WHICH ECONOMIC PULL INCENTIVE MAY BE RIGHT FOR YOUR COUNTRY?

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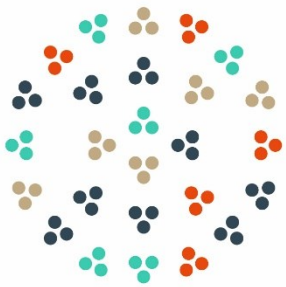

INTRODUCTION

"Pull" incentives for antimicrobial innovation aim to ensure that important antimicrobials meeting public health needs, particularly antibiotics and antifungals, are developed and accessible. An estimated 1.3 million people die every year from antibiotic-resistant infections.[1] Yet there are only two truly innovative antibiotics in clinical development targeting critical priority pathogens.[2] Conventional innovation and access mechanisms have failed for antibiotics, due to multifaceted and well documented reasons.[3,4]

There are several different types of pull incentives (see The Incentives), and the differences may not always be readily apparent.

This guide aims to assist policymakers to identify which pull incentive may be best suited for their national context and trigger discussion on the topic. Literature is given for each model for further reading (see Additional Reading).

WHICH ECONOMIC INCENTIVE?

This guide asks a series of questions to help policymakers hone in on the incentives most suitable for a specific context. Start at question 1 in the table below and follow the 'Next Steps' instructions. The questions are valid for diverse healthcare systems, including public and private, and those with federal, regional, hospital, or private pharmaceutical procurement. Remember when answering these questions that although most antibiotics under development will be used solely in hospitals, there are also antibiotics for primary care use (like those to treat drug-resistant gonorrhea). Please see The Incentives for further information on each of the incentives A-E referred to below.

QUESTION ?	SUPPLEMENTARY INFORMATION	NEXT STEPS
1 **Is your country a low or middle-income country?**	Global Antibiotic Research & Development Partnership (GARDP) and WHO are in the process of rolling out SECURE[5], with the aim of improving access to antibiotics in low and middle income countries (LMICs).	YES A NO 2
2 **Is your country bound by the European Commission's (EC) regulatory decisions based on the recommendations of the European Medicines Agency (EMA)?**	The EC has included the transferable exclusivity extension voucher in its proposal for changes to EU pharmaceutical legislation[6]. It is uncertain whether the voucher's inclusion will be approved by European Union's (EU) legislative bodies.[7] If approved, this would be a binding obligation on all EU Members States that recognize the EMA's approval of centralized marketing authorization applications (which include almost all novel medicines, including antibiotics). Given the uncertainty of the inclusion of the voucher in the legislation, it may be worth - at this current time point - considering other incentives in this table.	YES B&3 NO 3

QUESTION	SUPPLEMENTARY INFORMATION	NEXT STEPS
3 **Can your federal government pay to ensure access to medicines?**	Some federal governments, particularly those with regional healthcare provision, may not be legally permitted to pay for the supply of medicines. This is a complex question requiring careful legal investigation. The aim is not for the federal government to directly purchase antimicrobials, but to have the ability to pay for securing access to important antimicrobials. Previous legal precedents may include paying to ensure priority access to important vaccines (e.g., influenza or covid-19). Alternatively, federal research and innovation funding may also be used as a top-up financing, as demonstrated by Sweden despite its regional healthcare system.	YES 4 NO C
4 **Might your country benefit from multi-country collaboration?**	Expanding your market size will likely expand your negotiating power. Do you have neighboring (or other) countries that you could partner with on an incentive? Do you already participate in existing partnerships for health technology assessments (HTA) or medicines procurement? If so, consider the subsequent questions not only in regards to your own country but also in regards to a potential coalition of countries[8].	YES 5 NO 5

QUESTION

SUPPLEMENTARY INFORMATION

NEXT STEPS

5

Are you able to agree to one unit price for the antimicrobial throughout your country or coalition of countries?

The remaining incentives are delinked incentives, meaning that the total revenues are not determined by unit sales. A country (or coalition of countries) pays an agreed amount for guaranteed access to the antibiotic, not based upon the consumption of the antibiotic. Yet, the antibiotic cannot be made freely available to the healthcare institution or patient (the consumer) because this would encourage overuse of the antibiotic. Therefore, the consumer pays a transaction cost for consuming the antibiotic (similar to unit prices paid for other medicines).

