EU-JAMRAI

Joint Action
Antimicrobial Resistance and
Healthcare-Associated Infections

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Supporting antibiotic access and innovation

Work Package 9, Research & innovation
WP Leaders: Marie-Cécile Ploy and Christine Årdal
Date: July 8, 2021
Author: **Christine Årdal**

Inserm
La science pour la santé
From science to health

Norwegian Institute of Public Health

Disclosures

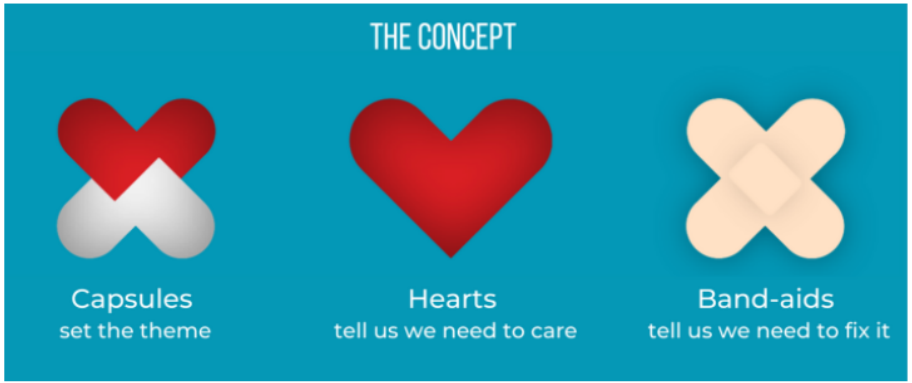
Christine Årdal is a senior researcher at the Norwegian Institute of Public Health (NIPH) and the co-lead of the research and innovation work package of the EU Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI).

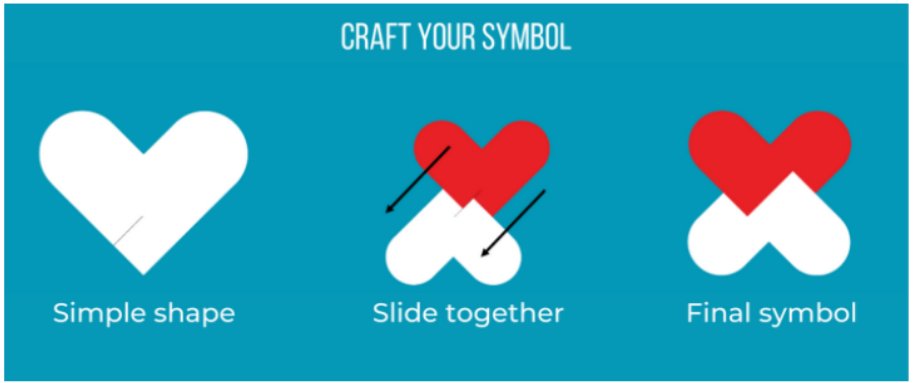
The views expressed in this presentation should not be considered to reflect the positions of NIPH, the Norwegian government or participating governments in EU-JAMRAI.

She is currently receiving external grant financing from the Norwegian Research Council (#300867), the World Health Organization (Regional Office for Europe), and the Norwegian Agency for Development Cooperation (Norad), and recently from the European Union (EU-JAMRAI, #761296).

About EU-JAMRAI

Joint Action's mission is to **foster synergies** related to AMR and HAI among EU Member States (26 participating countries)





Terminology

The focus of this presentation is antibiotics and **antibiotic** resistance.

Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis

Alessandro Cassini, Liselotte Diaz Högberg, Diamantis Plachouras, Annalisa Quattrocchi, Ana Hoxha, Gunnar Skov Simonsen, Mélanie Colomb-Cotinat, Mirjam E Kretzschmar, Brecht Devleesschauwer, Michele Cecchini, Driss Ait Ouakrim, Tiago Cravo Oliveira, Marc J Struelens, Carl Suetens, Dominique L Monnet, and the Burden of AMR Collaborative Group*

Summary

Background Infections due to antibiotic-resistant bacteria are threatening modern health care. However, estimating their incidence, complications, and attributable mortality is challenging. We aimed to estimate the burden of infections caused by antibiotic-resistant bacteria of public health concern in countries of the EU and European Economic Area (EEA) in 2015, measur

Methods We estimate European Antimicrob population coverage. W the European Centre f in European acute car models for five types o

Findings From EARS-N interval [UI] 583 148–7 associated with health and 874 541 (768 837–9 people aged 65 years o

Interpretation Our res expressed, for the first and EEA is substantial

Lancet Infect Dis 2019; 19: 56–66

Published Online November 5, 2018 http://dx.doi.org/10.1016/S1473-3099(18)30605-4

See Comment page 4

*Members listed at the end of the Article

European Centre for Disease Prevention and Control, Solna, Sweden (A Cassini MD, L D Högberg PhD, D Plachouras PhD, A Quattrocchi PhD, A Hoxha MSc, M J Struelens PhD, C Suetens MD, D L Monnet PhD); Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands (A Cassini, M E Kretzschmar PhD); University Hospital of North Norway, Tromsø, Norway (G S Simonsen PhD); Research Group for Host-Microbe

"671k infections with antibiotic-resistant bacteria…accounted for an estimated **33,110** attributable deaths"

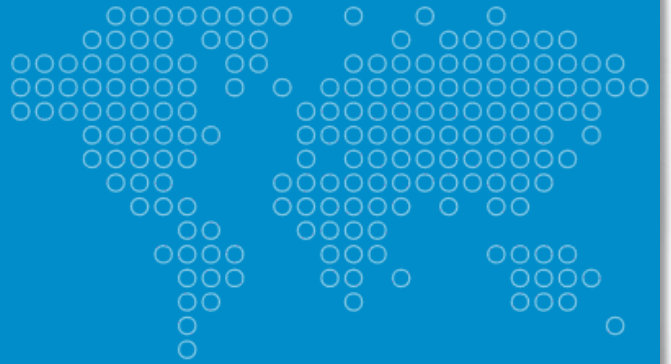

We’re making progress in combating
antibiotic resistance.

