Regulatory and market influences on innovation pathways for the development of new antimicrobial drugs

Regulatory and Market influences on Innovation Pathways for the Development of New Antimicrobial Drugs

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Acknowledgements

We thank the UK's Economic and Social Research Council (ESRC) for funding the project 'Independent Review of Antimicrobial Resistance', the findings on which this article is based.

Abstract

Focusing on Europe and the United States, and using policy/regulatory document analysis, qualitative interviews, and quantitative cost-scenario analysis, we explore regulatory and market influences on the commercial development of novel antimicrobial drugs and diagnostics to meet the global antimicrobial resistance crisis. We show that regulation of clinical trials previously inhibited firms' ability to develop commercially viable antimicrobials, but now unattractive commercial prospects are the main barrier. Our findings improve understanding of the challenges of drug development in the context of market failure and highlight unique problems of antimicrobial resistance in terms of the alignment of different incentive structures and value(s), including clinical norms and practices.

Introduction

Antimicrobial resistance (AMR) – the evolutionary ability of microbes to acquire resistance to drugs targeting them – is a global crisis (Davies, 2013) requiring national and international policy responses (O'Neill, 2016; OECD, 2016; WHO 2014; HOC, 2014). The danger is a return to a pre-antibiotic era, bringing catastrophic consequences for public health, and taken-for-granted medical advances over the past 50 years. For example, reducing risks of routine surgery sometimes requires prophylactic use of antibiotics, and life-threatening infections have been treatable for decades through antimicrobials. However, resistance is outpacing the discovery of novel drugs. Data from the Organisation for Economic Cooperation and Development (OECD) show from 2005 to 2015, AMR increased on average by 5% in 23 out of 26 OECD countries, with some infections increasing four-fold (OECD, 2016).

AMR is a systemic and complex global problem, with salient differences between high and low-resource countries in the quality of healthcare and access to diagnostic testing and therapy providing unique selection environments. A range of solutions are needed that integrate knowledge and understanding of innovation communities, regulatory bodies and governance processes, stakeholder groups, and broader socio-economic factors that drive transmission dynamics. We explore the drug development challenges for AMR, focusing on regulation-innovation interactions and market factors that can inhibit or incentivise antimicrobial drug development. Focusing on Europe and

the US, we show that regulation previously inhibited firms' ability to develop commercially viable antimicrobials, but now lack of financial incentives is the main barrier.

The following section outlines our methods. We then provide some background to the AMR problem, before looking at regulatory challenges and their impact on antimicrobial drug development. We discuss a tiered labelling approach for antimicrobials, illustrating changes in regulatory standards, and consider subsequent R&D investment scenarios. Finally, we discuss how lack of financial incentives for industry and prevailing clinical norms and diagnostic practices hinder AMR drug development. Note that we see two likely settings in which new antimicrobials will be used. These are: (1) in the hospital setting for patients with serious acute infections where there is evidence that established drugs are unlikely to be effective given the resistance profile of the pathogens at hand; and (2) as high priced "orphan drugs" in certain high-risk populations outside of hospital, e.g. patients with cystic fibrosis with chronic Pseudomonas aeruginosa infection. However, we would expect initial approval for use primarily in hospital populations with serious acute infections, where the drug is likely to be delivered intravenously (although reimbursement would be similar for an oral medication), so our analysis applies mainly to this scenario.

Methods

Data were collected in 2014 as part of an ESRC project, 'Independent Review on Anti-Microbial Resistance', which contributed to the O'Neill 'Review on Antimicrobial Resistance' (O'Neill, 2016). We reviewed academic and policy literatures to identify key themes and challenges, and conducted semi-structured interviews with senior regulators from the European Medicines Agency (EMA) and the UK's Medicines and Healthcare Regulatory Agency (MHRA), senior executives from industry with expertise on AMR (including drug/diagnostic firms and pharmaceutical trade associations and consulting firms); and an NHS consultant microbiologist on the practicalities of diagnosis and susceptibility testing. Where consent was given, interviews and meetings were recorded and transcribed. Otherwise, interview notes were used. All respondents requested anonymity, so we refer to respondents only by interview number. We focus here on 15 interviews from industry, given our interest in how commercial drug development is affected by policy and regulatory incentives and disincentives. We also conducted a 'sensitivity analysis' of the effect of different regulatory approaches on antimicrobial R&D costs (detailed later). We also had informal discussions (by phone, email, and at conferences) with venture capitalists. Their views were consistent with the 15 interviews, but are not a focus in this paper. We acknowledge some limitations of this data, specifically that our interviewees had an interest in achieving a higher price for antimicrobial drugs. However, given our aim to identify factors affecting industry's interest in antimicrobials, it was important to focus on these actors.

