INDEPENDENT REVIEW ON ANTI-MICROBIAL RESISTANCE

REGULATION-INNOVATION INTERACTIONS AND THE DEVELOPMENT OF ANTIMICROBIAL DRUGS AND DIAGNOSTICS FOR HUMAN AND ANIMAL DISEASES

MAIN REPORT

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SUMMARY

This report contributes to the Review on Antimicrobial Resistance chaired by Jim O'Neill[1] and considers regulation-innovation interactions, including whether, to what extent, and how, regulatory system adaptation can inhibit or incentivise the development of antimicrobial (AM) drugs and in vitro diagnostic devices (IVDs). Although its focus is mainly on the EU and the USA, its findings are relevant to the widely varied nature of AMR-related problems, in different diseases and different regions of the world.

Over the past decade, given the prevailing mix of incentives and deterrents and the lack of new leads emerging from scientific research, very few novel antimicrobials have been developed. An important policy lever to incentivise innovation in drug development has been through adaptation of the regulatory system, for example through fast-tracking or support for 'orphan drug' products with societally desirable properties. This report focuses on the regulatory systems of the EU and the USA, these being the systems that other nations look to as models of best practice when developing their own regulations.

New AM drugs that are brought to market in future are likely to have a narrower spectrum of action or, for reasons of stewardship, a narrower recommended use. This will require the development of new IVDs and better microbiological processes for rapid identification of microbial strains. Regulatory systems for innovative diagnostic technologies will require to be at least as adaptive as those for the drugs themselves if the complex range of future AMR-related problems is to be addressed effectively.

In addition to our focus on regulatory systems, our research identified the nature and scale of future markets for new AM drugs as a major deterrent to innovation in this area and thus to the resolution of antimicrobial resistance (AMR) problems. This will require a focus on innovative funding models to support product development for such markets on an equivalent scale to regulatory adaptation.

Drawing on evidence from: (i) a literature review; (ii) interviews with senior regulators; and (iii) interviews with senior industry managers, this report considers the interactions between innovative developments related to AM drugs and associated IVDs and the regulatory and policy drivers that relate to them. Different issues will arise depending on whether the innovation concerned is disruptive/path-breaking or incremental/path-dependent for the company developing it. This report has adopted an interdisciplinary approach that has been developed over the past fifteen years by staff at the Innogen Institute for health related issues (regenerative medicine, stratified medicine, drug development per se).

In considering the need to develop more new AM drugs, it is necessary to consider the degree of novelty and to distinguish between novel drugs and novel drug classes. Between the mid-1990s and early 2000s, industry drug discovery based on genomics and high-throughput screening failed to discover any attractive broad spectrum candidates. Also, regulatory systems at that time made clinical trials very difficult, particularly for the narrow spectrum drugs which appeared more discoverable than broad spectrum agents, but with only mediocre profit potential. The majority of the relatively few new molecules that are in clinical development or have come to market recently have been members of existing drug classes, so are likely to experience similar AMR problems to currently available drugs.

Considering the impact of regulatory systems on drug development, for the scenario calculated in Section 4, the total R&D cost per drug following the conventional approval route, including the cost of failed projects and the time cost of money, was ~$2190m, and the direct out of pocket cost was $975m. In contrast, the average R&D cost per pathogen-specific drug approved via the recently adapted regulatory pathway described in Section 3, again adjusting for failures and the cost of capital, would be 'only' $752m, and out of pocket cost $419m. These R&D cost estimates are

[1] Review on Antimicrobial Resistance. Antimicrobial Resistance: tackling a crisis for the health and wealth of Nations, 2014.

extremely sensitive to failure rate assumptions and these are, in turn, sensitive to the quality of preclinical drug candidates, their novelty, regulatory hurdles, and the diagnostic tools available to enrich trials for patients whose pathogens are likely to be sensitive to the drug in hand. Nevertheless these regulatory adaptations do appear to be encouraging at least some companies to begin to invest in discovery and development of AMs. The prevailing view among industry interviewees for this project is that a lack of financial incentives is now the main barrier to AM innovation, rather than regulatory constraints.

IVD industry interviewees reported that the EU regulatory system is more supportive of innovation than that of the US. In contrast to the global pharmaceutical market, the scale of US/EU regulatory differences means that IVDs are sometimes brought to market and sold successfully in the EU, without seeking or gaining approval in the US. Over the next 5 years, however, EU regulation is likely to become more stringent and there was concern among interviewees that this will increase development costs for products that already struggle to gain a place in health service markets.

Main conclusions

1. Given the probable lack of new broad spectrum AM drug classes for future development, along with lower technical barriers to the discovery of narrow spectrum agents, accurate, rapid, and inexpensive diagnostic tools will be required to detect the nature of the infectious agent and its susceptibility to specific AMs.
2. There has already been considerable regulatory adaptation in the US and the EU to enable more rapid and cost-effective development of novel AM drugs. According to our calculations these adaptations may have more than halved the development cost of a narrow spectrum AM drug with a novel mode of action[2]. Most of the interviewees from both large and small companies believed that regulatory constraints on the development of AM drugs are no longer an important factor inhibiting innovation.
3. In the context of IVD development where the more demanding US regulatory system was seen as currently problematic, and where IVD regulations in the EU are set to become more challenging in future, it will be important to ensure that any such changes can be tailored to support innovation in the development of AM-related IVDs while continuing to ensure safety and efficacy.
4. Uncertainty about future markets for AMs and associated IVDs was seen as the most important factor currently discouraging company investment in development of AM drugs and IVDs. HTA bodies, such as NICE in the UK, along with health service purchasers, were seen as overly conservative and unlikely to appreciate the benefits of novel IVDs. However, the most serious constraint of all was related to the presumption that a novel AM that is effective in cases of AMR will be reserved for use in the most serious cases. Thus future profits appear small, and returns on the investment that would be required to bring the drug to market appear poor.
5. AM use in animals is likely to be increasingly restricted, particularly in the case of drugs with a novel mode of action that will be useful for treatment of human cases involving AMR. This is seriously curtailing commercial R&D for AM drugs for use in animals. As a result, health care in animals is likely to be increasingly based on a range of alternative options including vaccines, genetics and breeding, potentially opening up new commercial opportunities. Restrictions on AM use should also create opportunities for greater use of IVDs but this is countered by the current regulatory situation, with low barriers but wide variation across countries, coupled with a lack of market incentives.

[2] Although all cost estimates are extremely sensitive to assumptions about clinical development success rates – see Section 4.

Suggestions for further investigation

Innovative business model foresighting

If the regulatory adaptations delivered to date are not sufficient to enable a small company to develop an AM product all the way through to a market without some form of collaboration with a multinational company (as seems to be the case), and if narrow spectrum or more radical innovations are too path-breaking to be attractive to a multinational company, then there is a chance that they will languish as potentially interesting developments that never make it to a market, for example transcription factor traps or phage based products. It will be important to adopt interdisciplinary approaches, of the kind suggested in this report, to explore future scenarios involving the development of novel business models for the optimal exploitation of new scientific knowledge in the context of future regulatory adaptation, innovative funding models and market developments. Such scenarios will need to take account of the variability in the nature of the AMR challenge for different disease organisms, in different disease contexts and in different regions of the world, particularly Asia, Africa and South America. These scenarios could also consider under what circumstances some potentially disruptive developments in AM or IVD could lead to a sufficiently broad range of different classes of narrow spectrum AMs, to enable their use to be stratified, e.g. between human and animal markets, as a means to resolve the lack of innovation incentive arising from severely restricted markets for novel products.

Market related incentives

There is a general view that direct public involvement in the creation of markets or other such support for innovation is likely to distort prices and cause private capital to withdraw. However, an alternative perspective has recognised that, *for truly path-breaking technologies*, the state has always played a role in shaping technology trajectories and creating markets, generating economic activity that would not otherwise have happened and opening up new markets that private investors can subsequently move into. It will be important to keep an open mind, if and when path-breaking, disruptive technologies emerge to meet the AMR challenge, on the need for innovative funding models with a significant public or philanthropic component as part of the overall support system for their development, along with an element of state-supported market creation and targeted adaptive regulation.

Public sector support for diagnostics as an economic complement to commercial drug R&D.

Better pathogen identification could reduce the cost of AM drug trials. For example, for an idealised example and holding all else equal, doubling the proportion of subjects recruited into a trial with a pathogen that should be sensitive to the experimental drug can reduce the required trial size by as much as 75%. Better diagnostics could also create new drug markets, particularly for narrow spectrum drugs. Diagnostic R&D appears to be between one and two orders of magnitude less expensive than drug R&D. However, diagnostics are less profitable than drugs, and adoption and reimbursement are problematic. There may be a case for major public sector investment in diagnostic technologies and microbiological services that are most likely to reduce the cost of commercial drug trials, and thus stimulate commercial drug investment.

Public sector support for sample banks to reduce the cost of diagnostic test validation.

One of the main barriers to R&D for IVDs is getting samples for test validation. Public sector institutions would be well placed to work as sample collectors and repositories at relatively low incremental cost and could be encouraged to collaborate with private sector test developers.

Precompetitive preclinical models for new therapeutic technologies.

Work in preclinical development (regulatory requirements for toxicology and safety, animal models of disease, drug absorption, metabolism, excretion, drug-drug interactions, routes of administration and formulation) is easier for therapies for which there is long commercial and regulatory experience. However, for new therapeutic technologies such as bacteriophages or transcription factor traps, there are few existing standards. Agencies such as the MRC and

Wellcome Trust could devote more funds towards the development of the preclinical models that are a necessary pre-requisite for regulatory scrutiny of potentially disruptive technologies.

Analysis of the commercial assumptions of firms that are investing in antimicrobial R&D today.

It is important to characterise the clinical and late preclinical pipeline of antimicrobial drugs to understand better the commercial opportunities that attract current investment and what this means for the design of future incentives for AM and IVD development.

Creating and maintaining AMR data resources.

A secretariat could be established that collates and publishes on a timely basis data likely to be of use to a wide range of people working on the AMR problem but which are currently scattered. For example, those engaged in AMR policy should be able to obtain information on drug pipeline status, including AM drugs in clinical development, the indications for which they are being tested, their phase status, and their mode of action. This could then inform changes in regulation, technology, or financial incentives. Such information, if stored on an open portal would allow sharing of information amongst all AMR interested parties.

AM and IVD developments for veterinary use

Improved information will be needed on: the extent of AMR transfer relevant to human disease control from animal sources, particularly arising from companion animals; the potential for an increased contribution to global AMR problems for human disease control where animal production is transferred from the EU to less restrictive regulatory jurisdictions; and any change in the risk of zoonotic disease (non-AMR) in human populations arising from reductions in AM use in animals. Additional research could usefully focus on alternatives to AM drugs for animal disease control.

