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Antibiotic reimbursement in a model delinked from sales: a benchmark-based worldwide approach

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Despite the life-saving ability of antibiotics and their importance as a key enabler of all of modern health care, their effectiveness is now threatened by a rising tide of resistance. Unfortunately, the antibiotic pipeline does not match health needs because of challenges in discovery and development, as well as the poor economics of antibiotics. Discovery and development are being addressed by a range of public–private partnerships; however, correcting the poor economics of antibiotics will need an overhaul of the present business model on a worldwide scale. Discussions are now converging on delinking reward from antibiotic sales through prizes, milestone payments, or insurance-like models in which innovation is rewarded with a fixed series of payments of a predictable size. Rewarding all drugs with the same payments could create perverse incentives to produce drugs that provide the least possible innovation. Thus, we propose a payment model using a graded array of benchmarked rewards designed to encourage the development of antibiotics with the greatest societal value, together with appropriate worldwide access to antibiotics to maximise human health.

Introduction

Antibiotics have transformed modern medicine and society, but the development of resistance is inevitable with their use. Resistance is of particular concern as a result of the weak development pipeline and the emergence of strains for which there are few therapies.^{1,2}

The causes of the thin pipeline are well understood: the discovery of antibiotics is difficult, clinical development of antibiotics is constrained and costly, and economic return on new antibiotics is generally poor.^{3–5} The first two challenges are being addressed via collaborative public–private partnerships⁶ and updates to regulatory pathways.^{7–10} However, the economic challenge of antibiotics is rooted in a fundamental tension between the need for antibiotic conservation and the need for a sales-based return on investment to recoup development costs. New antibiotics are appropriately restricted from use, thus lowering sales. This decrease in sales leads to a low projected value and has reduced private antibiotic investment.^{5,7,11–13}

Furthermore, estimating the market for a novel antibiotic is difficult. For example, carbapenem-resistant Enterobacteriaceae (CRE) are one of three urgent pathogens listed in the 2013 threat assessment produced by the US Centers for Disease Control and Prevention (CDC);² however, predicting the size of the market a decade from now is a struggle for companies. For example, the market in Sweden for such a drug effective against CRE is currently exceedingly small: the entire country recorded only 94 cases of isolation of CRE during 2007–13, with only 24 cases of symptomatic infection.¹⁴ Furthermore, an entirely new drug might not have been needed since 73% of the isolates were susceptible to at least three classes of antibiotics. In the USA, the CDC has estimated about 9000 clinical cases of CRE per year,² but many of these will be susceptible to a few existing drugs. Thus, the actual number of CRE cases per year in the USA requiring a new antibiotic is likely to be less than 9000. If infection prevention efforts

are successful, future trends would be even lower: the US National Strategy projects a 60% decrease in CRE infections in US hospitals by 2020.¹⁵ These reductions are excellent public health targets but make the commercial case even more daunting.

Addressing the economic challenge via a delinked model

Breaking the link between sales volume and return on investment is one possible approach to resolving the tension between antibiotic stewardship and business imperatives. Antibiotic delinkage pays companies on some basis other than sales volume, such as value or milestone-based payments. Delinkage could be implemented through payments of a predictable size and duration after successful registration of a new qualifying drug. Such payments would guarantee regulatory maintenance of the drug (eg, initial registration, maintenance of registration, pharmacovigilance, etc) and continuity in the supply chain (manufacturing base), whether the drug was prescribed or not.^{5,16,17}

Calculation of the size of delinked payments

Economic models might be useful in estimating the size of potential delinkage payments on the basis of recovering research and development costs. One model of net present value (NPV) of a new antibiotic transforms a money-losing drug to one with an NPV of US\$300 million at the start of the research and development process through the promise of future payments of \$500 million per year for the first 5 years after initial registration.¹⁸ The Review on Antimicrobial Resistance¹⁹ commissioned in the UK estimates a range from \$2 billion to \$4 billion for a full global patent buyout (depending on discount rate, costs, and probabilities of success), paid in a lump sum 3 years after registration. A model prepared for the US Department of Health and Human Services estimated that the US market for one new antibiotic could be covered with cash payments over

the product development cycle and at registration totalling \$919 million.¹¹ These models make assumptions that should be verified in a transparent process, and need to account for the cost savings arising from government support. However, they provide a useful starting point for discussing buyout prices adequate to encourage work in this specialty (table 1).

