Joint Action
Antimicrobial Resistance and
Healthcare-Associated Infections

D 9.2

A strategy for implementing multi-country incentives in Europe to stimulate antimicrobial innovation and access

WP9 | Prioritizing and implementing research and innovation for public health needs

Leader acronym | INSERM, FHI

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List of abbreviations

AMR: AntiMicrobial Resistance

HCAI: HealthCare Associated Infection

MS: Member States

WP: WorkPackage

Summary

Background: Several prominent reports have assessed the challenges to antibiotic innovation and recommended implementing "pull" incentives, i.e., mechanisms that give increased and predictable revenues for marketed, important antibiotics. We set out to understand countries' perceptions of these recommendations, through frank and anonymous dialogue.

Methods: We performed in-depth interviews with national policymakers and antibiotic resistance experts in 13 countries (ten European countries and three non-European) for a total of 88 individuals in 34 separate interviews.

Results: Interviewees expressed high-level support for antibiotic incentives in 11 of 13 countries. There is a general recognition that new economic incentives are needed to maintain a reliable supply to essential antibiotics. However, most countries are uncertain which incentives may be appropriate for their country, which antibiotics should be included, how to implement incentives, and how much it will cost. There is a general preference for a multinational incentive, so long as it is independent of national pricing, procurement, and reimbursement processes. Nine of the eleven countries supporting new incentives indicated a preference for a model that ensures access to both old and new antibiotics, with the highest priority for older antibiotics. Twelve of 13 countries indicated that shortages of existing antibiotics is a serious problem nationally. Since countries are skeptical about the public health value of many recently approved antibiotics, there is a mismatch regarding revenue expectations between policymakers and antibiotic innovators.

Conclusions: This report presents important considerations for the design and implementation of antibiotic pull mechanisms. We also propose a multinational model that appears to match the needs of both countries and innovators.

Introduction and objectives

WorkPackage (WP) "Research & Innovation" objectives.

The main objective of the WP "Research & Innovation" is to contribute to a coordinated European response against AMR by assisting MS in devising policies to prioritize, stimulate and utilize research and innovation related to AMR and HCAI.

This deliverable focuses on the second specific objective of the WP "Research and Innovation" whose overreaching goal is to propose tools to stimulate innovation and access to antibiotics.

Predictable access to life saving antibiotics is under threat.

Antibiotic resistance imperils global health, with multi-drug resistant bacterial infections accounting for over 33,000 deaths in Europe alone in 2015.[1] The number of annual global deaths is unknown but predicted to be large. Yet contrary to the public health need, antibiotic innovators and manufacturersarestruggling.

New antibiotics are unable to generate revenues large enough to sustain the interest of multinational players and even small developers are failing to cover their costs, resulting in bankruptcies of small antibiotic innovators.[2] Melinta, an American antibiotic innovator went bankrupt in December 2019, after receiving regulatory approval in the United States and Europe for an antibiotic judged as "innovative" against a "critical" priority pathogen by the World Health Organization. Physicians use new antibiotics as a last resort in order to preserve their efficacy. Whereas this is sound stewardship, it dis-incentivizes innovation since unit sales determine revenues.

Simultaneously, shortages of older antibiotics are increasing.[3] Due to antibiotic resistance patterns and prescribing habits, the markets of some essential antibiotics are small, including those for children. Tendering processes based solely on price and automatic price reductions for generic medicines reduce profitability, leading to a consolidation of supply. The dependency on sole manufacturers may come as a surprise, when there is suddenly no medicine available. For example, in 2017 a fire at a raw material factory in China resulted in a global shortage of

piperacillin/tazobactam.[4] During the COVID-19 pandemic, supply chains have been unable to meet demand as well as challenged by supply disruptions due to lockdownsand border closures.[5]

Several prominent reports have assessed the challenges toantibiotic access and innovation and have made recommendations, including calls for “pull” incentives, aiming to increase revenues for marketed, innovative antibiotics.[6-7]

The EU-JAMRAI setting out to understand MS perspective on AMR research, access to antibiotics and incentives.

As a part of the EU Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI) we set out to understand countries’ perceptions regarding several topics including antibiotic incentives, through frank and anonymous dialogue. The aim was to understand the barriers and facilitators of implementing incentives for antibiotic access and innovation.

Methodology

As a part of the EU Joint Action on AMR and Healthcare-Associated Infections (EU-JAMRAI), we wanted to better understand MS perspectives on AMR research, access to antibiotics and incentives. We performed **in-depth interviews** with **human health policymakers** in ten European countries: Belgium, Denmark, France, Germany, Luxembourg, the Netherlands, Norway, Romania, Spain, and Sweden. We also interviewed **policymakers from Ministries of Agriculture** in all countries except Romania.