This question relates to this transaction cost – can your country (or coalition of countries) agree to one transaction cost, i.e., one unit price? Conventional medicine unit pricing is complex with significant variation across countries. Many countries have standard medicine pricing formulas. It is also commonplace that hospitals purchase their own medicines. These practices translate into different prices for the same medicine. Whereas this may be current practice, it is important to ask if this is desirable. There is an advantage to agreeing to one unit or transaction price, since this allows you to set a reasonable unit price based upon stewardship principles, i.e., a price set to encourage physicians to follow the antibiotic prescribing guidelines (more on this under Incentive E – Subscription Model). There is also an advantage to not setting one unit price since it may be simpler to use your existing pricing mechanisms.

YES E

NO D

THE INCENTIVES

Pull incentives are policy tools to reward the successful development and availability of a product by increasing or ensuring future revenues.

Proposed and implemented mechanisms are described below:

A. SECURE
B. TRANSFERABLE EXCLUSIVITY EXTENSION VOUCHER
C. HIGH UNIT PRICE MODEL
D. ANNUAL REVENUE GUARANTEE
E. SUBSCRIPTION MODEL

A. SECURE

Incentive	Status & Examples	Provisions			Will this incentive impact my country's current…			
		Stimulate R&D	*Access*	*Stewardship*	*Method of determining medicine unit prices?*	*Health technology assessment processes?*	*Medicine procurement processes?*	*Medicine reimbursement processes?*
SECURE	Under development	✓ *Combined with GARDP's development efforts*	✓ LMICS	✓	NO	NO	Likely *SECURE may not participate in public tenders*	NO

SECURE is being developed by the World Health Organization (WHO) and the Global Antibiotic Research and Development Partnership (GARDP) with input from the United Nations Children's Fund (UNICEF) and the Clinton Health Access Initiative (CHAI). SECURE is designed to accelerate the access of essential antibiotics that meet countries' health needs and improve treatment options for people suffering from drug-resistant infections. SECURE will achieve these goals by developing appropriate market shaping interventions, while strengthening local capacity to ensure appropriate use of these antibiotics. SECURE runs in parallel to GARDP's and partners' cefiderocol access project, which will manufacture and commercialize cefiderocol in all low-income countries, most middle-income countries, and select high-income countries (135 countries in total).[9]

B. TRANSFERABLE EXCLUSIVITY VOUCHER

Incentive	Status & Examples	Provisions			Will this incentive impact my country's current…			
		Stimulate R&D	*Access*	*Stewardship*	*Method of determining medicine unit prices?*	*Health technology assessment processes?*	*Medicine procurement processes?*	*Medicine reimbursement processes?*
TRANSFERABLE EXCLUSIVITY EXTENSION VOUCHER	Under development	Expected	**X** *Novel antibiotics* *X* *Generic antibiotics* *X* *LMICs*	**X**	NO	NO	NO	NO

As currently proposed by the EC, a transferable exclusivity extension voucher[6] is an incentive for the development of priority antimicrobials. The voucher would give the developer of a priority antimicrobial one additional year of data protection from competition for a selected medicine. It would be awarded to a marketing authorization holder that receives regulatory approval for an antimicrobial that brings significant clinical benefit. If the antimicrobial developer does not want to use the voucher, the company can sell it, giving the purchaser the right to extend the exclusivity of a non-related medicine. In this way, companies with potentially high-earning medicines may be willing to pay a large amount for an additional year of monopoly. Antimicrobial innovators would be incentivized to bring important new antibiotics to market in order to receive and subsequently sell their vouchers. Whereas the purpose of the voucher is to stimulate innovation, it will not secure access to the recipient antimicrobial in all EU Member States[10]. An additional incentive within the proposed pharmaceutical legislation extends data protection from competition by two years for a medicine made available in all Member States within the first two years after regulatory approval. Depending upon the economics of these two incentives in combination, an innovator may be incentivized to make the priority antimicrobial available in all EU Member States. Yet, industry is calling for the EU to also implement a revenue guarantee (D) to secure access to the priority antimicrobial[10].

C. HIGH UNIT PRICE MODEL

Incentive	Status & Examples	Provisions			Will this incentive impact my country's current…			
		Stimulate R&D	*Access*	*Stewardship*	*Method of determining medicine unit prices?*	*Health technology assessment processes?*	*Medicine procurement processes?*	*Medicine reimbursement processes?*
HIGH UNIT PRICE MODEL	• France & Germany - active	Expected *for larger markets*	✓ *Novel antibiotics* X *Generic antibiotics* X *LMICs*	✓ *via existing national provisions*	YES *a new process must be implemented for new antimicrobials*	YES *since HTA or other valuation processes will need to reflect different evidence standards*	NO	NO