1. Introduction

The ESRC report on Antimicrobial Resistance (AMR) (ESRC, 2014) emphasises the need for solutions that integrate knowledge and understanding of innovation communities, regulatory bodies and governance processes as they interact with the economic and other incentives that then determine the nature of viable industry business models. The report of the UK Chief Medical Officer (Davies, 2013) that formed an important part of the background to this ESRC report focused mainly on scientific research related to the emergence of AMR-related problems, disease surveillance and the use of genomics-related rapid diagnostic devices, along with vaccine developments. There was no reference in the Davies report to the development of new antimicrobial (AM) drugs, apart from a brief reference to the need "… to support small businesses that could spin out new therapeutic breakthroughs from academic research" and to bridge the gaps between researchers, clinicians and policy makers so as to improve the implementation pathway. However, the related report from the UK Department of Health (DH) and the Department of Environment, Food and Rural Affairs (Defra) (DH & Defra, 2013), covering both human and animal related issues, identifies 'Development of new drugs, treatments and diagnostics' as one of seven Key Areas for Future Action and recognises low commercial return on investment, the scientific difficulty of finding new active agents, and the cost, complexity and (in some cases) uncertainty of regulatory processes as key constraints on the development of novel AMs.

Coping with the complexity of the AMR problem will require integration of measures to address where and how AMR is acquired, and how its progression can be moderated, particularly through adjustments in the behaviour of medical professionals and patients and their use in primary care and hospital settings. Analysis of this broader context is outwith the scope of this report but could usefully be informed by the 'drivers-sources-pathways-outcomes' model developed for risk analysis in the UK Foresight programme *Detection and Identification of Infectious Diseases* (Brownlie *et al.*, 2006; Tait *et al.*, 2006).

Section 2 of this report provides a baseline integrated analysis; sections 3 and 4 deal with AMR problems and the regulation and development of new AM drugs in the context of human disease control; section 5 covers AMR issues as they relate to animal disease control, particularly in the context of human/animal disease interactions (British Veterinary Association (BVA), 2013)[3]; and section 6 brings together the various aspects dealt with in the report and suggests further research needs in these areas.

Our research has focused on regulation-innovation interactions, particularly whether, to what extent, and how, regulatory systems can inhibit or incentivise the development of AM drugs. We also considered the future markets for new AM drugs that may be developed in the context of the AMR problem and the related need for innovative funding models to support product development for such markets. Until recently, given the prevailing mix of incentives and deterrents, large pharmaceutical companies had the capacity to develop new antimicrobials but little incentive, while smaller companies had the incentive but not the capacity (Tait, 2007).

An important policy lever to incentivise innovation in drug development generally has been through modification of the regulatory system, for example through fast-tracking or support for 'orphan drug' products with societally desirable properties (Milne and Tait, 2009). Given that the AMR problem is global, international solutions will be required. However, this report focuses on the regulatory systems of the EU and the USA, these being the systems that other nations look to as models of best practice when developing their own regulations.

As we describe in Section 3, there has recently been substantial revision to regulatory systems in the EU and USA with the aim of encouraging the development of novel AM drugs. We consider the

[3] We also considered briefly the role of vaccines in resolving AMR-related problems. However, the expected treatment regimes, business models, product development pathways, regulatory issues and markets are all very different from those of AM drugs, requiring a different integrated analysis approach. Therefore, although vaccines will be an important component of our future ability to meet the challenges of AMR, analysing fully this potential was beyond the capacity of this short project.

extent to which this is resulting in the development of more innovative products, whether further adaptation of regulatory systems might be required, and what companion measures, particularly in the nature of future markets and innovative funding models, might be needed to incentivise innovation in this area.

Producing more effective new antimicrobials will be only one component of the answer to the AMR problem and an important part of our analysis is the parallel development of new in vitro diagnostic devices (IVDs) for rapid identification of microbial strains. Adaptive regulatory systems as they apply to innovative diagnostic technologies will also contribute to the overall mix of incentives and constraints supporting resolution of the AMR problem.

Policy and regulatory systems may need to become even more adaptive and flexible than they are today if we are to meet the AMR challenge and we will also need related incentives to de-risk further the development process and pathways for novel approaches to the AMR problem. In particular, this may include new approaches to market creation and management and devising innovative funding models where current conventional models are failing (Omidvar *et al.*, 2014, submitted to ESRC).

Three supplementary reports, (1) *An Evaluation of Drug and IVD Regulation* by John Purves, (2) *An Evaluation of Drug and IVD Industry Views* by Jack Scannell, and (3) *Veterinary Antimicrobial Drugs and Diagnostics,* are attached to this report by Jack Scannell and Ann Bruce. They describe in more detail the literature reviews and interviews with key players in regulatory and industry communities that are summarised in Sections 3, 4 and 5 of this report.

2. Research approach and background

2.1 Research approach

This report draws on evidence from:

(i) literature reviews covering academic research, including journal publications and reports, policy papers and reports from government departments and non-government organisations, and reports from company sources;

(ii) interviews with senior regulators to develop an understanding of recent and potential future adaptations of regulatory systems to support the development of solutions to the AMR problem;

(iii) interviews with senior industry managers to inform our analysis of the important constraints and incentives in AM and IVD development and to highlight opportunities to adapt regulatory systems or other incentives or constraints in a manner that could support the future development of AMs.

We analysed the role of regulation as a driver of current global trends in AM development for human and animal use and, in consultation with pharmaceutical companies, explored how this impacts on current AM and IVD development pathways and business models, in multinational companies, medium-sized and smaller enterprises. Recent changes to regulatory systems, including the work of the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR, 2014), may already have begun to influence the amount of incremental innovation in antibiotic development and may be able to support further incremental innovation. However, more fundamental adaptation in regulatory systems may be needed to deliver the path-breaking innovation that could lead to radical new solutions to the AMR problem (Tait, 2008) and this is only likely for products related to human disease.

2.2 Policy interactions relevant to disruptive and incremental innovation

Considering the interactions between innovative developments and the regulatory and policy drivers that relate to them, different issues will arise depending on whether the innovation concerned is disruptive/path-breaking or incremental/path-dependent for the company developing it (Tait, 2007).

Incremental or path-dependent innovation

Most life science innovations have been 'incremental' or path-dependent in that they are easily accommodated within a sector's current innovation model; the challenge is to find the right niche within that model for a specific innovation. Incremental innovation enables stepwise improvement in a company's current innovation system, creating competitive advantage within the same sector without challenging the prevailing business model, and the value returned to the innovator can be significant, although less than for disruptive innovation. However, the innovation process is also much less risky than for disruptive innovation. The innovation is likely to be developed by an existing large multinational company and there is usually a clear regulatory precedent, avoiding a major source of uncertainty in the development of a disruptive innovation.

Disruptive or path-breaking innovation

Innovation that is path-breaking or 'disruptive' steps outside existing paradigms, leading to discontinuities in innovation pathways, to major shifts in product types and their place in the market, and even to the creation of new industry sectors or radical re-structuring of existing sectors. Such developments cannot be accommodated within a company's current business model. They require new areas of R&D, new modes of production, new routes to market and there is often no clear regulatory precedent. The innovation process is more uncertain but has the potential to generate significantly greater value than for incremental innovation. However, it is more difficult to find investors who are willing to support such developments, partly because of uncertainty about future regulatory requirements, their costs and timescale, and also future funding models and markets.

Policy support for innovation

The more demanding the regulatory systems in a sector (as is the case for health care) the more the innovation strategies of the sector are dominated by those of large multinational companies, and therefore the greater the preponderance of incremental innovation (Tait, 2008). The difficulties faced by multinational companies in developing disruptive innovations and the challenges that largely prevent smaller companies from doing so explain the relatively poorer innovative performance of the life sciences across most innovative sectors, compared for example to information and communication technologies.

Disruptive innovation is more likely to lead to revolutionary improvements in healthcare or to address unmet clinical needs and the tension between the incentives for life science companies to develop path-breaking innovation and their capacity to do so is one reason for the focus on regulation and policy initiatives that could improve the innovative capacity of companies developing AMs and IVDs.

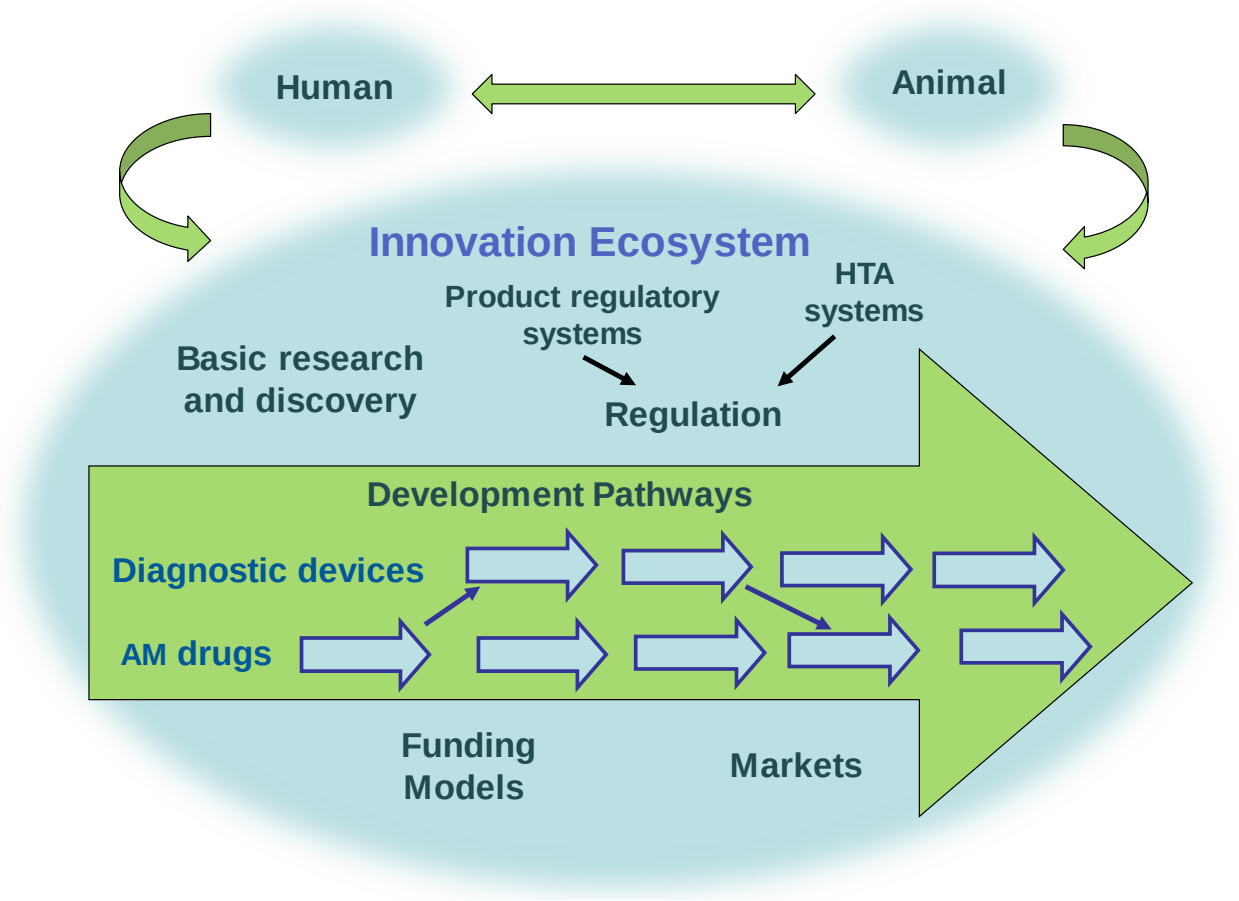
A governance framework to address the problems raised by these policy-innovation interactions would need to distinguish between the different challenges presented by path-breaking and incremental innovation. For example, for a path breaking innovation it is important to consider: how soon in the emergence of a new technology it is appropriate to establish a regulatory pathway; whether there is a regulatory precedent and if so how appropriate it may be; what problems might emerge in its application; and how it can be made adaptive to future scientific and technological developments.

