projects has gained much attention in the past decade. Companies whose intrinsic value depends on the yield of projects still in development stages rely on these valuation methodologies for effective resource allocation and for justification of investment. These valuations generally rely on 3 main factors: cash, timing and risk³⁵⁰. The risk involved is complex, but can be broadly divided into two main components: technical and commercial. Technical risk arises from the inability to successfully develop a viable vaccine; commercial risk describes the uncertainty of whether the vaccine will be purchased³⁵¹. It is the appropriate balance of each of these factors (cash, timing, risk) and their effect on cash flows that valuation methods aim to characterize. Historically, decisions on corporate projects have been undertaken using a discounted cash flow (DCF) model. This involves estimating the net cash flow for each year over the life of the project, where the net cash flow is equal to the difference between the costs and the revenues. Each year's estimated cash flow is then discounted to correspond to a present value, using an appropriate discount rate, such as the risk free interest rate or more appropriately, the company's weighted average cost of capital (WACC). The WACC factors in the effect of debt and taxes on investment decisions and can reflect the value gained from the project in the form of interest tax shields³⁵⁰. The sum total of the present values of each cash flow is referred to as the Net Present Value (NPV). The decision rule in this model is simple: if the NPV is positive for the project and meets a certain threshold then investment should be undertaken. DCF evaluations require estimates of cash flow and costs, but may not take into account risk or the potential to abandon projects. Stewart^{352 353} proposes that the risk-adjusted NPV should be employed when valuing biotechnology projects. The technique is similar to that of traditional DCF, however, all cash flows would be discounted by a factor that appropriately reflects the chances of success and failure for

the project. Yet, this does nothing to accurately characterize the decision structure needed for pharmaceutical R&D since it does not consider the value of the abandonment option – that companies can cut their losses and do not need to continue pouring money into a losing project^{354 355}.

Dixit et al³⁵⁶ examine the optimal investment rule which companies should use in deciding whether or not to invest in a project with fluctuating payoffs. They describe the ability to invest as similar to that of a call option and suggest that a firm will invest only when the returns exceed the costs – a practice similar to the exercise of a call option that is well above its strike price. Damodaran³⁵⁵ also suggests that R&D can be thought of as a call option, although he characterizes the entire amount spent on R&D as the cost of the option, while the resultant product is the payoff. Therefore, an alternative to the DCF method described above is that of real options valuation (ROV). Real options are essentially an opportunity to invest in a product as a result of development or research in that product³⁵⁷. It is widely accepted that the development of a drug by a corporation can be thought of as a series of decisions as to whether to continue or discard a particular project. Having an *opportunity* to invest means that companies have the potential for profitable return on investment as well as the ability to minimize loss by abandoning a project.

Schwartz³⁵⁸ uses ROV analysis to determine the real options value of a pharmaceutical project, along with the value of its abandonment option. Rogers³⁵⁴ also argues for the use of Real Options Valuation (ROV) analysis for decision making in the pharmaceutical industry. ROV allows companies to quantify value added to the project from the potential to invest, and the potential to abandon. Furthermore, ROV could be applied to evaluate a portfolio of projects³⁵⁹ or to rank projects within a portfolio³⁶⁰. A typical NPV calculation might yield a different investment decision than one undertaken with an ROV analysis. Real options demonstrate that projects may have greater value than previously determined under DCF analysis since the distribution of expected project returns is shifted more towards the positive side³⁶¹. This would be primarily due to the fact that a negative NPV project would treat all investment decisions as determined at the present time. An options approach would leave these decisions as flexible, therefore adding value to the overall project.

Thus, the idea of financial options concepts being applied to pharmaceutical practice is not a new one. However, previous analyses were undertaken from the perspective of the pharmaceutical firm as a method to determine when to continue or end R&D for a particular drug. It is possible to extend this concept to the traditional push and pull programs to create a new mechanism to stimulate antibiotic research for neglected diseases.

Some evidence is available to support the idea of combining push and pull mechanisms. Hsu and Schwartz¹⁵ created an ROV model to evaluate the ability of different incentive mechanisms (push, pull and hybrid) to stimulate development of effective treatments. They concluded that a hybrid mechanism of payments to the developer to help cover R&D costs combined with purchase commitments offered the greatest hope. This combined method spurs additional research as the initial payment increases. It also addresses two conflicting problems – first, the cost of the firm’s early stage R&D can be covered (at least in part) by the early payment. This drives more initial R&D but gives no incentive to create a final product. However, the purchase commitment solves this second problem by providing a market and profits only for working pharmaceutical products.

In our COV model, a potential purchaser would buy a right (during development) to purchase a specified amount of the drug at a later date, for a specified price. If the drug never makes it to market, the purchaser only pays a premium equal to the cost of the initial “option” contract. A fair valuation of an option will make the current value of the premium equal to the expected future profit from holding the option. Thus, the purchaser is protected from the down side risk of the cost of development, while the developing company is given an additional, earlier incentive to continue development. The greatest challenge is to persuade companies to invest in a market with low returns. Conventional thinking suggests that if it is possible to increase returns, at the very least giving the project a positive NPV that meets a predetermined threshold, then profit maximizing companies will always invest.

There are two ways to increase the NPV of a project involving large development costs: increase expected future cash flows or lower current costs. Thus, while pull mechanisms seek to increase future payouts, and push mechanisms help to lower current costs, our strategy does both. Once a company brings a drug to a specific phase of testing - for instance, Phase I clinical trials - a potential purchaser could be allowed to examine all of the data on the product in question and make an independent assessment of its potential. Ideally, this would be an international non-governmental organization or charitable foundation, with adequate funding to make several investment decisions and create a credible investment commitment, such as The Global Fund or GAVI. If the purchaser believed the drug to be a good investment, it would pay an agreed upon amount (the methodology for determining this will be discussed later) and in exchange have the contractual right to buy a certain number of doses at a reduced price if it made it to market. If the drug ran into problems during clinical trials and did not receive marketing approval, then the development company would retain the initial investment and the purchaser would have neither an obligation to buy nor a benefit from investment. However, any contract negotiated would need provisions ensuring access and ownership of all products developed from the initial, funded line of research. If one avenue proved promising, only to spawn a successful antibiotic from a

related mechanism, the purchaser would have an equal right to the new antibiotic, as it came from the intellectual property of the funded research. Likewise, if a company were to acquire the option and wanted to stop development, the contract could call for financial penalties.

This mechanism can perhaps best be understood with the aid of several examples, as seen below.

Options in Financial Markets

Call options stem from the financial world - in their traditional role the purchase of an option allows the holder of the option to buy a stock for a pre-determined price at a later date, if they so choose to. For example, an option might be bought on a share of Stock X (which currently trades at \$ 40 per share) for \$1, with a strike price of \$45. If the stock price moves above \$45 per share prior to the option expiration date, the holder of the option may then purchase one share of Stock X for \$45. Therefore, 3 scenarios are possible: 1) the share price never moves above \$45 and the option is never exercised, resulting in a net loss of \$1 for the option purchaser; 2) the share price reaches \$46, in which case the option may be exercised, a share will be bought for \$45, and could then be sold immediately for \$46 by the option holder, who will essentially break even (given the initial outlay of \$1) – Note that if the stock price is between \$45 and \$46 the option will still be exercised, but the holder will still have a net loss of < \$1; 3) the stock price moves above \$46, in which case the option is exercised, the holder purchases a share of stock at \$45 and can immediately sell it for the current stock price – making a net profit of the difference between the current stock price and \$45, minus the initial outlay of the cost of the option (\$1).

The most famous of the options valuation formulas is the Black-Scholes model, which is a specific model of a much more general formula to evaluate the forward price of a contract. This formula is given as³⁶²:

$$C_0 = PV [F_0 \times N(d_1) - K \times N(d_1 - \sigma\sqrt{T})] \quad (1)$$

$$d_1 = \frac{\ln F_0 / K}{\sigma\sqrt{T}} + \frac{\sigma\sqrt{T}}{2} \quad (2)$$

$$F_0 = S_0 \times (1 + r_f)^T \quad (3)$$

Where C_0 is the price of the call option (the cost of the future opportunity to buy). F_0 (defined in Equation 3) is the forward price of the stock - the value of the asset in the future, calculated by taking the current market value (S_0) and multiplying it by the risk free interest rate (r_f) raised to the time in years to expiration (T). When calculating an option for a stock, the current market value is simply the current share trading price. In equation 1, $N(d_1)$ is the normal distribution of the parameter d_1 . d_1 essentially represents the overall effect of volatility of the stock price, σ . Volatility is calculated for stocks by looking at the standard deviation of stock price over a period of years. K is the strike price – the price at which the option purchaser can redeem the option in the future to obtain the asset.

Example of the COV Model Applied to Antibiotics

The purchase of an antibiotic using the COV model can be illustrated using an example that closely follows the one above. For instance, a drug company called Pharma1 may develop a new antibiotic – AbX that could have remarkable efficacy in a particular bacteria afflicting a third world country. The target population may not represent a market share significant enough to make further testing and development profitable based on a traditional NPV analysis. However, an NGO, or interested health ministry may help stimulate further R&D through the COV model. In this scenario, the NGO would pay a small upfront fee for every single dose of drug they might anticipate buying in the future, at a fraction of what the actual dose will cost, but this will in turn assure them of the right to purchase the drug (if it ever reaches the market), at a significantly reduced price. In our example, they may spend \$0.10 in the present to purchase an option for each dose they need – perhaps 10 million doses. Therefore, at the present time, the NGO would pay \$1 million to Pharma1 in exchange for 10 million options to buy a dose of AbX at \$5 per dose in the future. Several years from now, AbX might make it to market, with a market price of \$10 per dose. Any individual or health ministry wishing to purchase AbX must pay this price, except for the NGO holding the 10 million options on AbX. The NGO will then exercise its option and purchase 10 million doses of AbX at \$5 per share. It may then sell these doses to health ministries at the market price of \$10 per dose, gaining a net profit of approximately \$49 million (\$50 million difference between market value and strike price, minus the initial cost of the outlay). (A more accurate assessment of the net profit would take into account the interest lost on the initial \$1 million over the years, thus the actual profit margin would be slightly less than \$49 million.) If the NGO was not interested in gaining profits from the sale of the drugs, it might then distribute the drugs at no cost or reduced rates according to the need of its constituents. The exact details of this would vary with the mission and aims of each organization. Of course, the flip side of this scenario is that AbX never makes it to market, in which case the option would go unexercised and the initial investment of \$1 million would never be recovered.

