COMMENTARY

Global Pull Incentives for Better Antibacterials: The UK Leads the Way

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The article from Leonard and the team from the National Institute for Health and Care Excellence, NHS England, and NHS Improvement [1] asks the question whether the UK subscription program can restore the antibacterial pipeline, with an insiders' description of the process and strategy that led to implementation (briefly, a 'pull incentive' of reimbursement for new antibacterials that is delinked from volume of sales with payments based on the added value to the whole health and social care system).

Governments [2–9], academics [10–12], civil society [13, 14], think tanks [12, 15–18], and other key stakeholders [19, 20] have clearly articulated the problems with the pipeline for antibacterials, with an increasing focus on pull incentives that do not depend on the volume of sales, also known as delinked pull incentives. This delinked approach is recognized as the key because it resolves the tensions that create the underlying market failure of antibacterials: via delinked pull incentives, companies are rewarded for innovation while stewardship is simultaneously supported by eliminating any incentive to generate sales through marketing efforts. Although these tensions are also potentially true for any class of antimicrobial therapeutic, they are most acute for antibacterials because of the frequency of use and the presence of prior generations of antibacterials with partial but declining effectiveness.

As described in their article, the UK has now become the first country to implement a delinked pull incentive for novel antibacterials. To appreciate this monumental achievement, three analogies may be helpful.

First, one can think of antibacterials as the fire extinguishers of medicine [21]. Fires (and infections) move quickly, the fire (infection) can spread if not controlled promptly, and control requires immediate access to fire extinguishers (antibacterials). Although carrying a cost, modern building codes recognize that inclusion of such systems in new commercial construction is a necessary and appropriate preparedness measure.

Extending this perspective, a second analogy is to consider antibacterials as infrastructure. Modern societies have built significant physical infrastructure to support our way of life. Consider water and sewer lines: clean water is a signal public health achievement, but water supplies require maintenance, surveillance, and eventually repair or replacement. Departments within our cities are responsible for these tasks, with long-term planning and financing through municipal bonds. Antibacterials can also be considered infrastructure for modern medicine. Surgery, cancer treatment, and many routine procedures would be more dangerous without this safety net. But no agency is charged with maintaining these important assets for civilization.

Finally, antibacterials have important insurance value. Perhaps you own life insurance on your life. Are you upset that your life insurance did not pay off today? Certainly not—the goal was to protect your family from financial distress. Antibacterials that are used sparingly today and saved for future use are a form of insurance protection for all of us.

In each analogy above, the UK subscription program neatly responds to the issue at hand. In a subscription, the government pays a fixed fee for however much is needed, with the firm hope that for several years the volume will be exceedingly low. This is purchasing the fire extinguisher well in advance of the fire, funding the infrastructure maintenance well in advance of a total collapse, and buying protection through insurance.

Through the UK process, these concepts have been articulated as five unique values that were not being fully captured in traditional health technology assessment (HTA): spectrum, transmission, enablement, diversity, and insurance (STEDI) [22, 23]. The published HTA reviews from the UK subscription program are the first time to our knowledge that a government has applied these broader values that are unique to antibacterials [24, 25].

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As further support for this approach, a recent study projected the impact of a 30-year program using principles similar to that of the UK's pilot. The study found that lives saved approached 100,000 in the UK and 9.9 million globally, with return-on-investment ratios of 11:1 and 125:1, respectively [26, 27].

One important question with any subscription program is the lack of precise clarity as to which antibacterials could be selected in future years [28]. Timelines for clinical development of antibacterials have been lengthening, and the median clinical development time now exceeds 8 years [29], on top of preclinical development times of 4–5 years starting at hit-to-lead [30]. Any pull incentive needs to give clear signals to drug developers, more than a decade out, so they understand what is required to receive the subscription. In the US, the PASTEUR Act [31] allows any drug developer entering clinical trials to ask for an analysis of the magnitude of the reward that could be earned for any given target product profile. On this important question of which drugs qualify for subscriptions, the UK has published point-based guidance [1] and the PASTEUR Act describes "favorable characteristics" [31], building on earlier work [21]. These approaches can be improved and clarified as we gain experience.