Progress on National Action Plans…

Impact

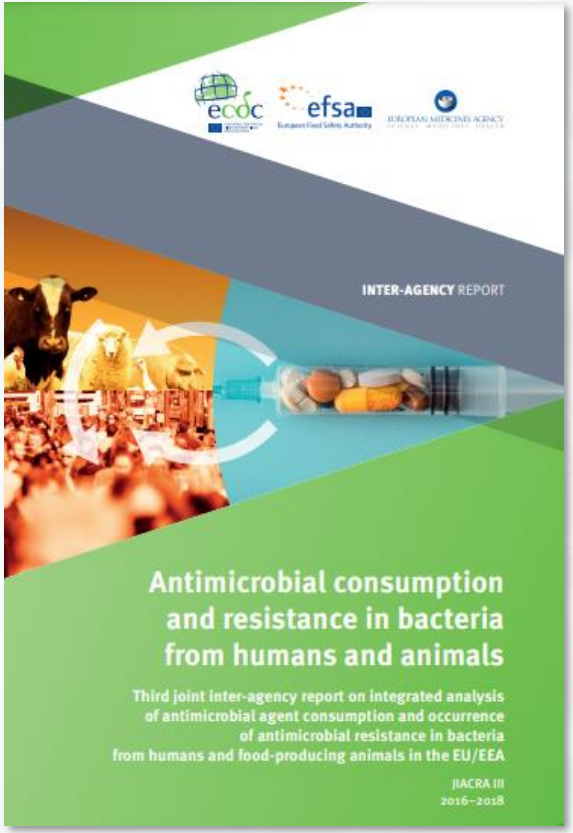
144
countries

have finalized their National Action Plan, aligned with the objectives of the GAP (as of May 2021)



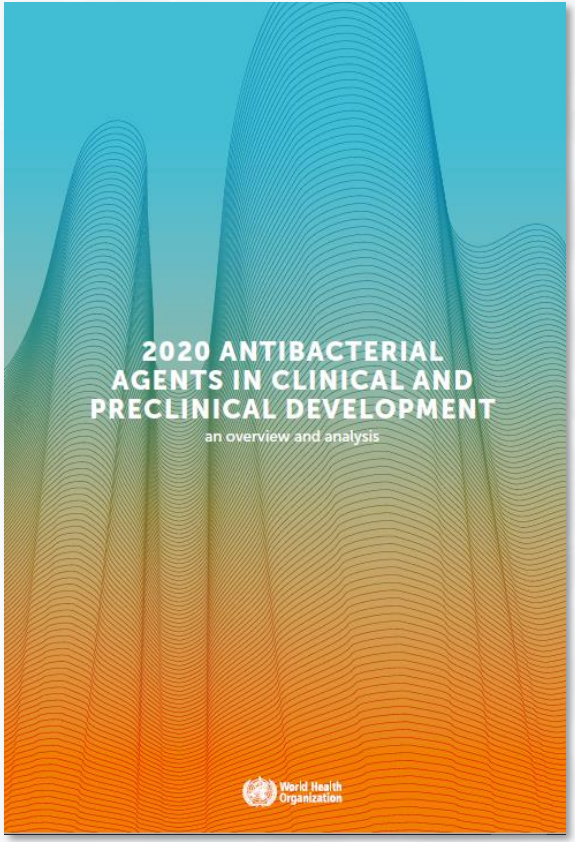
Source: WHO, https://www.who.int/activities/supporting-countries-with-national-action-plan-implementation

European veterinary use of antibiotics is decreasing…



"…the overall antimicrobial consumption was **lower in food-producing animals** than in humans during the timeframe covered in this report (2016–2018). This is the **first time** this has happened since JIACRA was initiated (2011)…"

Preclinical pipeline is greatly improved…



"The WHO **preclinical** pipeline database is **dynamic** and **innovative**, including a wide range of drug development projects that are using different approaches to target the WHO bacterial priority pathogens list."

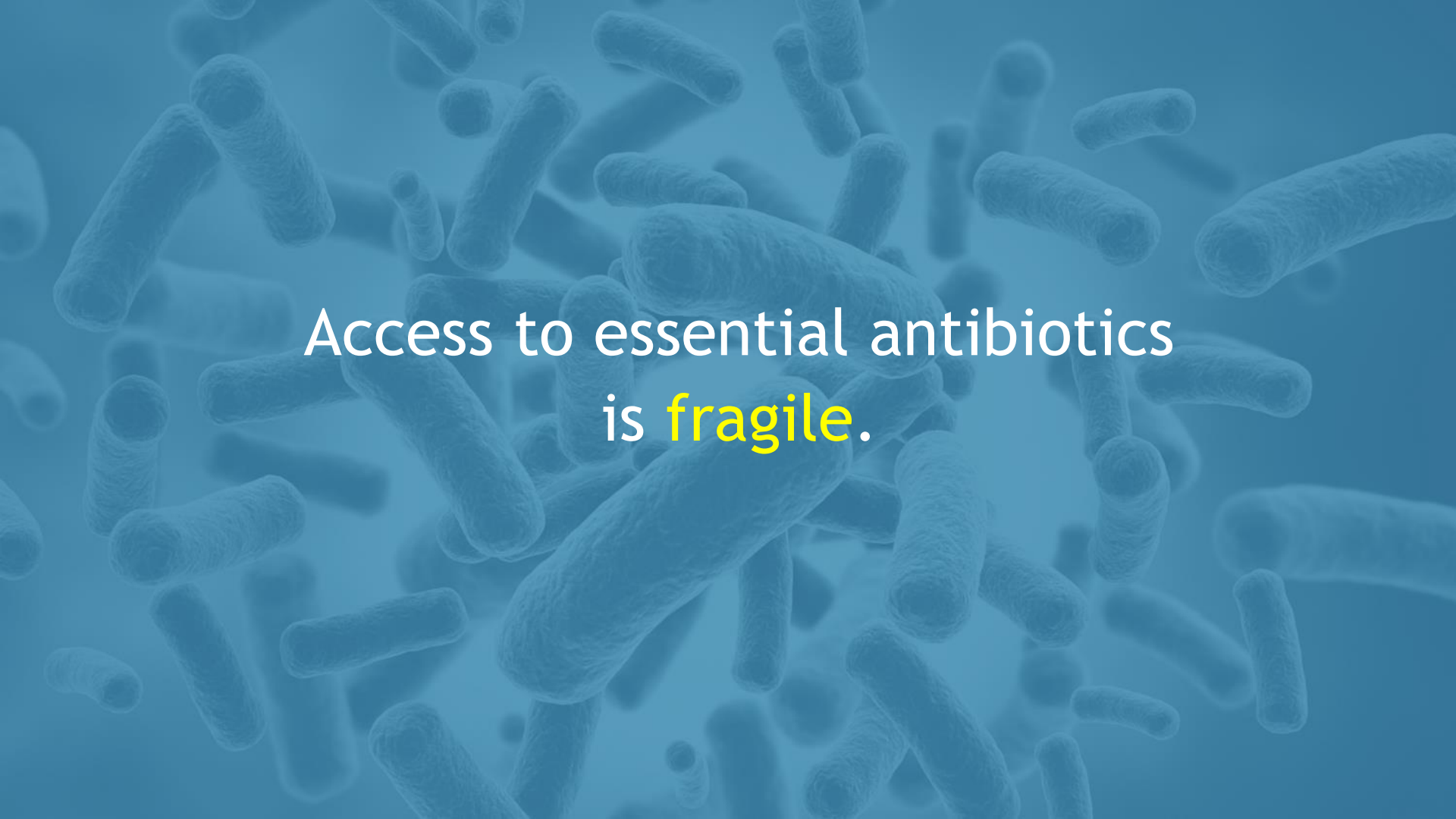
Availability of new antibiotics in countries with high need…

