Policy Brief

A Pan-EU/EEA Pull Incentive for Antimicrobial Innovation and Access

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We, alumni of the DRIVE-AB Consortium, academic experts in the area of antimicrobial pull incentives, are excited to see the Council Recommendation from June 2023 regarding European Union (EU) actions to combat antimicrobial resistance (AMR) in a One Health approach, including "*contribute to the design and governance of a Union multi-country pull incentive scheme in order to improve innovation, the development of new antimicrobials and access to existing and new antimicrobials where Member States can participate on a voluntary basis.*"[1]

In 2018 DRIVE-AB recommended the implementation of a delinked pull incentive to stimulate antibiotic innovation.[2] In the past five years, additional evidence demonstrates even more clearly that such a pull incentive is necessary, feasible and impactful.[3,4] In this policy brief, we present our recommendation for a pull incentive, to be led by the EU Directorate-General Health Emergency Preparedness and Response (HERA), aiming to both stimulate antimicrobial innovation and ensure homogenous access across the EU and European Economic Area (EEA) countries.

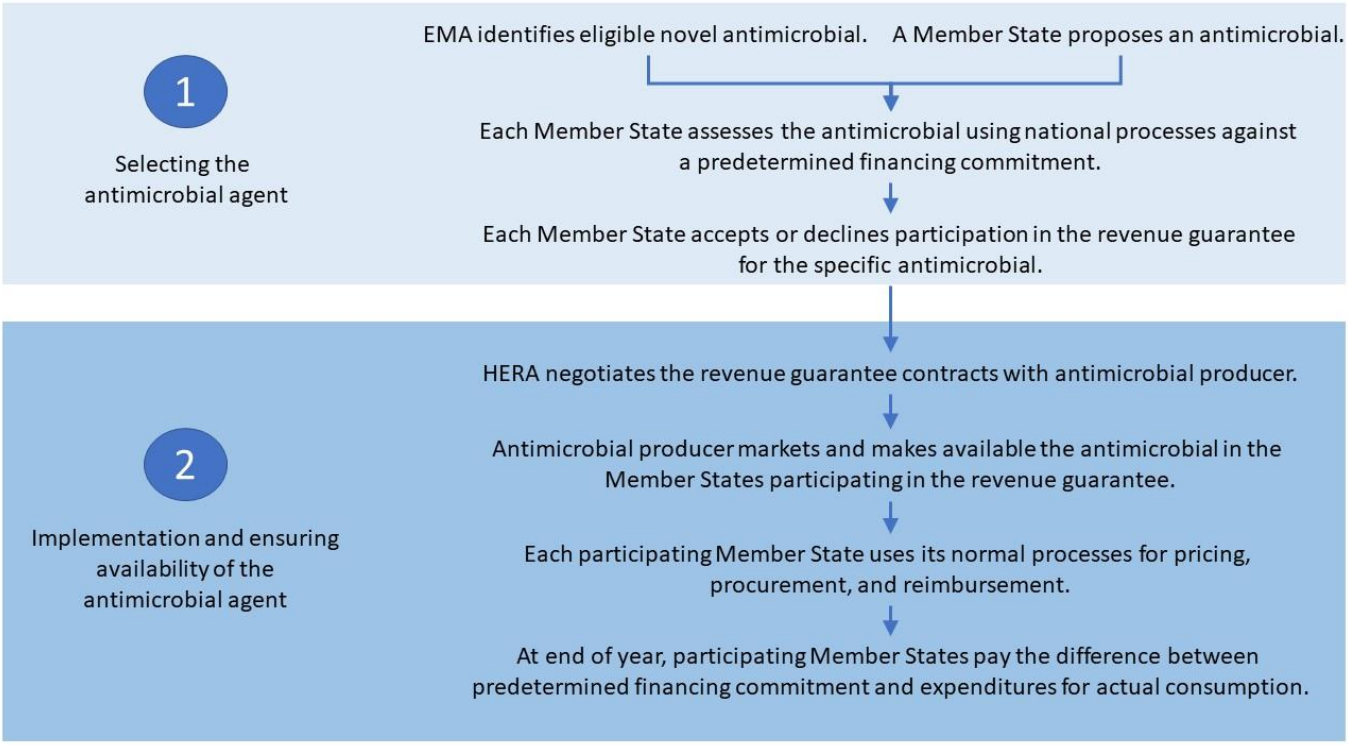
The incentive

A pan-EU/EEA flexible revenue guarantee (Diagram 1) led by HERA with sufficient financial resources is the most promising and feasible incentive to stimulate innovation of and secure access to antimicrobial agents that meet public health and clinical needs.