Background to AMR

Das and Horton (2016) suggest AMR has become both fashionable and politically visible, but focusing on 'resistance' ignores the scarcity of antibiotics in some global

contexts, where mortality from poor access to effective antimicrobials is higher than that from resistant pathogens. Laxminarayan et al (2016) argue that policy must recognise the multiple and overlapping value(s) of antibiotics, which includes 'option value' (in the case of influenza pandemics they provide additional options for treatment as interactions between influenza and secondary bacterial infections are a major cause of death during pandemics); 'enablement value' (antimicrobials make surgical procedures safer) and 'diversity value' (new antimicrobials reduce selection pressures on existing drugs). This calls for a multilayered, evidence-based response. Although the link between overprescribing of antimicrobials and resistance appears obvious, many factors drive resistance, including low vaccine uptake, population density, sanitation, and migration/tourism (Holmes, 2016: 178).

Global dynamics highlight the socio-economic and political dimensions that cannot be disentangled from basic science and clinical norms. A UK report from an ESRC working group on AMR (ESRC, 2014) suggested effective responses to AMR require changes in social practices, including: 'how regulatory and fiscal frameworks incentivise or deter antimicrobial development, production and use; and how public and healthcare professionals behave in relation to infection and use of antimicrobials' (ESRC, 2014: 1). Drug development is only part of the solution, as antimicrobial 'stewardship' depends on normative social systems of negotiation involving prescribers, dispensers and patients/consumers. It also requires effective public engagement, where messages rooted in notions of catastrophe may indeed be counterproductive (Davis et al 2017). We focus on business models and economic incentives for developing antimicrobial drugs, but these are structured by socio-political contingencies, including dystopian narratives of security and trauma (Brown and Nettleton, 2016). Commercial viability of antimicrobials is also shaped by prescribing behaviours, transmission dynamics, regulatory/pricing structures, and underlying scientific complexity, which problematize technology foresight and crisis management.

Four factors explain the paucity of novel antimicrobial drugs. First, traditional antibiotic discovery methods, based on fermentation broths and extracts of soil-derived microorganisms, became difficult given: (a) a shift to target-based drug discovery by the pharmaceutical industry; and (b), the practical challenge of de-replication in natural product-based antibiotic discovery (Silver, 2011; Balz, 2007). Second, investment in genomics and target-based drug discovery failed to deliver viable broad and narrow-spectrum antimicrobials (Payne et al, 2007, Silver, 2011). Third, regulatory guidelines previously made it difficult to undertake clinical trials, particularly for novel narrow-spectrum antimicrobials (IDSA, 2011).

Fianlly, newer antimicrobials do not generate large profits (Sertkaya et al, 2014), because they tend to be used in hospitals in patients with serious infections caused by pathogens resistant to older, cheaper generics. Most episodes of in-patient care in the US are reimbursed at a capitated rate where the payer provides a fixed fee for the 'episode of care'. Medicare Part A, for example, defines "Disease-Related Groups" (DRGs), such as a hip replacement or a coronary artery bypass graft, and pays a fixed fee based on the average cost of providing such an 'episode of care'. If a patient contracts a serious infection requiring an expensive new antimicrobial, the hospital loses money on the patient. In contrast, specialist drugs used in the out-patient setting (e.g. cancer drugs), are reimbursed under Medicare Part B, which pays the treating

institution the average sales price (ASP) of the administered drug plus 4.3%. Outpatient drugs thus become profitable for the dispensing institution. The difference between DRG-based in-patient reimbursement (where novel antimicrobials are used) and ASP-based out-patient reimbursement (where novel cancer drugs are used) explains why it is easier to commercialize new cancer drugs that cost $150k per course of treatment than new antimicrobials that cost $15k per course. Additionally, clinicians often hold back on prescribing new antimicrobials for 'tough cases' instead of basing decisions on treatment guidelines or lab testing, which exacerbates the commercialization challenge.

In summary, novel and effective drugs that might have been discoverable were viewed by much of the drug industry as too difficult to develop given a market restricted by conservative stewardship in much of the developed world, and by the economics of drug choice in US hospitals.

Impact of Clinical Trial Regulation on Antimicrobial Drug Innovation

Onerous clinical trial requirements were previously considered by some academics, the drug industry, and the Infectious Disease Society of America (ISDA) as a barrier to antimicrobial drug innovation (Rex et al, 2013, IDSA 2011, 2014). This was confirmed in our interviews. IDSA suggested FDA guidelines in force in 2010 prioritized 'experimental purity' over 'clinical pragmatism' such that it was impractical and unethical to recruit patients into antimicrobial trials (IDSA 2011, 2014). FDA guidance for hospital-acquired and ventilator–acquired bacterial pneumonia (HABP/VABP) required that prior use of antibiotics effective against the microbe presumed to be causing the infection be avoided in non-inferiority trials. The FDA argued that prior antibiotic use would reduce observable differences between the two treatment arms and bias conclusions. However, the IDSA contended this requirement made studies unfeasible as most trial participants would be selected from seriously ill hospitalized patients likely to have received prior treatment. Subsequently, the 2014 guidance (FDA, 2014) allowed enrolment of patients who had received up to 24 hours of treatment in the previous 72 hours.