Nevertheless, it does not seem reasonable to assign all antibiotics the same delinked reward. Experience shows that the usefulness of antibiotics varies, with some proving useful over time and others being withdrawn for a range of reasons.²⁰ New antibiotics have historically been valued via marketing on the basis of product differentiation. A manufacturer would be motivated to select and develop candidate drugs that are medically relevant, distinguishable from existing drugs on the market, and hence commercially viable. Additionally, a manufacturer is motivated to continue development after the initial registration, generating incremental data that further support the drug's use in preference to other drugs.

In a delinked model, however, these incentives will not be present in the same fashion. Offering the same reward to all newly developed antibiotics would create a perverse incentive, spurring the development of drugs that offer the least possible incremental advantage over existing drugs. Furthermore, there would be no incentive for development beyond the minimum requirements. Most fundamentally, the cost of creating an antibiotic would not necessarily relate to the value of the drug to patients and society.

The notion of reimbursing for value is generally attractive, with value defined as incremental improvements in human health.²¹ In the USA, Medicare and other payers are experimenting with paying for value in health care.²² Although this is a theoretically promising solution, concerns over how the effect of the antibiotic on health is measured and reimbursed need to be resolved. This research is underway via DRIVE-AB and the Innovative Medicines Initiative.

Analogy to the insurance value of fire prevention and control services

Antibiotics could offer insurance value merely by being available for use, hence creating an environment wherein medical care, travel, and commerce can be confidentially pursued. In this regard, antibiotics and infection control bear a striking resemblance to the fire-fighting infrastructure: the microbiology laboratory serves as the smoke detector, medical personnel are the fire fighters, and antibiotics are the water supply. All of these elements have to be established before the fire (infection), since buildings burn (and patients die) far more quickly than infrastructure can be built. For example, an outbreak of plague in India in 1994^{23,24} caused as many as 200 000 people to flee the vicinity and cost the local economy an estimated \$600 million. The

	Payments from governments	Expected NPV benchmark at commencement of R&D
Sertkaya et al ¹¹	\$919 million (spread over entire R&D process and at registration; USA only)	\$100 million
Sharma and Towse ¹⁸	\$2.5 billion (\$500 per year for 5 years)	\$300 million
Review on Antimicrobial Resistance ¹⁹	\$2–4 billion (paid 3 years after registration)	Not stated
All values are in US\$. R&D=research and development.		
Table 1: Nominal and expected net present value (NPV) estimates of the needed size of antibiotic delinkage payments		

costs of facing a hypothetical pandemic strain of CRE in London or New York are almost incalculable. The availability of an effective therapy would doubtless have reduced the overall level of public anxiety; however, the insurance value of the drug would have been present whether or not the actual epidemic had occurred, just as the fire department is needed even if no fires occur in a community. Calculations of the insurance value of antibiotics are in their preliminary stages,²⁵ but the consequences of not having insurance^{26,27} should encourage participation in a worldwide scheme ensuring antibiotic availability.

Benchmarks for delinked incentives

Delinked incentives should require delivery to market of a qualified drug; however, they equally need to recognise that initial approval is only one step towards understanding a new drug. The updated regulatory pathways that permit initial registration with small datasets in many ways implement an adaptive (or progressive) licensing approach²⁸ in which initial registration is presumed to be followed by further investigations. Thus, delinkage should not be front-loaded at the moment of registration, but instead spread across the period of time during which clinical evidence is still being developed.