- Case of cefepime-taniborbactam
- Targets WHO "critical" priority pathogens
- Considered an innovative antibiotic by WHO
- Currently in Phase III clinical trials

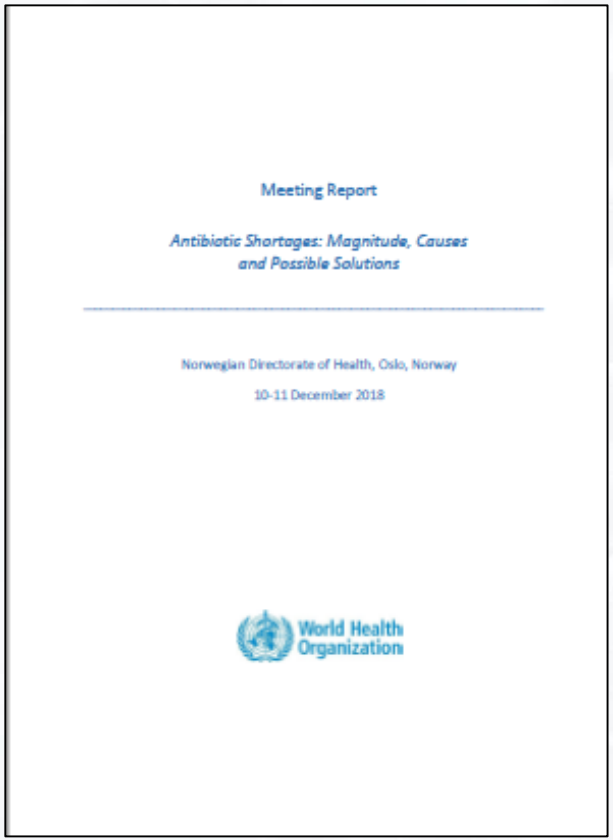
Collaboration with the Global Antibiotic Research and Development Partnership (GARDP)

In April 2020, Venatorx and GARDP announced a collaboration to accelerate the development of, and access to, cefepime-taniborbactam. GARDP is collaborating with Venatorx to complete the development of cefepime-taniborbactam, including the Phase 3 cUTI trial; additional clinical trials in adults with multidrug-resistant infections; and clinical development activities and trials to enable cefepime-taniborbactam to be used for children, including newborns with serious bacterial infections. Venatorx is committed to working with GARDP to distribute cefepime-taniborbactam on an affordable basis worldwide. Venatorx has granted GARDP exclusive rights to distribute and sub-distribute cefepime-taniborbactam, once it is approved for clinical use, in most low- and lower middle-income countries.

Source: https://www.venatorx.com/cefepime-taniborbactam/


Access to essential antibiotics
is fragile.

Unpredictable access to older antibiotics



Meeting Report

Antibiotic Shortages: Magnitude, Causes and Possible Solutions

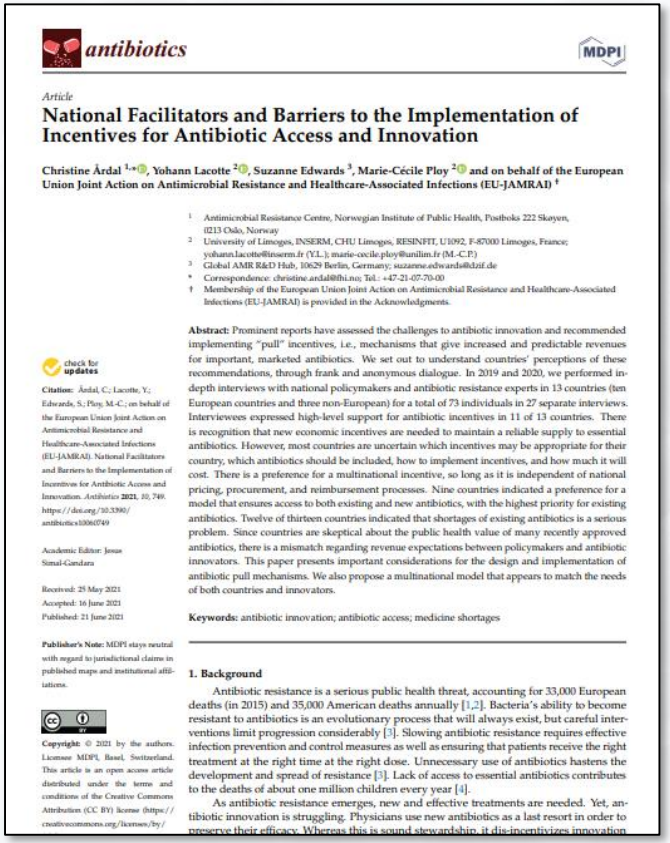
Norwegian Directorate of Health, Oslo, Norway

10-11 December 2018

World Health Organization

"The experiences of several European countries indicate that **shortage of antibiotics is common**, and the frequency of shortages seems to be **increasing**, despite Europe's position as the second largest regional manufacturing center of antibiotics."

Unpredictable access to older antibiotics



antibiotics

MDPI

Article

National Facilitators and Barriers to the Implementation of Incentives for Antibiotic Access and Innovation

Christine Årdal [1,*], Yohann Lacotte [2], Suzanne Edwards [3], Marie-Cécile Ploy [2] and on behalf of the European Union Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI) [†]

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† Membership of the European Union Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI) is provided in the Acknowledgments.