Other regulatory challenges included shifting targets, statistical hurdles that demanded large trials, and situations where no trial design appeared satisfactory. Coates et al (2011) provide an illustrative example. Having agreed to a clinical trial protocol for the drug *televancin* (for HABP and VABP) using clinical response as the primary endpoint, the FDA requested further data to support an evaluation of 'all-cause mortality' as the endpoint. This increased cost of development, because it is more difficult to demonstrate a statistically robust survival effect of a drug than a clinical response. To simplify, deaths are rarer events than drug responses, and statistical power depends on the number of events during the trial. Furthermore, death depends on many factors, not just the drug, so signal to noise ratio is reduced, which requires larger trials. This paradoxical situation applied to anyone considering a trial for a novel antimicrobial against multi-drug resistant gram negative pathogens: 'With no standard therapy [since these are multi-drug resistant pathogens], non-inferiority studies are not possible [as there is no commonly accepted standard treatment for the control arm]; historical controls are considered irrelevant and superiority studies are not ethical as patients cannot be randomized to ineffective therapy for infections with high mortality'

(Coates et al, 2011: 191). The point here is that it appeared impossible to satisfy regulatory guidelines in terms of trial design.

Today, the FDA and EMA have adapted regulatory guidelines to enable practical and ethical trial designs. There have been statistical requirement changes that allow for smaller trials, and changes in recruitment criteria to simplify enrolment. Progress has also been made in reducing regulatory burdens for new drugs for patients with limited treatment options. Industry no longer considers regulation a significant barrier to the development of antimicrobial drugs, evidenced in our interviews:

> *In broad terms, the regulatory environment has improved over the last 5 years.* (Interview 1)

> *The FDA and EMA have put in a lot of work. [Regulation] is not regarded as a major bottleneck. [We have] nothing yet in the clinic, but we could probably access the patients, testing etc. to run the trials we need to today if we had to* (Interview 2)

Regulatory adaptations to incentivise innovation are relatively recent. In 2013 and 2014, the FDA issued guidelines for the development of drugs for several important classes of infection. These followed the Generating New Antibiotics Now (GAIN) provisions of the FDA Safety and Innovation Act 2014, which provided guidance for the design and conduct of preclinical and clinical antimicrobial studies. The EMA issued similar guidance (EMA, 2011; EMA 2013) to allow for flexibility in the development paths and labelling for novel antimicrobials for unmet medical need. Pathogen-specific approval for serious infections with few treatment options was particularly innovative. For the first time, patients in clinical trials could be pooled, when their infections were at different anatomical locations, if they shared a common infectious agent. Such trials can demonstrate a positive risk-benefit profile against the pathogen, without having to prove definitively that the drug has a positive profile for each particular infection caused by the pathogen. This made it cheaper to run trials for rare pathogens, or those with rare resistance profiles (Rex, et al, 2013).

Tiered Labelling for Antimicrobial Agents and the Impact of Regulation on R&D Investment Cost Scenarios

The tiered labelling of antimicrobial agents illustrated in Table 1 summarises these regulatory changes. Although our terminology is slightly different from that used by the FDA and EMA, which does not officially use tiered labelling, the classification maps current guidance from both agencies.

Table 1. Tiered Labelling Framework for Antibacterial Agents (adapted from Rex et al, 2013, our additions in bold)

Typical efficacy data requirements	How the drug would be marketed
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 infection Y [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.**

The table shows four 'tiers' of approval. Tier A corresponds to conventional standards for which most antibiotics have been approved, but also reflects recent adaptations that have made clinical trials viable. For Tier A, the clinical trial is structured to support approval for use of 'drug X' in 'infection Y', (e.g. community or hospital acquired pneumonia). The sponsor must run specific clinical trials to show drug X has a positive risk-benefit profile in each infection for which the drug can be marketed. Thus, if novel drug X is to be marketed for use in hospital-acquired (VABP/HAPB) and community-acquired pneumonias (CAP), three trials are required; two for the initial VABP/HAPB indication and one for the additional CAP indication.