We think that concerns that antibacterial subscriptions will not encourage innovation [28] are ill-founded. While it is true that the first two agents selected are from (or closely related to) the existing class of beta-lactams, chemical novelty is only one useful proxy for clinical impact [21]. Both drugs offer useful therapeutic activity as described in the HTA undertaken in England. Similarly, critiques that suggest value is not shown when products are approved primarily on non-inferiority trials [32] fail to recognize the ethical requirement to design anti-infective trials to avoid demonstrations of superiority if at all possible [33, 34]. While these comments come from a shared and admirable desire that all new drugs be better than what has come before, the pragmatic realities of antibacterial drug R&D must also be understood. We think that the type of metrics for intrinsic value (e.g., spectrum, mechanistic novelty, unmet need) used by the NHS pilot can be refined to cause the R&D community to respond with innovation that is motivated by the potential for rewards reflecting the value of innovative antibacterials. Most importantly, the presence of a subscription program with high (but attainable) standards will itself improve the quality of the pipeline.

In addition to our hope for stability and clarity on the UK selection process, we have four suggestions for improvement.

First, it would be useful for the UK to make long-term budget plans to issue several additional subscriptions in the coming decades, similar to the long-term plans that are made for public utility infrastructure. These plans, if transparently shared with the public, make the process more efficient by encouraging companies to make long-term investments that result in these new drugs. Secret, uncertain, or shifting plans add risk to the R&D process.

Second, the application process must recognize that some of the small companies applying may have modest financial statements, given the current state of the industry. While governments typically set high financial standards for procurement processes, for this subscription program these standards must select the best products, even if the company has no other revenues.

Third, the UK subscription program was capped at £10M per drug per year. This cap was an administrative expediency at the time, but now we know that the HTA-estimated value for both drugs exceeded the cap. We hope to see the cap removed, as higher performing drugs should receive an appropriate reward. At present, the UK is leading the world by creating the first antibacterial subscription program and paying significant amounts, but modest increases would ensure that the program continues to pay the UK's "fair share" of a global antibacterial pull incentive [30].

Finally, the contracts implementing the subscription program guarantee supply in the UK, but do not explicitly address important topics like global stewardship and access. Ideally, pull incentives would coordinate so such standards were reasonable and effective, building on the contractual commitments that many companies have already made as a condition of funding at CARB-X (Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator) [35]. Similar language is found in the PASTEUR Act [31].

The UK government has delivered a revolutionary innovation, changing the way antibacterials are paid for in England. This model from a G7 country leads the world and sincere flattery of its approach can be seen in the design of the PASTEUR Act and other discussions by G7 countries. The design was based on the foundation from more than a decade of academic and policy research. Policy innovation on this scale is never complete on the first iteration, so we look forward to how this program continuously improves over the coming years.

Declarations

represent the official views of any CARB-X funders. During the period 2019-2022, JHR is Chief Medical Officer & Director, F2G, Ltd., Editor-in-Chief, AMR.Solutions, Operating Partner & Consultant, Advent Life Sciences, and Adjunct Professor of Medicine, McGovern Medical School, Houston, TX; has received grant support from Wellcome Trust; sits (or sat) on the scientific advisory boards of Basilea Pharmaceutica, Novo Holdings, Roche Pharma Research & Early Development, Bugworks Research, Inc., Forge Therapeutics, Inc., Sumitovant, and the AMR Action Fund (AMRAF); and received consulting fees from Forge Therapeutics, Inc., Roivant Sciences, Pfizer Pharmaceuticals, GlaxoSmithKline, and Bugworks Research, Inc. He is currently a shareholder in AstraZeneca Pharmaceuticals, F2G, Ltd, and Advent Life Sciences. The opinions expressed are his own and do not necessarily reflect the opinion of any of the groups with which he works.

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