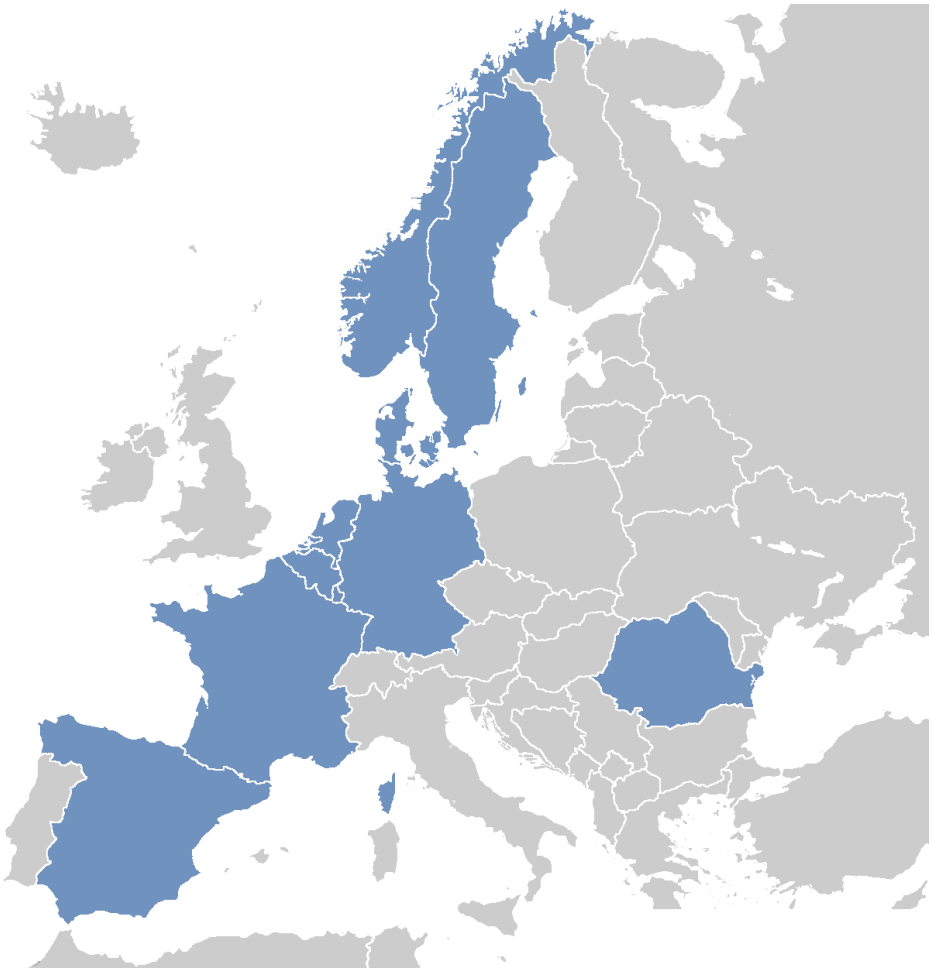


Figure 1: European countries interviewed

These insights were made more globally representative with the help of the Global AMR R&D Hub which supported the inclusion of a further three countries from other continents (Canada, Japan, and South Africa). In these three countries, we were only able to interview human health and research experts.

In total we interviewed 88 individuals in 34 separate interviews.

A standard interview guide was used (Appendix 1). All interviews were held under Chatham House Rule, meaning that "participants are free to use the information received, but neither the identity nor the affiliation of the speakers, nor that of any other participant, may be revealed." The intention of the interviews was not to secure government commitments, but rather to gain a better understanding of facilitators and barriers of incentives in order to suggest refinements to proposed mechanisms.

Interviews were not recorded due to the political sensitivities of the conversations. However, extensive notes were taken which were reviewed within two days following the interviews. The results describe and summarize the content of the interviews by theme.

Table1: Date and location of the meetings organized.

Country visited	Date	Type of meeting
France	23-24 May 2019	Physical
Netherlands	25 June 2019	Physical
Norway	27-28-29 August 2019	Physical
Luxembourg	16-17 October 2019	Physical
Sweden	18-19-20 November 2019	Physical
Denmark	15-16 January 2020	Physical
Spain	29-30 January 2020	Physical
Belgium	11 February 2020	Physical
Romania	04 September 2020	Virtual
Germany	16 September 2020	Virtual

Results

A high level support for antibiotic incentives

Interviewees expressed high-level and general support for antibiotic incentives in 11 of 13 countries. That is, there is a general recognition that new economic incentives are needed to maintain a reliable supply to essential antibiotics. However, there was little depth of understanding, with less than half of the countries familiar with the literature on antibiotic incentives. Indeed with all of the activity regarding new entities providing push funding, policymakers were often confused regarding the roles and differentiation of the new actors like CARB-X and GARDP.

Countries were uncertain which incentives may be appropriate for their country, which antibiotics should be included, how to implement incentives, and how much it will cost. The majority of countries are waiting for clear and concise recommendations from a recognized authority like the European Commission or the Global AMR R&D Hub, utilizing evidence from the pull mechanisms implemented in Germany, Sweden, and the United Kingdom.

Countries would prefer a multinational incentive

Eleven of the 13 countries interviewed would prefer a multinational incentive, that is, one where countries may opt in, so long as it is independent from national health technology assessment, medicine pricing, and reimbursement processes. These national healthcare processes are complex and heterogeneous. There was no interest in a new incentive that would disrupt these national processes, especially since new antibiotics are expected to be used rarely.

Countries would prefer an incentive ensuring access to both old and new antibiotics

Whereas almost all countries stated a concern about the lack of antibiotic innovation, this was not the principal driver to support new incentives. Rather, nine of the eleven countries supporting new incentives indicated a preference for a model that ensures access to both old and new antibiotics, with the highest priority for older antibiotics. Indeed, countries do not have predictable access to generic antibiotics. Twelve of 13 countries indicated that shortages of existing antibiotics is

a serious problem nationally. Eight out of 13 indicated that this resulted in greater use of broad-spectrum antibiotics and thereby potentially increasing antibiotic resistance. As important antibiotics continue to be unavailable, doctors change prescribing habits, potentially away from evidence-informed prescribing guidelines.

