

97039: Global Health, Antimicrobial Drugs and Vaccines

Module 2: The crises of new antibiotic development

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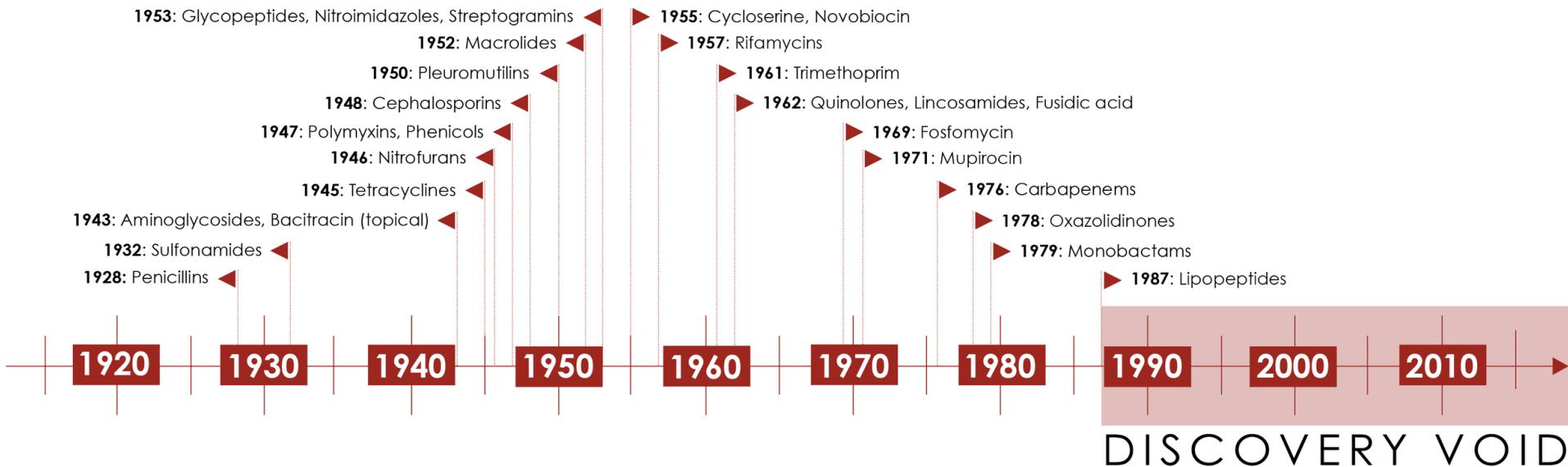


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Learning objectives

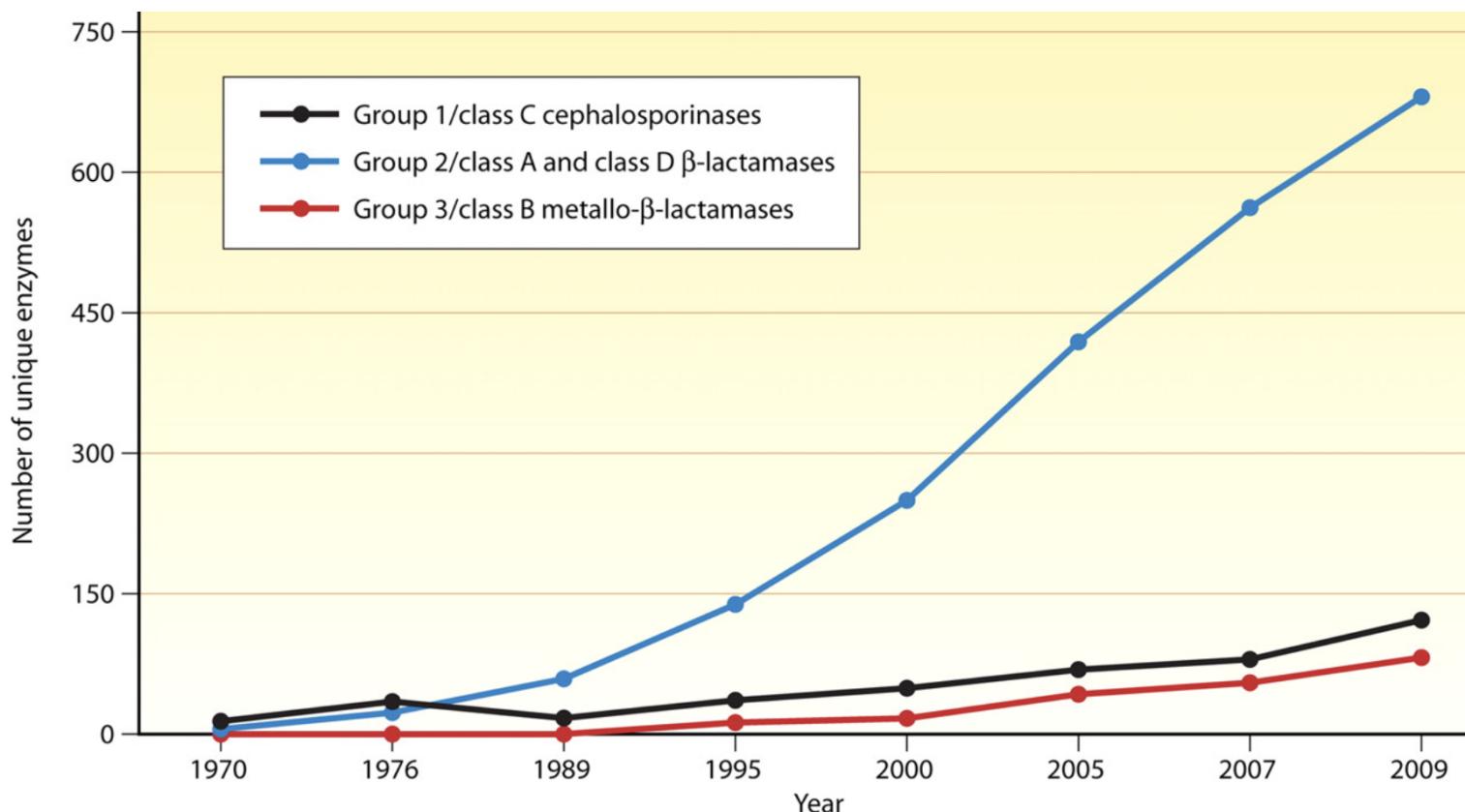
- Discuss factors contributing to the lack of new antibiotic development
- Compare and contrast economic incentives proposed to enhanced antibiotic development
- Examine challenges in ensuring antibiotic access in low and middle income countries (LMICs)