To address these intertwined issues and in recognition of calls for research in this specialty (eg, from a 2015 report by the European Parliament²⁹), we discuss a delinked approach based on a combination of benchmarked payments (table 2). In this proposal, qualifying novel antibacterial antibiotics receive delinked reimbursement for a standard term of 5 years beginning at the time of initial registration. This base amount would be paid to every qualifying drug via a single global buyer. The benchmarks provide a dynamic range by offering additional payments up to four times greater than the base amount for unambiguous delivery of features that are more valuable to society. This benchmark payment is intended to be the net profit earned by the developer.

The standard base reward amount should be calculated globally on the basis of reported models,^{11,18,19} and be sufficient to create a reasonably positive NPV for

For the DRIVE-AB initiative see <http://drive-ab.eu>

	Annual payment*
Drug approved at US FDA and European Medicines Agency to treat at least one defined infection‡ caused by at least one or more pathogens listed on the CDC 2013 threat assessment as either urgent, serious, or of concern to public health†	Base payment†
Has a clinical spectrum of activity on the label that includes one or more urgent pathogens on the CDC 2013 threat assessment§	Bonus equal to one base payment
Has a clinical spectrum of activity on the label that includes one or more serious pathogens on the CDC 2013 threat assessment§	Bonus equal to 50% of a base payment
Is the first approved drug to act via a given mechanism of action¶	Bonus equal to a base payment
Is the second, third, or fourth agent approved to act via a given mechanism of action	Bonus equal to 75% of a base payment for a second agent, 50% for a third agent, or 25% for a fourth agent
Is the fifth or subsequent agent to act via a specific mechanism of action but offers a medically relevant improvement in safety, efficacy, or ease of dosing	Bonus equal to 10% of a base payment
Delivery of agreed paediatric commitment studies	Payments based on model or separate contract open to tender
Is approved for a second, third, or fourth defined infection‡ for a specific agent	Bonus equal to 25% of a base payment
Approved in oral dosage form	Bonus equal to 25% of a base payment

Benchmark payments are paid annually for 5 years from the date the benchmark is first met. *Payments are additive and new drugs can earn various benchmarks. The payment for an oral drug labelled for an urgent pathogen that has a novel mechanism of action (eg, multidrug-resistant *Neisseria gonorrhoeae*) would be 3.25 times the base amount (one base amount, one bonus for urgent, one bonus for new mechanism of action, and a 0.25 base rate bonus for oral formulation). Additional bonuses could be earned for this drug in subsequent years by up to three label extensions in other infections, up to 0.75 of a base amount. †All new agents are expected to earn this payment (it is the minimum bar). ‡Defined infections are aggregated broadly rather than narrowly. §A new drug can earn one or both of these payments; the payment in each category can only be earned once (coverage of various urgent pathogens does not earn several payments). ¶Mechanisms of action are defined broadly rather than narrowly. ||If a benchmark is met as part of the initial drug approval, these benchmark payments will be paid annually for the full 5-year contract term provided that the sponsor maintains the drug on market. If a benchmark is met subsequently, payment will be made annually for a full 5-year contract term; however, this additional payment will start at the date the benchmark was met.

Table 2: Estimated benchmark payments for new antibacterial antibiotics

initial registration for a single indication. Additionally, the amount should cover the cost of paediatric co-development and account for previous public funding. Further modelling and public debate would be needed to ensure consensus on the base reward rate, but base payments around \$200 million per year over 5 years would be consistent with present modelling data. Five conditions would increase the benchmark payments over the base amount: novel mechanism of action; addressing serious unmet medical needs; reducing health-care costs; targeting priority resistant pathogens; and post-approval label changes to expand the indications. Each additional benchmark payment would be made for 5 years and can start at or after initial registration.