For countries where the federal government is unable or uninterested to make payments to ensure access, they can increase antimicrobial innovators' revenues by allowing for substantially higher unit prices. In some countries antibiotics are automatically bound to low unit prices because they utilize non-inferiority clinical trial designs, meaning that the new antibiotic is found to be not inferior to a comparator (often generic) antibiotic. There are several complex and valid reasons for this clinical trial design. New antibiotics are usually tested on non-resistant bacterial infections and therefore cannot demonstrate an added value against (multi)resistant bacterial infections (the instance where we want to use new antibiotics). Without a valid demonstration of their efficacy on resistant infections, they are as good as the comparator in treating site-specific, non-resistant infections. The result is that many countries set the price of the new antibiotic to that of the generic comparator. This is an understandable budgetary measure, since additional clinical benefit has not been demonstrated. Clinical trial networks, like ADVANCE-ID[11] and ECRAID[12], are working to gather more clinically useful data. The high unit price model may only work for large markets that are relatively insensitive to medicine prices. Otherwise, high unit prices have been shown to deter use,[13,14] and therefore not act as an incentive. The high unit price model would apply only to novel antimicrobials and would most likely not be adjusted to improve access to generic antimicrobials.

- **France & Germany - active**

Both countries have implemented incentives where antibiotics that meet a minimum clinical data standard may negotiate higher unit prices. For example, to qualify for the German scheme, the antibiotic must demonstrate efficacy data against priority pathogens, using in vitro data and results from at least one clinical trial and demonstrate that no or only limited therapy options or possibilities of prophylaxis are available[15].

D. ANNUAL REVENUE GUARANTEE

Incentive	Status & Examples	Provisions			Will this incentive impact my country's current…			
		Stimulate R&D	*Access*	*Stewardship*	*Method of determining medicine unit prices?*	*Health technology assessment processes?*	*Medicine procurement processes?*	*Medicine reimbursement processes?*
ANNUAL REVENUE GUARANTEE	• Sweden - active • Japan – not active	Potentially *depends on level of revenue guarantee*	✓ Novel antibiotics ✓ Existing antibiotics X LMICs	✓ *via existing national provisions*	NO	Potentially *since the HTA will likely inform the guarantee amount*	NO	NO *Since the healthcare institution will pay the unit price as per normal. Yet a public body will need to pay the difference between the guarantee and the actual consumption.*

An annual revenue guarantee is a delinked pull incentive where a federal agency (or other suitable organization) contractually guarantees the marketing authorization holder an annual revenue so long as all contractual stipulations are met. These stipulations include access and stewardship requirements, for example, guaranteed delivery of the antibiotic within a specified time, a national/regional stockpile, reporting requirements including notifications of extreme use, requirements that company employees are not remunerated based upon sales volumes, and more. Failure to meet the contractual stipulations may result in financial penalties. Existing pricing and procurement processes are unchanged. At the end of the year, the difference between the revenue guarantee and national unit sales (from both the public and private sectors) is paid out by the federal agency to the marketing authorization holder. With a goal to both stimulate innovation and secure access, the revenue guarantee should always be larger than unit sales, except in extreme situations. In these extreme situations, the marketing authorization holder would keep the higher unit sales – no guarantee amount would be paid out. As the revenue guarantee amount is flexible, it can also be adjusted to secure access to generic antibiotics with vulnerable supply. Award amounts could vary based upon the antibiotic's ability to meet public health needs (see How much will it cost?).

- **Sweden – active:** Sweden implemented a revenue guarantee in 2019 to secure access to antibiotics, not to stimulate innovation[16]. All applicants to a public tender meeting the criteria were accepted into the scheme. The criteria were: (i) reviewed by the European Medicines Agency (EMA) in the previous six years, (ii) proven activity against World Health Organization "critical" priority pathogens, and (iii) a good safety profile. Five antibiotics qualified including one generic antibiotic, fosfomycin iv, that had recently been reviewed by the EMA. Sweden required suppliers to hold a minimum stock in Sweden and deliver the antibiotic the next working day after an order. An assessment report[16] found the scheme successful at ensuring access but found that the stockpile resulted in wastage, with the recommendation to consider regional stockpiling instead. Sweden chose to award the same guarantee amount to each of the qualifying antibiotics for simplicity.

- **Japan – not active:** A three-year 'support program to secure antibiotics' is due to begin in 2023. Further information available here (in Japanese).

