

Financing Pull Mechanisms for Antibiotic-Related Innovation: Opportunities for Europe

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(See the Editorial Commentary by Shlaes on pages 2000–1.)

Antibiotic innovation is in serious jeopardy as companies continue to abandon the market due to a lack of profitability. Novel antibiotics must be used sparingly to hinder the spread of resistance, but small companies cannot survive on revenues that do not cover operational costs. When these companies either go bankrupt or move onto other therapeutic areas, these antibiotics may be no longer accessible to patients. Although significant research efforts have detailed incentives to stimulate antibiotic innovation, little attention has been paid to the financing of these incentives. In this article, we take a closer look at 4 potential financing models (diagnosis-related group carve-out, stewardship taxes, transferable exclusivity voucher, and a European-based “pay or play” model) and evaluate them from a European perspective. The attractiveness of these models and the willingness for countries to test them are currently being vetted through the European Joint Action on AMR and Healthcare-Associated Infections (EU-JAMRAI).

Keywords. antibiotic resistance; economic incentives; pull incentives; antimicrobials.

Antimicrobial resistance (AMR) is one of the most serious threats challenging modern medicine. The European Centre for Disease Prevention and Control (ECDC) found that in 2015 antibiotic-resistant infections resulted in 33 000 deaths in the European Union (EU), an increase from 2007 [1]. At the same time, antibiotic innovation is in serious jeopardy with a weak pipeline and companies abandoning the market. The Antimicrobial Resistance Benchmark Report, an independent assessment published in January 2018, analyzed companies with “the largest [research and development] R&D divisions, the largest market presence, and specific expertise in developing critically needed medicines and vaccines” [2]. Two years later, 37% of the 19 innovative companies included in the report (including small, medium, and large ones) have either left the market, gone bankrupt, or dramatically reduced their R&D efforts [3–7].

Companies are not leaving due to insufficient push funding, that is, financing that facilitates R&D. Indeed publicly and philanthropically financed push funding for AMR-related R&D has increased significantly in the past 5 years with actions at both

European and international levels [8]. Companies are leaving because the anti-infective market is not profitable once the product has been commercialized. The sales of 5 of the newest antibiotics (4 of which are produced by small companies) in the United States are reported to be each USD 1 million or less per month, which likely does not cover operational costs [9]. This is not to say that these new antibiotics should be selling in greater quantities. It is likely best for antibiotic stewardship to reserve these new antibiotics while older antibiotics are still effective. Yet companies, especially small ones, cannot survive on these low revenues. When these companies either go bankrupt or move onto other therapeutic areas, these antibiotics may be no longer accessible to patients.

Several reports have called for new incentives to reward the commercialization of new antibiotics that meet unmet public health needs [10–13]. These incentives focus on paying for the innovation rather than utilization, so-called pull financing. For example, a market entry reward is an incentive designed to pay a fixed sum over a number of years for the commercialization of an antibiotic that meets a predefined public health need, as long as the company meets the negotiated stipulations regarding access and stewardship. The European Parliament has called on the Member States to consider these incentives [14]. Yet countries balk due to the large amount of financing needed. An effective pull incentive is estimated to cost 1 billion US dollars per antibiotic globally [10, 11]. However, the true amount of a pull incentive will most likely be negotiated and vary by antibiotic and healthcare system.

Both Sweden and the UK have committed to pilot pull incentives, paying the innovator an annual fee in return for an access guarantee [15, 16]. Both countries state that these pilots

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Table 1: Potential European Financing Models for Antibacterial Pull Incentives

Financing Model	Definition	Requires Regular National Appropriations	Financed Through National Healthcare Budget
DRG carve-out	Paying separately for the antibiotic, outside of the standard DRG used for hospital reimbursement	No	Yes
Transferable exclusivity voucher	Granting a voucher in exchange for the successful regulatory approval of an antibiotic meeting's predefined specifications; the voucher gives a saleable legal right to extend the monopoly time period of any patented medicine	No	Yes
Stewardship taxes	Any national tax aimed to encourage antibiotic stewardship, for example, a tax on veterinary antibiotic utilization	Possibly	Possibly
EMA antibiotic fee ("pay or play")	A fee on all marketing authorizations (human and veterinary) to the EMA, except those for human antibiotic medicines	No	Indirectly

Abbreviation: DRG, diagnosis-related group; EMA, European Medical Agency.

are not meant to stimulate research and innovation, as the rewards are expected to be only high enough to ensure access for national needs. If these pilots can demonstrate that they have maintained secure supply to important antibiotics for a justifiable price, other countries may follow suit.