Eight countries indicated that companies recently decided to stop marketing an essential, older antibiotic in their country. Three countries managed to reverse this decision by awarding higher unit prices. One country secured the commitment of a small company willing to produce an older antibiotic for a higher unit price and assisted in the transfer of the marketing authorization to the new company. Yet in some countries important older antibiotics have never been registered. One country actively encouraged manufacturers to market an older antibiotic never previously marketed by offering mutual recognition of existing regulatory dossiers. The manufacturer responded that no countries were interested in this older antibiotic. Only later, through ad hoc communications, the country learned that several countries wanted access to this older antibiotic. These examples of successfully securing access are the exception. In many instances, countries lost access to the antibiotic. Older antibiotics with fragile availability mentioned in interviews include ampicillin, benzylpenicillin, benzathine penicillin, cefotaxime, cloxacillin, nitrofurantoin, phenoxymethylpenicillin, temocillin, and trimethoprim.

Unpredictable access is not only a challenge for older antibiotics but also for new ones, which are often not widely available, even in high-income countries. Only six of the 13 countries were aware that the availability of new antibiotics, especially those manufactured by small producers, may be delayed in their country, and these six all represented smaller market countries. Large market countries were generally unaware that, despite their size, they may be considered an unattractive market.

Countries concerned about how to finance incentives

Countries were often concerned about the estimated price tag of potential incentives, as the literature has estimated global revenue amounts in the billions needed to invigorate innovation. Many policymakers expressed frustration regarding the lack of engagement from large multinational pharmaceutical companies, given that the revenues of other (often high priced) medicines are dependent upon effective antibiotics. Most countries are uninterested in estimates of revenues

needed to stimulate innovation. Rather they are interested in paying amounts aligned with the national value to ensure access, meaning that the antibiotic is marketed and available in country. The majority of countries were uninterested in incentives that dramatically increased antibiotic prices, often referring to WHO's Fair Pricing Forums.[8]

To address this issue, the EU-JAMRAI published a viewpoint in Clinical Infectious Diseases on opportunities to finance an European pull mechanism. The article is available in Appendix 2.

Countries looking for more transparency on supply chain to prevent shortages

In interviews with six countries we were able to discuss supply chain transparency of these older antibiotics. In all cases countries were unaware that factory information is generally considered a business secret and is not shared, even between national regulators. One asked "*why isn't it public, after all we can see where our meat is produced?*" Countries were concerned that these older antibiotics are reliant on few manufacturers, particularly active pharmaceutical ingredient manufacturers. All six countries expressed interest in further pursing transparency of regulatory dossier information.

To address this issue, the EU-JAMRAI has recently published an article in the WHO bulletin advocating for more supply chain transparency to enable sustainable and continuous supply of antibiotics and essential medicines. This article is available in Appendix 3.

Countries want to see superiority trials

Yet there was little concern about not having immediate access to new antibiotics. There was skepticism regarding the public health value of many recently approved antibiotics. All antibiotics that have received regulatory approval in the last five years have been approved with non-inferiority clinical trials. That is, the new antibiotic is found to be *not* inferior to a comparator (often generic) antibiotic. There are several reasons for this clinical trial design, particularly that it is difficult (and therefore expensive) to gather patients with antibiotic resistance today. Policymakers are uninterested in new antibiotics that show no greater benefit than existing antibiotics. As one policymaker said, "*Antibiotics are being approved for*

indications where there is no intention that they will be used. This sends the wrong signal…would prefer that antibiotics are tested against drug-resistance instead. If the trials need to be done in [high-resistance countries] and they are performed according to existing standards, this is preferable." Policymakers were clear that incentives should only apply to antibiotics that meet public health needs, i.e., either those on antibiotic prescribing guidelines or new antibiotics that show benefit in clinical situations for unmet public health needs.

Conclusions

Barriers and facilitators to implement incentives for antibiotic access and innovation.

Through interviews with policymakers and AMR experts in thirteen countries we have explored the facilitators and barriers to implementing incentives to promote antibiotic access and innovation.

The barriers and facilitators to implementing incentives for antibiotic access and innovation as stated by national policymakers and AMR experts are summarized in Table 1.

Table 1: Facilitators and barriers to implementing incentives for antibiotic access and innovation

Facilitators	Barriers
• Countries generally agree that new economic incentives are needed to maintain a reliable supply of essential antibiotics. • Evidence regarding the effectiveness and operational cost of implementing pull incentives is being generated in Germany, Sweden, and the United Kingdom. • Pull incentives can ensure access to both old and new antibiotics, which is desirable since predictable access to existing antibiotics is a serious challenge in many countries. • Pull incentives can be designed to only reward antibiotics that meet public health needs. • Almost all countries agree that the WHO's Priority Pathogen List represents their unmet public health needs for antibiotic innovation. • The EU has committed to trial a pull incentive in 2021.	• Most countries are uncertain which incentives may be appropriate for their country, which antibiotics should be included, how to implement incentives, and how much it will cost. • Most countries prefer a multinational incentive and are waiting for a first mover to organize the process. • Countries are skeptical about the public health value of many recently approved antibiotics, which have all been approved through non-inferiority clinical trials. • There is a mismatch between the estimated price tag of new pull incentives and the public health value.