Tier C represents the important regulatory change of pathogen–specific approval (such as MRSA or highly resistant gram-positive anaerobes), which can be granted on tentative evidence from infections across multiple anatomical locations. Tier D is approval without human efficacy trials. This can be approved for cases where efficacy trials would be either unethical or unfeasible, which occurred in 2012 when the FDA approved *raxibacumab*, a monoclonal antibody for treatment of inhalation anthrax, solely on animal studies using the FDA's 'Animal Rule' (Tsai and Morris, 2015). The drug was destined for a US stockpile of agents to combat potential bioterrorism, so this is an example of regulatory innovation being adopted as part of a securitisation agenda. The FDA's Animal Rule has resulted in the approval of approximately one product per year since its inception in 2002, and over half of these are for bacterial infections. Tier B

applies to any drug that has robust efficacy data for one infection such as pneumonias, but more limited data for other infections (a hybrid of Tiers A and C).

Implications of Tiered Approval for R&D Costs: 'Sensitivity analysis'

We have estimated the effect of new approval routes on expected costs of antimicrobial R&D. Before we present the detail, we note some general points about drug R&D cost estimates.

First, R&D costs have been contested as the drug industry has used them to justify high prices. Scannell (2015) argues this has led to undue criticism of what are relatively straightforward analyses (see also Scannell et al. 2015). For our purposes, we assume that pharmaceutical firms are not committing systematic accounting fraud by misreporting their R&D costs, and that it is possible to triangulate on industry R&D costs from public sources (e.g., FDA drug approvals and audited financial accounts of drug companies). Specifically, we assume that the cost of individual activities in antimicrobial drug development correspond broadly with those set out by Sertkaya et al. (2014). We also note that these cost estimates are consistent with the R&D investments made by stand-alone biotechnology companies developing antimicrobials, such as Polyphor and Archaogen.

Second, drug R&D in general has the economics of a lottery, albeit one that plays out slowly (Grabowski and Vernon,1990; Grabowski et al, 2002; Scannell, 2015). Most projects fail, and those that succeed take time to complete. Thus the attractiveness of drug R&D to commercial investors who fund most clinical development is sensitive to their view of: (1) the probability that a given project will be a technical success; (2) the out of pocket (OOP) costs of individual clinical development activities; (3) the project's commercial prospects; and (4) the time cost of money (generally calibrated against other projects perceived to carry similar levels of financial risk).

Third, private sector actors have different views on factors (1) to (4). A company with robust pre-clinical toxicity data might assign a higher probability to ultimate approval than a company whose pre-clinical toxicity data looks marginal. A company whose drug shows low levels of cross-resistance with other antimicrobials, and whose drug shows high barriers to the evolution of resistance, may have high commercial expectations. Different companies invest, or not, accordingly.

Given these considerations, our assessment of the R&D cost implications of Tiers A, C and D pathways (Table 2) should be regarded as a 'sensitivity analysis', where the relative differences in cost estimates are more informative than absolute numbers. Given these caveats, and using Sertkaya's estimates for the Tier A path for HABP/VABP and CABP- including the cost of failed projects and time cost of money of 11% (Paul et al, 2010) - we get expected R&D costs of $1.6bn and $2.2bn respectively. It is probable that the costs per Tier C approval for a narrow spectrum agent would be nearly two-thirds less ($752m), while a Tier D approval would cost a tenth as much. If we ignore the cost of failure and the time cost of money – something that commercial R&D funders are unlikely to do at the point at which they decide whether or not to fund the project – the cost differential narrows. The Tier A path for HABP/VAPB and CABP would cost $150m and $81m, with Tier C costing $111m, and Tier D costing $37m.

Table2: R&D Investment Scenarios for New Antimicrobial Drugs (Cost in 2012 US $)

	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 $m	**1673.7**	**193.1**	**91.1**	**229.9**	**2.4**	**2190**
Memo item: Total market size ($m)						*3470*
Memo item: private ENPV of project ($m)						*-4*
CABP with conventional regulatory route						
Phase duration (years)	5.5	0.9	1.3	1	0.8	**9.5**
Time to commercial launch (years)	9.5	4	3.1	1.8	0.8	
Phase midpoint vs. launch (years)	6.8	3.6	2.5	1.3	0.4	
Real cost of capital	11%	11%	11%	11%	11%	
Time cost of money vs. launch	2.0	1.4	1.3	1.1	1.0	
OOP cost per successful candidate $m	21.1	9.7	9.1	38.8	2.0	**81**
Capitalized cost per successful candidate $m	42.6	14.0	11.8	44.5	2.0	**115**
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	32.1	68.2	2.3	**843**
Capitalized cost including R&D failures $m	**1289.3**	**148.8**	**41.4**	**78.1**	**2.4**	**1560**
Memo item: Total market size ($m)						*7940*
Memo item: private ENPV of project ($m)						*37*
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**
Tier D Approval Scenario						
Drug that cannot be prospectively tested in man						
Phase duration (years)	5.5	0.9			0.8	**7.2**
Time to commercial launch (years)	6.3	1.7			0.8	
Phase midpoint vs. launch (years)	3.6	1.25			0.4	
Real cost of capital	11%	11%			11%	
Time cost of money vs. launch	1.4	1.1			1.0	
OOP cost per successful candidate $m	25.3	9.7			2.0	**37**
Capitalized cost per successful candidate $m	36.6	11.0			2.0	**50**
Phase success probability	25%	100%	100%	100%	85%	
Candidates required per successful launch	4.7	1.2	1.2	1.2	1.2	
OOP cost including R&D failures $m	119.1	11.4	0.0	0.0	2.3	**133**
Capitalized cost including R&D failures $m	**172.5**	**12.9**	**0.0**	**0.0**	**2.4**	**188**