Many publications have investigated barriers for antibacterial innovation and potential solutions [8, 10–12, 17]. The primary focus of this previous work has been on incentives, that is, detailed descriptions of mechanisms that are meant to stimulate antibiotic innovation. In this article, we take a closer look at 4 potential financing models for pull incentives (Table 1), that is, how to pay for the incentives. Few financing models have been developed. These 4 have been gathered via expert input and are seen as the most promising financing models. We evaluate them from a European perspective, including the source of financing and whether regular national appropriations (ie, government-approved funding) would be required.

DIAGNOSIS-RELATED GROUPS (DRG) CARVE-OUT

Often when contemplating the unattractiveness of the antibacterial market, the obvious solution seems to simply allow the unit price of the antibiotic to increase. Yet this is not straightforward. Many countries determine a medicine's price based upon its clinical evidence [18]. For example, in France medicine prices are determined by incremental clinical benefit. Any medicine with clinical evidence based upon noninferiority trials, meaning that the medicine is found to be "not inferior" to a comparator medicine rather than "superior," automatically receives the lowest scoring, translating to a stipulation that the medicine's price must be lower than the comparator product [18]. Due to the still uncommon occurrence of resistant infections, most new antibiotics are tested through noninferiority trials.

Some countries are examining the potential to adjust the prices of new antibiotics to be commensurate with the value not only for the patient but also society. Several different types of indirect societal values have been described and formulas devised, including transmission value (an antibiotic's ability "to

reduce transmission rates in the general population") and diversity value (an antibiotic's potential "to curb resistance through a reduction in selection pressure") [19, 20]. Including indirect effects may allow an antibiotic to achieve a higher unit price.

Yet increasing the antibiotic's unit price may have little impact due to hospital reimbursement methods. Most European countries use DRG for hospital reimbursement, which allow procedures and treatments to be grouped and reimbursed per procedure, rather than the itemized actual costs [21]. Because antibiotic resistance in most cases is still uncommon, the DRG reimbursement amount is based upon the use of an inexpensive, generic antibiotic. The hospital is not reimbursed for the use of a high-priced antibiotic even when there is demonstrated clinical need.

Some have suggested that the reimbursement value of the antibiotic should be removed from the DRG, a so-called DRG carve-out [17, 22]. In this way, antibiotics could be reimbursed independently. A DRG carve-out is a financing mechanism because it allows hospital antibiotics to be reimbursed at higher prices and potentially removes any economic disincentive for use [23]. However, there are several drawbacks to a European DRG carve-out.

DRG carve-out aims to achieve profitability through unit sales, which may not be possible given the modest rates of multidrug resistance. In 2018 across all European countries there were 1799 cases of confirmed pan-drug resistant *Klebsiella pneumoniae*, 731 for *Pseudomonas aeruginosa*, and 2848 for *Acinetobacter* spp. [24]. Of course, new antibiotics may be preferable to administering multiple individual antibiotics, thereby allowing for greater sales. Yet there are multiple new antibiotics targeting gram-negative pathogens, so each individual antibiotic's market share will likely remain modest, potentially necessitating very high prices.

These high prices may create access inequalities if antibiotics are priced out-of-reach for some countries, even high-income ones. Additionally, countries with higher resistance levels will be the primary payers, whereas countries with low resistance will only need to purchase small amounts. Because all countries benefit from new antibiotics, either as an insurance measure or

as a necessary treatment, DRG carve-out cannot be the sole financing mechanism to stimulate antibiotic innovation. It must be paired with another incentive that balances the financial burden. It appears that the United States is moving forward with a DRG carve-out that will test the mechanism's impact [25].

TRANSFERABLE EXCLUSIVITY VOUCHER

One financing mechanism that would equally impact all European countries is a transferable exclusivity voucher, a saleable voucher awarded to the innovator of a novel antibiotic meeting predefined specifications that can then be used to extend the monopoly time period of any patented medicine [26, 27]. For example, if a company developed "Antibiotic A," it would receive an exclusivity voucher that can prolong the monopoly period of its own "Blockbuster Medicine" or sell the voucher to the innovator of another "Blockbuster Medicine." A transferable exclusivity voucher is both an incentive to stimulate antibiotic innovation and a way to pay for it. It is a theoretical untested model that has been deemed legally feasible in Europe [28]. This incentive was unsuccessfully proposed in a bill to the US Congress in 2018, as a 12-month transferable extension [29]. To better understand this incentive, we offer a concrete example.