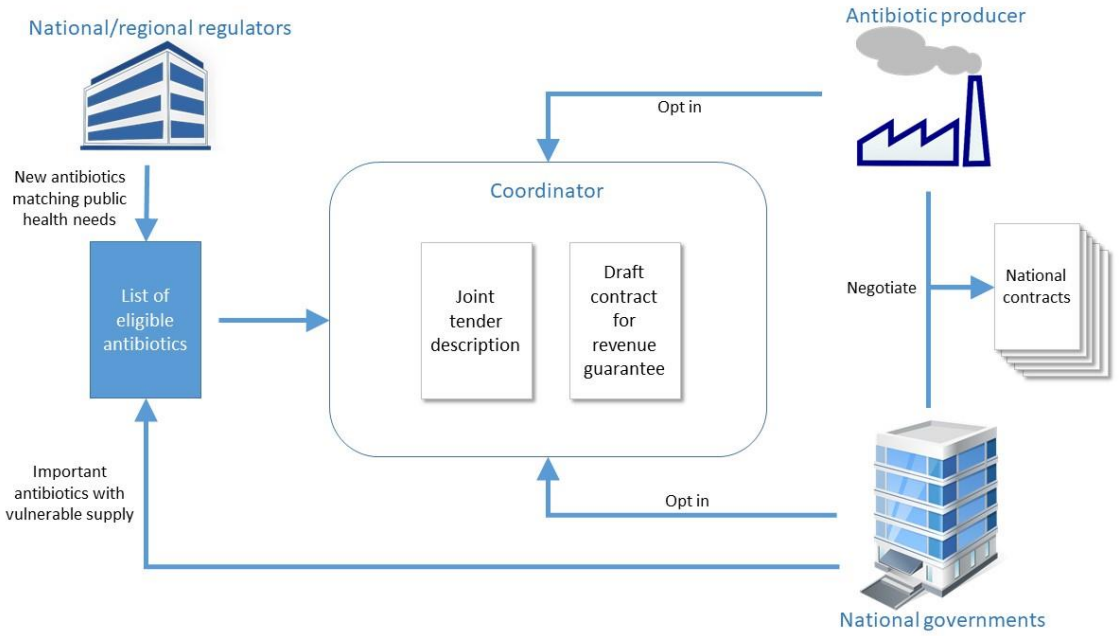
EU-JAMRAI proposition to implement a multi-country incentive for antibiotic access and innovation.

Country representatives expressed general support for antibiotic incentives with a number of caveats. Countries are uncertain about incentive design and cost. The main aim of any incentive should be to secure access to antibiotics of public health importance, including existing antibiotics. This means new antibiotics will need to more clearly demonstrate public health value through clinical evidence. Almost all countries would prefer a multinational incentive, but this must be completely independent from national regulatory, pricing, procurement, and reimbursement processes, as these are national responsibilities.

An adjusted version of the Swedish pilot incentive could meet these criteria well. Sweden guarantees annual revenues of SEK 4 million (about € 400,000) for patented antibiotics meeting specified requirements.[9-10] Producers are guaranteed an annual revenue, with the difference between the guarantee and actual annual sales paid through the new incentive. If sales exceed the guarantee amount, the innovator keeps the additional revenues as well as receiving a 10% bonus so long as all contractual conditions have been met. Sweden has entered into two-year contracts with the antibiotic producers and has included national access and stewardship provisions.

The principles of the Swedish model could be extended to a multinational incentive, with the aim that countries could participate in a joint tender with a common contract template (excluding the guarantee amount). Each country would negotiate a separate revenue guarantee with the producer. The process is visualized in Box 1. This pull incentive would allow countries to delink antibiotic revenues from sales volumes allowing innovators to have greater revenue predictability.

Box 1: Potential multinational pull incentive based upon principles of the Swedish incentive



Firstly, eligible antibiotics would be selected either by a country requesting their inclusion or based upon regulators' recommendations. As most countries require open tendering processes, these calls for tender would likely need to specify eligible antibiotic characteristics (e.g., antibiotics approved for antibiotic-resistant infections, antibiotics approved against specified Gram-negative pathogens, narrow-spectrum antibiotics for treatment of pneumococcal infections, etc.). We understand that no antibiotics today have a therapeutic indication against antibiotic-resistant infections because of the way that clinical trials are performed. However, the Wellcome Trust and others are establishing antibiotic clinical trial networks in countries with higher resistance patterns, meaning that new antibiotics should be able to perform superiority trials for resistant-infections.[11] This should enable the clinical evidence desired by policymakers.

Once eligibility requirements have been defined, a joint tender would be developed, with a contract template including national access and stewardship requirements. A suggested revenue guarantee would be included, such as a country-specific calculation of 1.5 times the predicted annual national volume of the antibiotic multiplied by the national price. (For especially small volume antibiotics, the revenue guarantee may need to be two or three times the predicted annual national volume to make the market attractive.)

Participation would always be voluntary, on behalf of both national governments and producers. Once the tender participants are agreed, each country would negotiate individually with the producer and ultimately enter into a contract. Global medicines distributors (like WHO/GARDP's SECURE initiative and UNICEF) should also be invited to participate in the tender in order to facilitate access in low and middle-income countries, with their guarantee amounts equaling their expected annual demand. All of the abovementioned process could be coordinated by a multinational organization like the Global AMR R&D Hub or the European Commission.

The aim of this model is to make it easy for countries to implement a pull incentive ensuring sustainable access to antibiotics while at the same time providing market certainty to antibiotic producers. Some may argue the revenues generated through these agreements will be insufficient to provide an attractive market for innovators. Calls to stimulate antibiotic innovation have primarily centered on the needs of antibiotic innovators with price tags of over USD 1 billion per antibiotic globally. Yet through this model the revenue guarantee amount would be negotiable. National unit prices may also be informed by a health technology assessment (HTA), which may include societal value in addition to patient value. Both the United Kingdom and Norway are trialing this approach.[12-13] With better clinical evidence, the national unit prices per antibiotic should increase. It was clear through our interviews that there is currently a mismatch between national policymakers and innovators regarding the perceived value of specific, new antibiotics. This incentive offers an opportunity for countries and innovators to find the middle ground, while giving predictability in both demand and supply.

Dissemination of these findings.

These findings have been disseminated through a joint policy brief written with the Global AMR R&D Hub (Appendix 4).