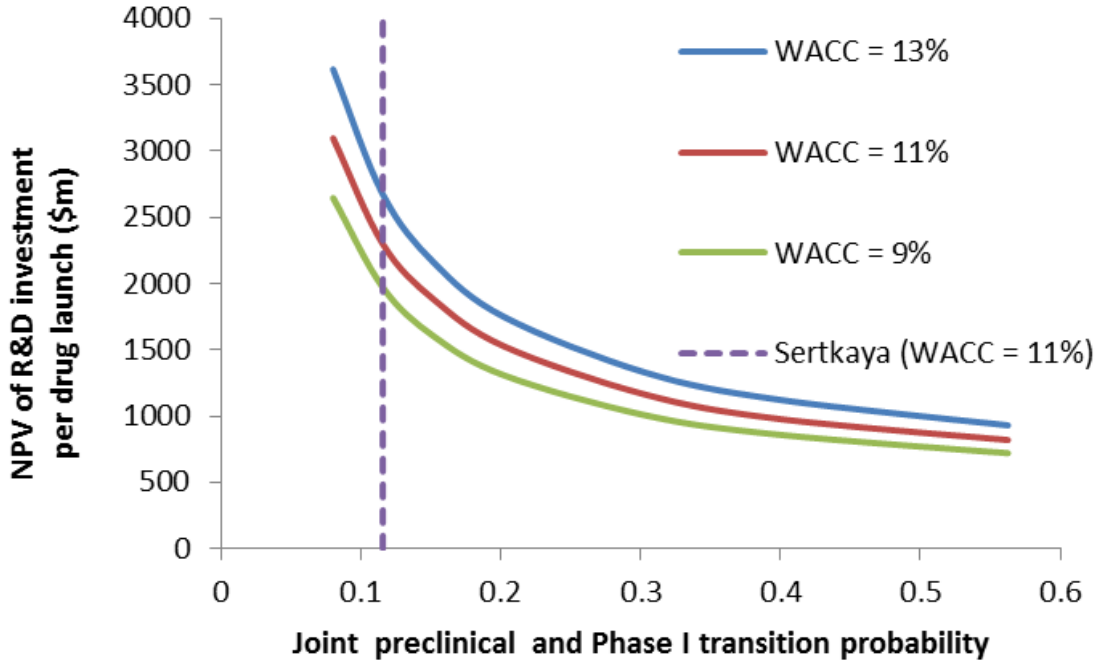
Sources: (Sertkaya, et al., 2014), (Rex, et al., 2013), and project team analysis and estimates

Table 2 shows that the R&D process for HARB/VABP takes 12 years from the start of preclinical studies to drug launch (top panel). The direct OOP cost for a molecule that successfully completes the entire process is $150m. However, if we include the cost of failures (30 preclinical programmes were required to yield one successful molecule) and the cost of capital in the pre-launch years (between 9.5 and 12 years of development) then the total capitalized cost of R&D at time of launch is $2,190m per drug. Furthermore, the HABP/VABP market is small, so investment returns are generally poor. The R&D process for CABP is marginally less expensive. It takes 9.5 years from the initiation of preclinical studies to drug launch (bottom panel), as the clinical trials are quicker. The direct OOP cost for a molecule that successfully negotiates the process is approximately $81m, due to lower phase 3 trial costs. Adding the cost of failures and of capital, the total capitalized cost of R&D by time of launch is $1,560m. The CABP market is also larger, so investment returns are at least higher than the cost of capital.