As can be seen from the example above, much of the viability of the COV model depends on the balance between the risk of the investment, the cost of the initial option, the market price of the final drug, as well as the strike price (what the negotiated price of the drug will be for option holders at the redemption time). High option prices or excessive risks make the investment unattractive to most investors, while low option prices erode the profitability of the project for the pharmaceutical firm and hinder the ability to continue development. Similar problems are encountered in pricing options in the financial world, where mathematical models have been employed to determine the likelihood that a stock will reach its strike price (the COV equivalent is the drug making it to market). The trouble with these valuation methodologies is that they assume volatility with a normal distribution. This is clearly not the case in the drug development world, since the cost of drug development at any given time is clearly dependent on stage of development, and the probability of failure in any given stage is also not normally distributed. Thus, a more accurate representation of the modeling of options as they pertain to drug development lies in a binomial evaluation of options. Intuitively, this makes sense – development at any given stage will either succeed or fail, and each outcome can be independently modeled for each stage.

Cheng discusses at length the Binomial Option Pricing Model³⁶³, in which he outlines its utility in helping companies to assess whether or not to engage in research projects, based on a value maximization approach. In the binomial model, a call option can be priced using the following equation:

$$C = \frac{S_u \times R - S_u \times d - X \times R + X \times d}{(u - d) \times R}$$

In this equation, the above variables represent the following:

C = the value of the call option

S_u = the value of the stock of the company if the project succeeds

S_d = the value of the stock of the company if the project fails

X = strike price of the option (the price of the stock at which the option would be redeemed)

R = $(1 + \text{risk free interest rate})^{T(\text{years})}$ (essentially accounting for the time value of money)

$$u = S_u / S$$

$$d = S_d / S$$

S is the current value of the company after the project is undertaken but before the final outcome is known. It essentially an average of the value of each state of success or failure based on their respective probabilities. It can be mathematically represented by:

$$S = P_u \times S_u + P_d \times S_d$$

In this equation, P_u represents the probability of the project succeeding (achieving the up state), while P_d represents the probability of achieving the down state (failure). These will necessarily be a function of the project's current state of development. The nature of pharmaceutical development is such that each independent stage carries dramatically different risks of success or failure. The success of the overall project can be viewed as the probability of success of a series of independent events. We must assume that the chance of success in any given stage is independent of the probability of success of any future stage. Also, success of past stages has no effect on future probabilities, other than success being a precondition to continue moving forward. Therefore the probability of success from any given stage is equal to the product of the probabilities of success for all future stages:

$$P_u = \prod_{i=m}^n P_i$$

where m is the current stage of development, n is the final stage of development and P_i is the probability of success for any given stage. Conversely, the probability of the project reaching the down state, P_d , is simply:

$$P_d = 1 - P_u$$

The value of the company if the project succeeds can be obtained from the following:

$$S_u = (S_0 - I) \times R + M$$

This effectively states that the net increase in the company's value after the initial investment required for the project, I , will be equal to the payoff M from the project's revenues at some future date. In our applications, M would be a function of the payoff deemed necessary by society to stimulate development for a particular class of drugs. The CGD concept of the Advanced Market Commitment could play an integral role in determining the socially acceptable payout for development of a new drug. This could easily be integrated into the COV model, by introducing a variable, AMC , which would be equal to the pre-determined dollar amount appropriate to stimulate research for that particular class of drugs. For instance, \$3 billion was the AMC amount deemed necessary to stimulate vaccine development. The variable AMC would be related to the project payout by the following equation:

$$M = \frac{AMC \times Q}{N}$$

Here we introduce two new variables, Q and N . Q is a parameter measuring the efficacy and novelty of the drug when compared to its peer group, and will range in value from 0 to 1. Q could be determined by an independent advisory panel which would assess the likelihood of the drug to contribute novel therapeutic benefit. Drugs with questionable efficacy or improvement over existing pharmaceuticals would be scored with a lower Q , meaning that their intrinsic project payoff would also be lower. Similarly, N is the

number of drugs in the same therapeutic class currently available. This would function to encourage development of drugs in novel therapeutic classes, as opposed to finding isomers and creating Me-Too drugs to gain marginal market share. Therefore, with these parameters, a truly unique drug with high likelihood of efficacy would yield a prize of the full advanced market commitment. A drug with little proven efficacy, entering into an already crowded field would have a much smaller, M , and thus less likelihood of securing a favourable return for the potential costs of development. This mechanism actively encourages novel drug development and targets financial rewards to that innovation.

The company value in the down state (project failure) must also be defined, and follows from the above equations to be:

$$S_d = (S_0 - I) \times R$$

Finally, the strike price (or exercise price), X , must be defined. In traditional financial call options, this price determines whether or not the option will be redeemed, since the redemption condition is whether or not the stock price reaches the strike price. However, in our model, the condition of redemption is approval of the drug (i.e. successful development). Thus, we have chosen to set the strike price as the marginal cost of production. In this way, the manufacturer of the drug does not lose money for each additional unit sold to holders of the call option, however the cost of development should not be borne at later stages by holders of the call option (they have invested previously to support development by purchasing the call option).

The COV model depends critically on accurate characterization of the probability of success at any given stage of development. Payne et al³⁶³ succinctly summarize data from the Centers for Medicines Research on drug development probabilities per stage, as well as length in years. The exact probability for any given stage will vary depending on the pharmaceutical class, but the numbers displayed in Table 6.4.1 are nevertheless instructive.

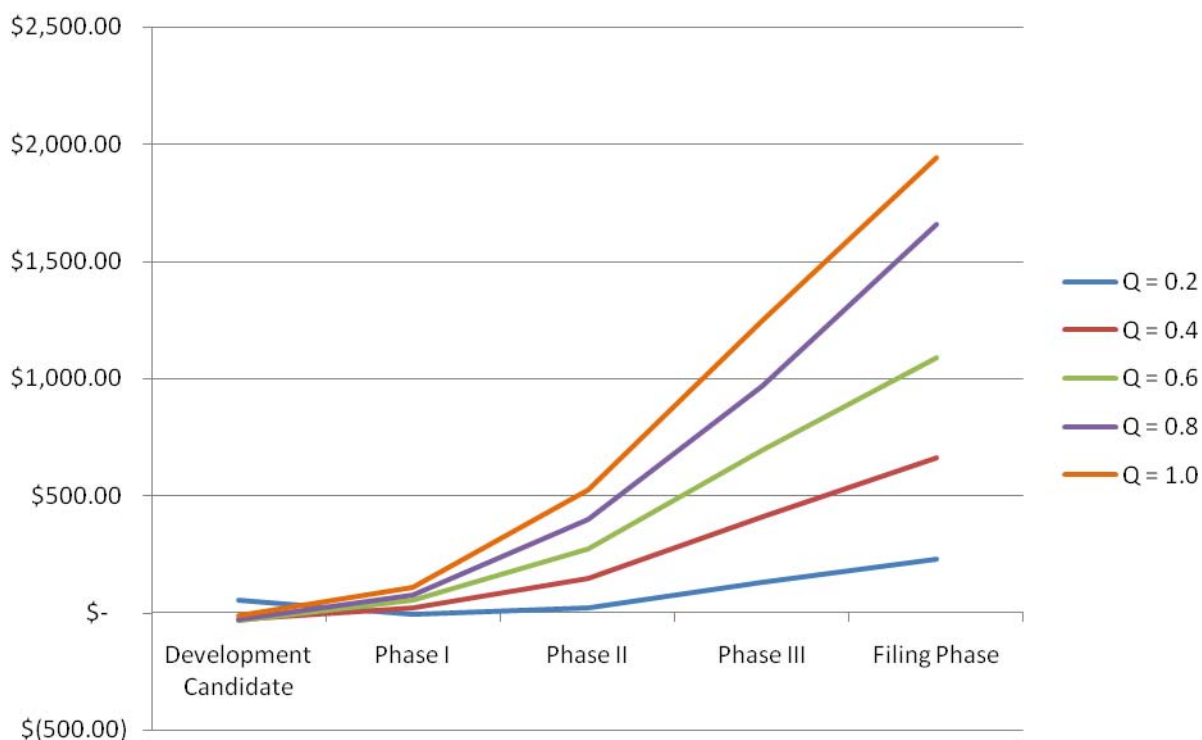
Table 6.4.1. Length of Time & Estimated Success per Development Phase

Phase Description	Length (in years)	Probability of success	Cost per phase (millions)	I (millions)
High Throughput Sequencing to Lead	2	0.0702	\$ 148.15	\$ 1,000.00
Lead to Development candidate	5	0.5	\$ 370.37	\$ 851.85
DC to Phase I start	1	0.75	\$ 74.07	\$ 481.48
Phase I to Phase II start	2	0.25	\$ 148.15	\$ 407.41
Phase II to Phase III start	2	0.5	\$ 148.15	\$ 259.26
Phase III to File	0.5	0.67	\$ 37.04	\$ 111.11
File to Launch	1	0.75	\$ 74.07	\$ 74.07

The last two columns were not taken from the article by Payne, but instead represent back-of-the-envelope calculations estimating the cost per phase. This assumes a total development cost of \$1 billion, which is in line with previous estimates of drug development. Assuming that the cost is spread evenly over the various stages depending on their length of time (a gross over-simplification, but a useful one for the purpose of illustration), then the cost per phase can be calculated. The investment cost (I) at any given phase can then be calculated by summing the costs per phase over the remaining phases.

Using the above data and the equations outline for the model, a very rough estimate of the aggregate price of all call options for a drug at any stage of development can be given, and is shown in Figure 6.4.1.

Figure 6.4.1: Call Option Price (in millions) as a Function of Development Stage and Q



Optimal Phase of Investment

As can be seen by the graph above, the optimal investment phase will be determined by a particular purchaser's appetite for risk and available funds. At the very least, it is instructive to consider the two extreme possibilities – early stage investment of development candidates, or investment at the filing phase. Investment in the earliest stages carries a significant amount of risk, the chances of any single given project making it to market are very small. Consequently, the purchase price of a call option at this stage is correspondingly cheap. If the project does succeed, a substantial savings will accrue to the holder of the call option when they redeem it for a discounted drug. Investment at this stage could be useful for an organization wishing to fund a number of competing projects or significantly different tracks of research to solve a given problem. They could invest widely across a spectrum of projects for a relatively small amount of money.

