The antibiotic subscription model: fostering innovation or repackaging old drugs?

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Antimicrobial resistance was associated with 4·95 million deaths worldwide in 2019.[1] Although broadening access to affordable health care and sanitation are the most promising means to reduce morbidity and mortality associated with antimicrobial resistance, novel classes of antibiotics are urgently needed.[2] However, low profitability means that most large pharmaceutical companies have withdrawn from antibiotic research and development. Meanwhile, reviews of compounds that remain in the research and development pipeline note that many such compounds are modifications of existing drug classes and do not constitute the molecular innovation needed to stay ahead of antimicrobial resistance.[3] Although some commentators have proposed non-market-based solutions, others emphasise the role of taxpayer-financed pull mechanisms to attract larger companies back into antibiotic research and development.[4,5] But will paying more for existing antibiotics promote molecular innovation, and if so, at what cost? Details from one of the largest pull-oriented policy experiments are emerging from the UK.

In the UK, reports and policies on antimicrobial resistance have promoted a so-called subscription model to stimulate the antibiotic pipeline for the past decade.[6,7] This model pays one flat-rate price to a company per year—a subscription—for an antibiotic used by a country's health system. The aim is two-fold: to avoid antibiotic overuse, and to guarantee a viable market for pharmaceutical companies even if their drugs are reserved as antibiotics of last resort. A subscription scheme is seen to be most useful to promote availability of high-value, low-use antibiotics, such as novel compounds that target multidrug resistant and priority ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* spp.). This policy experiment was put into place in June, 2020, and the first two drugs to be financed by the new UK subscription model were announced in April, 2022: ceftazidime–avibactam and cefiderocol. Both drugs had commercially launched before the subscription model even existed. Originally developed by AstraZeneca, ceftazidime–avibactam was approved in the EU in 2016 and subsequently sold to Pfizer, who launched it in the UK in 2017. Cefiderocol, which was developed by Shionogi, was approved by the US Food and Drug Administration in November, 2019, and by the UK in April, 2020. Both drugs are part of the cephalosporin family, of which the first member, cephalosporin C, was discovered in 1953; molecular modification of this drug has been one of the backbones of 20th century antimicrobial development. In hospitals, ceftazidime-avibactam and cefiderocol are used intravenously to treat multidrug-resistant pathogens—usually carbapenem-resistant Gram-negative infections (although ceftazidime–avibactam is not effective against class B-type beta-lactamases).

Proponents of this model highlight that paying a flat-rate, delinked to use, for current drugs will prove that the UK National Health Services is committed to derisking research and development and to supporting markets for future drugs. However, despite the UK's official aim to incentivise investment in antimicrobial research and development,[8,9] the current subscription funding does not convincingly reward innovative research into new chemical space, a field that many small and medium-sized enterprises are struggling to attract funding for. Instead, the annual price of £10 million per drug will support the antibiotic portfolios of two large pharmaceutical companies. Whether the volume of funding will be sufficient to lure companies of this size back into antibiotic investment is unclear.[10] Little exists in the fine-print to prevent companies from further derisking existing development pipelines by lobbying for reimbursement hikes or focusing on so-called me-too updates of old formulations.[11] Rather than supporting a resilient, innovative, commercial antibiotic ecosystem, there seems to be a marked risk that the UK subscription model could fall prey to what is termed the folly of rewarding A when hoping for B.[12]

Because the subscription pilot is currently being rolled out only in England, domestic stewardship misalignment—in which the same two drugs remain available at lower costs in the National Health Services of Scotland, Wales, and Northern Ireland—is also a risk.

According to current plans, the pilot will add two to three drugs every year. If the policy lasts 5 years, and

all drugs are licensed or contracted for the maximum 10 years, then this scales up to a committed cost of £1 billion split across ten drugs. This is substantial public funding. Greater transparency regarding decision making and more public debate on the ultimate goals of this process are needed. Adding safeguards, such as ringfenced funding for truly new drugs and robust and regularly published trackers of the effects of subscriptions on antibiotic research and development for novel drug candidates, could help to mitigate some of the identified risks. Ultimately, providing financial incentives is not the same as creating a functioning investment ecosystem for urgently needed antibiotic innovation.[8,13]

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