For incremental innovative developments, accelerated approval is a potentially useful approach, requiring consideration of the circumstances in which such approval would be most appropriate, and the mechanisms that could be used to maximise benefits and mitigate risks. For both path breaking and incremental innovation, scientific research can also lead to innovative developments that could support smarter product regulation, for example by eliminating some aspects of a potential risk or by providing faster, cheaper or more ethical routes to generation of evidence on which to base regulatory decisions, as could be the case for some IVDs in accelerating AM drug development.

2.3 Factors relevant to the development of drugs and diagnostics to meet the AMR challenge

The main focus of this project is on the interactions between regulatory constraints or incentives and product development decision making by companies, relating these interactions to other aspects of the innovation ecosystem, which will have a significant impact on companies' willingness and ability to develop novel AM drugs and IVDs. Figure 1 shows the main elements of our baseline analysis, including parallel and occasionally interacting development pathways of AM drugs and diagnostic tools, embedded in an innovation ecosystem where we have identified: basic scientific research relevant to drug and diagnostic discovery; regulatory systems and their adaptation; health technology assessment (HTA) systems and related market size; and funding models for innovative narrow spectrum AM drugs and IVDs; as the most important elements for consideration here.

Figure 1. AM drug and diagnostic tool development pathways



Basic scientific research relevant to AM drug development.

Between around 1995 and 2005, major genomics-related investments by multinational pharmaceutical companies to identify AM drug targets along with high throughput screening (Payne *et al.*, 2007; Silver, 2011) failed to identify any new broad spectrum AM drug classes. These screening activities identified small numbers of narrow spectrum AM drug candidates but they have typically languished undeveloped. Bumann (2008) has suggested that 'nature' has already found all the broad spectrum drug targets, these being proteins that are vital to the survival of a broad range of bacterial species and which can be attacked by a molecule that can penetrate most bacteria. ('Nature' as used here refers to organisms like actinomycetes and fungi from which most antibiotic drug classes were first identified). Most products in current pipelines are relatively broad spectrum, are close analogues of existing drugs, and are members of existing drug classes

(Coates *et al*., 2011). There are few truly novel drug classes[4] in clinical development, yet these will be the products best able to meet the AMR challenge in the long run

Drug regulatory systems.

One starting point for this project was the perception by industry that the regulatory systems of the European Medicines Agency (EMA) and the US Food and Drugs Agency (FDA) were major barriers to the development of new AM drugs (Coates *et al.,* 2011; Rex *et al*., 2013; Mittra *et al.*, 2014). However, since approximately 2010 the regulatory agencies have become more pragmatic and the FDA has lowered statistical hurdles which previously meant trials had to be very large, and has relaxed patient enrolment criteria, which previously made it impractical to recruit patients into certain kinds of trial. Both the FDA and EMA have also clarified regulatory paths for new AMs to help patients with AMR related infections for whom there are few good treatment options.

Basic scientific research relevant to IVD development.

As with AM drugs, genomic-related science has not yet delivered the expected breakthroughs in the development of IVDs, particularly for point-of-care devices that can accurately identify infectious agents or measure the patient's response to infection (NIH and EU Directorate for Health Research, 2011). However, several new technologies could speed up pathogen identification and AM drug selection. PCR-based tests have been standard in virology for some time (e.g. for HIV and hepatitis C testing) and a range of commercial tests are now available to screen for bacterial species and resistance genes in some common infections. MALDI-ToF is a spectroscopic method that allows rapid identification of bacterial species. Next Generation Sequencing (NGS) is being piloted in public health laboratories but is not yet in routine clinical practice. When mature, NGS should allow identification of bacterial species, and provide a good estimate of likely AMR. Our starting assumption for this project, based on previous research (Mittra and Tait, 2012), was that innovative IVD development would be particularly sensitive to the costs arising from any increase in the demands of EU regulatory systems, because of the lower price commanded by diagnostic products and the greater complexity of the adoption context.

Regulatory systems for diagnostic tool development.

Regulatory complexity for IVDs arises when there are multiple arrays that test for a range of different pathogens simultaneously. Regulatory costs for IVDs are also a more significant disincentive for companies than those for new drugs, in part because of the lower overall value of the diagnostics market. Diagnostics are also generally reimbursed using cost-based rather than value-based criteria, which further reduces incentives for innovation (Goldman *et al*, 2013). The current EU regulatory system is generally considered to be less onerous than that of the US, where extensive clinical trials are often required for diagnostics, although changes designed to make the EU testing regime more rigorous are now under consideration. In the EU, regulatory systems are therefore not currently seen as a major barrier to innovation. FDA regulations are, on the other hand, seen as significantly inhibiting innovation in diagnostic development. Although regulatory approval for a minor modification to an existing device is relatively painless, registration of novel devices generally requires expensive and time consuming clinical trials. The result is that many devices are launched first, or only, in the EU.

Health technology assessment (HTA) and markets for products to meet the AMR challenge.

The market size for a narrow spectrum AM drug is likely to be insufficient to incentivise commercial R&D investment, even if the price per dose of AM were to be relatively high. Also with IVDs, markets are smaller and less lucrative than for drugs, making it unattractive to invest in such developments. This is an issue that arises more generally in the stratified medicine approach, which requires the combined use of drugs and diagnostic tools in order to deliver more targeted treatments. The relevant drugs and IVDs will each need to negotiate their separate regulatory hurdles (thus increasing development costs) while the reduction in remuneration that arises from

[4] We include antibiotic resistance breakers in the term "drug".

a stratified market can be exacerbated by HTA requirements imposed by purchasers (Mittra and Tait, 2012). In the EU, for IVDs, commercialisation and adoption issues are seen as much more serious constraints on development than regulation. Also, across EU countries the UK is seen as the least attractive country in which to market a new IVD due to purchasing restrictions in UK hospitals, given that diagnostics are generally reimbursed using cost-based rather than value-based criteria (Goldman *et al*, 2013).

Innovative funding models to support the development of products for un-met medical need.

There are many parallels between novel AM drugs and regenerative medicine (RM) therapies in terms of the difficulty of finding sustainable business models and viable pathways to the clinic. Given the relatively slow pace of development of RM therapies, the UK House of Lords Science and Technology Committee Report on Regenerative Medicine (HoL S&TC, 2013) identified regulation, the lack of viable business models, NHS procurement strategies, and HTA evaluation processes, among the barriers to the delivery of RM therapies. A recent report from the Innogen Institute (Omidvar *et al.*, 2014) considered how innovative funding models could contribute to enhancing the viability of future innovation pathways for RM therapies. The following conclusions from that report are also relevant to the AMR problem:

- Industry reluctance to invest in novel products may be well justified and inducements to develop specific products should take account of the reasons for this caution, including lack of effective business models, regulatory uncertainty, and uncertainty about future pricing and reimbursement models.
- The funding models that are most likely to work in the short term are those with a significant public or philanthropic element.
- Support for disruptive innovation may require government involvement in market creation and support.

This report considers how all of the above factors and interactions among them will affect the future development of AM drugs, particularly the need to meet the AMR challenge. It is clear that regulators have already begun to make significant adaptations to regulatory systems with the intention to facilitate the development of new AM drugs in view of the AMR crisis. However, similar regulatory initiatives have not been undertaken to support the parallel development of diagnostic tools. In the drugs context, the failure of very significant research programmes in multinational pharmaceutical companies to find new broad spectrum AM leads is pushing innovation pathways towards a stratified medicine approach, involving the development of narrow spectrum AMs and the parallel development of diagnostic tools to identify the susceptible organisms. However, here there are also disappointing levels of innovation despite advances in genomics related science.

Even in the absence of AMR, stratified innovation pathways for new AM drugs will require segmented markets with much lower returns on investment for the companies developing them, and companies are also likely to have to support the cost of development of the associated diagnostic tools. If a new AM drug is a candidate for the treatment of patients at serious risk from an organism that is AM resistant, such a product is likely to be retained for emergency use only and not to be made available on the general market. These market related factors are seen as considerably greater deterrents to innovation in AM drugs and diagnostics than current regulatory systems.

3. Regulatory systems relevant to the development of AM drugs[5]

This section considers the regulatory systems in the EU and the US that have an impact on AM development, including the basis of the general regulation of medicinal products and how that has evolved to the current position.

[5] See Supplementary Report 1 from John Purves for more detail on the analyses summarised here.

3.1 Regulatory background – pharmaceutical regulation in general

The basis of European legislation lies in the Regulations, Directives and Guidelines issued by the European Commission. These tools are generated by the Commission's services but they are subject to extensive consultation amongst the Member States and their experts and discussion at European Council level. For Guidelines which supplement the legislation there is additional consultation with a wider group of interested parties, including the pharmaceutical industry and trade associations. The Commission also undertakes impact assessments for new legislation to establish the need, costs and benefits. Such consultation is designed to strengthen the transparency and value of the Commission's proposals.

Other jurisdictions globally have their own legislation and administrative procedures to deal with the review of dossiers for Marketing Authorisations. In the 1980s, recognising the difficulty faced by the pharmaceutical industry in satisfying regulatory requirements from many different regions, where varying data requirements could cause problems in the manufacture and licensing of medicinal products, Japan, the United States and Europe collaborated with the pharmaceutical industry to harmonise regulatory requirements for quality, safety and efficacy through the International Conference on Harmonisation (ICH), set up in 1990. As time has passed, other regions including Brazil, Russia, India and China - the BRIC countries - have expressed interest in being involved in such harmonisation. Furthermore, since 2003 the EMA and the FDA have progressively worked more closely together on a wide range of topics, including antibiotics, and have offered parallel scientific advice to the industry at an early stage of product development.

Although there has been significant movement towards harmonisation at the level of scientific requirements, because of the distinct legislative and administrative procedures in different countries / regions, the outcome of the review of dossiers may vary. To establish a better understanding of the UK and European positions interviews were undertaken with EMA and MHRA staff, and information sought from web-sites and other relevant publications.