EU-JAMRAI proposal for a multi country incentive will also be published in a peer-reviewed journal (to be submitted) and disseminated to policymakers through a policy bried (under writing).

WP9 leaders also actively disseminated these findings in various international meetings.

Acknowledgements

We kindly thank all the representatives form ministries and national agencies who accepted our interviews as well as all the people who facilitated these meetings.

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Appendix

Appendix 1: Country visit interview guide.

1. **Areas of greatest concern or vulnerability regarding research, innovation, and access.**
    - Briefly describe your country's biggest concerns regarding AMR & HCAI research, innovation, and access?
    - What are your greatest concerns or vulnerabilities regarding AMR and HCAI within animal and plant health?
    - What are your research priorities?
    - Do you feel like research priorities are being adequately funded and researched?

2. **Areas of greatest financial concern related to AMR and HCAI?**
    - Has your country assessed the cost of AMR?

3. **National processes to determine national research priorities.**
    - What national processes do you use to determine your research priorities? (including priority technologies, infection prevention and control (IPC) knowledge gaps, and behavioral change interventions)

4. **Incentives.**
    - Incentives for new antibiotics and other treatments
        - Access - What steps are your country pursuing (if any) to secure access to new antibiotics (or other treatments)? Are you concerned that your country will not have access to the newest antibiotics developed by small companies?
        - Pull - What focus does your country have on pull incentives? What are the biggest barriers to implementation?
        - Pooled funds - Would your country be willing to pool funds with other European countries? If so, which facilities are considered the strongest candidates for a pooled fund? (European Investment Bank?)

- Selecting products worthy of a reward - Does your country feel that the priority pathogens identified by WHO are aligned with your unmet public health need?
- Higher unit prices – Is your country open to assessing the societal value of a new antibiotic as a part of the health technology process in order to award a higher unit prices?
- Pilots – Sweden and the UK are moving forward on pull incentive pilots.
    - How open is your country to attempting to pilot new incentives within well-defined parameters and financing constraints? For example, an innovative new antibiotic for WHO critical pathogen.
    - Or would your country prefer a European-based pilot? If so, how many other countries would need to commit?
    - What are the barriers and influencing factors?
    - What might be the first steps towards a pilot?

- Incentives/measures to maintain access to older antibiotics
    - Are you experiencing shortages of antibiotics?
    - Is your country pursuing measures to secure availability of older antibiotics?
    - Which older antibiotics are you most concerned about? Do you have a list of critical antibiotics?
    - Is your country attempting to grow its consumption of older antibiotics through expanded susceptibility testing?
    - Is there a willingness to pay higher unit prices for older antibiotics? Or what other incentives might your country be interested in? Netflix models?
    - Piloting
        - How open is your country to attempting to pilot new incentives within well-defined parameters and financing constraints?
        - Or would your country prefer a European-based pilot? If so, how many other countries would need to commit?

        - What are the barriers and influencing factors?
        - What might be the first steps towards a pilot?
    - Are you experiencing shortages of veterinary antibiotics and/or vaccines?
    - Are there any incentives or regulations in place to support veterinary vaccinations?
    - Might your country be open to attempting to pilot new incentives for veterinary vaccines within well-defined parameters and financing constraints? What are the barriers and influencing factors?

- Incentives/measures to support IPC
    - OECD has demonstrated that significant cost savings can be achieved by improving IPC measures. Do you feel that this is relevant for your country?
    - If so, these often require upfront financing to achieve the savings. Are there mechanisms in your country to finance these efforts?
    - Could economic incentives be useful for infection prevention and control? For example, upfront financing in line with expected outcomes, followed by sharing of cost savings between the healthcare institution and government?

5. Financing national positions and ambitions.

- Are there national mechanisms to assist companies to bring products to market or support small businesses? Could these mechanisms be used to finance potential pilots for new or old antibiotics?
- Are there other mechanisms that may be potentially used to finance pilot for new or old antibiotics?
- Does your country work with the European Investment Bank regarding financing for health research?
- Has your country considered carving out the antibiotic reimbursement from the DRG?

- What are your thoughts about placing a fee onto EMA registrations of all other medicines with the exception of anti-infectives in order to finance antibacterial innovation?
- Is there any consideration of lessening regulatory requirements for SMEs, for example, local office for pharmacovigilance?

6. **Guidelines.**
   - Do you have national stewardship or IPC guidelines?
   - In animals and/or plants too?

7. **National processes to update clinical guidelines, IPC routines, and other AMR and HCAI-related policies and practices.**
   - What processes and procedures do you have to update the above? How often? How do you incorporate new evidence?
   - Are there any barriers to gathering the evidence and updating the policies/guidelines?

Appendix 2: EU-JAMRAI viewpoint on opportunities in Europe to finance a pull mechanism.

Clinical Infectious Diseases

VIEWPOINTS

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

Christine Årdal,[1] Yohann Lacotte,[2] and Marie-Cécile Ploy[2], on behalf of the European Union Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI)

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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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Appendix 3: EU-JAMRAI article on the need for more supply chain transparency to enable sustainable access to antibiotics and essential medicines.

Supply chain transparency and the availability of essential medicines

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Sustainable access to essential medicines is crucial at all times, especially during a pandemic when health-care systems are operating at maximum capacity and there is an increased demand for life-saving supplies. Moreover, in pandemics, not only health-care systems but also global medicine supply chains are under severe stress. Shortages of medicines, which were common before 2020,[1,2] have been exacerbated by the coronona-virus-2019 (COVID-19) pandemic because of increased demand, lockdowns, border closures and hoarding.[3,4] The supply of medicines could be improved by increasing the transparency of the complicated and fractured supply chain, starting upstream at the sources of active pharmaceutical ingredients.