Abstract: Prominent reports have assessed the challenges to antibiotic innovation and recommended implementing "pull" incentives, i.e., mechanisms that give increased and predictable revenues for important, marketed antibiotics. We set out to understand countries' perceptions of these recommendations, through frank and anonymous dialogue. In 2019 and 2020, 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 73 individuals in 27 separate interviews. Interviewees expressed high-level support for antibiotic incentives in 11 of 13 countries. There is 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 preference for a multinational incentive, so long as it is independent of national pricing, procurement, and reimbursement processes. Nine countries indicated a preference for a model that ensures access to both existing and new antibiotics, with the highest priority for existing antibiotics. Twelve of thirteen countries indicated that shortages of existing antibiotics is a serious problem. 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. This paper 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.

Keywords: antibiotic innovation; antibiotic access; medicine shortages

check for updates

Citation: Årdal, C.; Lacotte, Y.; Edwards, S.; Ploy, M.-C.; on behalf of the European Union Joint Action on Antimicrobial Resistance and Healthcare-Associated Infections (EU-JAMRAI). National Facilitators and Barriers to the Implementation of Incentives for Antibiotic Access and Innovation. *Antibiotics* **2021**, *10*, 749. https://doi.org/10.3390/antibiotics10060749

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1. Background

Antibiotic resistance is a serious public health threat, accounting for 33,000 European deaths (in 2015) and 35,000 American deaths annually [1,2]. Bacteria's ability to become resistant to antibiotics is an evolutionary process that will always exist, but careful interventions limit progression considerably [3]. Slowing antibiotic resistance requires effective infection prevention and control measures as well as ensuring that patients receive the right treatment at the right time at the right dose. Unnecessary use of antibiotics hastens the development and spread of resistance [3]. Lack of access to essential antibiotics contributes to the deaths of about one million children every year [4].

As antibiotic resistance emerges, new and effective treatments are needed. Yet, antibiotic innovation is struggling. Physicians use new antibiotics as a last resort in order to preserve their efficacy. Whereas this is sound stewardship, it dis-incentivizes innovation

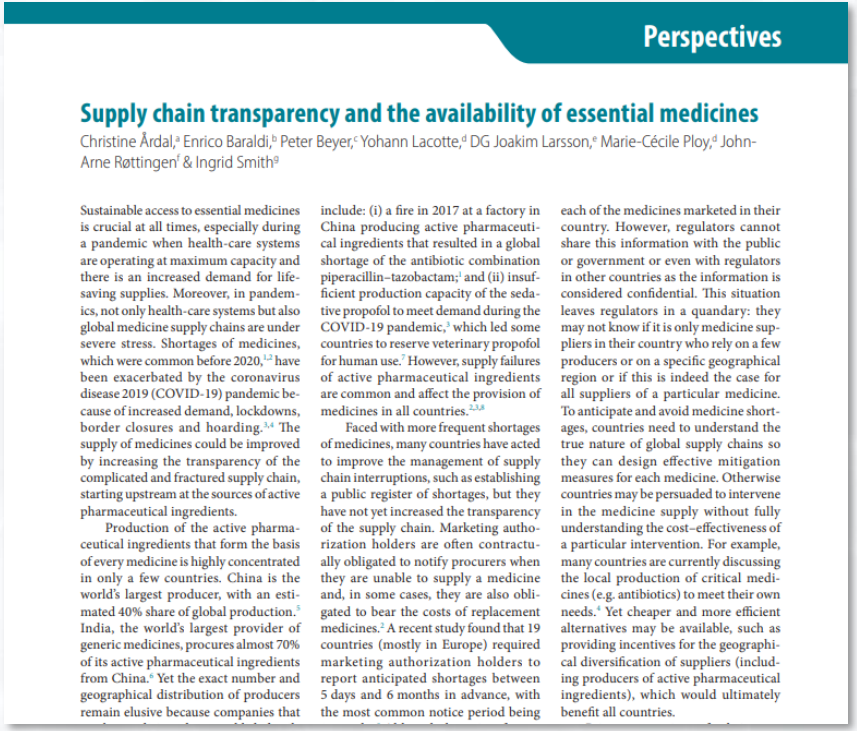
"12 of 13 countries indicated that **shortages** of existing antibiotics are a **serious problem** nationally…

8 of 13 indicated that this resulted in **greater use of broad-spectrum** antibiotics, thereby potentially increasing antibiotic resistance…

8 countries indicated that companies recently decided to **stop marketing** an essential, existing antibiotic in their country"

Case of antibiotic combination piperacillin/tazobactam

- Included in WHO's Essential Medicines List as a "watch" antibiotic
- When unavailable, some evidence points to increased hospital-associated infections*
- History of shortages, including fire at API manufacturer in 2017, resulting in global shortage
- Still unclear today how many API producers



Perspectives

Supply chain transparency and the availability of essential medicines

Christine Årdal,[a] Enrico Baraldi,[b] Peter Beyer,[c] Yohann Lacotte,[d] DG Joakim Larsson,[e] Marie-Cécile Ploy,[d] John-Arne Røttingen[f] & Ingrid Smith[g]

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 coronavirus disease 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 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 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 geographical 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.

* Gross et al. The Effect of a Piperacillin/Tazobactam Shortage on Antimicrobial Prescribing and Clostridium difficile Risk in 88 US Medical Centers. Clin Infect Dis. 2017 Aug 15.


A worrying trend of delayed availability
for new antibiotics in Europe.

The case of meropenem/vaborbactam

- Targets WHO "**critical**" priority pathogens
- Considered an **innovative** antibiotic by WHO

- Innovator – medium-sized American company
- FDA approval in 2017
- EMA approval in Nov. 2018
- Bankruptcy in 2019, restructuring
- Marketed in handful of European countries

BUSINESS NEWS DECEMBER 27, 2019 / 4:59 PM / 17 DAYS AGO

Antibiotics maker Melinta files for Chapter 11 bankruptcy

2 MIN READ

(Reuters) - Melinta Therapeutics Inc said on Friday it had filed for bankruptcy protection, becoming the latest casualty of a persistent cash burn in the antibiotic industry.

The drugmaker, which has four antibiotics on the market, warned that it was running out of cash last month.


European market is less attractive because of
low sales and low prices for new antibiotics.

Opportunity #1:

Medicine tendering processes award contracts to **multiple** providers, with additional rewards for those with **independent** supply chains.