Conversely, investment in the later stages of development carries far less risk. Investment at the time of filing for drug approval carries little to no risk, consequently the cost of the call option is correspondingly higher. In fact, if the call option is fairly priced, it will reflect nearly the market cost of the soon to be approved drug. The savings by purchasing a call option at this stage are minimal, but so is the risk. This highlights the versatility of this model to a wide array of potential purchasers with different interests. The risk and return can be customized to each purchaser depending on their appetite and objectives.

While these two extremes are useful examples, they are unlikely to be the phases that most interested parties will invest in. The selection of candidate drugs for development is a difficult task at best, one that pharmaceutical companies struggle with. Similarly, purchase of an option on a drug at the final stages of development holds little value to the purchasers. It is more likely that interested parties will purchase options in Phase I or Phase II, where the mechanism and benefits of the drug have become clear, along with preliminary data on efficacy. Investment at this point will also allow substantial savings at further stages of development, with a moderate amount of risk involved. In this way, the model could also help to revive previous projects that had been abandoned due to lack of access to capital. Projects could be restarted at any stage if the appropriate mix of risk and payment makes them viable once again.

Areas to Address

The evaluation of the proposed new drugs will be of critical importance to making the system work efficiently. A committee of financiers, economists and scientists would all be needed to determine if the options contract provided good value for money and was worth investing^{liv} (see Appendix B). Full disclosure of all test results (both from animal models and regulatory trials) would be necessary by the company, in a manner similar to that required for licensing approval. Reluctance to disclose such proprietary information should be overcome by the desire to obtain preliminary funding – confidentiality would of course be essential. The group to evaluate the drugs could be an extension of the purchasing organization. Their evaluation should include not only a review of the drug and its potential prospects, but also an examination of the viability of the company and its infrastructure. It is possible that promising drugs might be conceived by companies ill-equipped to carry their development through. This must be taken into account when making the decision to invest, thus the need for a multi-disciplinary group to evaluate potential projects.

The obvious rationale for such scrutiny of potential option purchases is that bad investment decisions could quickly lead to a large loss of money with no real benefits. This is similar to one of the critiques of push mechanisms – that project managers might prove incapable of deciding on the most promising research plan. This could be rectified by the formation of an independent body to assess which ideas to fund. It relies heavily on full disclosure of all relevant documents, which may not be achievable. Thus, great emphasis should be placed on the skill and qualifications of the drug evaluators, as well as on the free exchange of information between the companies and potential purchasers. International purchasers would need to hire people with specific skills in

^{liv} A short discussion of existing funding tools provided by the European Investment Bank (EIB) can be found in Appendix B at the rear. These include risk-sharing finance facility (RSFF) and Competitiveness and Innovation Framework Programme (CIP).

financing, project valuation and/or ROV assessment. However, it is reasonable to think, if information is shared appropriately, that the skills of the purchasers could closely match those of the drug developers in this area.

One could also envision a situation where additional regulatory trials mandated for the marketing approval would increase the total cost of development. The possibility of this might deter some companies from engaging in a contract with a pre-determined price. This could be solved in a number of ways: first, by setting aside a special emergency fund (paid for by the purchaser), which could only be accessed in the specific case where additional government trials are required. Secondly, the probability and cost of this scenario could simply be built into the model, thus the premium for the call option might be slightly increased. A third possibility is the formation of an alliance between companies with specific, synergistic advantages in complementary areas. This would add to the value of the option for the purchaser since it would increase the likelihood of development, by adding experience and capital investment during a critical period. Danzon et al³⁶⁴ have recently shown that alliances tend to be more successful than solo companies in drug development.

Another criticism might be the number of projects would be limited, and this might narrow the amount of potential antibiotics in development. However, it could be argued that exactly the opposite would occur. If companies were contractually obligated to sell their first antibiotic at a lower price, they might also intensely work on more effective antibiotics in parallel, with the hopes that purchasers would have to buy the better antibiotic at full price due to public pressure. They would still have an incentive to make a good faith effort to bring the original to market, because if they did not, the global purchaser would see this as a breach of contract and be less likely to invest in them in the future. Some might also point out that this competitive environment could hinder the sharing of ideas, particularly when compared to the free exchange of data and information seen in academic and government funded labs. While this is true, it is no different than the current business climate of for-profit scientific research. Thus, while this model would not help academic labs, it should spur on private development, and that is its intent. If it was felt that data sharing among companies was absolutely critical, particularly for a product funded in part by international organizations, then the potential loss in sales from generic manufacturing would need to be compensated for by an increased premium price for the drug. The key is to maintain a financial incentive for the developer, thus the release of proprietary information would and should come at a high cost.

Similarly, if the intellectual property developed during initial R&D from one project stimulated further drugs or new revenues, the holders of the options on the original project would get dividends from the new revenue stream. These dividends would be a function of the number of options they purchased and the time they bought them. The

exact terms of agreement could be negotiated at the time purchase of the original option. However, it is imperative that purchasers of options share in the fruit of any research produced by the project they are essentially investing in.

Another important aspect to consider is the scope of the advanced market commitment used in pricing the call option. If a European health agency or NGO invested in purchasing options for a drug specific to the health needs of Europe, the *AMC* variable should reflect the European market. However, if after development the market for the drug was expanded to include a much wider audience, the *AMC* variable would also essentially expand, thus the effective value of the European market call option would increase. The holders of the initial European market call option should be reimbursed for this, through either further discounting of their drugs, or claw-back provisions which would allow them to receive an appropriate portion of the revenues from the expanded market. This claw-back provision would need to utilize a formula that takes note of disease burden and market possibilities.

Finally, some may argue that larger companies may be more effective at “gaming the system” to secure funding for their compounds over smaller biotech startups. Thus, those that need the early infusion of capital the least would be most likely to receive it. There are two responses to this critique: 1) The purpose of this mechanism is to correct a market failure and make certain projects more attractive, not to sufficiently capitalize any and all comers. 2) If one of the goals of certain NGO’s is to facilitate development of drugs by smaller companies, one could envision a two tiered system of investing – one high risk and one low risk that sufficiently adjusts the upfront options price in return for even more substantial savings at the time of drug approval. In this way, the mechanism can be tailored to fit the particular objectives of the options purchaser.

A Way Forward

As mentioned previously, the CGD *AMC* and the COV model have been previously proposed as independent mechanisms to stimulate vaccine development. Both also hold promise in stimulating antibiotic development. In fact, the combination of the two may offer the best mechanism to date for stimulating neglected drug development. At its core, the CGD *AMC* seeks to create an appropriate market for pharmaceuticals that may otherwise not exist. It does this by offering subsidies at the time of purchase of these drugs by the end users (developing countries, NGO’s etc). The COV model also attempts to correct these market imperfections, but offers injections of money at earlier stages of development. The CGD model helped to define what the appropriate market is to stimulate development. The COV takes that one step further by allowing the market to function at different points in a drug’s life cycle, instead of simply at the time of marketing. The COV effectively takes the subsidy proposed by the *AMC*, and transfers that to companies at earlier stages, appropriately discounting it for the time vale of money, as well as the risk assumed. The underlying tenets of the need for a subsidy are

the same, however the two mechanisms simply advocate this subsidy at different stages in the product life cycle.

As pharmaceutical companies continue to search for blockbuster drugs to be sold at a premium price, attention must be paid to the continued research and development of vital, but less profitable antibiotics, vaccines and other neglected pharmaceuticals. Much work has been focused on this in the past, with mixed success. Now, as newer models to stimulate R&D are developed, a more critical examination of the risks and benefits must ensue. Perhaps the combination of the COV model and the AMC developed by the CGD may prove even more effective in the near future.

7. CONCLUSIONS

7.1 Rationale for Intervention in the Antibiotics Market

There are currently too few antibacterial agents with new mechanisms of action (MoA) under development to meet the growing challenge of multidrug-resistance (MDR)¹⁵⁴. Among the 15 largest pharmaceutical companies in 2004, only 1.6% of drugs in development were antibiotics⁴⁰ and overall the industry pipeline has few late-stage candidates for antibiotics that can effectively combat the emergence and spread of drug-resistant bacterial strains³⁸. Without urgent action to spur investment in discovering new products, health facilities will be increasingly unable to effectively treat bacterial infections. Already an estimated 175,000 people die each year from incurable hospital acquired infections within the EU alone⁴. Eventually this trend will begin to negate the advances achieved in medical care broadly. For example, advanced surgical procedures and cancer chemotherapy might be impossible to perform without effective antibiotics⁵. Faced with this potential health crisis, current incentives to promote R&D in antibiotics are clearly insufficient⁴². A European strategy to address this lack of new antibiotics – based on the best available evidence – is urgently needed¹⁵⁴.

The reasons behind the lack of investment in new antibiotics are numerous. First, there is the existence of generic antibiotics on the market that are still (although to varying degrees) effective in treating the large majority of infections faced by health services. Second, there is the emphasis by European public health authorities on conserving the existing antibiotics intended for severe infection by using generics as first-line therapy wherever possible. This sends a message to industry that effective new antibiotics, when developed, will be dispensed infrequently and kept as last resort treatments even if rates of resistance to widely-used antibiotics are high. Third, the limited duration of antibiotic regimes, along with their fully curative nature (as opposed to just mitigating symptoms as in the case of chronic diseases) increases marketing costs (to keep the product salient in the minds of potential prescribers), and decreases expected returns on investment. Therefore, relative to other therapeutic areas, antibiotics do not appear profitable. One estimate suggests an net present value (NPV) of 100 for antibiotics, compared to 300 for an anticancer drug, 720 for a neurological drug, and 1150 for a muscular-skeletal drug¹⁰. Fourth, as antibiotic that develop resistance rapidly has a shorter clinical lifespan, it is argued that if a developer invests billions of dollars and takes over a decade to develop a new antibiotic they may not reap the full benefits of their efforts¹⁰. So, in theory, the NPV for an antibiotic falls when resistance to a drug develops and spreads amongst the general population¹⁰. Fifth, with the lack of appropriate assessment within pricing and reimbursement agencies, the prioritization and corresponding price paid by public purchasers does not reflect the relative effectiveness of antibiotics in reducing morbidity and mortality. For example, much higher prices are paid for some drugs—for example cancer drugs or central nervous system (CNS)-related drugs—that offer only a few months of additional life.