- The incentive can be used to stimulate innovation of **high-value new** antimicrobial agents as well as to secure access to both new and **priority generic** antimicrobial agents. Please see definitions of potential criteria in Table 1.
- Member States participate on a **voluntary** basis according to a **predetermined** financing commitment.
- Each participating Member State uses its **normal processes** for pricing, procurement, and reimbursement.
- The reward is based upon the antimicrobial agent's value, with higher rewards for **innovative** agents with demonstrated **evidence** of treating the World Health Organization's priority pathogens.

In this brief, we consistently use the term "antimicrobial" agents. Yet we expect that eligible agents will most likely include antibacterial and antifungal treatments, including antibacterial combination therapies. Member States include all countries utilizing the European Medicines Agency (EMA), which includes both EU and EEA countries. Generic antimicrobials are those antimicrobial agents no longer protected by intellectual property rights within EU/EEA jurisdictions.

Diagram 1: Proposed operationalization of a pan-EU/EEA revenue guarantee for antimicrobial agents



1 – Selecting the antimicrobial agent

Selection of antimicrobial agents for the revenue guarantee is done through a two-stage process:

1. The EMA identifies eligible novel agents and assigns a reward tier. The reward tier is determined by the antimicrobial agent's activity, innovativeness, and evidence (Table 1). For a generic product, a Member State proposes the agent.
2. Each Member State then determines its participation, using health technology assessments (HTAs) or other national methodologies for prioritization or inclusion in reimbursement or similar.

The rationale for this two-stage process is to create a clear and expedient process. EMA's selection of the reward tier is associated with predefined, non-negotiable financial commitment per country. The Member State, after sufficient time to perform its assessment, can then decide to participate or not in the revenue guarantee.

The selection process for inclusion in the revenue guarantee differs between newly approved and generic products. For a newly approved antimicrobial agent, the EMA will apply criteria suggested in Table 1 and recommend a reward tier of high, medium, low, or no reward. To be categorized as eligible for a "high" reward, the antimicrobial must be expected to make a sustainable reduction in mortality and morbidity. This will require innovative products (including factors such as absence or low level of known cross-resistance and at least one of the following WHO innovation criteria: new chemical class, target, or mode of action[5]), with clinical evidence demonstrating efficacy against at

least one “critical” World Health Organization (WHO) priority pathogen or multiple “high” and/or “medium” pathogens. This includes both WHO lists for priority bacterial pathogens and fungal pathogens.[6,7] The requirement of innovativeness considers veterinary antimicrobials as well, i.e., an already approved veterinary antibiotic unused previously in humans should not be considered innovative.

It is common that multiple innovators develop similar medicines simultaneously. Since it is undesirable to incentivize innovators to rush clinical trials to be the first-to-market, similar and next-in-line agents will be considered innovative so long as, at the time of regulatory approval of the first-to-market, the similar agent has commenced dosing within a clinical trial in patients.

If the antimicrobial treats only one “high” or “medium” WHO priority pathogen it will be classified according to the scheme we propose on Table 1 as a “medium” reward since the utility, and thereby the value, is narrower. Those less innovative agents which nonetheless offer some patient benefit, such as treatment of a WHO priority pathogen with limited treatment options, are classified as “low”. Finally, undifferentiated, non-innovative antimicrobials will receive no reward.

Companies should be able to consult with EMA in advance of regulatory approval regarding the likelihood of an agent meeting the innovation requirements. This is non-binding, public feedback from the EMA about the agent’s likelihood to qualify for the revenue guarantee.

The eligibility requirements are strict but attainable. Europe should aim to incentivize innovation that has a real clinical impact, reducing morbidity and mortality. Today’s advanced clinical pipeline demonstrates a lack of novelty and diversity and a failure to address the most urgent resistance threats.[8] It is anticipated that few antimicrobials would qualify for a “high” reward, now and in the future. For planning purposes, we use an assessment which determines that five agents currently in clinical trials may qualify for a “high” designation and three for “medium”.[9] Yet many of these agents will likely fail for scientific reasons, never receiving regulatory approval.

