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Joint Action
Antimicrobial Resistance and
Healthcare-Associated Infections

Policy brief

Improving access to essential antibiotics

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The problem

Countries' access to essential antibiotics is fragile

Antibiotic resistance is a serious public health threat, with multi-drug resistant bacterial infections accounting for over 33,000 European deaths in 2015.[1] Hindering antibiotic resistance requires multi-pronged strategies, integrating surveillance, infection prevention and control, antibiotic stewardship, and access to antibiotics. This policy brief focuses on the latter, improving access to essential antibiotics, that is, both old and new antibiotics meeting public health needs.

Unpredictable access to generic antibiotics is a frequent problem globally, including Europe.[2] The markets of some 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 and fragile supply chains.

Unpredictable access is not only a challenge for older antibiotics but also for new ones. It is generally assumed that companies, receiving approval from the European centralised procedure, steadily make their antibiotics accessible across Europe. Yet this is not necessarily the case. For example, meropenem/vaborbactam, an antibiotic assessed as "innovative" against "critical" priority pathogens by the World Health Organization (WHO), approved by European Commission (EC) in 2018, is not yet available in most European countries, even the large ones.[3]

The rationale for these delays is complex and multifactorial. New antibiotics provide little clinical evidence of improvement over older and more affordable antibiotics. This is because it is difficult to locate enough patients with multi-drug-resistant infections, and antibiotics need to demonstrate efficacy in indicated infections (e.g., abdominal infections). This lack of evidence translates to automatic low prices in many European countries. Physicians rightly use new antibiotics as a last resort in order to preserve their efficacy. Small innovators struggle to cover their operational costs. Three small companies with marketed antibiotics have gone bankrupt in the past two years. Large pharmaceutical companies have largely abandoned the development of new antibiotics.

The consequences

Patients may not receive the right antibiotic at the right time

Shortages of antibiotics have been increasing globally over the last decade. In 2020, the EU Joint Action on Antimicrobial Resistance and Healthcare Associated Infections (EU-JAMRAI) set out to understand European countries' perceptions and needs regarding innovation and access to antibiotics. Through the facilitation of the Global AMR R&D Hub, participating countries were expanded to include Canada, Japan, and South Africa. Through in-depth interviews, 12 of 13 countries indicated that shortages of existing antibiotics are a serious problem nationally. Eight out of 13 indicated that this resulted in greater use of broad-spectrum antibiotics, thereby potentially increasing antibiotic resistance.[4]

Antibiotic innovation will always be needed as bacteria continue to evolve new resistance mechanisms. Patient outcomes regarding secondary bacterial infections of COVID-19 patients in countries with higher levels of antibiotic resistance is alarming. A recent study found than 3.6% of

Indians admitted to intensive care units with COVID-19 had highly resistant secondary bacterial infections, with a mortality rate of over 50% compared to 10% of COVID-19 patients without bacterial infections.[5]

The opportunities

Three interventions, already with documented impact, are needed to stimulate innovation and secure access

Firstly, to improve supply of existing antibiotics, medicine tendering processes should award contracts to ***multiple*** providers, with additional rewards for those with ***independent*** supply chains. Many European countries award contracts to a single provider for the national supply of a medicine based solely on price. This pushes antibiotic prices as low as possible and incentivises companies to consolidate to achieve even greater economies of scale. When a sole provider has production problems, this may result in a regional or global shortage, potentially costing healthcare systems millions trying to alleviate the situation.

Today a lack of transparency complicates an ability to fully understand supply risks.[6] National medicines agencies and procurers know which factories produce the raw materials and finished medicines *only for their own marketed medicines*, but do not have access to data about the *regional or global market* for a specific medicine. Factory information is generally interpreted as a business secret, although not in New Zealand where it is public information. When procurers are notified about 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 global supply of active pharmaceutical ingredients is concentrated in a few countries. A lockdown in one geographic region can have significant implications for the world's medicine supply.

Nordic countries implemented new criteria to award antibiotic tenders to multiple providers in 2020, with the following weights:

- 30% Good environmental practices
- 20% Reliable delivery
- 30% User preferences
- 20% Price

Some European countries have started awarding contracts to multiple providers. However, to actually strengthen a diverse supply base, more countries must join them, resulting in stronger global supply chains for the benefit of all countries. Tendering criteria that also value good environmental practices hinder the development of antibiotic resistance.

There are some hurdles to overcome to implement this intervention. The majority of existing antibiotics predate the European centralised procedure. This means that the marketing authorisation holders of older antibiotics vary across European countries. For countries with few marketing authorisation holders, this opportunity would require them to recognise marketing authorisations from other European countries. It also may take time for manufacturers to adjust their supply chains and may result in different prices for the same medicine.

