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Time for a change in how new antibiotics are reimbursed: Development of an insurance framework for funding new antibiotics based on a policy of risk mitigation

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ABSTRACT

Healthcare systems depend on the availability of new antibiotics. However, there is a lack of treatments for infections caused by multidrug resistant (MDR) pathogens and a weak development pipeline of new therapies. One core challenge to the development of new antibiotics targeting MDR pathogens is that expected revenues are insufficient to drive long-term investment. In the USA and Europe, financial incentives have focussed on supporting R&D, reducing regulatory burden, and extending market exclusivity. Using resistance data to estimate global revenues, we demonstrate that the combined effects of these incentives are unlikely to rekindle investment in antibiotics. We analyse two supplemental approaches: a commercial incentive (a premium price model) and a new business model (an insurance model). A premium price model is familiar and readily implemented but the required price and local budget impact is highly uncertain and sensitive to cross-sectional and longitudinal variation in prevalence of antibiotic resistance. An insurance model delivering risk mitigation for payers, providers and manufacturers would provide an incentive to drive investment in the development of new antibiotics while also facilitating antibiotic conservation. We suggest significant efforts should be made to test the insurance model as one route to stimulate investment in novel antibiotics.

1. Introduction

One key challenge of developing new antibiotics is that expected returns and associated risk are not competitive with other therapeutic areas [1–8]. The conventional pharmaceutical business model with reward based on sales volume and price puts the twin objectives of (i) developing new antibiotics to tackle growing antimicrobial resistance, whilst (ii) restricting use of antibiotics to encourage appropriate stewardship, in opposition to each other. Initiatives to try to solve this problem are being implemented, but have focused primarily on providing funding for early stage research and development (R&D) [9,10] and on regulatory changes [11,12] with, in some cases, additional market exclusivity. Recent analyses [5,13,14] have identified other types of incentives required to make R&D for new antibiotics more attractive. In this paper we model three policy options. Firstly, we explore whether public support for R&D with regulatory change and market exclusivity is likely to be sufficient to stimulate new R&D. Secondly we model a premium price model in which the pricing mechanism is used to restrict use and to provide a return on R&D. Thirdly we look at the impact of introducing a new "insurance-type" commercial model, which involves the partial de-linkage of returns on R&D from the volume of sales. This is the only option which meets the twin objectives referred to above. We then discuss how this can be made to work in the context of other proposals for de-linkage.

2. Our economic model for evaluation of incentives

Our approach was to combine a global estimate of the costs of developing a new antibacterial drug with global demand and revenue estimates scaled up from detailed modelling of demand and resistance estimates. We based our analysis on a hypothetical antibacterial drug targeted against specific, multi-drug resistant

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Table 1
Global cost of R&D for a new antibiotic and effect of incentives on R&D and eNPV.

	PCRD	Phase I	Phase II	Phase III	Registration	Post-launch study	Total (excl. post-launch)
	Base case without incentives						
Global cost (million)[a]	$19	$16	$54	$196	$29	$40	
Progression rate[b]	0·35	0.67	0·46	0.70	0·87	N/A	
Duration	5 years 0 months	1 year4 months	2 years2 months	2 years5 months	0 years11 months	6 years	11.8 years
Total programs[c]	15.22	5.33	3.57	1.64	1.15		15.22
Global capitalised cost (million)[d]	$708	$153	$292	$393	$35	$40	$1581
eNPV ($m)							-$1510
	With matched (50%) co-funding as part of Public-Private Partnerships for R&D						
Global capitalised cost (million)	$354	$76	$146	$197	$17	$20	$791
eNPV ($m)							-$701
	Implementation of the Tier B[e] framework for registration						
Global cost (millions)	$19	$16	$54	$98	$29	$40	
Global capitalised cost ($m)	$708	$153	$292	$197	$35	$40	$1385
eNPV ($m)							-$1313
	With matched funding as part of PPP for R&D and implementation of the Tier B framework for registration						
Global capitalised cost (million)	$354	$76	$146	$99	$17	$20	$692
eNPV ($m)							-$603