The clinical evidence requirements necessitate meaningful clinical data to guide clinical decision-making and prescribing practices according to antimicrobial stewardship principles. These do not require the agent to demonstrate superiority in a clinical trial due to antimicrobials’ inherent challenges[10,11] but do require evidence regarding activity against pathogens and resistance mechanisms as well as the relative effectiveness in clinical outcomes and activity against unmet public health need. We encourage innovators to make use of global clinical trial networks like ECRAID and ADVANCE-ID.[12,13] If significant new clinical evidence develops after regulatory approval, the sponsor can apply to the EMA to nominate the agent for inclusion in a revenue guarantee or recommend an adjustment in the reward tier of an existing guarantee at time of contract renewal.

A Member State may also request HERA to include an antimicrobial agent at a specified reward tier. Requests may concern both on-patent and generic antimicrobial agents. On-patent agents that are suitable for inclusion are those already marketed in Europe. Generic agents that are suitable for inclusion in the revenue guarantee are those where consumption is insufficient to secure a stable market, like child formulations. Additionally, the revenue guarantee would be negotiated with finished product manufacturers of the generic agent, since on a European basis there will be many different marketing authorization holders for the same medicine. This may require tendering procedures to select at least two (or more) producers. The finished product manufacturers would then be responsible for securing marketing authorization holders in each of their participating Member States.

Table 1: Suggested revenue guarantee reward tiers and EMA eligibility criteria

Reward tier	EMA's criteria	Comments
High	Activity against at least one WHO "critical" priority pathogen, or activity against multiple "high" or "medium" WHO priority pathogens	Antimicrobial agents effective against only one pathogen may not be used empirically. Thereby the value of having a novel agent that is effective against a wide variety of pathogens is higher. However, the need is urgent for "critical" priority pathogens.
	Considered "innovative"[1]	"Innovative" means that the antimicrobial agent according to EMA's judgement provides evidence of an absence or low level of cross-resistance and at least one of the three WHO innovation criteria: new chemical class, new target, or new method of action. For non-traditional agents (of which there are many in the preclinical pipeline), EMA must use its own discretion to assess if innovativeness has been achieved. New types of evidence may be required.
	Provides meaningful clinical evidence of the agent's ability to meet clinical needs	Demonstrates that the medicinal product is effective against WHO priority pathogens, based on meaningful in vitro data and based on the results of at least one clinical study, and demonstrate that no or only limited therapy options or possibilities of prophylaxis are available.
Medium	Activity against one "high" or "medium" pathogens included in the WHO priority pathogen list	For pathogen-specific agents, the company must provide information on the use and availability of diagnostics.
	Considered "innovative"[1]	See above for "innovative" and clinical evidence requirements
	Provides meaningful clinical evidence of the agent's ability to meet clinical needs	
Low	Activity against susceptible pathogens	
	Provides meaningful clinical evidence of the agent's ability to meet clinical needs	See above for clinical evidence requirements
No reward	Undifferentiated, non-innovative antimicrobials	Little to no added clinical and public health value
Priority generic	(Proposed by a Member State)	Important generic antimicrobials at risk of either shortages (due to e.g., fragile supply chains) or deregistration (due to e.g., low profitability), including child formulations

[1] Agents will be considered innovative so long as, at the time of regulatory approval of the first-to-market, the similar agent has commenced a clinical trial.

By opting into the revenue guarantee, a Member State has made an informed financial commitment to HERA. New antimicrobials targeting highly resistant pathogens will almost always be considered reserve products, only to be used as a last resort, based on WHO's AWaRe (Access, Watch, Reserve) list classification. As a delinked incentive, the revenue guarantee amount for these agents should always be larger than expected sales. In this brief, we propose European-wide payment amounts (Table 2) and break these down by Member State (Table 3). We believe that these amounts need to be predetermined, i.e., be fixed amounts defined before joining the scheme, so that each Member State has a financial threshold to use for their HTA (or alternative) processes. Thereby, each Member State will receive the cost-effectiveness data for the agent from the sponsor company[a] (as happens today with HTA assessments), well in advance (e.g., six months) of HERA's deadline for deciding whether to join or not this pull incentive scheme. Each Member State assesses the agent using national processes against a predetermined, non-negotiable financing commitment. Member States are encouraged to consider refining their HTA processes to recognize all values of antimicrobials, including population-level values like the UK has done[14].