In addition to the lack of relative profitability in the antibiotics market, there are also inherent market failures that further deter R&D from this therapeutic area. The existence of externalities is the key failure^{lv}. In the case of antibiotics, a positive or “public health” externality exists—appropriate antibiotic usage helps treat infections that otherwise could spread to the community^{62 9}. Therefore, the general public benefits when an individual consumes appropriately prescribed antibiotic therapy. According to economic theory, the antibiotic developer will not produce enough antibiotics since the firm does not obtain all of the benefits. Indeed, discovery and development of new antibiotics has slowed dramatically over the past 25 years. Another key externality surrounds inappropriate antibiotic usage and ensuing resistance. Developers choose to mass-market their product to increase sales. Individual companies cannot control the sales of antibiotics by other companies, and therefore all companies aggressively market the drug, resulting in a “tragedy of commons” leading to greater rates of resistance. This in turn extinguishes demand for the product. Private companies may not have an incentive to take into account the affect of their sales of antibiotics on future antibiotic effectiveness due to the potential for cross-resistance across different antibiotics produced by various companies in the market⁶³. Consequently, the market price of antibiotics does not adequately reflect the true social cost of antibiotic resistance and there may be too many antibiotics sold to achieve a socially optimal level of consumption. The positive “public health” and negative “antibiotic resistance” externalities associated with antibiotic consumption represent market failures given that developers, patients, physicians, and other consumers of antibiotics do not directly reap the full benefits of antibiotic consumption nor incur the full costs of resistance. It is, therefore, recommended that policies be implemented which aim to curb the rapid spread of antibiotic resistance push developers to internalise the costs of resistance as well as reap the full benefits of antibiotic drug R&D.

The potential savings from the discovery of new antibiotic agents is also significant, as better treatment of bacterial infection would lead to fewer and shorter hospitalisations as well as lower costs associated with lost productivity due to disability or death. Smith et al (2005) suggest that antibiotic resistance causes GDP to fall by between 0.4 and 1.6% (equivalent to a £3–11 billion loss in monetary terms in the United Kingdom [UK]). Household income, government tax revenues, and total national savings are estimated to fall by up to 0.3, 0.35, and 2%, respectively¹¹⁴. In the EU, the cost associated with MRSA infections alone has been calculated to be €117 million in 2001¹⁹.

^{lv} An “externality” exists when an individual’s behaviour has positive or negative effects on another person that is not directly involved in the transaction.

7.2 Preserving the Effective Life of Existing and New Antibiotics

Currently, the high growth of resistance stems in part from over-prescription of antibiotics. There is a naive acceptance that infections encountered in hospital and especially in community practice are most effectively managed on the basis of clinical assessment⁶. As cultures currently require 36–48 hours to provide results⁷ few infections are microbiologically confirmed sufficiently quickly to guide treatment decisions⁶. This presumptive treatment of patients means that viral infections are often misdiagnosed as bacterial infections, leading to inappropriately prescribed antibiotics. Risk aversion on the part of physicians (which is compounded by mounting tendency for litigation in some countries) and ensuing over-prescription of antibiotics will continue to amplify the growth of resistance until doctors have more sophisticated and effective diagnostics that are quick and easy-to-use at the point of care (POC).

In terms of the need of these technologies, the degree of sophistication of rapid diagnostic tests (RDTs) could range from the simple to the complex. Indeed as regards the former, Finch suggests that a test that indicates whether bacterial infection is present or absent would have value. More sophisticated tests that indicate pathogen species, resistance markers, and virulence factors would also have a role⁶. Rapid progress made in recent years suggests that numerous technical barriers to the development of these technologies have been overcome. Also, recently several patents on key platform technologies (such as with PCT) have expired. This has led many researchers to suggest that the major barriers to the technological improvement of RDTs have been removed. The key bottleneck preventing large-scale marketing of these vital technologies is therefore seemingly not driven (at least not solely) from supply.

From the demand side, all immediate signals would suggest that the size of the diagnostics market is potentially large—especially if RDTs were to be developed for use at the primary care level. Together the evidence would suggest that—unlike for antibiotics themselves—there are no inherent market failures within the diagnostics market. Rather the key bottlenecks may lie in the perceived disincentive for antibiotic-producing companies to produce technologies that may limit the use of their drugs. Under policies supporting presumptive diagnosis, a developer whose antibiotic has a good chance of being prescribed will unlikely be compelled to produce a formal diagnostic device that would potentially limit prescription of the antibiotic. Indeed the current absence of large pharmaceutical companies from the diagnostics market could suggest that there may be a perceived disincentive. In systems in which formal diagnosis is properly incentivised, on the contrary, the use of the diagnostic could increase the chance of prescribing a given antibiotic. The decision of whether or not to invest in accompanying diagnostic technologies lies in the expected effect on prescribing practices and developers are ambivalent regarding which direction the effect would likely take³⁶⁵. In addition, there are

concerns amongst diagnostic developers surrounding the uptake and diffusion of a developed RDT given previously expressed budget priorities, which could also be affecting the rate of development¹³⁴.

Although specific recommendations for promoting research and development (R&D) for RDTs lie outside the scope of this report, it should be underlined that both supply and demand side measures should be assessed to better understand and support the development of RDTs to guide antibiotic treatment. From the supply side, inputs could take the form of targeted support for basic research and increasing access to enabling technologies – although from an economic perspective there is little justification for incentives comprising large financial subsidy. From the demand side, a major review of incentives within the health system structure, financing and reimbursement arrangements, the legal framework (including liability issues), and clinical guidelines should take place. Addressing systems issues appears to hold the most promise in tackling both antibiotic resistance through more targeted and informed prescribing as well as in sending industry the signal that there is a large and lucrative demand for good RDTs for bacterial infections. Amongst the tools to help guide policy change, long-term cost-effectiveness analyses comparing the economic costs and benefits of presumptive treatment to procurement of advanced RDTs – given varying levels of pathogen resistance, varying diagnostic sensitivity and specificity, as well as varying price levels—should be performed.^{lvi} Such an exercise would help determine the price up to which the public purchaser could consider the procurement of the diagnostic to be cost-effective.

Beyond the development and use of diagnostics themselves, conservation of antibiotics will also require a re-alignment of incentive structures within health services in primary care services and hospitals as well as within the overall financing structures to ensure that prescribers are not perversely driven to overuse antibiotics. Policies relating to performance measurement and spending should take a longer-term perspective in weighing the risks and benefits of overuse. Financing structures, for example, are a key means through which both consumers and prescribers can be influenced and compelled to reduce the use of antibiotics. Performance targets are another means to influence prescribing practices. The Centers for Medicare & Medicaid Services (CMS) example (see Box 4.1) highlights the importance of a holistic approach to designing benchmarks to drive performance. If the time interval for achieving a benchmark excludes the possibility of performing diagnostic exams, physicians will not have the incentive to carry out appropriate procedures. Also, in the case of decentralised budgeting, if the prescriber's budget must cover the cost of the diagnostic while not covering the cost of treating the ensuing worsened infection, there is a greater chance that formal diagnosis will not take place. In sum,

^{lvi} Similar analyses, which take into account varying levels of absolute and growth rates of pathogen resistance, varying levels of diagnostic accuracy, varying treatment and diagnostic price levels, as well as a long-term perspective have been carried out in the past for malaria 8. Shillcutt S. Cost-effectiveness of malaria diagnostic methods in sub-Saharan Africa in an era of combination therapy. *Bulletin of the World Health Organisation* 2008;**86**(2):81-160.

it is crucial that policy-makers design *coordinated* policies that encourage physicians to meet quality care standards while also using discretion and diagnostic tools to determine the most appropriate treatment and use of this resource.

7.3 Key Concepts in Incentive Design

The potential for an impending health crisis due to the lack of new antibiotics, along with the inherent externalities in the market and the likely cost-savings from improving treatment, provide ethical and economic justification for some intervention in the market by a public body. However, the design of the incentive—in terms of the timing and size of the reward, the institutional driver, and the target beneficiary—will determine its chances of success.

The approach to designing incentives to promote R&D in antibiotics depends first and foremost on whether we believe that the number of antibiotics that can be discovered is finite or infinite. If it is finite and indeed we have, as some experts argue, already picked all the low-hanging fruit, then we must put the maximum amount of funding towards conservation and discrete investments in new product development, consecutively, one at a time. Ideally this process would be driven at a global level to ensure coordination amongst countries. However, if we believe that the obstacles faced in antibiotic development are merely a matter of investment and alignment of incentives, then our priority is to re-ignite R&D (alongside coordinated conservation initiatives), spreading our efforts amongst numerous promising products. This report cannot provide an answer to this fundamental question, however the incentives presented can help inform decision-making predicated on either of these crucial assumptions. However, the key recommendation made hinges upon the latter assumption, that the overall antibiotics market should be kick-started with some expectation of decreasing marginal returns to development investment. Indeed interviews undertaken for this project suggest that numerous targets for antibiotic development have already been discovered and have been collecting dust. New incentives are needed to clear away the dust and spark new interest in exploring the potential fruits of these molecules, including their potential to create narrow-spectrum products and use against gram-negative pathogens.

It is not obvious at which geo-geographic level the intervention should be undertaken. The fact that resistance is growing internationally suggests that it is a global problem requiring a common strategy³⁶⁶. Indeed, as society as a whole stands to benefit from new antibiotics, the ideal incentive would be constructed at the global level. This was suggested in 2005 under the auspices of the Global Medical R&D Treaty, which determined minimum levels of support for R&D with an outside body setting the contribution rate for each country and ensuring that countries meet their contribution requirements²⁴⁸. A global mechanism would also overcome or mitigate political sensitivity associated with governments needing to set aside such a large sum of funding. A global mechanism would also help improve credibility amongst developers vis-à-vis the viability of financial commitments. Unfortunately

the political dependence of creating a global approach is likely to prevent them from being able to provide solutions to the urgent innovation needs. However, global approaches to public health deserve far more attention than they have thus far received. They should be supported now in order to be properly implemented and functioning in the years to come. Short of constructing a global mechanism to promote R&D in antibiotics, the EU could partner with US agencies. Collaboration with the US could increase the size of the potential investment as well as capitalize on both the size of the US pharmaceutical market and the US experience (albeit limited) with establishing R&D incentives for pharmaceuticals. Common solutions should be explored with, for example, the developers of BARDA, even if the organization's focus remains currently on the development of pharmaceuticals associated with terrorism and natural disasters. However, given the urgency for developing new antibiotics, the EU should not hesitate to move independently in applying its own incentives in the short-term.