Which Antibiotics Might Receive a Transferable Exclusivity Voucher?

A World Health Organization expert group has judged 7 antibiotic candidates in late-stage clinical trials targeting priority pathogens as innovative [30]. If a transferable exclusivity voucher was introduced today, the owners of these 7 antibiotics are the most likely recipients of the voucher, depending upon the stringency of innovation requirement. Yet it is unlikely that all 7 products will make it to the market; most will fail for scientific reasons [31]. Possibly 2 antibiotics would be eligible for a transferable exclusivity voucher within approximately the next 5 years.

Which Blockbuster Medicine Might Likely Benefit From the Voucher?

There are many blockbuster medicines on the market today, whose producers would financially benefit from extending their monopoly time period. For example, AbbVie's Humira (adalimumab) is a treatment for multiple (12) autoimmune diseases and the largest selling global medicine with annual sales of USD 20 billion [32]. Adalimumab's sales outside of the United States were USD 6 billion in 2017 [33]. Alternatively, Pfizer's Lyrica (pregabalin) is an anti-epileptic (and other indications) with sales in Europe and Japan of USD 3.9 billion in 2017 [34].

What Might Be the Societal Cost of the Voucher?

If we hypothesize Pfizer's European revenues for pregabalin to be USD 2.5 billion per year, administrative costs for procuring the voucher to be USD 1 million, and Pfizer's minimum profit margin of USD 250 million, then Pfizer should be willing to

pay up to USD 2.249 billion for a 12-month European extension voucher. Whereas AbbVie, with the same expectations and USD 4 billion in European sales, would be willing to pay up to USD 3.749 billion for an extension for adalimumab. Yet as the highest selling medicine, AbbVie would not need to pay this amount, rather only outbid Pfizer (assuming that there are no other blockbuster medicines in between the 2) and thereby reap large profits. In this hypothetical example, *Europe would have access to 1 new important antibiotic but at a price of USD 3.2 billion to national healthcare systems* (ie, the cost of an additional year of sales at monopoly price [USD 4 billion] minus generic sales of the same medicine estimated 20% of the branded price [USD 800 million]). Additionally, adalimumab is an orphan medicine, meaning that the continued high-price burden would be shouldered by relatively few patients. This is significantly more than the estimated *global* market entry reward value of USD 1 billion, with Europe's share estimated to be approximately USD 300 million [10]. Some have argued that guard rails could be put in place to cap the financial impact to the insurer [12]. Although this may be possible in individual countries, it would be almost impossible in a multipayer European context.

Finally, the transferable exclusivity voucher does not guarantee that the market will have predictable access to the antibiotic because it is a one-off transaction. The antibiotic could be removed from the market for safety reasons, or the manufacturer could go bankrupt. For these reasons, if policy makers decide to move forward with the transferable exclusivity voucher, it should be awarded at the end of the antibiotic market exclusivity period, rather than at the point of the marketing authorization, even though this would lessen the value of the voucher due to the time value of money.

STEWARDSHIP TAXES

For countries with low resistance and therefore low utilization of new antibiotics, high unit prices cannot function as a pull mechanism. Norway and Sweden may only use a few packages of the new antibiotics each year [35]. Countries with low resistance rates will need to find alternative financing mechanisms to contribute to European pull mechanisms and thereby ensure access to new antibiotics. Both Sweden and the UK are pursuing such a model through their delinked models [15, 16]. Through these models, both countries will negotiate with companies to ensure access to important antibiotics. Although these models are meant only to ensure access, the negotiated payments must be high enough to cover the production and distribution costs as well as some profit margin for the company. Yet the pilots assume that other countries will also procure enough of these same antibiotics to ensure the viability of the producers.

The source of the financing for such an incentive is decided by the national policy makers. It may come from the health

budget. Alternatively, financing may be paid through taxes aimed to encourage stewardship, for example, a tax on veterinary antibiotic utilization. If Norway, a country with low antibiotic utilization in animals, taxed each antibiotic prescription designated for use in animals USD 7.00, it could raise over USD 1 million each year [36]. This amount could be used to either finance a national access scheme or alternatively be paid into a European fund in exchange for access guarantees and reduced pricing. However, such a tax may have unexpected consequences. Taxing antibiotic use in animals would place additional financial burden onto farmers, impacting price competitiveness. Farmers and veterinarians have successfully lowered antibiotic use in many European countries [37]. It would be undesirable to lose their goodwill. Alternative taxes include those applied to human antibiotic consumption or alternatively a tax on national insurance. The success of any of these taxes will depend upon national context and must be decided by national policy makers.