Table 2: Suggested annual reward amount per reward tier per antimicrobial agent

Reward tier	Suggested total annual amount for all Member States	Rationale
High	€ 120 million per year[1]	The calculated "share" of a global revenue guarantee for all EU/EEA Member States, based on academic assessment[15] and also requested by industry[16] (€1.2 billion per agent over 10 years)
Medium	€ 80 million per year[1]	A midpoint calculated "share" of a global revenue guarantee for all EU/EEA Member States, based on academic assessment[15,17] and requested by industry[16] (€800 million per agent over 10 years)
Low	€15 million per year[1]	This is an estimate based upon the recently applied Swedish revenue guarantee, demonstrated to effectively secure access to new antimicrobials[3], adjusted by GDP. For greater precision, HERA should ask Member States to complete Sweden's formula for each agent (estimated highest volume of safety stock needed per year * price per package * 1.5).
Priority generic	€ 3 - 30 million per year	There are little data available regarding sufficient revenues needed to sustain an older antibiotic. Sweden estimates that revenues of €100k are needed to induce a marketing authorization holder to maintain an antibiotic in Sweden.[18] Yet this number will likely vary depending upon national context (regulatory costs, distribution channels, etc.). HERA should ask Member States for their national estimate of necessary revenues to maintain access and consult industry. Unlike the other tiers, this guarantee is applied at a strength and formulation level, e.g., flucloxacillin oral suspension 50 mg/ml. This means that the same substance (e.g., flucloxacillin) could receive multiple guarantees (e.g., one for oral suspension and another for tablet form).

[1] If the EU/EEA has financed clinical trials for the antimicrobial, these amounts will be subtracted from the guarantee amount.

[a] Excluding generic agents

Each Member State determines whether it will participate in the revenue guarantee for the specified antimicrobial. Once an antimicrobial agent is identified and a reward tier assigned, HERA will ask each Member State for a participation commitment. The commitment will be for a multi-year contract (likely 3-4 years initially) with the ability to extend. Those Member States that do not opt into the revenue guarantee will have an opportunity to join at the time of contract renewal (3-4 years later). Until then, they will need to secure access independently.

Some Member States may decide not to participate in the revenue guarantee. If an antimicrobial meets public health and clinical needs, all European countries will want access to the antimicrobial. This has been demonstrated by France, Germany, Sweden, and the UK, countries experiencing different levels of AMR, with incentives that have selected the very same recipient antimicrobials, including for the high value award in the UK.[3,4,19,20] Therefore, we expect that European countries will want access to high-value antimicrobials. However, there may be instances where some Member States decline participation. For example, a "low" value agent may not be attractive for countries, particularly for non-critical priority pathogens. In these instances, the revenue guarantee amount will be reduced accordingly.

2 – Implementation and ensuring availability of the antimicrobial

HERA negotiates the revenue guarantee with the antimicrobial producer, where the value of the contract may be negotiated lower than the suggested values in Table 2 depending upon Member State participation. HERA enters the negotiation knowing the Member State financial commitments. A standard agreement is negotiated to be signed by the innovator and each participating Member State. If all 30 EU/EEA countries participate, 30 separate contracts will be signed.

At contract execution, the antimicrobial agent will be made available in all participating Member States. It is anticipated that the antimicrobial agent will have market authorization in all participating Member States at the contract start date. If the agent is not available in participating Member States, the revenue guarantee payments may be decreased. Availability will be defined in the contract and set to a clinically reasonable timeframe.

Ensuring appropriate global access and stewardship to the right antimicrobial hinders the spread of AMR. Therefore, it is essential that those countries with the highest burden of AMR, i.e., low- and middle-income countries, also have predictable availability to effective, new antimicrobials where needed. This can be a uniform provision in all European pull incentive contracts. The Global Antibiotic Research and Development Partnership (GARDP) with partners is currently undertaking such an effort with the novel antibiotic, cefiderocol, in 135 countries. This effort will provide valuable learnings about how to roll out and steward new antibiotics in low and middle-income countries. Expectations about global availability can be reinforced in high-income country pull incentive contracts.

A revenue guarantee entails the following set of obligations on the antimicrobial producer, whereby failure to comply may result in deductions from the revenue guarantee:

- Keeping a European-based security stock, ideally with the agent labeled for use in all Member States, containing enough units to serve the participating Member States' anticipated demand for a set period (contractually defined, e.g., three months)