From these sources, it is clear that the review of dossiers for Marketing Authorisations (MAs) has evolved over the years. In the early 1980's, the review of data focussed primarily on quality, safety and efficacy, with little post-authorisation monitoring. However, feedback from physicians about adverse drug reactions (ADRs) arising from the use of medicinal products became increasingly important strengthening post-authorisation data. The review of dossiers has progressively matured and now includes, in addition to quality, safety and efficacy, Risk Management Plans (RMPs), benefit-risk judgements, post-authorisation commitments, pharmacovigilance and moves towards adaptive licensing. To exemplify these points:

- In parallel and with the advent of the Regulation on Advanced Therapy Medicinal Products (ATMPs), it was clear that both the size of the clinical trials and the corpus of data for review would be smaller, but that the use of such products would have much closer monitoring by specialist physicians / healthcare workers before and after treatment. This significantly strengthened post-authorisation control. It also stimulated reflection on the balance between the data submitted to support an application for an AM and post-authorisation control with emphasis on benefit risk judgements at the EMA Committee for Medicinal Products for Human Use (CHMP).
- These same factors may require consideration in the context of narrow-spectrum AMs. The situation would be similar and the patient data-base / corpus of data for review would also be reduced. In such situations, the patients would have much closer physician monitoring which might allow more permissibility regarding a smaller data base as reflected in the guideline issued by the EMA CHMP Efficacy Working Party (EWP) in 2009 and finalised in 2012 (CPMP/EWP/558/95 Rev 2).

Another factor influencing the review process is the structure and capacity within a regulatory agency (Cone & Walker, 2005; Liberti *et al.*, 2013). The Centre for Innovation in Regulatory Science (CIRS) Workshop on regulatory review incorporated international regulators and multinational pharmaceutical company representatives to focus on the best practices that underlie

regulatory decision making, thereby facilitating the transparent, timely, procedurally predictable and good quality evaluation of new medicines. Key points made in the report were:

- A good quality review of a marketing authorisation dossier is dependent upon the processes used by the agency and its quality management system (QMS). Regulatory agencies require clear and defined processes and consistent application supported by well-trained personnel.
- The review of dossiers is science driven – a good quality review depends on two aspects, the quality of the review and the quality of the decision making.
- A decision framework should be established to ensure good quality decision-making (Liberti *et al.,* 2013). Agencies should continuously evolve their processes and practices to ensure implementation of optimised tools and techniques.

In addition to the evolution of the review of dossiers described above, steps were taken by the EMA to study benefit – risk methodology (EMA, 2011a). The mission was "the development and testing of tools and processes for balancing multiple benefits and risks as an aid to inform regulatory decisions about medicinal products". A key task of a regulatory agency is the review of dossiers throughout the life-cycle of a product, balancing the benefits (desirable effects) of the product against the risks (undesirable effects). This task is multi-factorial and thereby complex in that regulators have to bring together all available evidence provided by experts and evaluate the corpus of data. Expert judgement may be feasible for specific tasks, but integrating these evaluations and deciding on the overall balance of benefit and risk is not easy. The objective of this EMA project, therefore, was to move towards a more structured approach by examining various models for benefit – risk analysis (Honig *et al.,* 2007). When the results of the final work packages are finalised – 5 work packages in all - the Agency will initiate public consultation and seek stakeholder views through a workshop before adoption of a final position. The outcome of this project will further strengthen regulatory decisions by refining the benefit - risk methodology.

The review procedure undertaken by assessors is dependent upon the scientific data submitted by the applicant and the robustness with which it is generated by the company and subsequently the soundness of the review. Scientific / clinical guidelines are therefore important in bridging the gap between legislative requirements and the data to be submitted in applications for marketing authorisations.

Guidelines developed in Europe and through the International Conference on Harmonisation (ICH) have allowed the generation of regional and international guidelines, resulting in a growing global understanding of data requirements between the industry and regulators and reducing some of the uncertainty in product development. Most of these guidelines are generally applicable to the development of medicinal products, whilst others are more specific addressing particular needs of certain products and potential public health matters.

3.2 Regulation of AM products

In the context of AM products, additional clinical guidelines have been prepared by the EMA and experts from member states. These include:

- Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 revision 2), which came into effect in January 2012 and
- Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections (EMA/CHMP/351889/2013), which came into effect in May 2014.
- Concept Paper on revision of the points to consider on pharmacokinetics and pharmacodynamics in the development of antibacterial medicinal products (CHMP/EWP/2655/99) and conversion to a CHMP guideline. The consultation period ended in May 2014.

The EMA held a workshop on AMR in November 2013 entitled "Best use of medicines legislation to bring new antibiotics to patients and combat the resistance problem". The workshop report covered the major issues discussed and recommendations (EMA, 2013a).

- the approval process for new AMs in Europe and whether the new requirements in the guidelines are considered adequate for fostering rapid development of new AMs;
- encouraging appropriate use of AMs as one of the tools to reduce the speed at which antimicrobial resistance develops;
- aspects of research and development, including the importance of efficient and early dialogue between industry and the EMA to facilitate the development of medicines.

Presentations at the workshop included the following views on the new guidelines:

- "If the PK/PD analyses are convincing, it may be possible to completely omit clinical dose-finding studies
- A single pivotal study may be acceptable to support an indication
- Adult efficacy data in some indications can be extrapolated to children
- Guidance for SmPC sections most pertinent to antibacterial agents
- Simplified section 5.1 on microbiology, resistance mechanisms, pathogens treated in clinical trials, others expected to be susceptible
- Regarding rare infections / pathogens (e.g. some MDR pathogens) efficacy data can be collected in standard RCTs and / or separate targeted studies
- Studies that enrol patients with well-documented infections regardless of which body site(s) is / are affected may be the only way forward
- When only limited data can be obtained randomised study designs are preferred but may not need to be powered for inferential testing
- Minimum number of treated cases to support a specific claim for treating certain MDR pathogens to be judged on a case-by-case basis."[6]

The information in guidelines and the various tools available to facilitate the development of products for the submission of applications for Marketing Authorisations provides evidence of the evolutionary, proactive and ongoing responsiveness of regulators to current needs.

Another step towards quicker access of special medicines such as AM drugs to patients has been highlighted on the EMA web site "Adaptive licensing is an approach to the authorisation of human medicines that is currently being discussed and developed" (Eichler *et al.,* 2012). This involves the staggered or progressive licensing of a medicinal product, where it may be used in a restricted population and when, through an iterative process, more evidence is gathered the marketing authorisation may be adapted to allow access to a broader patient population. Thus, there is growing scope to provide medicines for serious and unmet medical needs (Eichler, 2014).

The range of interests involved in adaptive licensing includes:

- EMA and other medicines regulators
- Patient and consumer organisations
- Pharmaceutical industry
- HTA bodies
- Organisations issuing clinical treatment guidelines – Public Health Bodies

[6] Extract from EMA Web-page November 2014 - Dr Mair Powell – MHRA

- Healthcare professionals
- Researchers
- Academics

Adaptive licensing may further facilitate the development, evaluation and benefit-risk analysis of antimicrobials depending upon the nature of the product concerned i.e. whether it is a narrow rather than a broad spectrum product.

The EMA, being aware of their primary objective of evaluating the quality, safety and efficacy of medicinal products and the different drivers for HTAs in the development of medicines, promoted early dialogue to address potential problems from the outcome of clinical trials, where there may not be agreement on design and desired outcome. This dialogue resulted in agreement on the need for workshops to bring together all interested parties, regulators, HTAs and developers, to share views and plan how to deal with issues which may arise, to facilitate speedier access to medicinal products for patients (EMA-HTA, 2013; 2014). A key step in the 2014 EMA/HTA Guideline was the development of Best Practice guidance for Pilot EMA HTA Parallel Scientific Advice procedures. Therefore opportunities are available to discuss any perceived issue that may arise in the development of an AM drug.

The EC has established a European HTA Network, a voluntary step to bring together the competent authorities responsible for HTAs, to minimise delays in access to medicines arising from different views and decisions between regulators and HTAs. Currently this has to be achieved at national level due to different health policies and funding models across EU member states.

3.2 Impact of regulatory adaptation on AM development

The primary determinants of the impact of regulation on the development of AMs, as for many other medicinal products, will be:

- speed of development by the manufacturer and applicant (SME or otherwise) for the marketing authorisation
- nature (special conditions which may be applicable) of the application and quality of the dossier submitted to the regulator
- review and benefit risk evaluation by the regulators

In the following list of initiatives, the first two items are dependent upon the applicant, who could use one or a number of tools to speed up development. An SME could use 1 to 8 and the benefits of 14 and 15. Points 9 to 13 could only be used if applicable. The understanding and use of these tools in preparing an integrated strategic plan for development will dictate the impact of these measures on any business model. A good plan will provide an aggregated saving in the development and review phases, but it is only possible in one or two cases to quantify the time saved: (i) *"accelerated assessment" where the review time could be reduced from 210 to 150 days; and (ii) depending upon the nature of the product 'rolling review' could afford a similar reduction.* The remaining items are dependent upon other factors including the quality of the dossier. For a standard pharmaceutical company, point 1 would not be applicable but all others could be used. Also the quality of the dossier would be expected to be significantly better than from a small company with limited resources, resulting in speedier review and approval.

1. Small and medium-sized enterprises
2. Innovative Task Force
3. Orphan Drugs
4. Development of scientific and clinical guidelines
5. Medical devices and In-vitro medical devices
6. Scientific advice and protocol assistance

7. Adaptive clinical trial design
8. Pre-submission meetings
9. Accelerated assessment
10. Conditional marketing authorisation
11. Exceptional circumstances marketing authorisation
12. Compassionate use
13. Rolling review
14. Evolution of the review procedure
15. Adaptive licensing

Progress has been made on the benefit risk evaluation by the regulator over the last 14 years. New opportunities are available for applicants and regulators to work proactively on the development of new products through the Innovative Task Force, Scientific Advice and pre-submission meetings and the special conditions for SMEs and orphan drugs with fee reductions / exemptions. The evolution of the review of dossiers over that period has enhanced the approach to benefit-risk assessment, culminating in the concept of adaptive licensing. Provided applicants contact the regulators early in development of an antibiotic and establish a sound strategic plan, taking into account the opportunities available for development and submission of the application for a marketing authorisation, then the time for development can be reduced significantly, as described in Section 4.

4. Development of new AM drugs: the industry perspective [7]

4.1 Factors influencing drug development

The dearth of new antibacterial drug classes with novel mechanisms of action over the last ~30 years follows from four factors: (i) the economic exhaustion of traditional methods for antibiotic discovery, based largely on the fermentation broths and extracts of soil-derived microorganisms (Silver, 2011; Balz, 2007); (ii) the failure between the mid-1990s and early 2000s of industrialised drug discovery based on genomics and high-throughput screening to discover attractive looking broad spectrum candidates (Payne, *et al*., 2007); (iii) regulatory guidelines that made clinical trials very difficult, particularly for narrow spectrum drugs (Rex *et al*., 2013; IDSA, 2011; Coates *et al*., 2011); and (iv) only mediocre profit potential (Sertkaya *et al*., 2014). In short, even where substantially novel drugs were discovered, they were unlikely to be developed.