Those unfamiliar with drug investment might be surprised that the difference in capitalized R&D cost between the two scenarios does not emerge from different unit costs for phase 3 trials ($101m for HABP/VABP and $38.8m for CABP), but from the time cost of money. The CABP trials take less time than the VABP trials, so the OOP preclinical costs of $637m (identical for both programmes) have a capitalized cost of $1,673m in the case of HABP/VAPB, but only $1,289m in the case of CABP. We note that most of the OOP costs in both scenarios follow from transition probability assumptions that require 29 failed preclinical programmes for each drug that reaches market ('candidates required per successful launch' in Table 2). Assuming higher probability of success for each project, expected costs for each approved drug would be lower. These analyses are sensitive to failure rate assumptions, which in turn are sensitive to the quality of preclinical drug candidates, their novelty (Porges, Shi, and Pancratov, 2014), and the diagnostic tests available to enrich clinical trials for patients with pathogens sensitive to the drug. For example, for the $2.2bn Tier A estimate, the direct spending on the single drug that finally reached the market was only $232m, or just 11% of the average R&D spend per new approved drug.

Figure 1 illustrates the HABP/VABP scenario in Table 2, but varies the joint preclinical and phase 1 transition probability (the probability that a drug passes both phases) and the weighted average cost of capital (WACC). It shows the expected value of R&D investment required per drug approved varying by a factor of 4 as we change the probability of success of preclinical and phase 1 trials. Cost of capital assumptions, which vary the time cost of money, are also important but less so within the 9% to 23% range we have examined.

Figure 1: R&D Cost Estimate's Sensitivity to Transition Probability Assumptions



Looking now at Tier C regulations (Tables 1 and 2), it is much cheaper to run clinical trials for narrow-spectrum agents, which have higher success rates for several reasons. First, they are easier to discover given current technological capabilities, so there are more viable candidates to select for clinical trials. Second, there are plausible scientific reasons to expect them to be less toxic to humans than broad spectrum candidates. Sertkaya et al (2014) used concerns about toxicity to justify the low success rates of broad-spectrum drugs in preclinical and phase 1 trials. One interviewee argued that many broad-spectrum antibiotics have 'promiscuous' and 'messy' target binding profiles (they have to bind to a family of homologous but slightly different target proteins in various micro-organisms), which increases human toxicity (Interview 4). Third, narrow spectrum drugs have benefits with regard to resistance patterns:

> *There are huge benefits from the perspective of evolution of resistance if you use narrow spectrum agents. With broad spectrum agents, every bug in the patient is exposed to a selective pressure. With narrow spectrum agents, most bugs in the patient are not exposed to any selective pressure. There is also much less chance of horizontal acquisition of resistance (i.e. cross species DNA transfer) … narrow spectrum agents should have a much longer useful life* (Interview 5)

Our cost sensitivity analysis suggests that regulatory changes have created an environment more conducive to the successful clinical development of novel, narrow-spectrum antimicrobial drugs.

Financial/Market Barriers to Antimicrobial Drug Development

Our research suggests that other factors are hindering antimicrobial drug development: (1) the viability of markets; and (2) interactions between rapid pathogen identification

(through diagnostic innovation) and resultant impact on clinical trials costs for narrow-spectrum drugs.

Attractiveness of Markets and the 'Average' Drug

Industry interviewees identified the lack of market incentives as the main barrier to antimicrobial innovation:

> *[The] problem is a lack of clarity on commercialization 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 [some new antibiotics are now $15,000]… this is not an easy problem given payer resistance and the way different kinds of drugs are reimbursed. Most antibiotics for serious infections are prescribed within the hospital setting and are not reimbursed separately from the rest of the treatment episode [unlike most cancer or orphan drugs]* (Interview 6)

Prevailing norms of reimbursement mean novel antimicrobials prescribed within a hospital will never achieve the profits that have made other niche drug markets attractive for R&D investment. Furthermore, new antimicrobials will be reserved for patients that have failed to respond to existing drugs, reinforcing market failure.

Much attention has been given to this 'incentive problem' (Sciarretta et al, 2016; HOC, 2014; Sertkaya et al, 2014), and the following points arise from our analysis. First, we should be wary of analyses of the attractiveness of antimicrobial R&D based on historic average costs, probabilities, and sales, because R&D investment decisions are not predominantly driven by these factors, but by assessment of future costs, probabilities, and sales. Furthermore, financial returns on R&D at the project level are rarely 'average', and there is evidence that returns are highly variable and skewed across therapy areas (DiMasi and Grabowski, 2012; Scannell et al, 2015). Most projects lose money, and a small proportion of projects generate much of the value for the company. Nobody knows *a priori* which projects will be successful (Chia, Rifai and Sarraf, 2013).