Secondly, to ensure a steady supply of new antibiotics for unmet public health need, countries need to continue to support research and development grants targeting WHO's Priority Pathogen List. In the last five years public and philanthropic funding for antibiotic innovation has significantly increased, with more than € 1 billion invested over this time period.[7] According to the WHO, the

preclinical antibiotic pipeline is "dynamic" with almost 300 candidates in development, developed by a majority of small European companies.[8] The Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) is currently funding preclinical development of 18 new potential classes of antibiotics and 16 non-traditional therapies (e.g., antibodies, anti-virulence products, and bacteriophages).

Whereas the preclinical pipeline is promising, WHO assessed the current clinical antibiotic pipeline as "insufficient", with only seven candidates considered innovative.[8] In the short-term it may be necessary to repurpose existing medicines to treat emerging multi-drug resistant infections, develop new formulations, or reduce side effects. For example, the Global Antibiotic Research and Development Partnership (GARDP), in addition to its development of new antibiotics, is modifying existing antibiotics. Since repurposed medicines are generally older and not patentable, companies are not incentivised to undertake these trials. Public grant funding is essential to support this work, as in the case of evaluating existing medicines to treat COVID-19.

For promising candidates advancing in development, small companies struggle to secure late stage financing, with only the US' Biomedical Advanced Research and Development Authority (BARDA) providing grants. With the advent of the Health Emergency Response Authority (HERA), the EU has an opportunity to act as a pipeline coordinator, shaping and bringing promising new classes to market. Public funding ensures that critically needed antibiotics are financed as opposed to those most likely to be profitable. Public funding may also improve the quality of the clinical evidence, so that physicians have a better understanding of how to use new antibiotics when approved. The EU has supported the development of clinical trial networks that can improve evidence generation. HERA may also act to ensure a minimum level of regional production competencies that may be used for critical shortages.

Lastly, to ensure reliable access to essential, small market antibiotics, the implementation of "pull" mechanisms is urgent. Pull incentives are economic incentives that increase revenues for marketed, important antibiotics. Four European countries have implemented initiatives where new antibiotics can achieve higher rewards. France and Germany allow for higher unit prices. Sweden and UK are trialling delinked pull incentives, where the reward value is not linked to the units sold. Preliminary results show that Sweden and the UK now have access to more newly marketed antibiotics than any other country with the exception of the United States.[3] In the Swedish case, its pull incentive has successfully demonstrated that it improves access to prioritised antibiotics. However, to stimulate innovation and improve access, more countries need to implement pull mechanisms.

EU-JAMRAI found that many European countries support the implementation of pull incentives for essential antibiotics (old and new) but are uncertain how to proceed and would prefer multinational collaboration. The EU has committed to trial a pull incentive in 2021. EU-JAMRAI recommends a revenue guarantee (Figure 1).