Production of the active pharmaceutical ingredients that form the basis of every medicine is highly concentrated in only a few countries. China is the world's largest producer, with an estimated 40% share of global production.[5] India, the world's largest provider of generic medicines, procures almost 70% of its active pharmaceutical ingredients from China.[6] Yet the exact number and geographical distribution of producers remain elusive because companies that market medicines do not publish details of the sources of their active ingredients. Producers of the active pharmaceutical ingredients of a specific medicine are known only to the marketing authorization holder and the regulatory authority – neither buyers nor the public have access to this information. Thus, the fact that several companies may be selling a specific medicine in a particular country does not mean that there is a truly competitive market in that country capable of providing an ample supply. Prominent examples of global supply failures include: (i) a fire in 2017 at a factory in China producing active pharmaceutical ingredients that resulted in a global shortage of the antibiotic combination piperacillin–tazobactam;[1] and (ii) insufficient production capacity of the sedative propofol to meet demand during the COVID-19 pandemic,[3] which led some countries to reserve veterinary propofol for human use.[7] However, supply failures of active pharmaceutical ingredients are common and affect the provision of medicines in all countries.[2,3,8]

Faced with more frequent shortages of medicines, many countries have acted to improve the management of supply chain interruptions, such as establishing a public register of shortages, but they have not yet increased the transparency of the supply chain. Marketing authorization holders are often contractually obligated to notify procurers when they are unable to supply a medicine and, in some cases, they are also obligated to bear the costs of replacement medicines.[2] A recent study found that 19 countries (mostly in Europe) required marketing authorization holders to report anticipated shortages between 5 days and 6 months in advance, with the most common notice period being 2 months.[9] Although these time frames may be sufficient for procurers to react to impending shortages, they will be insufficient to avoid shortages caused by the failure of the sole producer of an active pharmaceutical ingredient.

With greater supply chain transparency, governments would be able to work more proactively and collectively to identify limiting factors in the supply chain and, thereby, avoid shortages. Each national regulatory authority knows which active pharmaceutical ingredient producers are affiliated with each of the medicines marketed in their country. However, regulators cannot share this information with the public or government or even with regulators in other countries as the information is considered confidential. This situation leaves regulators in a quandary: they may not know if it is only medicine suppliers in their country who rely on a few producers or on a specific geographic region or if this is indeed the case for all suppliers of a particular medicine. To anticipate and avoid medicine shortages, countries need to understand the true nature of global supply chains so they can design effective mitigation measures for each medicine. Otherwise countries may be persuaded to intervene in the medicine supply without fully understanding the cost–effectiveness of a particular intervention. For example, many countries are currently discussing the local production of critical medicines (e.g. antibiotics) to meet their own needs.[4] Yet cheaper and more efficient alternatives may be available, such as providing incentives for the geographical diversification of suppliers (including producers of active pharmaceutical ingredients), which would ultimately benefit all countries.

Private companies prefer their manufacturing and distribution practices to be kept secret for several reasons. For example, transparency would give competitors an insight into supply chains and could reveal supply weaknesses or financial details: an exact knowledge of the factories involved allows costs to be calculated fairly precisely. In addition, as many national and hospital medicine procurement agencies still tender almost solely on the basis of price,[2] transparency may enable larger manufacturers to utilize financial information to drive

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out competitors. However, procurers are starting to value the benefits of a predictable supply and are applying the principle of multiple sourcing (i.e. they have several providers for each medicine where possible).[10] Ideally, during the selection process, procurers should not only base their appraisals on price but should also consider whether supply chains are independent, resilient and meet environmental standards – characteristics that would give a company a competitive advantage in tendering and price negotiations.

Regulatory agencies should publish the source of the active pharmaceutical ingredients for each registered medicine along with the usual information. Through the efforts of the European Union's Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections and in light of supply challenges related to COVID-19, some European countries are considering moving towards greater supply chain transparency. As an example of how this can be done, the New Zealand Medicines and Medical Devices Safety Authority provides publicly available information on the names and locations of: (i) active pharmaceutical ingredient producers; (ii) finished product manufacturers; (iii) product sponsors; and (iv) the marketers of products.[11] Recent reports have called for similar actions in the United States of America, including active monitoring of medicine supplies and increased supply chain transparency.[3,10]

In addition to enabling countries to better anticipate shortages and avoid them, supply chain transparency has other collective advantages. The discharge of wastewater during the manufacture of drugs can promote the development and spread of antimicrobial resistance and cause serious local environmental pollution that may also have public health implications.[12] Greater transparency about the supply chain would increase pressure on international companies to monitor their sources of active pharmaceutical ingredients and enable engaged citizens to put pressure on governments and hospitals to ensure that any medicines they procure have been produced in a way that respects relevant environmental standards.

The practice of keeping medicine supply chains secret conflicts with public health needs. Without accurate information, procurers cannot proactively develop cost-effective plans for ensuring the sustainable, continuous supply of essential medicines. At the same time, procurers must ensure that suppliers are rewarded for maintaining robust supply chains and meeting environmental standards. Greater transparency is an essential first step in improving the medicines supply chain in a way that will benefit public health. ■

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Appendix 4: Policy brief "Incentivizing antibiotic access and innovation"

POLICY BRIEF

INCENTIVIZING ANTIBIOTIC ACCESS AND INNOVATION

Joint Action Antimicrobial Resistance and Healthcare-Associated Infections

GLOBAL AMR R&D HUB

PREDICTABLE ACCESS TO LIFE-SAVING ANTIBIOTICS IS UNDER THREAT

Antibiotic resistance imperils global health, with multi-drug resistant bacterial infections accounting for over 33,000 deaths in Europe alone in 2015. The number of annual global deaths is unknown but predicted to be large. Yet contrary to the public health need, antibiotic innovators and manufacturers are struggling.