- Delivery of the agent guaranteed within a clinically reasonable timeframe (e.g., 24 hours) specified in the contract, up to the contractually specified estimated demand[b]
- GARDP (or another organization, such as the Medicines Patent Pool, with similar public health goals) is offered an opportunity to license or distribute the agent at a low unit price for use in a specified list of low- and middle-income countries[21]
- Binding commitments to complete phase IV studies and pediatric studies as per EMA risk management plans[c] (payments can be reduced if the studies are not completed on time)
- If the agent is removed from the EU/EEA market for any reason, the contract is terminated
- No company employee or contractor is remunerated based upon unit sales targets of the agent
- Sharing all data regarding consumption of the agent in the EU/EEA Member States
- Monitoring and sharing all global post-marketing data regarding resistance levels to the antimicrobial[c]
- Sharing information on all direct financial clinical R&D support for the agent, so that the guarantee amount may be lowered correspondingly for those Member States that funded the agent's clinical development[c]
- Agreement of the latest possible date of generic entry of the agent for Member States, so there is clarity on when generic competition will start within EU/EEA countries[c]

Participating Member States also have obligations to participate in the revenue guarantee:

- Commit to steward all antimicrobials, especially those included in the revenue guarantee
- In the first year of the revenue guarantee to expedite accessibility, allow packages labeled for other Member States to be used
- Produce reliable national maximum demand estimate for the antimicrobial agent to be communicated to the antimicrobial agent's supplier to ensure adequate production capacity

To manage orders and product flows, each participating Member State uses its normal processes for pricing, procurement, and reimbursement. There is no change to these processes. These will determine the participating Member State's annual consumption, i.e., unit sales.

At the end of the contract year, each Member State will pay the innovator the difference between its financing commitment amount and actual consumption (i.e., unit sales). To stimulate innovation and ensure access, the revenue guarantee is always expected to be larger than actual revenues from consumption. Yet, unusual circumstances may occur. If a Member State has paid more for the antimicrobial than its financial commitment, no payment will be made to the company. There will be no clawback of funds to the Member State from the company - a revenue guarantee is not a cap on revenues. An overconsumption in one country will not lower other Member States' payments to the company. Potentially excessive use of the agent by any Member State will result in follow-up conversations between Member State representatives, HERA, and ECDC. Since each Member State will pay for its consumption based upon normal practices, there is no incentive to overconsume.

Basis for the recommended financial magnitudes of the revenue guarantee

Industry claims that EU/EEA Member States' share of the global amount necessary to stimulate antimicrobial innovation is € 640 million to 1,350 million per antimicrobial.[16] HERA's commissioned study recommended that between €650 million to €1,400 million was *globally* sufficient, which aligns

[b] If the antimicrobial exceeds the contractually stipulated maximum demand, the parties will collaborate to find a suitable solution. It is anticipated that hospitals will have stocks available at their pharmacy for patients with immediate needs.

[c] Not applicable for generic antimicrobials

with DRIVE-AB recommendations.[2,17] Yet, other academic work has calculated the global share as much higher, in line with industry expectations.[15]

Under the proposed EU pharmaceutical legislation, exclusivity (i.e., regulatory and market protection) may vary from 8 to 12 years.[22] New antimicrobials are expected to reach 10 years of exclusivity[d]. Thus, we assume that antimicrobial innovators have sufficient means to achieve 10 years of exclusivity and base annual recommendations on a 10-year period. To avoid evergreening of intellectual property, as a part of the revenue guarantee contract, the company agrees to the latest date of generic entry.

This brief proposes a tiered award system, where those antimicrobials that are truly innovative and meet previously unmet public health needs receive amounts in line with industry expectations and less innovative or less societally valuable antimicrobials receive lower or no rewards (Table 2). The aim of this revenue guarantee is to stimulate innovative antimicrobial R&D. Setting a high bar for innovation increases the cost of R&D because more products will fail for scientific reasons.

HERA will allocate each Member State's financial commitment according to gross domestic product (GDP). Those Member States with the greatest ability to pay are those that are expected to pay the highest amounts. Table 3 gives each Member State's allocation based upon World Bank GDP data 2021. HERA should update these figures including for inflation with each guarantee proposal.

Push financing

Whereas push financing has increased in the last five years, it is still insufficient to generate a truly innovative R&D pipeline. DRIVE-AB called for total investments of push financing of €750 million per year for antibiotic innovation, in addition to pull incentives.[2] In 2021, a little over €371 million was invested in therapeutic R&D for antibiotic innovation globally (including tuberculosis, which was excluded from DRIVE-AB's mandate), a reduction of €113 million from 2020.[23] Truly innovative research projects are riskier than incremental developments of known molecules, as has been noted by CARB-X, a large global push incentive. Therefore, a revenue guarantee is necessary to pull molecules to market, and public push financing is still necessary to ensure a truly innovative antimicrobial pipeline.[17,24,25]