Our interviews with industry managers suggest that, following recent regulatory adaptation (see Section 3), it would be feasible once more to bring drug candidates through clinical trials, although some frustrating differences remain between the EMA and the FDA. Clinical trials were a major barrier, perhaps *the* major barrier, to innovation. The FDA had placed such an emphasis on experimental purity that trials were unethical and impractical to run in certain specific indications, particularly HABP/VABP (IDSA, 2011; Coates *et al*., 2011). However, the FDA and EMA now guide the industry towards trials that are pragmatic. Some statistical hurdles have been lowered slightly, which means smaller trials. Trial recruitment criteria have become more permissive, which means it is easier to enrol patients.

Another regulatory innovation is pathogen-specific approval for serious infections with few good treatment options (FDA, 2013a, 2014a; EMA, 2013b, 2014a; 2014b). For the first time, this allows trials to pool patients with infections at different anatomical locations (e.g., pneumonias, wound infections, urinary tract infections, etc.) but which share a common infectious agent. Thus these clinical trials can show a positive risk-benefit profile against the pathogen, but are not powered to prove definitively that the drug has a positive risk-benefit profile for each particular kind of

[7] See Supplementary Report 2 from Jack Scannell, for more detail on the analyses summarised here.

infection caused by the pathogen. This regulatory change should make it much easier to run trials for pathogens that are rare, or which have rare drug resistance profiles (Rex *et al*., 2013).

The variety of development approaches that the FDA and EMA now propose to allow is illustrated in Table 1 (Rex, *et al*., 2013). The terminology here is different from that used by the FDA and EMA, but the classification system maps onto the current guidance from both agencies. Tier A corresponds to the conventional approach as exemplified by recent FDA guidelines for infections such as hospital-acquired (HABP) or ventilator associated bacterial pneumonias (VABP) (FDA, 2014), and with the current and more benign statistical hurdles and enrolment criteria. Tier C is the novel pathogen-specific approach. Tier D applies to drugs that cannot be tested for efficacy in humans for ethical or other reasons (e.g., potential bioterrorism agents such as anthrax). Tier B is a hybrid of Tiers A and C.

Table 1. Tiered Labelling Framework for Antibacterial Agents, from (Rex et al., 2013)

Typical efficacy data requirements	**How the drug would be marketed** **(**Note – our **emphasis** below**)**
Tier A. Two standard Phase 3 trials of drug X in infection Y. Additional indications for drug X can be added after single Phase 3 studies	Drug X is indicated for treatment of infection Y when proven or strongly suspected to be caused by drug X-susceptible strains of [list of pathogens]
Tier B. One standard Phase 3 trial of drug X in infection Y, plus small prospective studies and descriptive data focused on the tier C pathogen(s) in a range of standard infections	Drug X is indicated for treatment of infection Y and [list of studied infections from tier C database] when proven or strongly suspected to be caused by drug X-susceptible strains of [list of pathogens]. **Because data for drug X in these infections are limited, drug X should be used only if other alternatives are known or suspected to be less suitable**
Tier C. Small prospective studies for drug X and descriptive data focused on the tier C pathogen(s) in a range of standard infections	Drug X is indicated for treatment of [list of studied infections from tier C database] when proven or strongly suspected to be caused by drug X-susceptible strains of [list of pathogens]. **Because data for drug X in these infections are limited, drug X should be used only if other alternatives are known or suspected to be less suitable**
Tier D. Animal studies	Drug X is indicated for the emergency treatment of infection Y caused by susceptible strains of organism Z. **Drug X should not be used for infection Y unless other options are unavailable**

Table 2 gives estimates of the R&D cost implications of the Tier A and Tier C regulatory paths for antimicrobial drugs. Here we draw on estimates by Sertkaya *et al*. (2014); these figures were produced several years ago for the US Department of Health and Human Services to support policy development around the GAIN[8] provisions of the FDA Safety and Innovation Act, 2012. Based on discussion with the lead author, we understand that the figures were at the time subject to considerable scrutiny and debate.

We calculated the project lifecycle R&D costs implied by the Sertkaya *et al*. (2014) figures. The total R&D cost per drug approved for HABP/VABP, following the conventional approval route (Tier A), including the cost of failed projects and the time cost of money[9], and when viewed from the point of drug approval, is a hefty ~$2190m. The direct out of pocket cost ("OOP" in the table) is

[8] GAIN means "Generating New Antibiotics Now". A legislative attempt called the GAIN Act was subsumed within the Food and Drug Administration Innovation and Safety Act of 2012. For an overview, see Woodcock, 2014.

[9] We have followed Paul *et al*. (2010) and Sertkaya *et al*. (2014) and assumed an 11% real cost of capital for the entire R&D process. We have also expressed all costs in real 2012 dollars. The ~$2190m figure is also calculated by assuming that the costs are viewed retrospectively at the point of drug approval.

$975m. This is less than half of the "capitalized" cost of $2190m because R&D takes a long time (~12 years in this case), much of the money is spent on failed projects very early in the process, and because we assumed an 11% annual cost of capital[10].

In contrast, it is plausible that the average R&D cost per pathogen-specific drug approved via the new Tier C pathway, again adjusting for failures and the cost of capital, would be nearly two thirds less than for Tier A; at "only" $752m. The out of pocket cost in this case is $419m. The process takes less time (10.5 years vs. 12 years) so the spread between the out of pocket cost and the capitalized cost is also less than for the Tier A scenario.

Table 2. R&D Investment Cost Scenarios for New Antimicrobial Agents (in real 2012 dollars)

	Preclin	PI	PII	PIII	NDA/BLA sub.	Total R&D
Tier A / Conventional Approval Scenarios (Sertkaya, et al., 2014)						
HABP / VABP with conventional regulatory route						
Phase duration (years)	5.5	0.9	1.5	3.3	0.8	**12**
Time to commercial launch (years)	12.0	6.5	5.6	4.1	0.8	
Phase midpoint vs. launch (years)	9.3	6.1	4.9	2.5	0.4	
Real cost of capital	11%	11%	11%	11%	11%	
Time cost of money vs. launch	2.6	1.9	1.7	1.3	1.0	
OOP cost per successful candidate $m	21.1	9.7	15.6	101.4	2.0	**150**
Capitalized cost per successful candidate $m	55.4	18.1	25.9	130.9	2.0	**232**
Phase success probability	35%	33%	50%	67%	85%	
Candidates required per successful launch	30.2	10.6	3.5	1.8	1.2	
OOP cost including R&D failures $m	637.4	102.7	54.9	178.0	2.3	**975**
Capitalized cost including R&D failures $m	**1673.7**	**193.1**	**91.1**	**229.9**	**2.4**	**2190**
Tier C Approval Scenario						
Narrow spectrum agent (e.g., activity limited to Psuedomonas aeruginosa)						
Phase duration (years)	5.5	0.9	3.3	3.3	0.8	**10.5**
Time to commercial launch (years)	10.5	5.0	4.1	4.1	0.8	
Phase midpoint vs. launch (years)	7.8	4.6	2.6	2.6	0.4	
Real cost of capital	11%	11%	11%	11%	11%	
Time cost of money vs. launch	2.2	1.6	1.3	1.3	1.0	
OOP cost per successful candidate $m	21.1	9.7	10.4	67.6	2.0	**111**
Capitalized cost per successful candidate $m	47.3	15.5	13.6	88.2	2.0	**167**
Phase success probability	69%	54%	50%	67%	85%	
Candidates required per successful launch	9.4	6.5	3.5	1.8	1.2	
OOP cost including R&D failures $m	198.7	62.8	36.6	118.7	2.3	**419**
Capitalized cost including R&D failures $m	**446.2**	**100.9**	**47.8**	**154.9**	**2.4**	**752**

Sources: (Sertkaya *et al*., 2014; Rex *et al*., 2013), and Innogen project team analysis and estimates.

It is important to realize that these kinds of R&D cost estimates are *extremely* sensitive to failure rate assumptions. Failure rates are, in turn, extremely sensitive to the quality of preclinical drug candidates, to their novelty (Porges *et al*., 2014), to regulation, and to the diagnostic tools that are available to enrich trials for patients whose pathogens are likely to be sensitive to the drug in hand.

The high cost of the Tier A scenario follows from very high preclinical and phase I attrition rate assumptions. Thus ~30 preclinical projects are required for each drug launch (see the row "Candidates required per successful launch" in the table above). For the Tier C route, we have assumed industry average attrition rates for preclinical development and phase I trials. Thus, here we only require 9.4 preclinical candidates per drug launch. We think an assumption of higher success rates under Tier C can be justified for several reasons. Narrow spectrum drugs seem easier to discover so there should be more to choose from before initiating trials. There are also plausible

[10] To use different terminology, the net present value (NPV) of the average failure-adjusted costs when viewed from the point of drug approval is ~$2190. The NPV of these costs would of course be different if viewed from a different point in time. If viewed from the start of the R&D project, the NPV would be around $626m, based on the same direct out of pocket costs of $975m. However, the overall attractiveness of the R&D investment would be the same, because we would also apply the same higher discount to the value of any profits that the approved drug eventually yielded.

scientific reasons to expect narrow spectrum candidates to be less toxic to humans than broad spectrum candidates. We note that Sertkaya *et al*. (2014) used concerns about toxicity to justify the low success rates in preclinical development and Phase I trials.

No one knows, however, what the 'correct' assumptions should be for R&D starting today. It was perfectly plausible for Sertkaya *et al*. (2014) to assume high attrition rates leading to an overall cost of ~$2190m per approved drug. It is also plausible for us to assume low attrition rates via a Tier C path and a $752m figure. However, neither our cost analysis nor anyone else's provides a definitive cost figure. A precise consensus among analysts, investors, and drug companies on the average success-weighted cost of an R&D project starting today is unachievable. Different players will make different assessments based on the specific details of the opportunities they see, on their own experiences, and on the data they have at hand, and they will invest, or not, accordingly.

4.2 Financial incentives and the "average" drug

The view among our drug and biotechnology industry interviewees was that a lack of clear financial incentives is now the main barrier to antimicrobial innovation. As one of our interviewees put it: *"*[The major] *problem is lack of clarity on commercialisation route and pricing. No-one has yet got an antibiotic to market with modern 'orphan' type pricing. Even* [the most] *expensive antibiotics have never cost more than around $5000 per treatment…. This is not an easy problem given payer resistance and the way different kinds of drugs are reimbursed. So, for example, most antibiotics for serious infections are prescribed within the hospital setting and are not reimbursed separately from the rest of the treatment episode* [in contrast, for example, to most cancer drugs or high priced orphan drugs]*."*

There is a great deal of policy work already done on the incentive problem by academics, by the Innovative Medicines Initiative, Chatham House, the Office of Health Economics, and others. The range of financial incentive mechanisms is summarized in Section 2 of Sertkaya *et al*, (2014). Rather than rehearse these arguments, we want to make a slightly different point. As we suggested above, individuals deploying capital in the drug industry will disagree about the likely amount they will have to spend on R&D to bring candidates through discovery and clinical trials. They will also disagree on the value of future profits that can be tapped by investing in such R&D. Thus an incentive mechanism does not need very precise estimates of historical R&D costs or current antibiotic profits. It simply has to give enough investors and companies the belief that investing in AM R&D today will yield positive returns. The behaviour of companies and investors will provide the only reliable guide as to whether the incentives are plausible enough and big enough.