The direction of the incentive could perhaps be the biggest influence on its chances of success. Push incentives focus on removing barriers to developer entry largely by affecting the marginal cost of funds to the developer for investments in R&D and tend to impact the earlier stages of the development process^{11 #270}. Examples include any subsidy made to a developer in the early stages of drug discovery or development such as grants or early tax breaks. These injections lower the cost of R&D for the developer by reducing the cost of necessary inputs. Push incentives may come from public as well as private sources such as venture capitalists or large philanthropic donors. In providing early funding, push mechanisms are particularly useful for attracting SMEs who often operate with less than 6 months cash-in hand^{12 lvii}. However, they are also fraught with several difficulties. For example, developers paid through push mechanisms often lack the motivation to move into the next, more applied, phases of production. Indeed push incentives pose the risk of spending on activities that may not ultimately lead to the development of new products. There is also the danger for the eventual over-payment through push incentives to have a dampening effect on entrepreneurialism¹³. Push incentives also pose agency problems in that researchers are compelled to show their work in the best light possible, which may not accurately reflect the merits of investment. The funder, therefore, bears most of the risk of product development funded through push mechanisms.

In contrast to push mechanisms, pull mechanisms involve the promise of financial reward only *after* a technology has been developed. Examples include simple monetary prizes, the promise of tax credits to match eventual product sales, intellectual property (IP) extensions, or specified advanced market commitments (AMCs). Pull incentives offer financial reward upon completion of technological advances in order to lure R&D investments in a desired direction. Also, as profits increase with decreasing development costs, they better align internal incentives to

^{lvii} In the US, BIO currently estimates that 120 companies, comprising 30 percent of all publicly-traded biotech companies are currently in this situation.

rectify inefficiencies. Finally, as pull mechanisms provide a reward only upon full product development and authorisation, they provide researchers with the incentive to self-select the most promising products and thereby bypass many of the agency problems of push mechanisms. However, if the incentive relies only on the promise of rewards (as opposed to fully earmarked existing sum), pull mechanisms are at the mercy of the changing political and economic (and associated budgetary) tide. It has also been suggested that pull mechanisms may corrode existing non-financial incentives to collaborate and slow the overall search for solutions. Finally, as financial rewards in pull mechanism are reaped only following product development, the financial risk involved in all stages of R&D falls on the developer. This unequal distribution of risk is perhaps of the greatest limitations to pull mechanisms.

The basic elements of push and pull mechanisms can also be combined to create hybrid mechanisms. Hybrid mechanisms may help overcome many of the problems faced by uniquely push or pull incentives by covering (at least partially) the developer's early R&D costs while also providing the profit lure to go through with full product development. In a comparison of the ability of push, pull, and hybrid mechanisms to stimulate the development of effective treatments, Hsu and Schwartz concluded that a hybrid mechanism were the most viable. Indeed the merits of a hybrid approach are increasingly widely accepted. Hybrid mechanisms may provide crucial impetus to overcome developer reticence at the different (and perhaps key) stages of product development: early stage push funding provides the increased financial space to explore early discovery ideas without needing to understand their potential, while the larger pull element entices them to undertake the latter phases of development, including expensive Phase III trials. The evolution between the respective incentive forces within a hybrid incentive (push to pull) is important in that developers have been understood to respond more to profit incentives at the later stages of the research process than at the earlier stages¹⁶. In combining push and pull incentives, hybrid mechanisms also spread risk between the funder and the developer. This balance is especially important for antibiotics in that the development of an entirely new product (with a novel mechanism of action [MoA]) presents a significant technical challenge—and thus a high level of risk in going forward with development.

Incentives that use pull mechanisms in the form of specified rewards (e.g. monetary prizes, AMCs) present a good opportunity for public health authorities to communicate their therapeutic priorities as well as the price they are willing to pay for products responding to those priorities. However, the critical challenge of these incentives lies in the required *ex ante* estimation of the optimal financial reward. The size of the award should, on the one hand, be high enough to attract researchers with the necessary skill set while, on the other hand, avoid overpaying and thereby wasting scarce public or donated resources. Achieving this balance is crucial to the success of the incentive. However, the estimation is extremely difficult to make and a number of considerations must be taken into account, especially if the resistance profile is not well understood at the time the estimation is made. First, the size of the reward would need to compete with drugs that have higher NPVs²⁶⁶. Most

proposals also suggest the judging of the winner and distribution of the prize funds be proportional to the relative innovation or benefits, however the metric (usually quality-adjusted life-years [QALYs]) for assessing this also presents some challenges in practice. With regards to antibiotics specifically, one proposal suggests that an award US \$3 billion be granted to the first effective treatment for a high-priority pathogen²⁵⁷.

The use of any non-market reward for promoting R&D inherently presents the risk of overpaying for the innovation, and thereby producing significant social loss. As such, it is important not over-emphasize the lack of potential profitability in the antibiotics market. There is a profit to be made from sales in developed countries. Indeed with the growing rates of resistance to current treatments, we can expect legitimate sales of new products to increase in the years to come even with conservation measures in place. For example, it has been suggested that the temporal increase in the incidence of infections such as MRSA within hospitals and the emergence of community acquired MRSA (CA-MRSA) indicate that a market for new treatments does exist and it seems likely that it will increase over time with resistance to existing products³⁴⁵. Overall, the anti-infectives market is estimated to be worth US \$79 billion per year, the third largest pharmaceutical market globally after the CNS and cardiovascular markets¹⁵⁶. The antibiotic market itself is currently estimated to generate sales of US \$37 billion per year. Although with the significantly slower growth of this area relative to other therapeutic areas, this position is unlikely to be maintained. Also, while contrary to the theory that the NPV for an antibiotic falls substantially with resistance, some experts suggest that the fall in sales due to resistance actually occurs only post patent expiry. This would suggest that resistance fails to significantly affect the most lucrative life of the patent. In addition, the developer of a new antibiotic may stand to reap reputational (public relations) rewards in being able to claim contributions to life-saving products^{345 367}. While these advantages are clearly not sufficient to drive the desired level of R&D independently, they should be examined to some degree in the calculation of an appropriate award. In quantifying these gains, however, it should not necessarily be assumed that they will be equal to those reaped from research in neglected diseases. Another difficulty in calculating a reward *ex ante* lies in the political palatability of paying out large sums given competing priorities within the public sector. Indeed incentives that bypass the overt calculation of reward (e.g. IP extensions) may receive less opposition as the high cost of drug development can be hidden.

Some experts suggest that the key strategy for the promotion of drug discovery will be the development of focused cooperation between academic institutions and small and medium enterprises (SMEs)¹⁶¹. Indeed the smaller companies are already starting to fill the gap left by the larger companies that have pulled out of antibiotics. It has been suggested that SMEs require substantially lower annual sales to recoup investments (perhaps US \$100–\$200 million per year) compared to \$500–800 million for large companies¹⁶⁵. Precedent now exists for a relatively small company

to acquire promising molecules and carrying them through development and to market.^{lviii} To the extent possible, SMEs should aim to get involved in more collaborative approaches with the pharmaceutical industry. And the input of larger pharmaceuticals will be imperative. The COA model may provide a mechanism through which greater collaboration becomes more feasible. However, it should be noted that—while very attractive in theory—complicated partnerships or shared rights present the danger of repelling participants from any incentive scheme. This is especially true of the traditionally autonomous and financially self-sufficient large companies. Indeed the PDPs for neglected diseases have demonstrated that negotiations over rights can be lengthy and draining for large companies that are accustomed to independence and generally lead by IP-driven strategies. Antibiotics—a therapeutic area that lacks the positive public relations effect of neglected diseases—would be even less likely to compel large pharmaceutical companies to leave their IP comfort zones and accept shared rights agreements. The options here are two-fold: either limit industry participation to SMEs—which can provide most if not all the necessary expertise and resources—or simplify IP arrangements to attract the large pharmaceutical company participants.

7.4 Conclusions on Individual Incentives

7.4.1. *Direct public subsidy for basic research*

Addressing the decades-long exodus of specialist knowledge, skills and experience is vital for the development of new antibiotics in the future. Traditional tools, such as grants and fellowships for training can help attract new scientists to the field. However, in order to avoid losing existing knowledge that has strayed to other areas over the past decades, efforts should also be made to re-engage older researchers in the area of antibiotics. Without public funding for capacity building and re-training it seems unlikely that even the most interested developers will be able to find the necessary human resources for basic research to expand work in antibiotics. Specifically, funding could be made available for basic research into resistance and potential targets (biomarker discovery), gene identification, platform technologies and clinical development, as discussed in section 6.1.3. Efforts should be made to commit the necessary funds in advance, detaching them from annual budgetary negotiations that risk putting them at the mercy of political whims, the economic climate, and other perpetually changing forces.^{lix}

Support for open-access molecule libraries or open-access research more generally could also help remove barriers to participation and collaboration. Despite the fact that currently few of the requisite tools exist within the public domain to support

^{lviii} This refers to the development of Daptomycin (trade name Cubicin) by Cubist Pharmaceuticals, a single-product-driven company based in the US. They purchased the initial molecule from Eli Lilly. However, it should be noted that Daptomycin had already undergone some Phase II testing when it was purchased. Manufacturing of Daptomycin is outsourced to another small company.

^{lix} The 9 year budget commitment (for 2004–2013) apportioned in the in the US Project BioShield is an example of longer-term funding.

knowledge-sharing within the biomedical sciences and despite the strong proprietary history in the field, open access approaches should be publicly supported now so that they can help foster important developments in the (perhaps near) future. Indeed the reshaping of the business environment through technology as well as the changing drug development landscape more generally, would suggest that open source approaches may provide important contributions to product development quite soon. Efforts could be made to hasten this evolution. For example, free access could be made mandatory for all publically-funded projects.

7.4.2. Tax incentives

Despite their ability to foster creative accounting amongst companies²⁴⁵, tax credits have a successful record in stimulating innovation in the US by effectively lowering the costs of drug development^{243' #109}. It has also been suggested that, as the effectiveness of tax credits depends in part on the revenue potential of the final product, stimulating R&D for antibiotics, which lose value as resistance emerges, their application to the antibiotics market may require larger tax credits^{243' #109}. However, in Europe, as limiting consumption is an essential part of resistance control, tax incentives for antibiotics should not in fact not be placed on post-approval, revenue-related activities such as marketing or sale volumes. On the contrary, the use of tax incentives should be used for push purposes, not as pull mechanisms, which rely on the lure of high volume sales. The level of the tax credit or rebate should reflect the amount of risk that the donor is willing to take on, as indeed under such arrangements, the funder faces most of the risk of failure. Overall, however, push tax incentives, alone will be unlikely to attract interest from developers. For antibiotics, tax incentives would need to be combined with a pull mechanism (e.g. monetary prize, AMC). This would increase the revenue potential of the drug and create a clearly defined market^{18,243}. However, as the temporal dynamics of tax credits and capital allowances tend to benefit those with existing (or else upcoming in the case of deferrable credits) tax liabilities, SMEs with limited portfolios stand to gain very little unless the design specifically takes their needs into account.