Conclusion

The revenue guarantee proposed in this brief is intended to stimulate innovation and secure access to antimicrobials meeting public health and clinical needs. Our suggested award amounts assume that the transferable exclusivity voucher (TEV) proposed as a part of the EU pharmaceutical legislation is not implemented.[22] If the TEV is implemented, the amounts in Tables 2 and 3 must be reconsidered and adjusted downward or removed for on-patent antimicrobials. Likewise, if EU or its Member States subsidize clinical development of a drug selected for a pull incentive, the cumulative revenue guarantee must be directly reduced, Euro for Euro. Even if it may appear from this brief that our proposal is more complex than the TEV, this is not the case. The operationalization of the TEV has not yet been fully described.

We see minimal risks with implementing a revenue guarantee. As is widely acknowledged there are few innovative agents currently in the clinical pipeline. This means that those few high value agents can be tested with this agreement through a 3–4-year contract, limiting liability for public payors.

The revenue guarantee proposed in this brief offers a predictable and directly implementable solution to stimulate innovation and secure access to antimicrobials that meet public health needs.

[d] Regulatory data protection (6 years), market protection (2 years), market launch (2 years)

Member States voluntarily determine if they would like to participate, in alignment with the Council Recommendations. Innovators have clearly defined targets, and the rewards are high. In many ways, the proposed EU-level revenue guarantee is a scaling up of national pull incentive models that have already proven to be effective in the UK and in Sweden and could act as a complement to the US PASTEUR incentive, if enacted.

Table 3: Suggested annual financial commitment per Member State by reward category, if participating

	High	Medium	Low
	(thousands)		
EMA countries (as of 2023)	€ 120 000	€ 80 000	€ 15 000
Austria	€ 3 258	€ 2 172	€ 407
Belgium	€ 4 030	€ 2 687	€ 504
Bulgaria	€ 570	€ 380	€ 71
Croatia	€ 468	€ 312	€ 58
Republic of Cyprus	€ 193	€ 128	€ 24
Czech Republic	€ 1 911	€ 1 274	€ 239
Denmark	€ 2 702	€ 1 801	€ 338
Estonia	€ 252	€ 168	€ 32
Finland	€ 2 017	€ 1 344	€ 252
France	€ 20 063	€ 13 376	€ 2 508
Germany	€ 28 895	€ 19 263	€ 3 612
Greece	€ 1 457	€ 972	€ 182
Hungary	€ 1 233	€ 822	€ 154
Ireland	€ 3 420	€ 2 280	€ 427
Italy	€ 14 297	€ 9 531	€ 1 787
Latvia	€ 270	€ 180	€ 34
Lithuania	€ 451	€ 300	€ 56
Luxembourg	€ 580	€ 387	€ 72
Malta	€ 118	€ 79	€ 15
Netherlands	€ 6 870	€ 4 580	€ 859
Poland	€ 4 609	€ 3 072	€ 576
Portugal	€ 1 721	€ 1 147	€ 215
Romania	€ 1 927	€ 1 285	€ 241
Slovakia	€ 790	€ 527	€ 99
Slovenia	€ 419	€ 279	€ 52
Spain	€ 9 682	€ 6 455	€ 1 210
Sweden	€ 4 312	€ 2 874	€ 539
Iceland	€ 174	€ 116	€ 22
Liechtenstein	€ 41	€ 28	€ 5
Norway	€ 3 271	€ 2 180	€ 409

About DRIVE-AB

DRIVE–AB (i.e., Driving reinvestment in research and development for antibiotics and advocating their responsible use, www.drive-ab.eu), was a consortium of 16 public sector partners and 7 pharmaceutical companies supported by the Innovative Medicines Initiative (IMI) Joint Undertaking

(www.imi.europa.eu), resources of which were composed of financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and EFPIA (European Federation of Pharmaceutical Industries and Associations) companies' in kind contribution. DRIVE-AB was tasked with defining responsible use of antibiotics, identifying the antibiotic-related public health priorities, calculating the societal value of having new antibiotics available for these priorities, developing and costing new economic models to promote the desired antibiotic innovation, and sustainable use of the resulting, novel antibiotics. The purpose of the project was to transform the way policymakers stimulate antibiotic innovation and to ensure that these new antibiotics are used sustainably and available equitably. DRIVE-AB published its final report in 2018.[2] The opinions in this policy brief are those of the authors, not the entire DRIVE-AB consortium nor the authors' organizations.

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