Nordic initiative for a more reliable supply

Denmark, Iceland, and Norway 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

Split the market with at least two providers (not necessarily with independent supply chains)

Results: increased number of bidders; unit cost increase (but not due to environmental practices)

Feedback from industry: Higher prices help them to maintain production of older antibiotics; useful to demonstrate to headquarters that environmental practices are important

Opportunity #2:

Continue to **support** research and development **grants** targeting WHO's Priority Pathogen List.

“Push” funding is working…

- According to Global AMR R&D Hub, more than **€ 1 billion invested** in antibiotic innovation in the last 5 years
- The WHO calls the preclinical pipeline “**dynamic**”, with almost 300 candidates in development
- 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

Clinical pipeline is “insufficient”…

Clinical pipeline “insufficient” (WHO) with few late stage funders

BARDA	GARDP	Private*	European Investment Bank	AMR action fund
USD 960 m (2010-2019)	€ 270 m (2017-2023)	USD 166 (2017-2021) + USD 339 public/private	€ 60 m (2017-2021)	USD 1 b (2020-2030) (€ 20 m EIB)

Pipeline coordinators for public health

Portfolio investors – loans or equity

Role for HERA?

Case of murepavadin

- Inhaled antibiotic against *Pseudomonas aeruginosa* infections for cystic fibrosis patients
- Preclinical
- Narrow-spectrum
- Critical pathogen
- Innovative
- Swiss company
- Failed as intravenous form in phase III

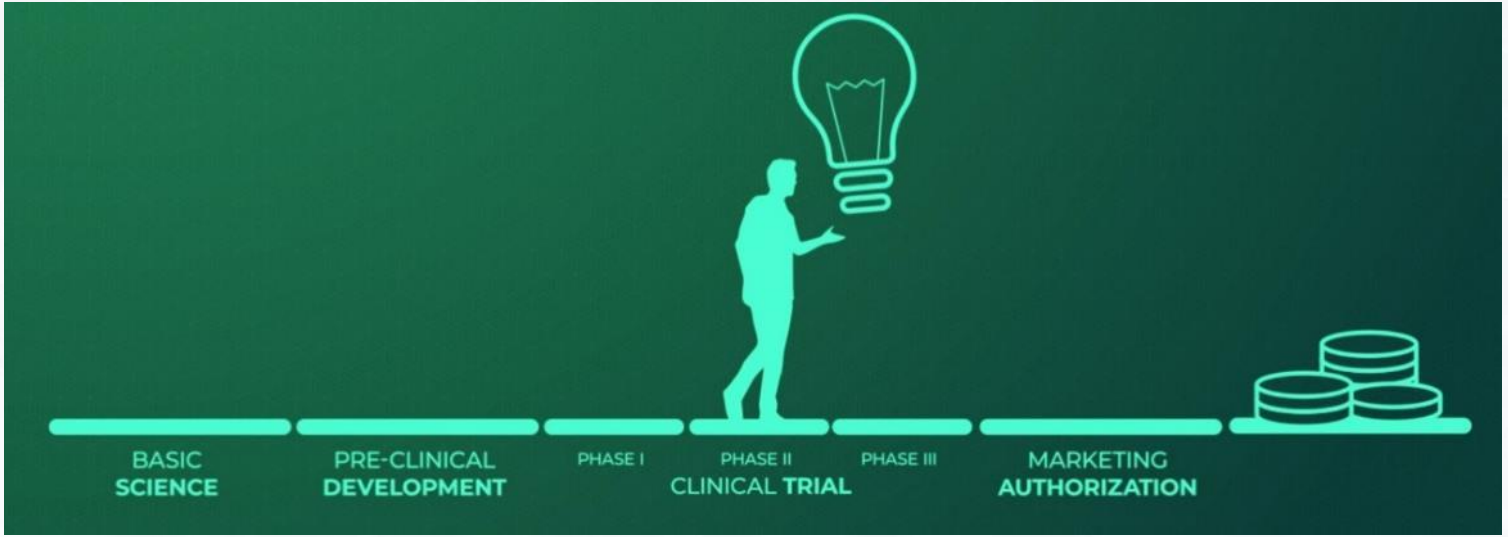
* Global AMR R&D Hub, Dynamic Dashboard, Investments in AMR R&D (criteria = human, development, bacteria)

Opportunity #3:

Implement **“pull”** mechanisms for essential, small market antibiotics.