On this point, we note that money *is* being invested today by a reasonable number of companies on antimicrobial projects throughout the R&D lifecycle. The FDA has given around 40 'orphan-like' QIDP[11] designations to AM drug candidates in clinical trials over the last ~2 years (Woodcock, 2014). These companies and their investors presumably think they *can* make money by investing now. Some are investing in the hope that incentives will improve by the time their drugs approach market. However, others appear to believe that they can make money sooner without a change in incentive structures. Perhaps the incremental investment required to move their drug candidate towards approval is low. This would be the case, for example for drugs that are reformulations of existing agents, or for drugs which were previously abandoned late in the R&D process with acceptable safety and a large package of regulator-ready data[12]. Yet others seem to see attractive commercial niches.[13]. This could apply to antibiotics used for prophylaxis in rare diseases in the outpatient setting, for example.

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[11] The FDA Safety and Innovation Act of 2012 provides for 5 years of "orphan-like" market exclusivity to new antimicrobial drugs (Qualified Infectious Disease Products, or QIDPs) active against a list of ~21 "Qualifying Pathogens"

[12] Dalbavancin is an example here. The drug was submitted to the FDA for approval by Pfizer, but in 2007 the FDA required more data. Pfizer withdrew its application for approval and sold the rights to the drug to Durata in 2009. Durata then initiated 2 new Phase III trials which led to FDA approval in 2014, and QIDP status.

[13] While we have not interviewed the company and do not know their commercial intentions, we wonder if Aradigm may intend to position its inhaled ciprofloxacin as a high priced specialty drug. Their drug candidate appears to be intended for chronic

It seems important to understand why companies such as Cubist, Durata, Bayer, Aradigm, Actelion, Merck, and others are behaving as if they disagree with what appears to be the wider industry, academic, and health policy consensus on the unattractiveness of antibiotic R&D in the absence of additional financial incentives. It would also seem important to understand the kind of agents that these firms are likely to bring to market in the next few years. Will these drugs really bear on the AMR problem? Or is the current late stage pipeline dominated by drugs that may provide good investment returns without improving the AMR pharmacopoeia?

4.3 In Vitro Diagnostics (IVD) Regulation

The regulatory situation for IVDs differs from that for AM drugs. The European and American regulatory environments have major differences in both philosophy and detail. Among the IVD industry interviewees, the view was that the EU approach is more innovation friendly. Europe applies self-certification to nearly all IVDs, while the US requires formal review by the FDA for most IVDs. European evidence is expected to be auditable, but US evidence will be rigorously scrutinized before a test can be sold into the US market. Europe focuses more on narrow validation (i.e. the test must perform as it claims to perform, but it is then up to the market to decide whether or not the test is useful in the clinic), while the US places more emphasis on clinical validation (i.e. the test can generally only be marketed after it demonstrates validity under the real-world usage conditions it would face in the US (Mansfield and Gutman, 2005).

In contrast to the branded pharmaceutical market which is global, the scale of these US/EU regulatory differences means that IVDs are sometimes brought to market and sold successfully in the EU, without seeking or gaining FDA approval in the US[14]. Over the next 5 years, however, EU regulation is likely to take a step upward in terms of stringency. This was a concern for industry interviewees in that it will increase cost. Our analyses suggest that the cost increases will be small (only a few percentage points) as a proportion industry-level R&D expenses, but that the new costs will fall more heavily on some companies than others.

As with drugs, and despite the substantial costs imposed by the FDA, IVD regulation was not regarded as the *primary* barrier to innovation, even among relatively small companies with nascent products. Our interviewees identified four major challenges for IVD innovation.

- *User adoption*. Tests struggle for acceptance if they change significantly health service work patterns.
- *Cost and reimbursement*. IVDs can fail if they increase costs. However, they can also fail if they reduce total costs, but in doing so, they move costs from one budget to another.
- *Esotericism*. Manufacturers struggle to make money from *"expensive, low-volume, non-routine"* tests. This matters because most AMR variants are rare.
- *The high cost of validating IVDs for less common diseases*. For example, if it requires 100 positive samples from patients to validate a test, and if only 1% of patients carry the pathogen in question, then test validation will require 10,000 patient samples.

4.4 Scope for Adapting Regulatory Models

Our interviews suggested several ways in which the regulation of drugs might be improved further. Two suggestions seem particularly important.

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outpatient use in a patients with non-cystic fibrosis bronchiectasis. Chronic outpatient use means it will be directly reimbursed in the US by insurance companies who typically have limited pricing power. This could allow higher pricing than would be possible with a hospital-prescribed antibiotic. Furthermore, the agent is a reformulation of an old antibiotic, which means that the clinical trial programme is relatively unlikely to fail on the basis of safety or efficacy. Perhaps this combination of factors makes the investment in Phase III trials attractive. We note that there at least one other drug company, Bayer, which has recently initiated Phase III trials of a different inhaled formulation of the same antibiotic. Bayer's candidate has been granted orphan drug status by the FDA.

[14] This is very rare in the case of drugs, and when it occurs, it usually reflects some kind of failure in the clinical trial programme, and/or a difference in risk tolerance between the FDA and EMA.

1. Perhaps via TATFAR (TATFAR, 2014), the EMA and FDA should consider whether it is possible to produce a single integrated set of guidelines for the development of antibacterial drugs. As one interviewee told us: *"Although there has been a huge improvement in the FDA and EMA regulations, it would still be very helpful if there could be a single unified set of guidelines. When you get into the very gritty details of trial design and end-point measurement, there are still differences. These mean that you take a risk with at least one of the regulators if you optimise your trials for the other one."*
2. There should be coordination between any new mechanisms for incentivising antimicrobial R&D, and FDA and EMA regulation. New financial incentives for R&D will have important interactions with regulatory systems and vice-versa.

Here we are struck that the US already has an incentive system for new antimicrobial agents, which appears to be having an effect. The FDA Safety and Innovation Act of 2012 provides for 5 years of 'orphan-like' market exclusivity to new antimicrobial drugs (Qualified Infectious Disease Products, or QIDPs) active against a list of ~21 'Qualifying Pathogens' and perhaps against other pathogens too[15]. In just 2 years, the FDA has awarded QIDP status to around 40 AMs in clinical development (Woodcock, 2014).

The QIDP designation has no direct parallel in Europe. Thus the US is already sending commercial signals to the industry on where to direct AM investment in a way that the Europe is not. This is not necessarily a problem. It may well be a cost-effective way for Europeans to get new AM drugs. However, it will become a problem should Europe decide that it wants a different set of AMs to those incentivised by the US.

5. AMR, AM Drug and Diagnostic Development for Animal Diseases[16]

5.1 Patterns of AM drug and diagnostic use in animals

Antimicrobials (AMs) have long been used in the US and Europe to treat animal infections, to prevent animal disease (i.e., prophylaxis and metaphylaxis[17]), and to promote animal growth. As in humans, most animal AM prescribing is 'empiric' with the drug selected on the basis of the clinical syndrome, and microbiology performed in potentially serious cases and/or in the event of failure of the initial antibiotic chosen (Livermore & Wain, 2013). In most cases, susceptibility testing occurs only as a consequence of initial antibiotic treatment failure.

There are large differences in the range of livestock raised in different European countries. More intensively managed poultry and pigs tend to be given more AM drugs than extensively farmed sheep and goats. Even so, the differences in AM use between different European countries appear very large. Adjusted for livestock biomass, some EU countries appear to use 100 times more AM drug than others (Figure 2) (ESVAC Project, 2013; 2014). The pattern of usage also varies, with different countries favouring different drugs. Both the quantity and pattern of consumption appear to reflect idiosyncratic national differences in prescribing habits and not simply differences in the local livestock population or its pathology (ESVAC Project, 2014; De Briyne *et al*., 2014).

This variation in national prescribing patterns extends to the antimicrobial agents that the WHO defines as most important for human health, the so-called Critically Important Antibiotics, or CIAs, including 3rd and 4th generation cephalosporins, macrolides, and fluoroquinolones. The veterinary use of CIAs causes the highest level of policy concern in some countries - in Bulgaria for example,

[15] https://www.federalregister.gov/articles/2014/06/05/2014-13023/establishing-a-list-of-qualifying-pathogens-under-the-food-and-drug-administration-safety-and

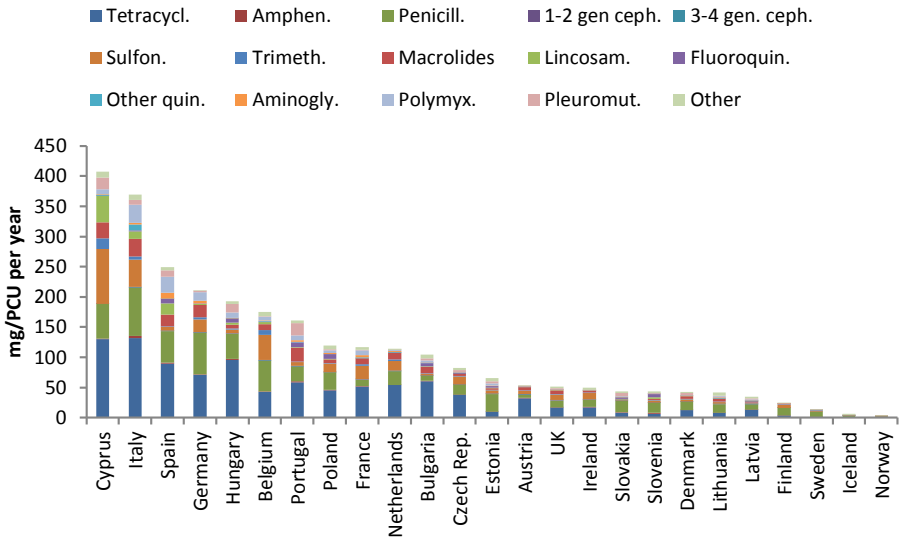
[16] See Supplementary Report 3 from Jack Scannell and Ann Bruce for more detail on the analyses summarised here.

[17] Metaphylatic use typically involves treating a group of animals once an index case has been identified and where epidemiology suggests the group is likely to be or become infected. Treatment is over the incubation period of the disease. Prophylactic use involves lower doses administered to groups of animals in feed or water during vulnerable periods e.g. for two weeks when pigs are weaned and mixed into new groups.

CIAs constitute nearly 20% of all antimicrobials prescribed to animals while In Norway CIAs are hardly used at all.

Much serious infectious disease in animals, often viral in origin, is managed by culling of the animals and not by medical treatment. The EU lists 'notifiable diseases' that pose a serious economic risk or a welfare risk to animals (e.g., foot and mouth disease, brucellosis), and/or which pose a threat to human health (e.g., bovine tuberculosis, avian influenza).