Second, estimates of R&D returns to firms and investors are sensitive to these actors' estimates of R&D success rates and future market potential. Such actors rarely consider themselves 'average', particularly when they see promising new technologies (e.g. rapid diagnostic testing) to support highly selective antimicrobials. Third, returns on incremental investment change during R&D. For investors in early stage drug discovery, the expected cost of the entire R&D process, including failures, is salient. The investment's attractiveness is shaped by the fact that profits will not accrue for many years, as our analysis in Table 2 illustrates. However, specific decisions on incremental investment during the R&D process are different. 'Surviving' drug candidates acquire higher value as they move through development. When the decision comes to initiate phase 3 trials, much of the R&D costs have been sunk, but potential profits are imminent. Profit margins too narrow for investment in early stage drug discovery

activities now look attractive when relatively modest investment will likely bring a late-stage candidate to market.

From 2012-1014, the FDA granted 40 antimicrobial drug candidates 'orphan-like' Qualified Infectious Disease Products (QIDP) status (Woodcock, 2014). According to our respondents, money is being invested in antimicrobials by a number of companies (Cubist, Durata, Bayer, Aradigm, Actelion, and Merck). Among firms we interviewed, the dominant view was that money was being invested in hope that incentives would improve and clinical trials for narrow spectrum agents would become cheaper and less prone to failure. If new incentives do not materialise, and diagnostics do not improve, many believed R&D investment would stall.

Diagnostic Innovation and Narrow-Spectrum Antimicrobial Drug Trials

Current enthusiasm for narrow-spectrum antimicrobial drugs rests on the assumption that clinical trials can be run more quickly and cheaply. This requires the availability of appropriate diagnostic tests:

> *There is a huge economic complementarity between rapid diagnostics and antimicrobial drug R&D. The need to pre-treat severely ill patients with a broad-spectrum agent while waiting for conventional microbial identification means that trials are bigger, noisier, more expensive. If you really could do rapid diagnosis … you could run the antibiotics trials much more like some of the recent anti-cancer drug trials; fewer patients recruited, better signal to noise ratios, hence easier and more profitable R&D* (Interview 7)

This reflects the need to improve systems for managing patients in hospitals and clinical trials. Many respondents hoped that development of routine diagnostic tools and services could shift narrow-spectrum agents into more widespread use, which would create commercial opportunities without an unacceptable increase in AMR.

Our research uncovered four factors that impact on diagnostic innovation for antimicrobials: (1) the ability of diagnostic tools to fit into existing health system workflows and practices; (2) the ability of diagnostic tools to fit into existing health care budgets; (3) the scale economics of laboratory supply and (4) the cost of validating diagnostics for rare diseases. The first three have an indirect effect in that they reduce clinical adoption, which affects financial incentives for R&D investment.

In terms of health system workflows, one respondent observed that the ideal in vitro diagnostic (IVD) is 'boring', in that it should provide new information but not affect how physicians or health system operate. It is easy for health systems to substitute a better antibiotic for an older, less effective one. However, diagnostic technologies are more likely to require changes to conventional healthcare pathways and clinical practices. If they change workflows, even by adding just 5 minutes to a consultation (Interview 8), they are less likely to be clinically adopted. This applies to diagnostic testing for microbes as a precursor to providing narrow-spectrum antimicrobials in both hospital and community settings. If the constraint prevents more

effective treatment of disease, one regulatory solution might be to require doctors to administer a diagnostic test before prescribing antimicrobials.

In budgetary terms, success of IVD innovation depends on who pays for the test and how much it costs. For example, tools that save money in health systems may simply shift payment from one budget to another. Primary care physicians may be reluctant to use relatively cheap point of care tests, if they are paid from their own budgets and if similar results could be provided more slowly by sending specimens to a laboratory, where costs fall within another budget. Our interviewees suggested reimbursement, access, and adoption are challenges for diagnostic companies. New tests can also increase costs if health systems must continue running older services during transition.

National differences in price sensitivity and procurement processes for diagnostics also add complexity. In the US, physicians are often self-employed entrepreneurs, insensitive to the price of diagnostic tests that are paid for by the hospital/insurance company, but sensitive to the risk of litigation if they under-test. European physicians are often employees working within fixed budget systems. A specific test might benefit from pricing and reimbursement in one country, but not another. In the UK, one respondent stated:

> *The NHS insists on proving cost effectiveness. What this means is they expect the diagnostics firm to pay for a big study in various UK hospitals before they think about buying anything. However, it sometimes costs you more to prove to the NHS that your test is cost effective than you would ever make from the test if the NHS became your customer* (Interview 8)

In the US, there is the additional challenge of proving 'clinical utility' for reimbursement. How does one prove that the use of a diagnostic, a priori, and its companion drug results in better, more cost-effective outcomes versus the prescription of an 'off the shelf' broad-spectrum antibiotic with routine diagnostic testing and second line antibiotic treatment as back-up?