First, substantial payments might be earned via discovery and successful development of a drug with a novel mechanism of action. In this proposal, mechanisms of action should be construed broadly rather than narrowly, since otherwise the developer could argue that slightly different points of contact with a target qualify as a different mechanism. For example, inhibition of a multicomponent enzyme at the same site as an existing drug (eg, inhibition at the catalytic

site of GyrA and ParC, which are blocked by the fluoroquinolones) would not qualify as a new class of antibiotic, but inhibition at an entirely new location on these large molecules (eg, the ATP binding site of GyrB and ParE) would qualify. A public consensus led by a respected neutral body would probably be needed to delineate how new mechanisms of action and antibiotics withdrawn from the market are classified (eg, whether novobiocin, which is no longer marketed, is a previous example of an inhibitor of the ATP binding site of GyrB and ParE).³⁰

Second, although the full payment for a novel mechanism cannot be earned by subsequent class entrants, substantial payments should be offered to subsequent entrants solving problems such as toxic effects, dosing, and efficacy. This method deliberately encourages the development of improved drugs within a new class, since they provide substantial societal value.³¹

Third, additional benchmark payments should be made for reducing overall health system costs, such as oral administration of a drug, and adding value to society generally. Oral administration offers a substantial benefit to the overall health-care system by reducing the complexity of administration and by facilitating step-down and outpatient treatment. Furthermore, oral administration can promote access in resource-constrained populations.

Fourth, the development of drugs that target priority pathogens selected through a global threat assessment, similar to the one done in the USA by the CDC, should result in additional benchmark payments.² In the CDC threat assessment,² resistant pathogens were triaged through an expert assessment into three categories: urgent, serious, and concerning. Higher payments would be made for drugs that target pathogens in the urgent category and a lesser amount for those in the serious category. No additional payments would be awarded for the concerning category, since that is the baseline for entering the delinked reward structure.

Finally, additional payments should be made after further clinical studies that expand the drug's label to include new indications. These payments will provide an incentive for developers to pursue further study after initial registration. The developer should receive a suitable reward for the effort even if it cannot be part of the initial registration. Distinct indications could include community-acquired bacterial pneumonia, hospital-associated or ventilator-associated bacterial pneumonia, complicated and uncomplicated urinary tract infection, complicated intra-abdominal infection, acute bacterial skin and skin structure infection, endocarditis, meningitis, osteomyelitis, infectious arthritis, uncomplicated sexually transmitted diseases, and the Unmet Need indication proposed by the European Medicines Agency.

Similar to incentives pertaining to the mechanism of action, it will be important to avoid the distorted

incentives that might ensue if indications are too narrowly divided. Hence, fine distinctions should not be drawn (eg, uncomplicated cervical, anal, urethral, and oropharyngeal gonorrhoea would not qualify as four forms of uncomplicated gonorrhoea). Again, public consensus on defined indications would probably be needed.

Implementation of such a scheme has to consider the perspective of the companies investing in new agents. First, the values assigned to the benchmarks should be modelled against expected company investment and public benefit. They need to be robust enough to encourage companies, but not so large that society does not obtain excellent value. For example, if society expects a company to invest \$93 million in post-approval phase 4 studies over a 5-year period, then the expected NPV of these studies should be positive based on the models. By one model, the necessary reward for this scenario is \$70 million per year, paid over the following 5 years.¹⁸ This reward is surprisingly large because of the assumption of an 11% discount rate. Alternatively, post-registration research undertaken under contract with no connection to delinkage payments might be more efficient. Risk of failure is lower in post-approval studies and the research could be completed without the financial effects of discounting.

Second, low-cost worldwide access should be assured without patent-based mark-ups. The developer should not receive profit based on usage, and promotional activities should be eliminated. On the basis of projected and actual health needs, the developer will need to produce and make available via standard supply chains the needed volumes during the contract period. The net global price will be the audited marginal cost of production (including appropriate overheads to maintain the supply chain and address pharmacovigilance). To avoid incentives that could result from users perceiving a particular drug to be cheap, it might be necessary for the drug to have a price similar to that of other drugs already on the market and locally accessible. Thus, usage would be guided by medical need combined with good stewardship practice. The difference between the audited marginal cost and the price paid by the user could be rebated to the global purchasing facility.