Figure 2. Variation in Intensity of Veterinary Antibiotic Use across the EU (2011 Data)



***Legend**. Data are from the ESVAC Project (2013). The vertical axis shows the mg of active antimicrobial ingredient prescribed per unit of livestock biomass (PCU) per year.*

5.2 Policy Context: Growing Concerns over Antimicrobial Use in Animals

Policy consensus has emerged, first in Europe and in more recently in the US, that the use of AMs in animals can promote the evolution of resistant strains and increase the frequency of resistance genes and that this can pose a risk to human health. Although there is much less consensus on the magnitude of the risk there is now policy pressure on both sides of the Atlantic to reduce the use of antimicrobials in livestock production.

In the EU the use of antimicrobials as growth promoters in animal feed was banned in 2006 and there is a range of initiatives, some at the EU level, and others managed nationally, to assess and track the AMR problem and to reduce antimicrobial use (EMA, 2014a) (De Briyne *et al*., 2013). The EC is also introducing new regulations for veterinary medicinal products which may limit the use in animals of drugs that could promote the evolution of resistance to medicines for human use.

In 2008, the Netherlands implemented a policy to reduce antimicrobial drug use in food producing animals (NL Ministry of Economic Affairs, 2014) related to the contrast between antimicrobial use in the Dutch human health system (characterized by low levels of AMR and strict control of prescribing) and relatively liberal AM use in agriculture. There were concerns over the transfer of resistant bacterial strains from animals to humans.

Dutch consumption of AMs in food producing animals has fallen by ~50% since 2009, with large declines in their use in all major livestock segments, pigs, poultry, veal and dairy cattle (NL Ministry of Economic Affairs, 2014). Dutch agriculture has gone from being a relatively high user of AMs to a more median level.

In Denmark, (Aarestrup *et al.*, 2010) domestic concerns over the levels of antibiotic use in intensive pig production led in 2010 to a voluntary ban on the use of cephalosporins (some of which are among the WHO's Critically Important Antimicrobials), and a "yellow card" scheme that

tracks antibiotic use and imposes restrictions on farmers whose pigs consume twice the national average level of antibiotic. In the first year after introduction of the scheme, antibiotic use in pigs fell by ~25% (Alban *et al*., 2013) and vaccine use increased. There was also some evidence of an increased rate of certain bacterial infections during meat inspections, but the net effect on animal health appeared to be small.

The Dutch and Danish examples show that it is possible for national policies to have a large impact on AM use in animals, and the bulk of EU livestock resides in member states that appear to have consumption levels substantially higher than those in the Netherlands or Denmark.

Various research and policy initiatives are under way in the UK with the intention of reducing antimicrobial use in livestock and companion animals, but none has yet been implemented.

The EC has prepared draft veterinary medicines regulation, to be voted on by the European Parliament in 2015 and to come into force in 2018. While acknowledging some demand for new drugs for animals, the draft regulation and associated documents (e.g., impact assessments, annexes, etc.) tend to emphasize the AMR problem, and the potential risks to humans that follow from use of antimicrobial drugs in animals (European Commission, 2014). The EC also discusses options to make it easier to withdraw animal drugs should concerns arise over drug resistance that might become problematic in humans.

The EMA strategy paper for veterinary AMs also emphasizes the AMR problem, and the potential concerns that the regulator would have with substantially novel agents: *"Risks related to AMR are to be considered in the benefit/risk assessment and in case these risks are found unacceptably high and cannot be sufficiently mitigated marketing authorisation will not be granted….. **Of special concern are molecules that represent totally new modes of action (and thus resistances unrelated to those already evident on the market) and a very strict view will be applied where the molecules in questions are specifically reserved as last resort medicine for use in zoonotic infections in humans.**"* (EMA, 2011b) [Our emphasis].

Until recently, the US has taken a more relaxed view of AM use in livestock. The FDA has permitted the sale of AM drugs for treatment of animal disease, for prophylaxis, for metaphylaxis but also to increase feeding efficiency or to promote weight gain; so-called "production uses" (FDA, 2012). However, production uses are now being phased out in the US, and will have been eliminated entirely by 2016. Following FDA guidance (FDA, 2012; 2013b) nearly 20 drugs have been voluntarily withdrawn from production uses.

The FDA also stresses scrutiny of potential risks to human health that could arise from resistance that emerges as a consequence of the use of novel AM drugs in animals (FDA, 2003; 2012; 2013b). Drugs that are considered risky from a resistance point of view may be approved, but with restrictions: they will not be available without a veterinary prescription, off-label use may be prohibited, there will be more rigorous post-approval monitoring, and the FDA will likely seek public Advisory Committee review.

5.3 Impact of EU and US Regulation and Policy Environments on Veterinary Drug Innovation

Our interviews suggested that the current policy and regulatory environment has had a stifling effect on private sector investment on R&D for new AMs for animal use, with little or no private sector activity to bring novel AMs to the veterinary market. For veterinary users, new drugs that are merely close analogues of existing drugs (i.e., the new drugs that are cheapest to bring to market) will often share the same resistance problems as existing drugs. They will also tend to be relatively undifferentiated from very cheap generics. Yet genuinely novel drugs with new kinds of antimicrobial activity are likely to be those that are most jealously guarded for use in humans.

Veterinary markets also have a political problem: if governments incentivise R&D on novel AM classes for human use, involving large scale payments (~$500m) to a major drug company for a novel AM that would face extreme stewardship in human populations, they are then unlikely to allow that drug or its analogues to be prescribed to pigs and chickens.

The main hope of trade bodies that represent livestock producers and veterinary medicines companies is that future constraints on AM use are reasonable and moderate (e.g., NOAH, 2014). They are arguing, for example, to retain some veterinary access to WHO Critical Antimicrobial Agents such as 3rd and 4th generation cephalosporins and fluoroquinolones. They do not seem to be asking for, or expecting, much in the way of novel AMs.

5.4 Impact of EU and US Regulation and Policy on Veterinary IVD Innovation

Potential constraints on future usage appear to be a major disincentive to private sector investment in new veterinary drugs. The situation with veterinary diagnostics that could mitigate the AMR problem is different. In principle, demand ***should*** grow as various policy initiatives push vets and farmers towards more tailored use of antimicrobial drugs. In the Netherlands, for example, third line antibiotic use now requires prior susceptibility testing (which is also recommended before second line antibiotic use) (Ministry of Economic Affairs, 2014). Furthermore, at an EU level, regulatory barriers are low for many diagnostic tests. In the US, companies must gain approval for an IVD from the US Department of Agriculture (USDA) but the hurdles are lower than for human diagnostics.

However, our interviewees identified several barriers to IVD innovation. National regulation of veterinary diagnostics varies by country although the standards may not be individually challenging. Two further barriers to AM and IVD innovation are the relatively modest value of veterinary drug and diagnostic markets, and the price sensitivity of farmers who pay for most of the drugs and for diagnostic testing for non-notifiable infections. The cost of a diagnostic test must be weighted up against the economic value of the diagnosis. If the first and second line antibiotics are cheap and available, and the diagnostic costs more than, say, the lost milk production, there is little economic incentive to use the diagnostic.

5.5 Alternatives to AM drugs

Several interviewees expressed concerns over the animal welfare and/or economic implications of substantial restrictions on the use of AMs in animals and a number of alternatives were suggested: vaccines, biosecurity, probiotics and feed additives, and genetics. Most **vaccines** seek to prevent viral infections; the use of antibacterial vaccines is more limited and our interviews suggested that veterinary bacterial vaccines available today are somewhat dated and of limited use. On the other hand, improvements in **biosecurity and hygiene practices** appear to have been important adjuncts to the reduction of antibiotic use in farms in Denmark and the Netherlands (Alban *et al*., 2013) (NL Ministry of Economic Affairs, 2014) and elsewhere (Vergne *et al*., 2014). Vergne *et al*. (2014) consider alternatives to use of AMs in pigs and list a range of **feed additives** which may have an effect on pig health although few have been rigorously evaluated. **Genetics and breeding** can support the management of animal disease (Bishop & Woolliams, 2014), generally applied to quantitative traits (e.g. the *degree* of resistance to infection) which result from the combined effects of large numbers of genes. The changes in resistance in each generation are small, so selection pressume must be maintained over many years[18].

5.6 Relevance of animal disease and treatment to human AMR problems

The magnitude of the risk to human health from AM use in animals is contentious, even if there is consensus on the existence of the risk. In developed countries the most pressing AMR problem for human health seems to arise from nosocomial infection, often in severely ill, very elderly or immunocompromised patients. Resistant bacteria (or resistance genes) acquired from other humans in the community or from animals are less important although these routes of transmission do exist (FDA, 2012). This is not to suggest that the risk to human health from animal use of antimicrobial drugs does not matter. And the political focus on the AMR problem in human

[18] We are aware of work at the Roslin Institute to increase the resistance of chickens to Campylobacter and Salmonella, both of which can cause zoonotic infections in man. We are aware of work on resistance to bovine TB. In aquaculture species (e.g. salmon) selection for resistance to viral diseases such as Infectious Pancreatic Necrosis is being progressed.

health systems in the EU and US will probably continue to bring the veterinary use of AMs into the spotlight, almost independent of the actual risk to human health that veterinary use poses.

Both the desire and ability to manage AM drug use in animals varies within the EU. Some countries appear to use AMs with considerable caution (e.g. Sweden) while others seem more liberal (e.g. Spain). There has also been a major trans-Atlantic divide, with the EU banning the use of antimicrobials for growth promotion 10 years ahead of the US. We have not had the opportunity to explore antimicrobial use in China, Brazil, India, etc., but Europe and the US appear to lie towards the restrictive end of the spectrum.

Given the nature of international trade some production of meat for price-sensitive components of the European and US markets will probably migrate to countries where concerns over the AMR problem are less pressing and where veterinary antimicrobial drug use would not meet US or EUs standards. Thus some component of the AMR problem may be exported to countries whose public health systems are less well equipped to deal with it. The global movement of animal products has already led to calls for regulation on a worldwide basis (Herrera, 2013).

The following suggestions arise from this limited consideration of AMR and AM and IVD use in animals.

- Demand for susceptibility testing is likely to rise, but the European market for veterinary diagnostics appears to be unnecessarily complex. Innovation in, and adoption of, veterinary IVDs would probably improve if there was more coherent EU-level regulation, as has been the case for human diagnostics since 1998?
- Our interviewees suggested that there is a high degree of technological overlap between veterinary and human diagnostics, but that there is more limited overlap across the companies that sell to these different markets. It may be helpful to facilitate movement of ideas and people between the veterinary and human diagnostic fields
- There is little interaction between geneticists and veterinarians and research councils could usefully support more collaborative work in this area. The prevention and management of bacterial infection in animals in an environment of constrained antibiotic use becomes less of a conventional prescribing problem and more a broader interdisciplinary problem that must integrate drugs, diagnosis, vaccination, breeding, biosecurity, and husbandry.

6. Conclusions

6.1 General points

This project has yielded several important insights into the factors impacting on the development of novel products relevant to resolution of the AMR problem.