New antibiotics are unable to generate revenues large enough to sustain the interest of multinational players and even small developers are failing to cover their costs, resulting in bankruptcies of small antibiotic innovators. Melinta, an American antibiotic innovator went bankrupt in December 2019, after receiving regulatory approval in the United States and Europe for an antibiotic judged as "innovative" against a "critical" priority pathogen by the World Health Organization. Physicians use new antibiotics as a last resort in order to preserve their efficacy. Whereas this is sound stewardship, it dis-incentivizes innovation since unit sales determine revenues.

Simultaneously, shortages of older antibiotics are increasing. Due to antibiotic resistance patterns and prescribing habits, the markets of some essential antibiotics are small, including those for children. Tendering processes based solely on price and automatic price reductions for generic medicines reduce profitability, leading to a consolidation of supply. The dependency on sole manufacturers may come as a surprise, when there is suddenly no medicine available. For example, in 2017 a fire at a raw material factory in China resulted in a global shortage of piperacillin/tazobactam. During the COVID-19 pandemic, supply chains have been unable to meet demand as well as challenged by supply disruptions due to lockdowns and border closures.

Several prominent reports have assessed the challenges to antibiotic access and innovation and have made recommendations, including calls for "pull" incentives, aiming to increase revenues for marketed, innovative antibiotics. We set out to understand countries' perceptions of these recommendations, through frank and anonymous dialogue. As a part of the EU Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI) we performed in-depth interviews with policymakers and AMR experts in ten European countries.[1] These insights were made more globally representative with support of the Global AMR R&D Hub who supported the inclusion of a further three countries from other continents.[2] The aim of the interviews was to understand the barriers and facilitators for implementing incentives that promote antibiotic access and innovation.

EU-JAMRAI & Global AMR R&D Hub | Policy brief: Incentivizing antibiotic access and innovation

[1] European countries interviewed were: Belgium, Denmark, France, Germany, Luxembourg, the Netherlands, Norway, Romania, Spain, and Sweden. We interviewed policymakers from Ministries of Agriculture and Research in nine of these countries.

[2] Supplementary pool included interviews with the Ministries of Health and other AMR experts in Canada and South Africa, and an interview with an AMR expert in Japan.

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PREDICTABLE ACCESS TO LIFE-SAVING ANTIBIOTICS IS UNDER THREAT

EUROPEAN "PULL" MECHANISMS

The Pharmaceutical Strategy for Europe (2020) states that the EU will pilot a pull incentive in 2021. Three countries are already underway:

England will pay an annual fixed payment determined through a health technology assessment (including both patient and societal value) for the supply of a new antibiotic. The payment is not dependent upon sales volumes. The pilot has selected two antibiotics. Target implementation date is Spring 2022.

Germany has revised the way it assesses new "reserve" antibiotics, allowing for higher unit prices in line with the value of the new antibiotic.

Sweden has signed agreements with suppliers of five new antibiotics for an annual revenue guarantee. Swedish hospitals continue to purchase as normal with the funding from the pilot study paying the difference between the guarantee and actual sales. The agreements started July 15, 2020 and will continue for two years.

ELEVEN COUNTRIES EXPRESSED GENERAL SUPPORT FOR ANTIBIOTIC INCENTIVES

Interviewees expressed support for antibiotic incentives in 11 of 13 countries. Yet, it was clear from the interviews that policymakers' support is high-level and general. Almost all countries are uncertain which incentive is appropriate for their country, how to implement an incentive, and how much it will cost. They prefer to wait for evidence from Germany, Sweden, and the United Kingdom (see box). Nine of the 10 European countries interviewed would prefer a common, European or multinational incentive, as long as it is independent from national health technology assessment, medicine pricing, and reimbursement.

Policymakers were clear that incentives should only apply to antibiotics that meet public health needs and that the public health value must be demonstrated through showing benefit in clinical situations against multi-drug resistant infections (see quote).

Whereas policymakers expressed concerns about the lack of antibiotic innovation, this was not the principal driver for support for new incentives. Rather, countries (9 of 11) indicate a preference for a model that ensures access to both old and new antibiotics, with the highest priority for older antibiotics.

"Antibiotics are being approved for indications where there is no intention that they will be used. This sends the wrong signal...would prefer that antibiotics are tested against drug-resistance instead. If the trials need to be done in [high-resistance countries] and they are performed according to existing standards, this is preferable."

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COUNTRIES DO NOT HAVE PREDICTABLE ACCESS TO LIFE-SAVING ANTIBIOTICS

Predictable access to life-saving antibiotics is a common global challenge. Twelve of 13 countries indicated that shortages of existing antibiotics is a serious problem. Eight out of 13 indicated that this resulted in greater use of broad-spectrum antibiotics and thereby potentially increasing antibiotic resistance. As important antibiotics continue to be unavailable, doctors change prescribing habits, potentially away from evidence-informed prescribing guidelines. Interestingly, we also interviewed veterinary counterparts in European countries, who stated that there was no indication of shortages of veterinary antibiotics, despite often being comprised of the same active pharmaceutical ingredients.