These factors highlight the challenge of incorporating new activities or costs into complex health systems. Another factor relates to the economics of the IVD industry and laboratory practices, which discriminate against particular types of test. Complex tests that are rarely used are difficult to integrate into laboratory workflow and are unattractive to manufacturers. For example, for oncology drugs and their companion diagnostics, the diagnostics are cross-subsidised by the drug, which is the only way that IVD companies make money. The diagnostic only makes commercial sense where it supports the sale of an expensive cancer drug, and the drug company pays for the development of the test and its clinical use. Similar cross subsidies allow the health system to administer the test:

> *Panels of molecular tests often end up being costly [to administer], particularly if you are looking for relatively rare diseases. To give an example, in lung cancer, the drug crizotinib works very well in the 5% of lung cancer patients with an ALK mutation. That means you have to test 20 patients to get a single positive. Even if each test is only 500 euros [to*

the health system], this means you spend 10,000 euros per patient detected. The expectation is that the drug company ends up paying for the companion diagnostic (Interview 9)

The problem in the case of IVDs for rare pathogens, or rare forms of AMR, is that unlike the case of cancer treatment, there is no 'blockbuster' antimicrobial drug to subsidise the development costs of the diagnostic and its administration.

Finally, costs associated with the validation of tests for rare diseases are important given that most types of AMR are rare. Statistical assessment of test quality is both more complex and less familiar to most people than the assessment of drug efficacy. Many believe a clinical trial proves a drug 'works' if the difference in outcome between patients who received the drug and those who did not is 'statistically significant' at the $p < 0.05$ level. However, there is no simple rule to prove a diagnostic works (Greiner, Pfeiffer, and Smith, 2000). For most diagnostic tests, it is important that vendors, customers, auditors, and regulators understand at least four parameters: sensitivity, specificity, positive predictive value, and negative predictive value. The first two are intrinsic attributes of the test. The others depend on context of use. The test's usefulness depends on the acceptable trade-offs between these parameters. In general, if sensitivity rises, specificity falls. If the disease is severe and the diagnostic test expensive, while the curative drug is safe and cheap, one might be willing to accept false positives from the test, but would be concerned about false negatives, as the following account illustrates:

When you have multiplexed tests [a panel of tests for different pathogens run simultaneously using the same test kit and machine] the cost of validation [in R&D] goes up. So consider a panel of test for sepsis. Practically any bacteria can cause sepsis in certain patients. Technically, we could easily make a panel of 100 yes/no PCR tests. However, it is only the 10 most common pathogens that you encounter frequently enough to effectively validate the tests. With the very rare pathogens you cannot estimate your false positive and false negative rates without testing an inordinately large number of samples, the overwhelming majority of which will be negative. Importantly, AMR is still relatively rare and specific mechanisms of resistance are often very rare. Therefore, broad panels of PCR-based tests for resistant bugs will be expensive to validate (Interview 10).

Together, these factors highlight continuing challenges that inhibit commercial development and delivery of effective antimicrobial drugs and diagnostics to the clinic.

Conclusion

We have analysed the role of regulation in incentivising or inhibiting the commercial development of new antimicrobial drugs and diagnostics to address the global AMR challenge, and other market factors that make such innovation unattractive to the pharmaceutical industry - reimbursement and the complexities of diagnostic testing for narrow spectrum agents. Clinical norms and practices have a significant negative impact on new antimicrobial drug development, and regulatory changes can support the R&D

process. Commercialization challenges for new antimicrobial drug development are clearly not new, particularly on reimbursement. Most hospital use of antibiotics for serious infections is either paid from a fixed hospital budget, or else reimbursed on a DRG-basis. In both cases, institutions have a financial interest in using established antibiotics, which are now almost always generic and cheap. However, new stewardship concerns have a compounding effect on the economics of antimicrobial innovation.

In conclusion:

(1) Given the scarcity of broad-spectrum antimicrobial agents, accurate and rapid IVDs to detect the nature of the infectious agent and its susceptibility to narrow spectrum agents will become increasingly important. A new process will be required for these IVDs to enable co-development of the drug and diagnostic and a viable payment model.

(2) There has been considerable regulatory adaptation to enable rapid and cost-effective development of new antimicrobial drugs with social benefits, so regulation is no longer considered an important barrier to drug development. R&D costs per drug may have more than halved as a result of recent regulatory changes.

(3) However, the lack of market incentives is inhibiting antimicrobial drug innovation; particularly issues around hospital practices, workflows, and diagnostic/therapy reimbursement. Rather than focus on historical R&D costs or current profits, it is important to satisfy investors and companies that investment in antimicrobial development today will provide acceptable returns in future.

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