1. Given the scarcity of new broad spectrum AM drug classes for future development, accurate and rapid diagnostic tools to detect the nature of the infectious agent and its susceptibility to specific narrow spectrum AMs will be increasingly important. The development process for these IVDs will not follow the same pattern as that for IVD innovation related to cancer treatments where co-development of the drug and diagnostic is expected to be increasingly synchronised (Mittra and Tait, 2012). This should allow more flexibility and more rapid development of innovative IVDs relevant to AM use than in the case of cancer treatment, provided IVD regulatory systems are sufficiently adaptive to this circumstance.
2. As described in Sections 3 and 4, there has already been considerable regulatory adaptation in both the US and the EU with the intention of enabling more rapid and cost-effective development of drugs with significant societal benefits. Most of the interviewees from both large and small companies believed that regulatory constraints in the context of development of AM drugs are no longer the most important factor inhibiting innovation. For example, for the scenario calculated in Section 4, the total R&D cost per drug may have been more than halved as a result of regulatory adaptations already in train. Thus, regulatory adaptation does appear to be encouraging at least some companies to begin to invest in discovery and development of

AMs. The prevailing view among industry interviewees for this project is that a lack of market incentives is now the main barrier to AM innovation, rather than regulatory constraints. Our results suggest that an incentive mechanism for AM drug development does not need to be based on very precise estimates of historical R&D costs or current antibiotic profits. It simply has to give enough investors and companies the belief that investing in AM R&D today will yield positive returns in future.

3. These judgements were more qualified in the context of IVD development. The more demanding US regulatory system was seen as potentially problematic, and indeed several IVDs have been developed for use in the EU but not the US for this reason. However, IVD regulations in the EU are currently being revised and it will be important to consider their potential impact on AM-related IVDs to ensure that they can be tailored to the specific needs of such IVDs to ensure quality and efficacy without unnecessarily inhibiting innovation.
4. Uncertainty about future markets for AMs and associated IVDs was seen by interviewees as the most important factor discouraging company investment in development of such products. HTA bodies, such as NICE in the UK, along with health service purchasers, were seen as overly conservative and unlikely to appreciate the benefits of novel IVDs. The most serious constraint of all was related to the presumption that a novel AM that is effective in cases of AMR will be reserved for use in the most serious cases, making it impossible for a company to recoup its development costs.
5. As described in Section 5, AM use in animals is likely to be increasingly restricted, particularly in the case of drugs with a novel mode of action that will be useful for treatment of human cases involving AMR. This is seriously curtailing commercial R&D for AM drugs for use in animals. As a result, health care in animals is likely to be increasingly based on a range of alternative options including vaccines, genetics and breeding, potentially opening up new commercial opportunities. Restrictions on AM use should also create opportunities for greater use of IVDs but this is countered by the current regulatory situation, with low barriers but wide variation across countries, coupled with a lack of market incentives.

Despite the uncertainties outlined in point (4) above, and (perhaps) given the incentives outlined in points (2) and (3), several large and small companies are now investing in the development of AMs and associated IVDs for human use, although no products developed in the new regulatory context have yet reached the market so it is too early to tell if they will be effective in delivering innovative products with the capacity to address the AMR problem.

6.2 Radical and incremental innovation

These promising developments, and the comments elicited in interviews, relate to incremental innovation (see Section 2.2), that can be accommodated within the sector's current innovation model and potentially create competitive advantage for a company without challenging the prevailing business model, although in this case with considerable uncertainty about the value likely to be returned to the innovator. However, radical, and perhaps much more effective, solutions to the AMR problem that will arise in future from new scientific research in synthetic biology (e.g. from research on marine organisms and on phage technology) are more likely to be disruptive, path-breaking developments and the recent adaptations in regulatory systems that may have been effective in encouraging more incremental innovation in AM and IVD developments may not be sufficient to enable more disruptive innovation to proceed efficiently to market.

If the regulatory adaptations delivered to date are not sufficient to enable a small company to develop an AM product all the way through to a market without some form of collaboration with a multinational company (as seems to be the case), and if the more radical innovations are too path-breaking to be attractive to a multinational company, then there is a chance that they will languish as potentially interesting developments that never made it to a market, for example phage based technologies.

It is also possible that novel, potentially disruptive scientific developments could lead to a number of different classes of narrow spectrum AMs, providing a sufficient variety of options to deal with

AMR problems to enable general use (although targeted to specific organisms based on a related IVD) rather than reserving such products only for patients with no alternative treatment options. Such developments are likely to require an integrated approach to tailor a pathway to market involving further regulatory adaptation, innovative approaches to HTA questions, and innovative funding models including public support for market creation.

6.3 Innovative funding models

In parallel with discussions on the role of regulation in enabling or constraining innovative developments there has been also been a focus on the nature of innovative funding models that could help bring new technologies to market, particularly disruptive technologies such as regenerative medicine (Omidvar *et al.,* 2014). Where innovative solutions to the AMR problem are likely to be disruptive, there may be a need for state, or other non-commercial funding to enable such products to be adopted in health care markets. There is a general view in such contexts that the role of government should be to set the conditions for private capital success, addressing tax and capital formation conditions around particular technologies to *enable* private capital rather than to leverage or direct it. Direct public involvement in the creation of markets or other support for innovation is usually seen as likely to distort prices and cause private capital to withdraw.

However, an alternative perspective on such questions has recognised that, *for truly path-breaking technologies*, the state has always played an important role in shaping technology trajectories and creating markets, generating economic activity that would not otherwise have happened and opening up new markets that private investors can subsequently move into (Mazzucato, 2013). It will be important to keep an open mind, if and when path-breaking, disruptive technologies emerge to meet the AMR challenge, to the possibility that innovative funding models with a significant public or philanthropic component may need to be part of the overall support system for their development, along with an element of state-supported market creation and targeted adaptive regulation.

6.4 Relevant future initiatives and research requirements

Building on the above comments and suggestions, it would be useful to consider the following requirements for further research or adaptation to regulatory systems, markets and funding models.

Market related incentives

Given the market-related constraints relevant to the development of novel AM drugs and diagnostics, there is a strong case for considering innovative funding models that could incentivise such developments by small and medium sized companies and/or by multinational pharma companies. Potential precedents for such initiatives could be those relevant to regenerative medicine, currently facing a similar array of disincentives to those affecting AM drugs and diagnostics (Omidvar *et al.,* 2014).

Public sector support for diagnostics as an economic complement to commercial drug R&D.

Better pathogen identification could further reduce the cost of AM drug trials. In rough terms and in principle, doubling the proportion of subjects recruited into a trial with a pathogen that should be sensitive to the experimental drug, via the use of a diagnostic test, can reduce the required trial size by as much as 75%. In the long run, better diagnostics could also create new drug markets, particularly for narrow spectrum drugs. Furthermore, diagnostic R&D appears to be between one and two orders of magnitude less expensive than drug R&D. However, diagnostics are less profitable than drugs, and adoption and reimbursement are problematic. In oncology, an area where the drug industry is investing heavily to exploit the complementary nature of drugs and diagnostics, these problems can be overcome, but only because drug companies subsidise IVD development and IVD provision so that they can sell what are often very expensive drugs. Without highly profitable cancer drugs, there would not have been a flowering of molecular cancer diagnostics or small and efficient cancer drug trials highly enriched for responsive patients. Such cross subsidy is unlikely to occur with antimicrobials given the potentially restricted markets and

lower profitability of the drugs. There may also be a case for public sector investment in the diagnostic technologies and microbiological services that are most likely to reduce the cost of commercial AM drug trials and thus stimulate commercial investment.

Public sector support for sample banks to reduce the cost of diagnostic test validation.

Given that one of the main barriers to R&D for IVDs is getting samples for test validation, public sector institutions such as the NHS, the Health Protection Agency, or other European agencies, would be well placed to work as sample collectors and repositories at relatively low incremental cost, and could be encouraged to collaborate with private sector test developers.

Precompetitive preclinical models for new therapeutic technologies.

A great deal of often unglamorous but important work goes on in preclinical development (e.g., regulatory requirements for toxicology and safety, some animal models of disease, drug absorption, metabolism, excretion, drug-drug interactions, options for routes of administration and formulation). Preclinical development is easier for therapies for which there is long commercial and regulatory experience. However, for new therapeutic technologies such as bacteriophages or transcription factor traps, there are few existing standards. Agencies such as the MRC and Wellcome Trust could devote funds towards the development of the preclinical models that are a necessary pre-requisite for regulatory scrutiny of potentially disruptive technologies.

Analysis of the commercial assumptions of firms that are investing in antimicrobial R&D today.

It is important to characterise the clinical and late-preclinical pipeline of AM drugs to try to understand the commercial opportunities that attract investment today, and to understand what this means for the design of future incentives.

Creating and maintaining AMR data resources.

A secretariat could be established that collates and publishes on a timely basis data likely to be of use to a wide range of people working on the AMR problem but which are currently scattered. For example, it would be useful if those engaged in AMR policy were able to obtain information on drug pipeline status, including all the AM agents in clinical development, the indications in which they are being tested, their phase status, and their mode of action. This could then be compared, on a continuous basis, with changes in regulation, technology, or financial incentives. So, for example, have the GAIN provisions and QIDP status been correlated with an increase in clinical trial activity? How many agents are reformulations or combinations of existing products? How many are new drug classes? What is the mix of broad spectrum vs. narrow spectrum agents? How does the pattern of pipeline activity and progress match the perceived medical need? Where is venture capital flowing?

6.5 Integrated overview of regulatory and market-related stimuli of drug and IVD developments relevant to resolution of the AMR problem.

As described above, there is evidence that regulatory adaptation related to AM drug development is having a positive influence on the development of AM drugs and IVDs. However, it is possible that regulatory adaptation to date may not be sufficient to enable a small or medium sized company to take an AM product all the way through to a market without some form of collaboration with a multinational company. Narrow spectrum AM drugs may have too limited a market to be attractive to a multinational company, and more radically innovative products may entail too much future uncertainty. Also, where AM drugs and diagnostics with the capacity to address the AMR problem will face restrictions on the range of patients for which they can be prescribed, regulatory adaptation may need to be supplemented by some form of market creation or support, requiring further research on such interactions and how they can be integrated effectively.

There is a need to foresight the adaptations required for existing drug development business models and innovation pathways and, particularly for narrow spectrum and truly novel modes of action where an innovative business model may need to be crafted *ab initio* as an integral

component of the development process. There are also potentially complex interactions between AM drug and diagnostic use for humans and for animals that could have serious implications for the future development of AMR. These would also need to be taken into account in a future integrated analysis.

It would be useful to explore future integrated scenarios, taking account of all the factors included in the above analysis, as summarised in Figure 1, for the optimal exploitation of new scientific knowledge relevant to resolution of the AMR problem. Such scenarios should take account of the variability in the nature of the AMR challenge for different disease organisms, in different disease contexts and in different regions of the world, particularly Asia, Africa and South America. These scenarios should also consider under what circumstances some potentially disruptive developments in AM or IVD could lead to a sufficiently broad range of different classes of narrow spectrum AMs, to enable their use to be stratified, e.g. between human and animal markets, as a means to resolve the lack of innovation incentive arising from severely restricted markets for novel products.

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