7.4.3. Monetary prizes

The pull effect produced by a prize-based incentive is dependent on the appropriate calculation of the prize (see Box 6.2.2 for discussion). If given the appropriate contract agreement, this decoupling can help leverage market segmentation and lead to more economically appropriate pricing in the developed versus the developing world, thereby improving access. Also, in decoupling sales from the recouping of R&D costs, monetary prizes can help prevent the over-marketing and subsequent over-consumption of an antibiotic product that is ultimately developed. Monetary prizes will only be attractive to SMEs if they already benefit from early stage funding in the form of venture capital or other forms of push funding. SMEs may also be attracted to this type of pull-incentive if their strategy is to bring one product to market rather than develop a multiproduct portfolio. In addition, given the lower revenue requirements for SMEs, smaller sized awards could be used. The main disadvantage of prizes lies in the fact that consumers must not only subsidise

the monetary prize, they are also forced to pay monopoly prices for the eventual drug.

Under milestone monetary prizes developers are rewarded for reaching certain milestones within the product development process, such as for completing Phase I and Phase II trials. The incremental nature of the reward allows developers to recoup investment costs earlier than under single, post-development reward arrangements, thereby reducing the risk they face. As design proposals generally take a multiple winners approach, a greater number of researchers may be encouraged to participate, thereby increasing the overall amount of research focussed on a given issue. Naturally, conditions must be used to mitigate the risk of the funder paying more than once for a given development. Smaller companies would also be more attracted to this scheme as they receive reimbursement for development costs earlier in the development of the product, potentially making it easier to attract venture capitalists to provide funding for later stages of development. A disadvantage of milestone rewards is that the funding body would be rewarding some research on products that would never reach the market: a product might make it through Phase I and receive an award for reaching that milestone, but it may fail during Phase II trials. However, as significant proportion of molecules fail during Phase I, setting the first milestone for successful Phase I trials eliminates part of this weakness. Also, as the most expensive stage of clinical trials occurs with Phase III testing, providing a milestone payment after Phase II could help SMEs find the additional funds to conduct Phase III trials.

Optional reward systems²⁵⁴ would provide greater advantages to the developer than under traditional prize systems in that the developer would be given more time to assess the value of the finished product within a more up-to-date economic and competitive environment and make the choice of reward accordingly. In this regard, the optional reward system reduces the amount of risk faced by the developer, passing it to the funder. Further, given the asymmetry of information and the required 10–15 years of development, the developer will be in a better position to understand the potential resistance profile of the product. Therefore, despite even the strictest criteria for granting of the reward, as it is set at the outset, the risk to the funder is further compounded. Also, in accepting to be part of an optional rewards scheme rather than simply applying for a patent, one might question if a participating company in fact had doubts regarding the quality of the product that they were in a position to produce. Overall, the asymmetry of information combined with the uncertainty surrounding the growth of resistance suggest that this incentive would not be suitable for promoting R&D in antibiotics.

Research tournaments in which a sponsor provides a reward to the developer that has progressed the furthest in research by a specified date²⁴⁵ are similar to monetary prizes in that they rely on a pull mechanism and reward to promote competition amongst developers. The ability of such a mechanism to promote development progress depends largely on the number of developers, as well as the

level of collusion amongst them. The main advantage of this incentive design lies in its ability to attract developers who believe they have a competitive advantage—potentially those with existing molecules that have been previously set aside. Developers most likely to enter the competition would seemingly be those that have already undertaken some discovery work and believe they have found something promising. However, truly breakthrough technology could potentially be omitted due to confidentiality fears. Another major disadvantage of this proposal lies in the fact that donors would be forced to pay the reward regardless of the actual level of overall progress or whether the product is likely to ever make it to market. Generally such an incentive should be seen as a potential mechanism to overcome specific bottlenecks within the development cycle or to help spur creation of follow-on products. Their suitability for promoting progress in the development of novel antibiotics is seemingly limited.

7.4.5. Advanced market commitments

In specifying the number of doses to be purchased as well as their price AMCs have the benefit of aligning incentives for the funder, developer and user early in the development process. These arrangements both reduce the risk to developers and potentially increase the size of the market for the eventual product. Consistent with most pull mechanisms, AMCs reward successful outputs with predetermined characteristics rather than reward inputs into research that may not succeed²⁶⁶, explicitly linking payment to product quality²⁶⁷ and allowing the developer to pursue whichever R&D approach or mechanism it feels maximises its chance of success. They are seen to combine the incentives of patents and monetary prizes while eliminate the price distortions associated with patents, as the profit maximising developer does not set the final price^{237,255}. In applying AMCs to antibiotics, a few key challenges arise, including with product specification and quantity guarantee given the changes in the market and the unpredictability of resistance. One suggestion is to avoid contractually establishing a minimum threshold quantity, in order for the funder to be able to choose amongst all the products qualifying for the price guarantee²⁶⁷. This more closely mimics an actual market, however, it substantially increases the risk to the developer. Pricing structure and IP arrangements will also effect developer reward and hence risk. Another challenge in applying AMCs to antibiotics concerns the determination of the purchase volume given changes in the epidemiological environment. One option would be for the government to commit to purchasing a certain amount and stockpile the product if too much is purchased. However, to qualify for stockpiling, antibiotics will likely have to be formulated for simple consumption to ensure they can be disseminated widely to the public in the case of an epidemic. Indeed anecdotal evidence from the US suggests that antibiotics in their originally marketed parenteral formulations are generally not considered for stockpiling. This may have substantial cost implications for developers and must be accounted for in AMC designs with high volume commitments. In addition, there may be substantial risks in committing to purchase large quantities of the developed product prior to properly understanding its resistance profile as this leaves open the possibility that cross-class resistance with the novel product could render it obsolete before the product is even fully marketed.

Non-binding commitments would clearly present lower risk to the funder but may not appeal sufficiently to the potential developer. In addition, elements of push funding are likely to be needed if the AMC is to attract SME or public sector participants.

7.4.6. Licensing arrangements

A patent buyout takes place when a monetary award or fund is used to purchase the IP of a new product and secure it in the public domain. Awards that effectively buy the patent from the developer present advantages in terms of the ability to decouple sales from the recouping of R&D investment. In the case of antibiotics, this crucially eliminates the need for large-scale marketing and the related overuse of the product. If calculated appropriately, there may be some interest amongst smaller companies, public researchers or PDPs that combine the two as they may be more attracted to one-off payments as well as to a single product development strategy in order to be able to concentrate their limited resources. However, in buying out the patent from the developer, the incentive for the developer to produce “follow-on” generations of the product is extinguished.^{ix} Further exploration of the potential of the product would then require the licensing of the product out to developers for further exploration^{ixi} although new arrangements would have to be made for the reward of the incremental innovation.

A patent pool is a financing mechanism that enables the collective acquisition and management of IP for use by third parties for a fee. Patent holders from the public or private sector may contribute patents to the pool. A developer wanting to use the patent to develop a new product then seeks a license from the pool against the payment of royalties to produce the medicines. Efficiency gains are made through the collective management structure which centralises, simplifies and streamlines the administrative, legal and bureaucratic processes of obtaining and managing licenses from a multitude of patent holders. The possibility of a ‘one-stop-shop’ versus multiple individual agreements reduces costs and market entry barriers to potential new developers or manufacturers²⁷⁷. Further cost-savings may be achieved through the reduction of litigation costs for patent infringements. Also, perhaps more importantly, pools increase access to IP as developers and manufacturers no longer need to wait out the patent term, which can allow for faster downstream innovation, technology transfer and scale-up if and when necessary²⁷⁷. In the case of antibiotics, patent pools may be useful for fostering innovation where previously developers have abandoned efforts. However, it could be argued that the licenses placed into the pool would unlikely be those with the most promise (in this case those with novel MoA). In this sense, one could suggest that patent pools are more likely to foster incremental innovation than novel innovation. This does nonetheless present significant advantages in terms of

^{ix} While follow-on products are not generally novel enough to avoid cross-resistance with the earlier generation products over the long-term, they can slow resistance in the short term.

^{ixi} This could of course be the previous developer who has knowledge advantages in working with the product.

exploring fixed-dose combinations for creating new antibiotic treatments. The harmonization across all the licenses within the pool may facilitate this exploration substantially.

7.4.7. Regulation-based incentives

In theory, the reduction of clinical trial requirements could help speed authorisation and lower costs associated with the development of new antibiotic products. As discussed, there may be scope for delaying Phase III trials until post-launch for drugs for very serious infections, as is done for certain HIV/AIDS drugs, or limiting liability through expanded indemnification insurance. Another possibility may be to accept more evidence based on modelling predictions. While it is not in the remit of this report to present definitive answers regarding the appropriateness of regulatory options, it is hoped that serious analysis and consideration of them will be undertaken (or continue). However, it is strongly recommended that further progress be made towards providing developers with clear and consistent guidance for trials on relevant indications. Whilst altering regulatory requirements may be necessary given scientific understanding and biological evolution, further effort should be made to maintain transparency and consistency vis-à-vis the demands made on developers in attaining regulatory approval.

Incentives based on the promise to increase regulatory efficiencies should not be regarded as sufficiently lucrative rewards to stimulate the level of desired innovation in antibiotics. Antibiotics for serious infection in principle already qualify for accelerated regulatory assessment in both the US and the EU if they fulfil certain criteria. The existing empty pipeline would therefore suggest that these mechanisms are not in themselves a sufficiently strong lure for developers. Although the introduction of the voucher would increase the strength of the incentive in Europe, its application elsewhere would cause some distortion. Perhaps most importantly, incentives based on regulatory efficiencies may not be suitable to promote R&D for antibiotics given the fragmented regulatory structures of the EU. For even if the scientific assessment is accelerated, post-authorisation procedures that extend down to Member States are likely to continue to be time consuming without broader reforms. Better coordination of regulatory processes across European institutions and across Member States such as in the area of Health Technology Assessments (HTA) could help make incentives based on accelerated regulatory review a more viable incentive option.