Third, antibiotic research and development is a worldwide issue that cannot be solved by any nation alone.³² We propose an integrated worldwide reimbursement model with proportional financial contributions from, at the very least, members of the G20 (which includes Brazil, China, India, Russia, and South Africa). Broader participation can occur over time and a global institution would be needed to coordinate such a venture. Models include GAVI, MMV (Medicines for Malaria Venture), and the Medicines Patent Pool. The institution will require the ability to

contract with companies and enjoy stable funding from the USA, European Union, and other G20 governments. Alternatively, the USA and European Union could independently pursue delinked reimbursement programmes that are coordinated to align the basic incentives towards a common set of goals.^{33,34}

Limitations and further questions

This proposal has many limitations and questions for further study (panel). The benchmark payment values in table 2 need to be modelled on the basis of audited parameters and agreed by many stakeholders. Stable funding will be needed, with incremental worldwide funding in the range of \$2–4 billion per year. However, since the worldwide antibiotic market is roughly \$40 billion per year, investments of this magnitude are quite reasonable to preserve this life-saving class of drugs.³⁵ Creation of a suitable worldwide authority to implement this fund is another obvious constraint, in addition to the problem of free riders on the system and the absence of an incentive to reduce production costs.^{33,34}

Delinkage should guarantee maintenance of antibiotics after all reward payouts are completed. This can be partly addressed by making on-market maintenance a condition of receiving any reward payment. Since at least some of the reward payments are likely to be staggered (additional label-extending indication studies can take up to 2–4 years), individual drugs might be supported by remaining payments for up to a decade. However, longer-term maintenance is desirable and this would entail at least some ongoing contractual maintenance arrangements. Providing a steadily reducing percentage of the total earned reward for a further period of time should be considered, with the percentage falling to zero at a point corresponding roughly to the typical term of marketing exclusivity.

Panel: Next steps

The following steps are crucial to making a model delinked from sales a reality:

- Further modelling of the magnitude of payments needed to create an appropriate incentive, with such modelling to identify ways to account for previous government support
- Further modelling of the insurance value of antibiotics
- Consensus on the definition of a novel mechanism
- Consensus on the distinct indications that would earn a benchmarked payment
- Building commitment from the G20 countries for long-term support
- Creation of a global facility to manage the delinked purchase process
- Agreement on a process for drugs reaching the end of their benchmarked payment period

Drug production over a very long period of time could be contracted to the developer or others willing to undertake the tasks.

A further risk is that some investors might view a defined, fixed reward as contrary to the high risk–high reward model of the biotechnology industry. However, our view is that the present market model for antibiotics is high risk–low reward and that most investors would be pleased to have a predictable return on investment.

Conclusion

We need new antibiotics that have the greatest societal value. Delinked payments can be designed with a base payment linked to the registration of a new qualifying antibiotic and a set of incremental benchmark payments earned by demonstration of specific properties of the new drug. The strength of this proposal comes from the simplicity of benchmarks and their direct linkage to features offering societal value. The scheme encourages novel drugs, foresees the need for multiple drugs in a class, and encourages continuing work after initial registration.

Contributors

Both JHR and KO contributed equally to all phases of manuscript generation, from concept to writing.

Declaration of interests

JHR is an employee and shareholder of AstraZeneca Pharmaceuticals; a non-executive Board Member, Senior Advisor, and shareholder of F2G Pharmaceuticals; a consultant to and investor in Advent Life Sciences; an investor in F2G Pharmaceuticals; and an occasional scientific adviser to other pharmaceutical companies. KO is a member of the Roche/Genentech Anti-Infectives Strategy National Advisory Board, with 100% of his consulting fees donated by the company to Habitat for Humanity.

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