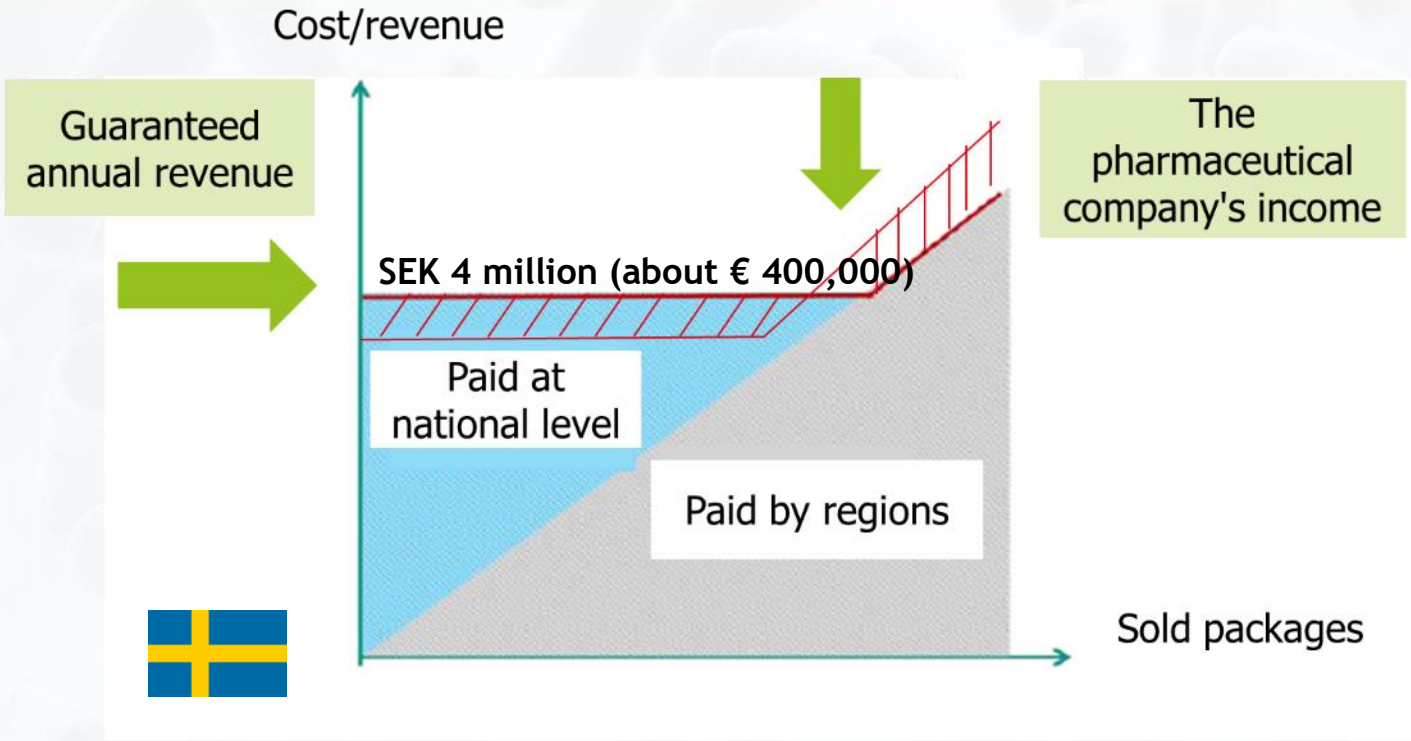
“Pull” incentives

“Pull” incentives improve the market conditions once an important antibiotic has received marketing authorization.



“Delinked” pull incentives provide revenues independent of unit sales.

Sweden and UK trialing “pull” incentives



Sweden now has access to more newly marketed antibiotics than any other country with the exception of the US and UK

Sources: Questions and answers about procurement in pilot study for new remuneration model. Public Health Agency of Sweden: https://www.folkhalsomyndigheten.se/contentassets/92ec9ceb2f2f428cb683add24b4f785b/faq-upphandling-pilotstudie.pdf

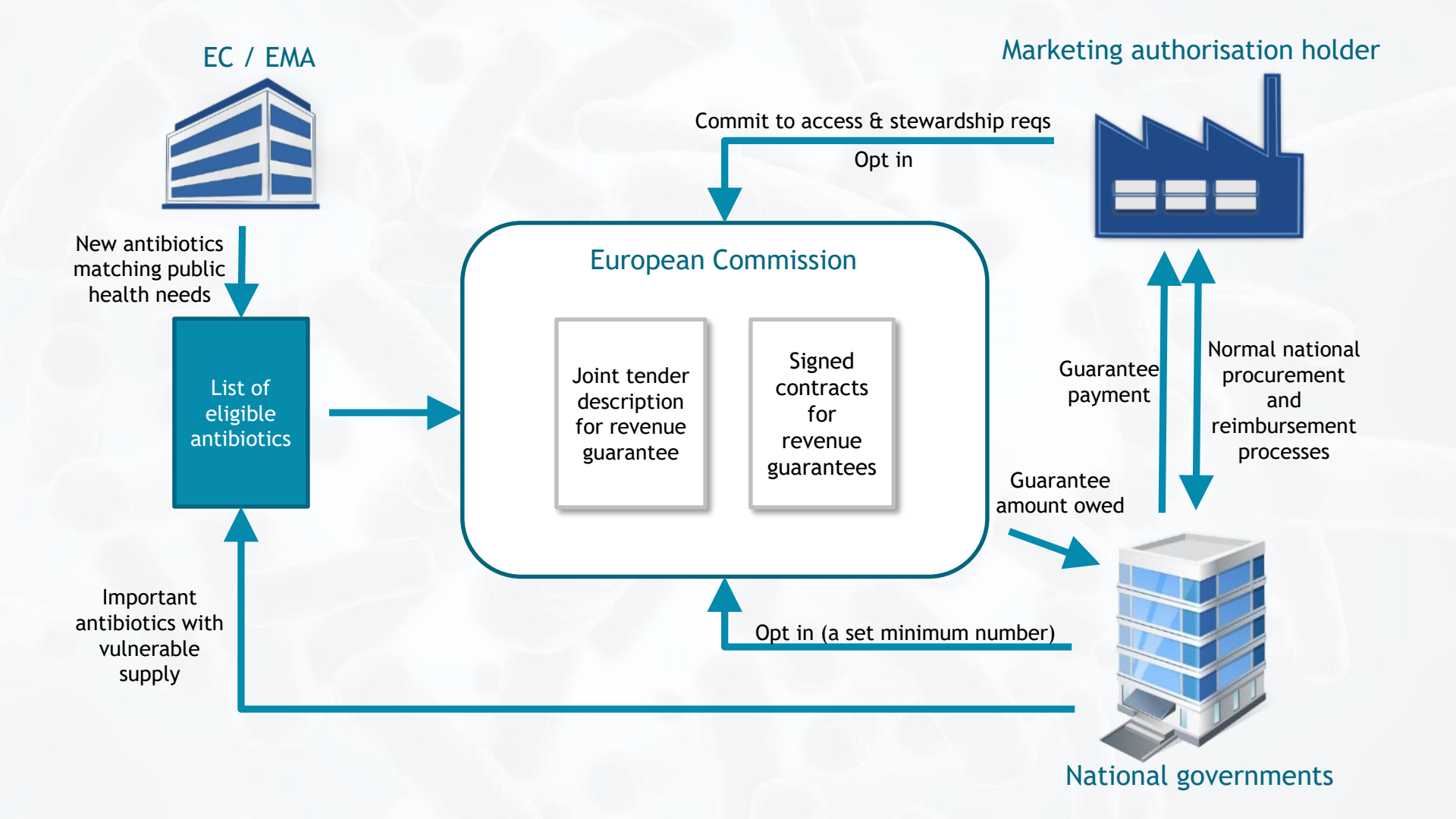
Outterson et al. Patient Access in Fourteen High-Income Countries to New Antibacterials Approved by the FDA, EMA, PMDA, or Health Canada, 2010-2020. (accepted in *Clinical Infectious Diseases*)

New incentives to ensure access to antibiotics (and innovation)

11 (of 13) countries expressed support for new incentives for antibiotics (high-level, general support)

- 11 of 13 countries would prefer a common, **multinational** incentive, so long as it is independent from national medicine pricing, procurement, and reimbursement processes.
- 9 of 11 countries indicate a preference for a model that ensures access to both old and new antibiotics, often with the **highest priority given to older antibiotics**.