THE EMA ANTIBIOTIC FEE OR “PAY OR PLAY”

The last financing option we discussed here is based on industry contribution. The UK's AMR Review recommended an antibiotic investment charge, meaning that companies “could either pay the charge or invest in R&D that is deemed useful for AMR” [11]. The logic behind the pharmaceutical industry cofinancing antibiotic innovation is appealing because effective antibiotics are a building block of a functioning healthcare system, making all medicines dependent upon their continued effectiveness and availability. However, undoubtedly these increased fees on other therapeutic areas will be passed on to health insurers and/or patients through higher prices. Patients may be reluctant to pay higher prices for a medicine from which they receive no direct benefit. Other therapeutic areas also suffer from a lack of investment and may ask to be included with antibiotics, making the scheme unsustainable. These are compelling arguments against any “pay or play” model.

If policy makers decide to pursue a pay or play model, the design is important so as not to incentivize gaming, that is, that industry invests minimally in antibacterial R&D to meet the required threshold but does not strive to bring new, high-value antibiotics to market. The design must also not require expensive administrative processes like formal audits of companies' investments.

A simpler and perhaps more impactful implementation would be to levy a fee on all marketing authorizations (human and veterinary) to the European Medical Agency (EMA), except those for human antibiotics (or alternatives). In this way, all nonantibiotics would pay for antibiotic innovation. If a 25% fee was charged on all initial marketing authorization applications and annual fees, we estimate that this would generate approximately €20 million per year [38]. Twenty-five percent may sound excessively high, yet this increase combined with

EU Member States' regulatory fees appears to be lower than US medicine regulatory fees [39]. The EMA already has reduced fees in place for small- and medium-sized enterprises (SMEs), and these would continue to apply across all therapeutic areas.

€20 million a year may seem a paltry sum when considering that the estimated European share of a market entry reward per antibiotic is estimated to be USD 300 million. However, a market entry reward is designed to be paid out over multiple years, with recommendations for a 5-year payout, that is, USD 60 million per year per antibiotic. It may take time to award the first market entry reward. In the meantime, the pay or play financing raised should be placed in an interest-earning bank account. Finally, pay or play is meant to supplement national financing, not completely finance a pull incentive.

BUNDLING THE FINANCING MECHANISMS

Because the EU has limited abilities to tax and healthcare remains a national responsibility, it is difficult to see a single European financing solution for antibiotic pull incentives. Transferable exclusivity voucher is the only financing mechanism that could finance antibiotic innovation on its own, however, at an extremely high cost and with little guarantee of access. The remaining 3 financing options should be viewed in combination.

As of December 2018, there were 42 new antibiotics in clinical development, with the potential to treat serious bacterial infections, and 95% of these candidates are developed by SMEs [40]. These companies do not have established distribution networks or global geographic presence. Large pharmaceutical companies will likely not be interested in licensing the antibiotics that make it to market due to the small expected revenues. SMEs may determine that the most financially viable option is to serve the US market only, due to its large size, moderate resistance rates, and single regulatory body.

If European countries want access to new antibiotics, solutions that ensure access and a reasonable profit for the company will need to be negotiated. A successful and sustainable manner for the EU may be to act collaboratively through the EMA and potentially the European Investment Bank (EIB).

Significant expertise will be needed to determine if the antibiotic qualifies for the pull incentive. The EMA is probably the most qualified to perform this role, already performing similar roles today regarding determining eligibility for orphan designation and accelerated regulatory review. If there is a desire to pilot the pay or play financing, the EMA would also need to collect these funds. However, it would be unusual for the EMA to pay funds back to industry and may be a conflict of interest. The EIB would be a better actor as it already creates and manages investment funds and regularly negotiates with and finances industry for specific projects. The EIB also has the ability to hold funds in interest-bearing accounts.

Countries interested in ensuring access to the antibiotic could contribute through a number of ways, including implementing a national access scheme potentially financed by a stewardship tax, contributing funds to the EIB in exchange for access guarantee and a lower unit price. For countries with higher resistance levels and budget constraints dissuading them from annual reimbursement guarantees, the DRG carve-out could also be an option. These funds would supplement the pay or play funds, which ensure that the antibiotic is registered in Europe.

The attractiveness of these models and the willingness for countries to test them are currently being vetted through EU-JAMRAI. If there is interest, a compilation model will be more granularly developed and balanced against the revenue needs of innovators to determine sustainable solutions. Further development must likely be facilitated at a higher level on the European agenda.

Notes

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