National medicines agencies and procurers lack the tools to work proactively to avoid antibiotic shortages. They know which factories produce the raw materials and finished medicines for only their own marketed medicines, but do not have access to data about the global market for a specific medicine. Factory information is generally considered a business secret and cannot be made publicly available. When countries are notified of a supply disruption, it is too late to find a solution if all companies are dependent upon the same raw material supplier. This is a common problem since the world supply of active pharmaceutical ingredients is highly concentrated in a few countries. A lockdown in one geographic region can have significant implications for the world's medicine supply. Transparency is needed to understand supply chain resilience. New Zealand has already taken steps, openly publishing the name and location of raw material and finished product factories for all its marketed medicines.

Unpredictable access is not only a challenge for older antibiotics but also for new ones. New antibiotics are not widely available. For example, the new antibiotic combination meropenem/vaborbactam, judged as "innovative" by the World Health Organization against "critical" priority pathogens, was approved by the European Medicines Agency in 2018 but is currently marketed in only five EU countries.

A lockdown in one geographic region can have significant implications for the world's medicine supply.

SPECIFIC, DETAILED INCENTIVES MUST BE COMMUNICATED TO FACILITATE IMPLEMENTATION

The results of these interviews point to a clear need for specific, detailed incentives that national policymakers can assess, tailor, and implement. These incentives must be designed with the aim of ensuring national access to important antibiotics that meet public health need. EU-JAMRAI aims to publish a recommendation in early 2021.

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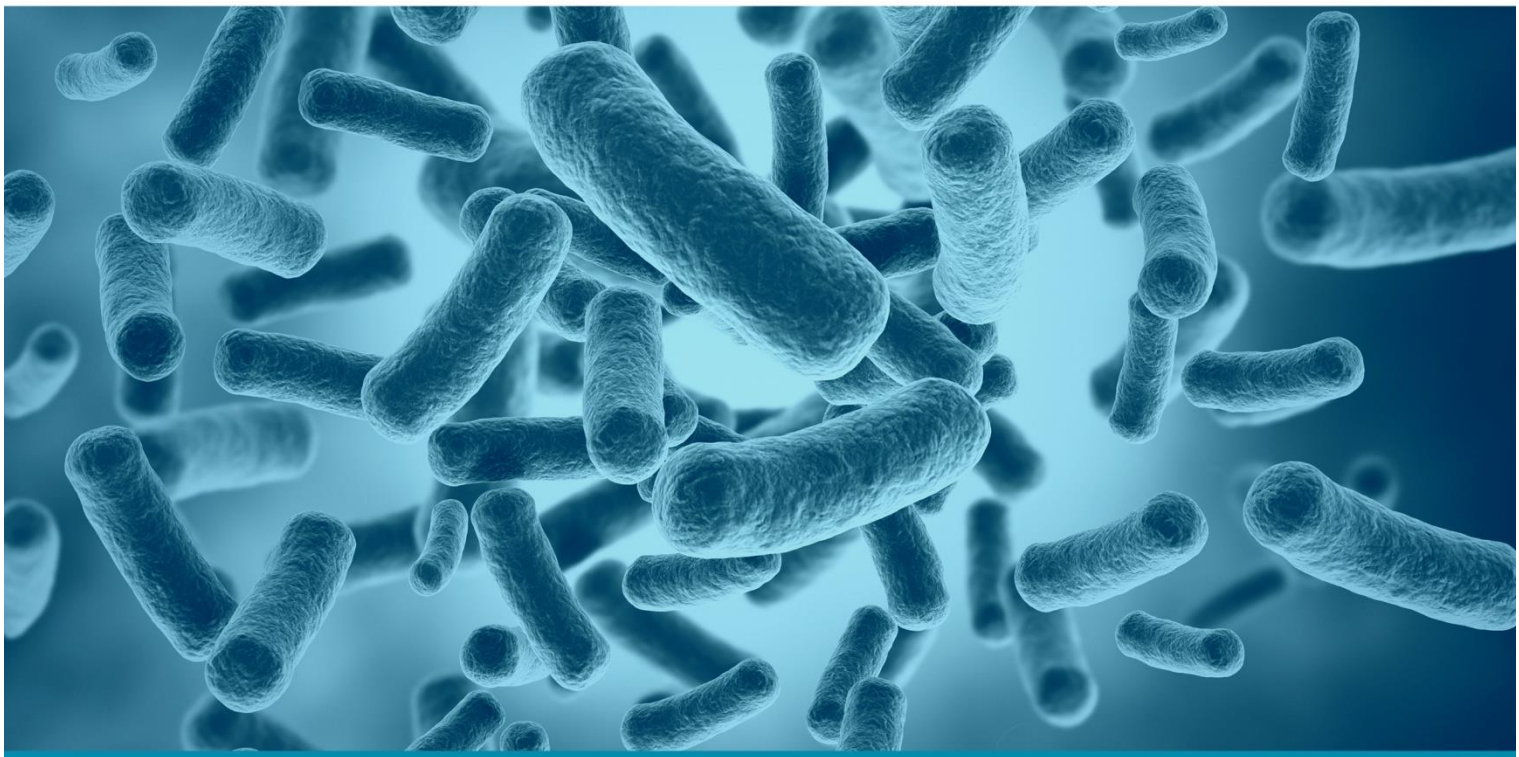
ABOUT EU-JAMRAI

EU-JAMRAI is a European Union Joint Action on Antimicrobial Resistance (AMR) and Healthcare-Associated Infections (HCAI) that brings together 44 partners and more than 40 stakeholders. Our mission is to foster synergies among EU Member States by developing and implementing effective One Health policies to fight the rising threat of AMR and to reduce HCAI. EU-JAMRAI started in September 2017 and will finish in February 2021.

Our mission is to foster synergies among EU Member States by developing and implementing effective One Health policies.

EU-JAMRAI

Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections



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