Based upon this feedback, **EU-JAMRAI has a proposal…**


EC / EMA
Marketing authorisation holder
Commit to access & stewardship reqs
Opt in
New antibiotics matching public health needs
European Commission
List of eligible antibiotics
Joint tender description for revenue guarantee
Signed contracts for revenue guarantees
Guarantee payment
Normal national procurement and reimbursement processes
Guarantee amount owed
Opt in (a set minimum number)
Important antibiotics with vulnerable supply
National governments


Other models are either
too expensive or ineffective.

Transferable exclusivity voucher – too expensive

"Innovative" antibiotic against "critical" pathogen

€ 2.5 b

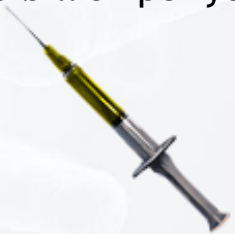
Approved on small clinical trials; turns out to not be so useful

EC/EMA

Voucher = 1 year additional monopoly

Offers up to € 2.5 b

Medicine A
€ 3 billion per year



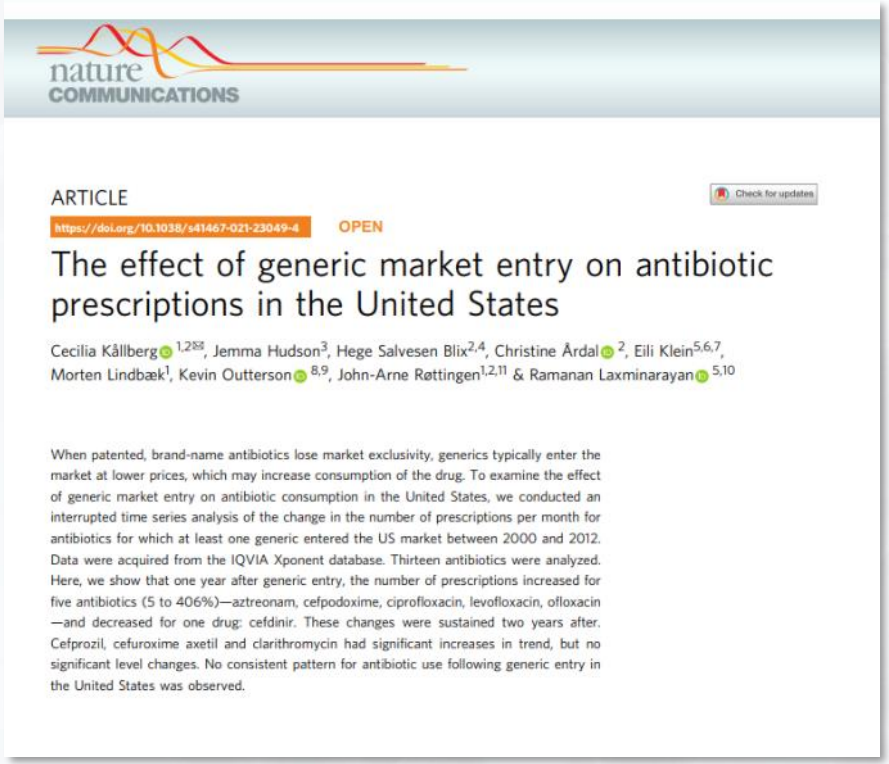
Offers € 2.5 b + € 1

Medicine B
€ 5 billion per year

Probably an orphan drug

Source: Årdal et al. Financing Pull Mechanisms for Antibiotic-Related Innovation: Opportunities for Europe (2020).

Patent extensions – ineffective



nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-021-23049-4 OPEN

The effect of generic market entry on antibiotic prescriptions in the United States

Cecilia Kållberg[1,2✉], Jemma Hudson[3], Hege Salvesen Blix[2,4], Christine Årdal[2], Eili Klein[5,6,7], Morten Lindbæk[1], Kevin Outterson[8,9], John-Arne Røttingen[1,2,11] & Ramanan Laxminarayan[5,10]

When patented, brand-name antibiotics lose market exclusivity, generics typically enter the market at lower prices, which may increase consumption of the drug. To examine the effect of generic market entry on antibiotic consumption in the United States, we conducted an interrupted time series analysis of the change in the number of prescriptions per month for antibiotics for which at least one generic entered the US market between 2000 and 2012. Data were acquired from the IQVIA Xponent database. Thirteen antibiotics were analyzed. Here, we show that one year after generic entry, the number of prescriptions increased for five antibiotics (5 to 406%)—aztreonam, cefpodoxime, ciprofloxacin, levofloxacin, ofloxacin—and decreased for one drug: cefdinir. These changes were sustained two years after. Cefprozil, cefuroxime axetil and clarithromycin had significant increases in trend, but no significant level changes. No consistent pattern for antibiotic use following generic entry in the United States was observed.

- US sales per new antibiotic does not exceed USD 17m per month*
- Out of 13 new antibiotics, only 5 had increased use after generic transition
- These were all very modest increases, with the exception of one (ciprofloxacin) being stockpiled

* Source: Alan Carr, Needham & Co., Sales of newly launched antibiotics in US

1. Medicine tendering processes award contracts to **multiple** providers, with additional rewards for those with **independent** supply chains.
2. Continue to **support** research and development **grants** targeting WHO's Priority Pathogen List.
3. Implement **"pull"** mechanisms for essential, small market antibiotics.

Thank you!