[a] Out-of-pocket costs to support a single program.
[b] Progression rates are defined as the probability of progression to the next stage of R&D or successful registration. Two progression rates for pre-clinical R&D (PCRD) have been published; 0·35 [35] and 0·10 [36]. We used the more optimistic estimate of 0·35 which results in lower R&D costs. Progression rates for the subsequent clinical development phases were estimated from our analysis of clinical studies for antimicrobials conducted between 2005 and 2011 (see supplementary material). Note that for Phase III, we use the (more optimistic) average of 0.70 reported by Paul et al. [35] which results in lower R&D costs.
[c] This is the total number of programs that are required to be initiated at the pre-clinical R&D stage to produce a single licensed product.
[d] A cost of capital of 10% was used to calculate the capitalised cost of R&D. It represents the expected return required from an alternative investment portfolio with a similar level of risk [17].The capitalised cost is risk-adjusted to account of failures i.e. programs that do not progress to next phase.
[e] Under Tier B pathway [11], there is one phase III trial rather than two (standard) phase III trial for each of two indications. Thus, we assume Phase III costs are a quarter relative to our base case, which is a conservative estimate of the cost of late-stage development.

(MDR) pathogens with expected use exclusively within acute care. Prevalence of the MDR pathogens would be very low at the point of registration of a new antibiotic, which would therefore, initially, be rarely used. Resistance prevalence and subsequent growth was based on a combination of high and low European country-specific prevalence data for healthcare-associated infections (HAIs) [15] and the most recently available data for rates of resistance of *E. coli* to third generation cephalosporins [16] (see the supplementary material). To model lifetime revenues we estimated an average price per course and, using increased prevalence of antibiotic resistance as the key driver, estimated volumes. We are not aware of any other modelling using this approach.

Economic viability was assumed to require a global estimated pre-tax NPV (eNPV) of $100 million [5]. Programs were assumed to target global registration. The model covered R&D from drug target to registration, and revenue, manufacturing and distribution costs for twenty years post-registration. To model the effect of recent efforts to streamline antibacterial development, our base case included estimated Phase 3 costs of four large non-inferiority studies (two for each of two different indications to obtain registration in the US and EU). We also include a single post-launch study costing $40 million to cover the costs of additional indications.

3. Cost of developing a new antibiotic and resulting estimated net present value (eNPV) – base case

Our assumptions for the base case model (i.e., with no incentives) R&D costs and eNPV are shown in Table 1. The estimated global cost of developing a new, targeted antibiotic, excluding the post launch study, was calculated at $1581 million (at 2011 US prices), which is similar to that of Mestre-Ferrandiz et al. [17]. Pre-clinical R&D contributes the greatest share of the capitalised development cost as (i) a large number of projects need to be initiated at this stage due to low probability of progression and (ii) from the long time remaining to drug licensing impacts the cost of capital.

For the base case, the market for a new antibiotic was based on an assumed 3% annual growth in the number of HAIs and a prevalence growth of MDR infections requiring treatment with a new antibiotic of half the growth in prevalence of infections caused by *E. coli* resistant to third generation cephalosporins. Data came from the European Centre for Disease Control Antimicrobial Resistance Interactive Database (EARS-Net) [16]. Assuming a price per day of $120, roughly comparable to recently launched branded antibiotics for certain Gram positive infections, and treatment duration of 14 days for a complicated Gram-negative infection [18], results in a treatment course cost of $1680. Operating cost assumptions are set out in the supplementary material. The global eNPV for the base case, including R&D and registration cost, and post-registration revenue and costs, was negative (- $1510 million).

We estimated the numbers of MDR infections that would be needed in our model to make the current price/volume arrangements viable for new drugs, i.e. generating the target eNPV of $100m. If the cost of treatment for each case of infection caused by a MDR pathogen remains at $1680, the total number of MDR cases for Europe and North America at the time of launch required to produce a positive eNPV would need to be more than 375,000 with cases of HAI needing to almost double from the 12.56 million cases in 2012–23.67 million with 1.58% caused by a MDR pathogen requiring a new antibiotic. If 80% of these MDR patients were treated with the new antibiotic, equating to an annual revenue of $630 million, the required eNPV would be achieved. This compares to our base case estimate of 200 cases in the first year post-registration based on data from EARS-NET for E. coli resistant to third generation cephalosporins. The analysis is set out in the supplementary material. Such a high prevalence of MDR infections would likely produce a large increase in attributable excess mortality [19], morbidity [20,21] and a decrease in the number of certain medical procedures (e.g. surgical implantation) that patients would be willing to risk and which hospitals would be willing to perform [22,23]. In short, relying on growth in MDR infections to make the existing commercial model for drug development work would require such a high prevalence of MDR infections that the sustainability of developed country health systems would be threatened. Patients would be reluctant to undertake routine treatment because of the