Unlike most therapeutic agents, antibiotics tend to be prescribed as short-course, fully curative regimens. While their extensive use in clinical practice reflects the expedient and often life-saving nature of these drugs, their advantages are not fully acknowledged by pricing and reimbursement agencies. Indeed pricing and reimbursement decisions appear to minimally reflect actual therapeutic benefits or cost savings that drugs provide. Suggestions are now being made to tie pricing and reimbursement to the social value of the product. Despite its many merits, social-value based reimbursement would, in practice, present numerous challenges. Notably, decisions surrounding the measurement of social value of a product is

contentious – although even an imperfect metric such as the QALY^{lxii} would likely suffice for such calculations in the short term. Limited pricing reform to better reflect therapeutic value may be possible in the short-to-medium term or while a more holistic, social-value based system is under development. The (fulfilled) promise of a higher prices would in itself go far in luring developers to antibiotics. Further, in contrast to patent-term extensions, reimbursement incentives would allow developers to recoup R&D costs early on and reduce the amount of risk faced by developers. Also, reimbursement incentives have a direct influence on prescribers and patients, which in turn would provide positive knock-on effects on resistance.

In some countries such as the UK similar proposals to price (all) drugs according to their social value have been considered³⁶⁸. One could also suggest that moves towards HTAs such as those performed by the German Institute of Medical Documentation and Information and the National Institute of Clinical Excellence represent a clear shift towards more value-based considerations in resource prioritisation. However, in the EU, antibiotic prices themselves tend to be consistently negotiated down as part of a display of monopsonist power in the form of item-by-item price negotiation, reference pricing, formulary pricing, as well as indirectly through rate-of return regulation.

Reimbursement and price re-structuring could have a significant impact on the investment of R&D for antibiotics. However, within a European context, the success of this type of reform as an incentive would depend largely on the number of Member States adopting such an approach. A standardised European approach to assessment would make the prioritization of antibiotics more credible and in turn greatly contribute to the strength of such an incentive. These major reforms will undoubtedly take time and, in this regard, reimbursement reforms should be perceived as a key approach for directing R&D investment towards long term needs rather than a solution to fill urgent treatment gaps. However, in the short term even minor price-restructuring within Member States could help pull investment.

7.4.8. Intellectual property extensions

The argument behind IP extensions lies in the fact that obtaining market authorization is usually a long process that reduces the effective life of a patent. Proponents suggest that profits a developer obtains from selling its product during the effective patent life may not be sufficient to justify the costs of R&D, particularly for treatments with a high cost of R&D and/or lower revenue potential. The high level of interest demonstrated by large companies for IP extensions suggests that they would be likely to continue or re-enter the search for new antibiotics if such lucrative incentives were put in place.

IP extensions have the political advantage of avoiding the need to overtly calculate the exact amount of public subsidy to be used to re-ignite R&D. They are more

^{lxii} The QALY design is currently under revision.

politically palatable in that they the high cost can be hidden. In this regard, extensions to IP protection may have significant appeal. However, it must be clear that these mechanisms do not imply the ultimate cost will be lower. Indeed the ultimate social cost of extended monopoly status could impose a significant social cost, especially if the extension can be applied to blockbuster drugs (as in the case of wildcard patent extensions). Further, increasing IP protection for antibiotics will delay generic competition and thereby postpone the availability of cheaper products. This will have major knock-on effects for developing countries that will likely already face a delay in accessing new drugs. The human toll of such a delay could be significant. Finally, and perhaps most crucially, offering extensions on IP for antibiotics risks sending the message that any drug category with underinvestment by industry will ultimately be granted similar privileged status. Obviously the repercussions of such a message would transmit to immense social loss on the longer term.

Allowing the patent extension to be transferable across products and companies (wildcard patent extension) could make the incentive even more powerful as well as make it more attractive to SMEs who could sell it on to companies with blockbuster drugs. However, there is a trade-off between luring SMEs to the scheme and minimising the distortionary nature of the wildcard as the application of the extension to other, entirely unrelated, products risks severely distorting the market in other therapeutic areas. Indeed this also creates problems in terms of equity and transparency³¹⁶. Further, as the extension would likely be transferred to blockbuster products, the potential social loss would likely be high.

Wildcard patent extensions should not be considered for promoting R&D in antibiotics. If one IP extension were to be most promising for antibiotics it would likely be orphan drug legislation. However, given the potential for dangerous precedent setting, the lack of antibiotics should be considered a full health emergency and one which must be determined by scientists.

7.4.9. Functional resistance groups

Another variation of patent extension incentives is to apply patents over functional resistance groups (FRGs) rather than by chemical classes, in order to reduce resistance arising from competition between drugs under different patents for the same condition¹. As mentioned, the inability of one firm to control the sales of antibiotics by other companies creates a 'tragedy of commons'^{259,294} resulting in aggressive marketing of the drug, thereby accelerating the development and spread of resistance. The FRG scheme would relax anti-trust laws to allow companies to sell the rights to their product to another company with a competing antibiotic in the same functional group, and thereby create monopolies through mergers. Patents for FRGs rather than individual drugs could then be created (see Box 6.2.4 and 6.2.5). Broad patents will stop companies from competing for the same pool of effectiveness within a FRG and provide an incentive for companies without a patent for a FRG to develop new antibiotics outside of the patented classes⁶⁵. This would

give developers the incentive to manage sales and related consumption patterns (and resistance), thereby forcing companies to better internalise the cost of resistance, and produce and sell antibiotics more closely to the socially optimal level^{38,65}.

As FRGs inherently require a collaboration that would be interpreted as collusion, the creation of FRGs would require reforms to current anti-trust laws. This would undoubtedly be seen as presenting a danger in terms of setting precedence for other sectors to base non-competitive activities upon. Aside from this immense challenge, the FRG proposal is fraught with numerous practical difficulties. The number of antibiotic patent owners, the number and variety of patents themselves, as well as varying levels of remaining IP protection on these patents would make the creation of FRGs an extremely complicated process. Also, with regards defining the group, the classification of the respective FRGs would likely need to be dynamic as resistance develops given that resistance could immerge across seemingly unrelated classes. Another major disadvantage is that developers would have no incentive to research drugs in other FRGs where patents already exist¹, which may hinder the development of both novel and follow-on antibiotics. In addition, as many classes of antibiotics have off-patent drugs or patents owned by different companies, the implementation of *sui generis* rights may also be necessary. A *sui generis* right would provide the holder of the original patent with the ability to produce the antibiotic in perpetuity, effectively eliminating the development of generics for off-patent drugs¹. A number of challenges arise from this proposal. For example, it is unclear who would receive rights for off-patent antibiotics. One proposed solution is to hold an auction for the rights over certain classes of antibiotics¹. Overall, and especially if they are considered for the long term, *sui generis* rights are likely to be politically contentious. Overall, at the time of writing, too little is known about how to tackle the practical challenges of FRGs to merit their recommendation. Significant research would be needed to understand how to amalgamate new groups while adequately compensating developers within such a system.

7.4.10. Product development partnerships

Partnering with pharmaceutical companies can provide basic researchers with the added expertise and infrastructure to move to further stages in the process. In the past, arrangements in the form of public-private partnerships for neglected diseases have sought to take on most of the risk through almost entirely push funding. However, in the case of antibiotics for the richer countries—where significant returns can be reaped even with volume conditions—more properly balanced risk-sharing arrangements should be sought. However, a key challenge for product development partnerships (PDPs) for developing antibiotics is that they may not provide sufficient attraction for developers, especially large ones, as negotiating an acceptable return for the private sector partner (in addition to the culture clashes discussed in section 7.4.10) can prove to be challenging. The necessary balance between improving public health and allowing profit maximisation for developers can be difficult to attain^{338,345}. Partnership arrangements for drugs developed for both developing and developed country markets are particularly difficult to

negotiate, especially surrounding IP rights and pricing³⁴⁶. A proposed solution is to separate the various stages of antibiotic development and licensing. Specifically, a not-for-profit foundation could be created for development stages up through Phase II trials. Products could then be licensed to commercial companies for sale in the industrialised market, while sales in the developing world would remain on a not-for-profit basis¹⁸.

The Innovative Medicines Initiative (IMI) is a specially designed PDP that—while not intended for full product development—is likely to foster essential collaboration between public and private entities as well as amongst traditionally competitive private entities to tackle key bottlenecks, thereby accelerating product development. While still in its infancy, the key to IMI’s success will likely be the focus on “pre-competitive” technology (means for predicting safety and efficacy), which increases the chances for close collaboration and sharing of knowledge amongst experts. The initiative has significant industry support and input. However, this industry support of the initiative may also present drawbacks. Namely, it has yet to be seen whether chosen areas of work will derive from pure financial interest or rather reflect the most socially beneficial areas of therapeutic need such as the area of antibiotics. In sum, the IMI should be considered as a promising collaboration to foster important developments in safety and efficacy in the long-term. However—as with PDPs in general—these arrangements are not a solution for satisfying urgent development needs.

7.4.11. Call options for antibiotics model

The Call Options model for Antibiotics (COA) is a hybrid push-pull mechanism, based on the principles of call options in equity markets as well as AMCs. It’s hybrid nature is in-line with the recommendations of a recent OECD report¹⁴. The COV model allows an investor to purchase the right to buy something at a later point in time. In this case, the potential purchaser buys the right to purchase a specified amount of an antibiotic at a later date for a specified price. Purchasing takes place during the early development phase of the technology, which allows for the spreading of risk between the developer and the purchaser. If the product does not reach the market, the purchaser has paid only the cost of the initial option contract and has no further obligations. If the project is terminated following problems during clinical trials, the purchaser retains access and joint ownership of the early findings of the research conducted using the funds from the option. The purchaser would therefore have joint rights to any later antibiotic based on that initial research. The COV model is like most pull mechanism in that it only gives the option to buy rather than a commitment to buy and thereby places substantial risk on the developer. However, the fact that the purchaser pays a premium early on in the development phase compensates for some of this demand-side risk.