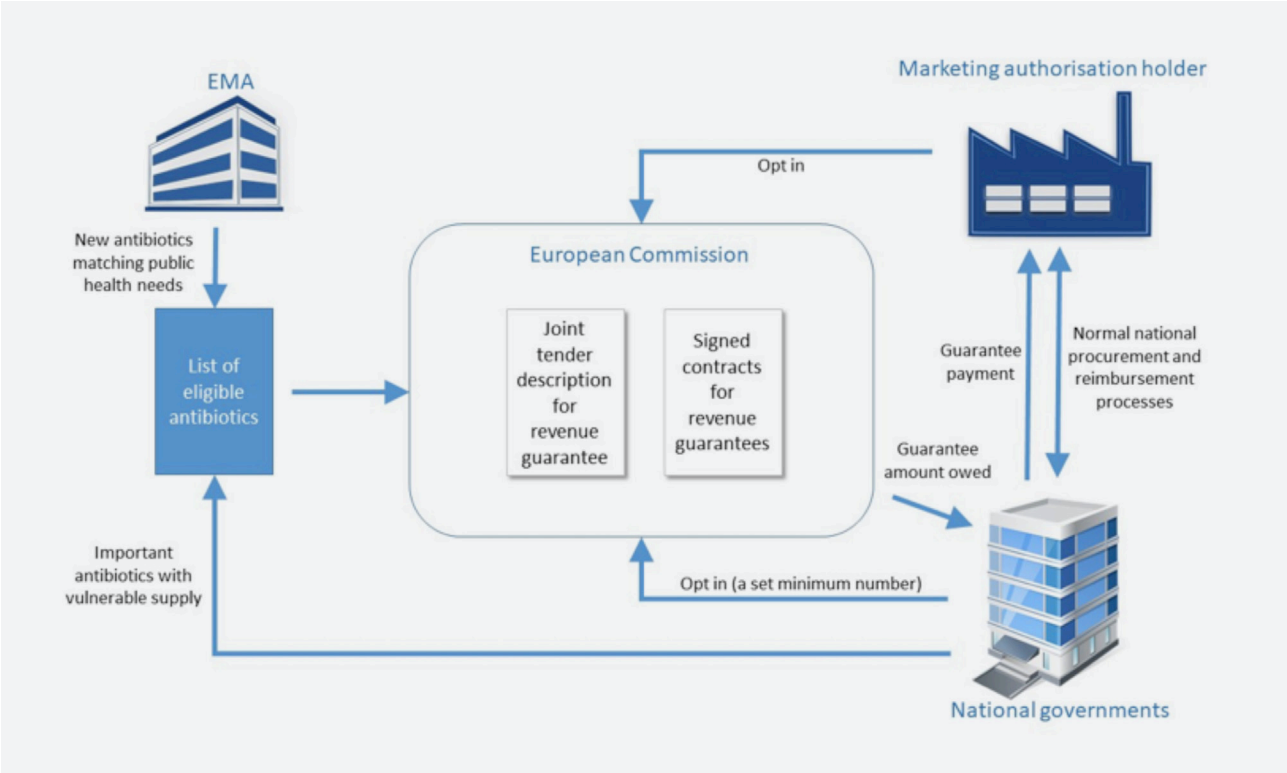

Figure 1: EU-JAMRAI proposed European pull incentive for essential antibiotics

Step 1: Eligible antibiotics

Newly approved antibiotics would be recommended by European Medicines Agency (EMA) based upon their ability to meet unmet public health need, as assessed by WHO and national governments through existing health technology assessments. Existing antibiotics would be nominated by European countries that are concerned with vulnerable supply.

Step 2: Tendered antibiotics

The European Commission (EC) would gather countries' willingness to participate in the revenue guarantee for each eligible antibiotic. A minimum number of countries would need to express interest for the antibiotic to be included in the tender. National financial responsibility for the guarantee would be apportioned and agreed.

Step 3: Negotiation

The EC would perform a tender for all of the antibiotics defined in step 2. To participate in the tender, a company would need to have either marketing approval through the European centralised procedure or marketing approval in at least one European country (which could be expanded through mutual recognition). Companies must commit to access and stewardship stipulations for all participating countries. For older antibiotics, ideally multiple companies would be selected. The revenue guarantee would be adjusted based upon the countries served.

Step 4: Fulfilment

Participating countries would continue to price, procure, and reimburse the antibiotics as per normal national practices. Companies would meet the access requirements as per the revenue guarantee.

Step 5: Payment

After the close of each year (or other specified time period), companies would report their total unit sales amount for each participating country to the EC. Governments would validate these figures. Each country would then pay the difference between its apportioned guarantee amount and actual sales to the company. If actual sales exceeded the guarantee amount, no further action would be taken.

Step 6: Repeat

This process would be repeated dependent upon the nomination of additional antibiotics, or at the expiry of the revenue guarantees. Ideally revenue guarantees would last 3-5 years.

The revenue guarantee amount is negotiable. Countries would submit their projected annual use and package price per antibiotic to the EC to inform its negotiations. A key principle of the revenue guarantee is rewarding companies for maintaining stable access to important antibiotics. Therefore, it is expected that the revenue guarantee would always be higher than projected sales. Revenue guarantees should be of a sufficient magnitude to ensure a reasonable profitability for antibiotic innovators and producers.

Appendix

In this brief we use the term "antibiotic" for ease of understanding, but the concepts in this brief apply equally to all antibacterial agents.

This policy brief is an output of the EU-JAMRAI is a European Union Joint Action on Antimicrobial Resistance (AMR) and Healthcare-Associated Infections (HCAI), eu-jamrai.eu, a collaboration of 44 partners and more than 40 stakeholders. Our mission was 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 finished in February 2021. Some of the text in this policy brief is from previous policy briefs of EU-JAMRAI. The text is used with permission.

This policy brief provides a high-level overview of promising interventions to improve access to essential antibiotics in Europe. For each of these topics, there are more detailed analyses available, meaning that these interventions may be implemented fairly rapidly, utilising and expanding upon existing structures. Over 30 models have been assessed in developing these recommendations.[9] The table below includes some of the prominent models that have been discarded and the rationale.

Selection of discarded pull incentives	Rationale for removal from consideration
Joint procurement mechanism	The revenue guarantee outlined in this brief is closely related to the EU's Joint Procurement Process. However, a pure procurement agreement where a government pays only for the amount used will not stimulate antibiotic innovation or stabilise fragile markets. The antibiotics included in the revenue guarantee are by definition small market products. Producers require revenue predictability and additional rewards for maintaining stable access. Governments need to pay for the guarantee of access, not consumption.
Patent extensions	Extending the monopoly time period by patent extensions or other exclusivities assumes that antibiotic consumption continually grows to a level of profitability for the innovator. Yet this is not the case as antibiotics are carefully stewarded. This incentive will also not work for non-patented antibiotics.
Transferable exclusivity vouchers	A transferable exclusivity voucher is a legal right to extend the monopoly time period of any other patented drug, in exchange for the successful regulatory approval of a specified antibiotic. The voucher would be transferable or saleable. Whereas transferable exclusivity vouchers may be straightforward to implement, in the end, the cost of these vouchers to healthcare systems is anticipated to far exceed the cost of revenue guarantees.

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