Acknowledgements to Marie-Cécile Ploy and Yohann Lacotte for their contributions

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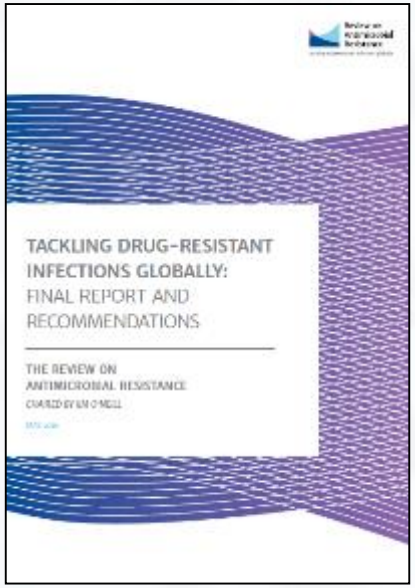
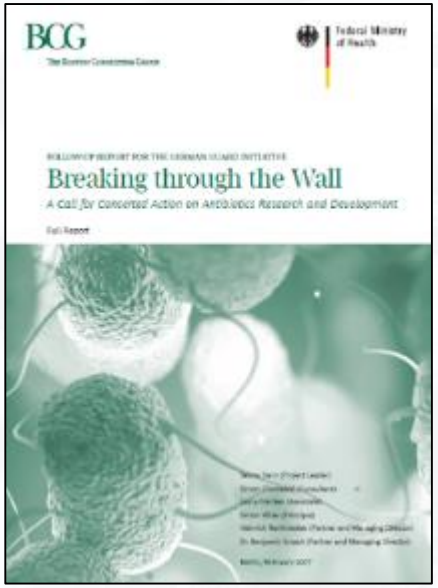
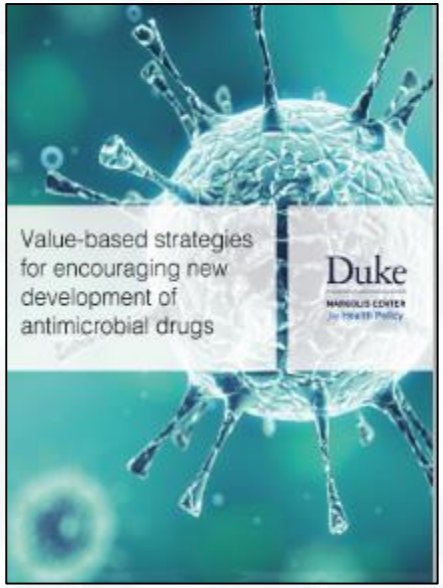
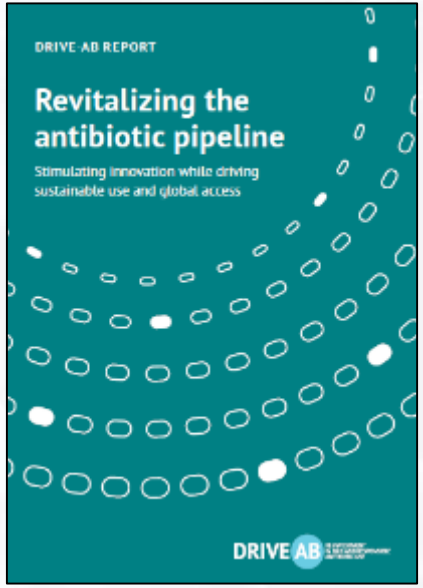
Common solutions to stimulate antibiotic innovation



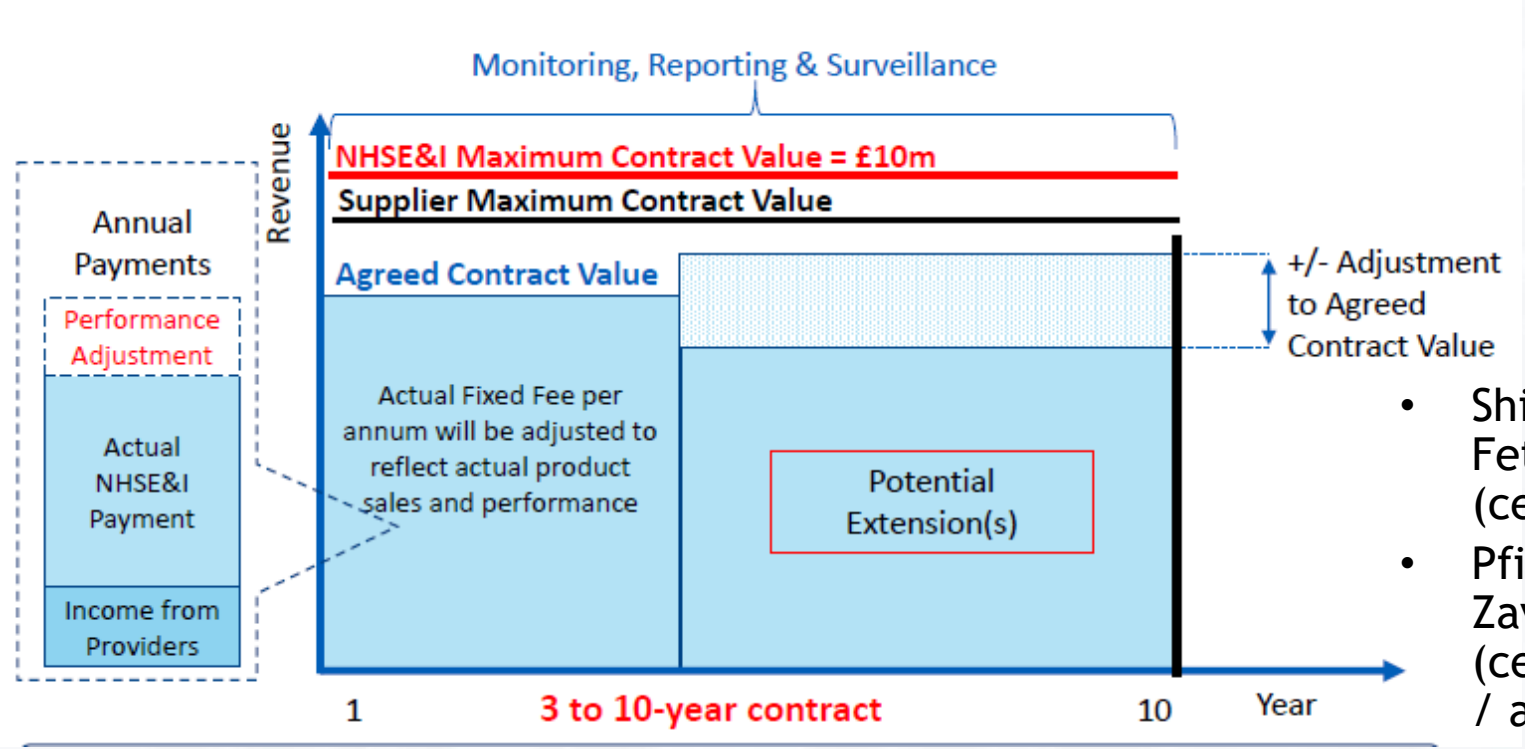






1. Invest in R&D
2. Fix the market by rewarding innovation and availability rather than sales

The English pilot of a fully delinked pull incentive



- Shionogi - Fetcroja (cefiderocol)
- Pfizer - Zavicefta (ceftazidime / avibactam)

Source: Crabb et al. Developing and testing innovative models for the evaluation and purchase of antimicrobials. March 2020.