E. SUBSCRIPTION MODEL

Incentive	Status & Examples	Provisions			Will this incentive impact my country's current…			
		Stimulate R&D	*Access*	*Stewardship*	*Method of determining medicine unit prices?*	*Health technology assessment processes?*	*Medicine procurement processes?*	*Medicine reimbursement processes?*
SUBSCRIPTION MODEL	• UK – active • US – not active	Expected	✓ *Novel antibiotics* *potentially Generic antibiotics* *potentially LMICs*	✓	YES *prices set to reinforce prescribing guidelines*	Potentially *since the HTA will likely inform the subscription amount*	NO	NO *Since the healthcare institution will pay the unit price as per normal. Yet a public body will need to pay the difference between the guarantee and the actual consumption.*

A subscription (often referred to as "Netflix" or fully delinked market entry reward) model is a delinked pull incentive where a federal agency (or other suitable organization) contracts the marketing authorization holder to supply its antibiotic for a fixed total price. Contractual stipulations include access and stewardship requirements, like those given under **Incentive D (Annual Revenue Guarantee).** Failure to meet the contractual stipulations may result in financial penalties. At the end of the year, the difference between the subscription amount and national unit sales (from both the public and private sectors) is paid out by the federal agency to the marketing authorization holder. With a goal to both stimulate innovation and secure access, the subscription amount will always be larger than unit sales, except in extreme situations. In these extreme situations, a contractual clause would be instigated that requires a re-negotiation of the subscription amount. A subscription model is very similar to an annual revenue guarantee with the exception that rather than determining the unit price (or transaction cost) using standard procedures, one unit price (i.e., a stewardship price) is set. The aim is to align pricing with antibiotic prescribing guidelines, so that a last-line antibiotic would have a high but affordable unit price, whereas a first-line antibiotic would have a low unit price. In this way, the unit prices reinforce the antibiotic prescribing guidelines.

- **UK – active:** In 2022, the UK implemented a subscription model in England[17]. Two antibiotics for priority pathogens were selected through a public tender competition. Post selection each antibiotic was subjected to an extensive HTA process to determine the annual subscription value. These HTAs included an assessment not only of traditional patient values but also non-traditional values, like the insurance value of having the antibiotic available, including the use of in vitro data. Accounting for non-traditional public health values is key to creating attractive markets for antimicrobials, and thereby stimulating innovation (see How much will it cost?). A stewardship price was set for each antibiotic. Currently, a consultation is being conducted on behalf of all nations of the UK who may participate in the Antimicrobial Products Subscription Model, on proposals for a subscription style contract that can be used to expand this approach to more antimicrobial products.
- **US – not active:** The draft US legislation PASTEUR (Pioneering Antimicrobial Subscriptions to End Up surging Resistance)[18] is also a subscription model. Yet rather than using HTA to determine the annual value, an expert committee will determine the annual subscription amount based upon the characteristics of the antibiotic or antifungal. The Act also requires the company to submit a plan for registering the antimicrobial in other countries with unmet public health needs, anticipated to benefit LMICs.

HOW MUCH WILL IT COST?

Aside from the mechanisms, an understanding of the overall cost of an incentive is, of course, decisive. Several research efforts have focused on the global magnitude of revenues needed to stimulate innovation and secure access.[3,4] The most recent estimates, which the pharmaceutical industry endorses[19, 20], range from USD 220 million to 480 million per year per antimicrobial for the remainder of its exclusivity period (generally 10 years).[21]

While these are global estimates, the expectation is that these amounts will be paid for by high-income countries. Investments in water, sanitation, and infection prevention and control by LMICs provide significantly greater impact against antimicrobial resistance and are therefore a better buy for scarce national funds in these countries.[22]

Distributing the global amounts down to a country level may be done according to Gross Domestic Product (GDP) or population.

Yet, these figures are purely based on the amounts that industry considers an attractive market – they are not aligned with public health need which varies based upon the specific antimicrobial. The public health value of a new class, oral, broad-spectrum antibiotic is immense; an undifferentiated, existing class antibiotic has a public health value of zero. The value of the incentive cannot only reflect industry's needs – it must also reflect the public health value, i.e., both the patient value and societal value.

The UK has demonstrated through its assessments that the public health values do largely align with industry's expected revenues[17,23]. It would be beneficial if other countries also performed similar assessments.

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ADDITIONAL READING

A – SECURE

- SECURE - https://gardp.org/secure/

B – Transferable Exclusivity Voucher

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C – High unit price model

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D – Annual revenue guarantee

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GLOBAL AMR R&D HUB

The Global AMR R&D Hub is a partnership of countries, non-governmental donor organisations and intergovernmental organisations to address challenges and improve coordination and collaboration in global AMR R&D using a One Health approach. The Hub was launched in May 2018 and is steered by a Board of Members.

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