The need for novel mechanisms to tackle the global antimicrobial resistance threat: are innovative payment models enough?

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Introduction

> Antimicrobial resistance (AMR) poses an urgent global health threat which continues to be on the rise, caused by inappropriate antibiotic prescribing and further exacerbated by COVID-19[1,2]
> It is estimated that antimicrobial resistant infections may result in 10 million annual deaths by 2050, with the global economy shrinking by up to 3.8% of its annual gross domestic product (GDP) in the same time period[3,4,5]
> This is coupled with low economic incentives to invest in research & development in this space due a unique market failing associated with antimicrobials.[5] Traditionally, the commercial success of a drug has hinged upon the sales volume and price. In the case of antimicrobials a higher sales volume may lead to higher rates of AMR and clinicians are discouraged from prescribing, leading to a decrease in the total volume of antibiotic sales over the years, particularly in countries which prioritise antimicrobial stewardship.[5] Secondly, the prices of antimicrobials are influenced by the abundance of low-priced generics, with the prices of new antimicrobials generally benchmarked on these generics.[5] Since 2010, there have been 18 antibiotics approved, with the median annual sales in the first year following launch to be $16 million United States (US) and four antibiotic developers subsequently filing for bankruptcy since April 2019.[6]
> Many incentives have been proposed to correct for this market failure in the development of antimicrobials and bolster the drug pipeline which can be broadly captured into two main types: push and pull.[5] Push incentives are strategies aimed at lowering the costs associated with the drug development which may include policy measures like early funding for manufacturers.[5] In contrast, pull incentives are those that reward the successful development of innovative antibiotics.[5] Two types of pull incentives exist: outcomes based or lego-regulatory.[5] Outcomes-based pull incentives are associated with advanced milestone reward payments associated with set milestones along the drug development process.[5] Meanwhile, lego-regulatory pull incentives are associated with policies that indirectly enable greater returns for the developer in the future, such as market exclusivity extensions like transferable exclusivity vouchers.[5,7]

Objective

> This review presents the current incentives to increase antibiotic research and development, focussing upon two payment models which have been piloted in the United Kingdom (UK) and Sweden as case studies. We aim to summarise their learnings to inform potential next steps at the European level.

Methods

> A search was conducted in Google Scholar using keywords including “novel payment models” and “value frameworks” currently used in health technology assessment (HTA) and antibiotics to combat "AMR". Additional keyword searches were conducted to include “lessons learned” and newly “proposed pull incentives” in “Europe”.
> Inclusion criteria were papers published from 2018 to 2023 and which described incentives which have been implemented, piloted, or proposed within Europe and any associated lessons learned.

Results

> 12 studies were identified that met the inclusion criteria. Overall, the literature highlights that pull, rather than push, incentives have been more popular with policy makers.
> In particular, outcomes-based pull incentives using volume delinked payment models for AMR have been piloted in the UK and Sweden.
  – The UK National Institute for Care Excellence (NICE) model assesses antibiotics for inclusion under Spectrum, Transmission, Enablement, Diversity, and Insurance (STEDI) framework elements.
  – The Swedish model is a partially volume delinked payment model which offers a minimum annual revenue.
> Lego-regulatory pull incentives such as transfer exclusivity vouchers, which grant extensions to the patent term of the approved antibiotic by up to 12 months in the European Union (EU) or to sell the voucher to another pharmaceutical company, were the second most cited form of pull incentive that policy makers are considering to implement within the literature.[6]
> An overview of novel reimbursement mechanisms for AMR is given in Table 1, from Gotham et al (2021)[8]

Table 1: Overview of novel reimbursement mechanisms

Country	Antimicrobials/pathogens targeted
France	• Antimicrobials with even a ‘minor’ added therapeutic benefit will be guaranteed a price not lower than the lowest price across 4 reference countries • Antimicrobials will be exempt from turnover liable to clawback • Manufacturers may request permission for a price increase from the reimbursement authority
Germany	• Ad-hoc exception of antimicrobials from internal price reference groups • Automatic exception of ‘reserve’ antimicrobials from internal price reference groups and accelerated reimbursement review process following European Medicines Agency (EMA) approval
Sweden	• PHAS Pilot Study: PHAS sets a minimum guaranteed annual revenue for selected originator antimicrobials, in exchange for a guaranteed supply volume
UK	• Innovative model for the evaluation and purchase of antimicrobials - annual fee, negotiated based on AMR-specific HTA, delinked from volume supplied

Sweden

Model type	• Novel partially delinked model
Eligible Products	• Patented • Efficacy proven against “Priority 1: critical group” of World Health Organisation (WHO) Priority Pathogen List • Acceptable safety profile
Evaluation	• Comparative effectiveness
Accessibility	• Made available to eligible patients
Price Setting	• The Public Health Agency of Sweden (PHAS) sets a minimum “guaranteed annual revenue” for each antibacterial, based on the cost of a “security stock” at 50% above the average European list price • PHAS also pays a bonus of 10% the “security stock” in case “guaranteed annual revenue” is exceeded through large volume of sales
Reimbursement	• Regional
Implication(s)	• Ensure availability of originator antimicrobials that may otherwise not be marketed in Sweden due to small market size.

UK

Model type	• Novel partially delinked model
Eligible Products	• New & existing antimicrobials (in pilot phase) • Efficacy proven against “Priority 1: critical group” of WHO Priority Pathogen List • Active in the clinical areas with highest unmet need (e.g., UK=gram-negative infections) • Degree of novelty, surety of supply, antimicrobial stewardship and manufacturing practices, antimicrobial surveillance and cost
Evaluation	• Cost-effectiveness
Accessibility	• Made available to eligible patients
Price Setting	• Multi-year contract paid via a set annual payment (or “fee”) for which the manufacturer would provide as many doses as possible • This maximum annual fee is based on a calculation what approximately England’s “fair share” would be of the proposed US $2–4 billion financial incentive needed, per new antimicrobial, globally, to revitalise the antimicrobial pipeline(i.e., £10 million per year per antimicrobial cap)
Reimbursement	• England only (in pilot phase)
Implication(s)	• This model will avoid development of “me-too” drugs and it will ensure cost-effectiveness outcomes are included from a societal perspective. • However, the annual fee-structure means that the use is not disincentivised by high unit prices, which could result in greater volumes of antimicrobials and consequent inappropriate use.

Conclusions

> Subscription-based payment mechanisms have proven to be a key step in combatting AMR together with incentivising the research and development of new antibiotics
  – However, there is a need to evaluate if the use of volume delinked payment models creates a sustainable and viable market for new antibiotics.
> There is a need for additional incentives amongst European countries to foster antibiotics research and development.
> Finally, the UK and Sweden have presented pilot innovative payment frameworks that could be implemented at a wider European level to maintain active antimicrobial pipelines.

References

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