In providing early funding to developers, the COA may lower barriers to entry and provide crucial funding for SMEs. Also, in contrast to other pull mechanisms such as AMCs and prizes, the COA spreads out the cost of drug purchase, which may be

more fiscally feasible. This increased feasibility is also likely to have knock-on effects in terms of increasing the credibility of the scheme by improving the chances that the funder can comply. Also, the quality marker within the model crucially allows for the size of the reward to be determined as a function of the type of product that is developed, more for innovative therapies, and less for me-too or follow-on drugs. However, the COA also has some shortcomings. For example, it hinges on thorough evaluation of the potential drugs, and—with asymmetry of information—this may hinder efficient allocation of resources to different projects. Also, the model allows potential gaming the system by developers as they could, in theory, take the early seed money and then prematurely terminate the project if it becomes more expensive than expected or less viable. However, reputation concerns could play an important role in preventing such offences. Also, when the number of call options purchased has been used up, the antibiotic returns to full price, instead of marginal cost of production. This would have a negative effect on prices for antibiotics in developing countries, which did not take part in the option scheme unless developed and developing country markets were appropriately segmented. One could argue, however, the higher prices in developed countries could help prevent over-diffusion and consumption of the product. Finally, the presence of sunk costs in certain projects may unduly influence organisations to purchase sub-par drugs when other, better options may have become available in the interim. However, despite these limitations, the COA model appears to be the most promising in terms of its ability to make antibiotic research attractive.

APPENDIX A: Global vaccine research

Table A. New Vaccines against Infectious Diseases: R&D status as of February 2006.
Adapted from WHO Initiative Vaccine Research ³⁶⁹.

Pathogen	Vaccine mechanism	Developer	Stage
<i>Streptococcus</i> Groups A (<i>S pyogenes</i>)	26-valent M protein N-terminal epitopes + conserved protein Spa	ID Biomedical	Phase II
	J14 moiety fusion peptide combined with 7-valent determinants on polymer backbone	Queensland Inst of Med Res, Australia	Ready to enter Phase I
	C-terminal half of M protein expressed as a fusion protein on surface of <i>Streptococcus gordonii</i>	Rockefeller Univ, New- York/ SIGA	Phase I
	Recombinant fusion peptide containing N-terminal M protein fragments from Group A Strep serotypes 1, 3, 5, 6, 19, and 24	Center for Vaccine Development, Baltimore, USA	Phase I
<i>Neisseria meningitidis</i>	Group A PS conjugate	Serum Institute of India	Phase I
	Trivalent A, C, W135 PS	GSK	Phase II
	Tetavalent PS conjugate	Sanofi-Pasteur	Licensure
	Heptavalent DPT-HepB-Hib-MenA/C conjugate	GSK	Phase II
	NZ Por A outer membrane vesicles	GSK	Phase II
	New membrane protein subunit	Chiron / Auckland Univ	Phase III/IV
	New membrane protein subunit	Chiron ; Microscience	Preclinical / Phase I
<i>Streptococcus pneumoniae</i>	Conjugate 13-valent (tridecavalent) vaccine containing serotypes 6A and 19A	Wyeth (Prevenar 13™)	13 March 2009 Biologic License Application (BLA) submitted to FDA. 'Fast Track' status.
	Conjugate 9-valent vaccine	Wyeth (Prevenar)	End of Phase III
	Conjugate 11-valent vaccine	Sanofi-Pasteur;	Phase III
		GSK Phase III completed (old formulation)	Phase II (improved formulation)
	BVH3/11V fusion protein	ID BioMedical	Phase I completed
	PspA+PsaA	Sanofi-Pasteur	Phase I in adults
	Pneumolysin, PspA, adhesins, PiaA, PiuA, etc, subunit or DNA vaccines	Various academic institutions	Preclinical / Phase I

C. difficile	clostridium difficile candidate vaccine	Acambis now part of Sanofi-Pasteur	Phase II
Enterococcus	E. faecalis and E. Faecium (enterococcus)	vancomycin	
S. aureus		StaphVAX (Nabi Biopharmaceuticals) V710 (Merck & Co/Intercell) SA75 (VRI plc)	StaphVAX, was based on patented technology that Nabi had licensed from the Public Health Service/NIH

APPENDIX B. Possible funding mechanisms for a COA scheme

The EC has mandated the European Investment Bank (EIB) and the European Investment Fund (EIF) to manage 2 financial tools aiming at supporting and encouraging innovation within the EU:

Risk sharing finance facility (RSFF):

Partly to address the dearth of funding for R&D – particularly the more high risk – in the EU area, the EC and the EIB set-up the RSFF under the umbrella of the knowledge economy to which the EIF also contributes. The RSFF programme runs for 2007–2013 the same as its supporting programme the seventh framework programme (FP7) the main financial tool through the EU supports R&D³⁷⁰. Each party is expected to provide up to €1 billion with this extra lending expected to attract a 4 to 6 times the community funds provided to the facility³⁷⁰ possibly upto €10 billion³⁷⁰. For each loan an average of 20% of the volume is set aside for risk coverage and for loans less than €7.5 million the RSFF is available indirectly through intermediary banks (and other institutions) in member states³⁷⁰.

The requirement for loan beneficiaries to be creditworthy (albeit riskier) limits the eligibility of many smaller SMEs and biotechs who perhaps do not have revenue-yielding products already on the market or the capacity to carry-out clinical trials within Europe. Research, Development and Innovation (RDI) projects and tend to be multi-annual (3–4 years)³⁷⁰. RSFF can support a range of RDI activities, from: basic research through applied and proof of concept to feasibility studies. Eligible investments can be tangible (construction and equipment) or intangible (salaries, operating cost, management and support staff, utilities, consumables, IP acquisition) assets and can cover up to 50% of eligible investments [1]. The need for a company to be ‘creditworthy’, in reality, means the loans are infrequently suitable for SMEs who don’t already have a pipeline yielding significant revenue. Due to the smaller loans being administered through intermediaries (such as banks) it is likely that the eligibility criteria are even more stringent for these smaller loans.

Upto the end of 2008 23% of RSFF funds had been allocated to life sciences, although predominantly to mid-cap companies such as Solvay and Teva. Very few SMEs or biotech companies have been successful in securing these loans with a notable exception of Pharmamar a Spanish biotechnology company with successful products launched aswell as in pipeline, which received a €30 million RSFF loan to assist them in continuing their work looking into innovative anticancer treatments from marine origin³⁷⁰.

Competitiveness and Innovation Framework Programme (CIP):

A €1.1 billion facility (€160 m of which is earmarked for eco-innovation) to encourage the competitiveness of European enterprises, support innovation and provide better access to finance for SMEs through a venture-capital style mechanism. The facility is split between venture capital and guarantees covering the period 2007–2013. The former capability being provided by the High-Growth and Innovative SME Facility (GIF; €550 million) and the latter by the SME Guarantee Facility (SMEG; €506 million). The EU Guarantees are provided by the EIF on behalf of the EC and cover a part of the risk of the financial intermediary relating to the relevant loans or lease transactions³⁷⁰.

- The GIF supports innovative SMEs through provision of risk-capital in their early stages through GIF1 (EIF investing 10–25% of total funds raised by the intermediary venture capital fund) and their expansion phase through GIF2 (EIF investing 7.5–15% by total funds raised). Additionally, for new funds likely to have a particularly strong catalytic role investments can be up to 50% in GIF1 and 25% in GIF2 to a maximum of €30 million. Thereby providing important leverage for the supply of equity to these companies³⁷⁰.
- Through the SMEG the EIF supports SMEs by providing co-, counter, and direct guarantees to financial intermediaries providing loans, mezzanine finance and equity to SMEs. The objective of the SMEG Facility is to reduce the particular difficulties SMEs face in accessing finance, either due to the perceived higher risk or to lack of sufficient collateral³⁷⁰.

APPENDIX C. Innovative Medicines Initiative (IMI) Call One

As indicated in Section 6.1.3 of the text, below is a full list of projects selected from the first IMI Call for Proposals along with their expected outcome (source IMI website).

1. *Non-genotoxic carcinogenesis*

Project is expected to provide proven reliable role of early biomarkers in the prediction of cancer development.

2. *Expert systems for in silico toxicity prediction*

Project is expected to provide in silico prediction and expert systems for secondary pharmacology prediction and for pure chemistry-related toxicity.

3. *Qualification of translational safety biomarkers*

Project is expected to provide new specific and sensitive safety biomarkers and their respective assays for human sample for improved predictivity between non-clinical and early clinical studies.

4. *Strengthening the monitoring of the benefit/risk of medicines*

Project is expected to provide new methodologies in pharmacovigilance and pharmacoepidemiology

5. *Islet cell research*

Project is expected to provide better understanding of β -cell proliferation, differentiation and apoptosis permitting the identification of approaches to preserve β cell function aiding the development of preventive and curative treatments for diabetes types 1 and 2.

6. *Surrogate markers for vascular endpoints*

Project is expected to provide biomarkers/surrogate endpoints for micro- and macrovascular hard endpoints in diabetes clinical research and new in vitro or in silico tools to test novel therapies.

7. *Pain research*

Project is expected to provide improved understanding of the pathways and mechanisms mediating different kinds of pain, and markers for patient stratification and quantitative pain assessment for efficient testing of new analgesics.

8. *New tools for the development of novel therapies in psychiatric disorders*

Project is expected to provide blood/CSF markers, imaging and/or electrophysiological measures suitable for clinical assessments to be used for preclinical models with sensitive pharmacodynamic markers that are closely linked with psychiatric disorders

9. *Neurodegenerative disorders*

Project is expected to provide translatable animal and human volunteer models for better prediction of clinical efficacy of new therapies in patients with Alzheimer's disease, Parkinson's disease and multiple sclerosis.

10. *Understanding severe asthma*

Project is expected to provide a large longitudinal patient cohort enabling validation of novel biomarkers and development of diagnostic criteria for mechanistic and therapeutic trials.

11. COPD patient recorded outcomes

Project is expected to provide a framework for better understanding of patients' experience of chronic obstructive pulmonary disease (COPD) leading to better strategies for measuring clinical trials outcomes

12. European Medicines Research Training Network

Project is expected to provide a European biopharmaceutical research training platform providing a sustainable academia-industry cross-disciplinary approach to efficient organisation of training courses on emerging science and technologies across Europe.

13. Safety sciences for medicines training programme

Project is expected to provide training programme integrating all safety-relevant disciplines linking animal and human/patient safety data thereby facilitating a more holistic evaluation of new medicines

14. Pharmaceutical medicine training programme

Project is expected to provide establish a network of academic centres that delivers postgraduate training programmes in pharmaceutical medicine including quality management of the processes and outcomes.

15. Pharmacovigilance training programme

Project is expected to provide customised training programmes for professionals in pharmacovigilance from industry and regulatory agencies to support proactive pharmacovigilance and risk management of medicines.

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