Antibiotic development timeline



© ReAct Group 2015

Increase in numbers of group 1, 2, and 3 beta-lactamases



Bush, K. & Jacoby, G. A. *Antimicrobial Agents and Chemotherapy* **54**, 969–976 (2010).

Global Research and Development Priorities for AMR

Priority	Pathogens included
Critical	<i>Acinetobacter baumannii</i> (Carbapenem-resistant) <i>Pseudomonas aeruginosa</i> (Carbapenem-resistant) Enterbacterales (3rd generation cephalosporin, carbapenem-resistant)
High	<i>Enterococcus faecium</i> , vancomycin-resistant <i>Staphylococcus aureus</i> , methicillin-resistant, vancomycin intermediate and resistant <i>Helicobacter pylori</i> , clarithromycin-resistant <i>Campylobacter</i> , fluoroquinolone-resistant <i>Salmonella</i> spp., fluoroquinolone-resistant <i>Neisseria gonorrhoeae</i> , 3rd gen. cephalosporin-resistant, fluoroquinolone-resistant
Medium	<i>Streptococcus pneumoniae</i> , penicillin-non-susceptible <i>Haemophilus influenzae</i> , ampicillin-resistant <i>Shigella</i> spp., fluoroquinolone-resistant

This table does not include *Mycobacterium tuberculosis*, which was already recognized as a global health priority pathogen

WHO Clinical Antibiotic Pipeline Report



- New antibiotic development is driven by small- or medium-sized enterprises (SMEs), with large pharmaceutical companies continuing to exit the field.
- Eight new antibacterial agents have been approved since 1 July 2017, but overall, they have limited clinical benefits.
- One new anti-tuberculosis (anti-TB) agent, pretomanid, developed by a not-for-profit organization, has been approved for use within a set drug-combination treatment for MDR TB.
- **The clinical pipeline remains insufficient to tackle the challenge of increasing emergence and spread of antimicrobial resistance.**



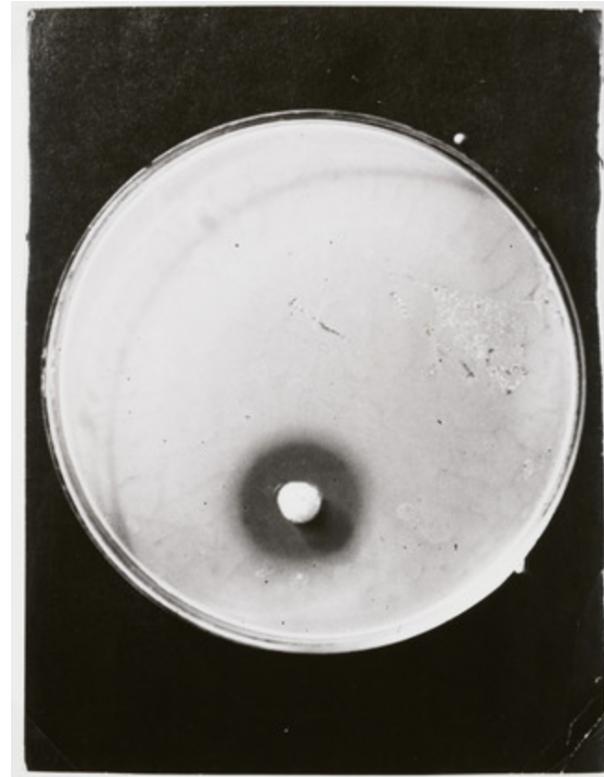
Why are new antibiotic not being developed?

The scientific challenges of antibiotic discovery

- Ideally must target multiple pathways in bacterial species (to avoid rapid resistance development) ...*but no human targets*
- Must be safe...drugs are *administered grams not mg or mcg*
- Must penetrate and be effective in multiple body sites
- Must be effective now and also against future forms of resistance (i.e. predict future resistance problems)

Natural product screening:

The "golden age" of antibiotic discovery before 1965 from soil streptomycetes and fungi



Penicillin culture flasks, 1942. Photo: James Jarche

1970s to 1990s- modified chemistry to overcome resistance

Penicillins → cephalosporins, carbapenems

nalidixic acid → fluoroquinolones

kanamycin → amakacin

glycyclines → tetracyclines

*resistance
mechanisms
develop to entire
classes*

Since 1970, the only indisputably new antibiotic classes to reach the market are: the oxazolidinones (discovered 1978, launched 2000) and lipopeptides (discovered 1986, launched 2003)



Regulatory requirements



United States Food and Drug
Administration



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA

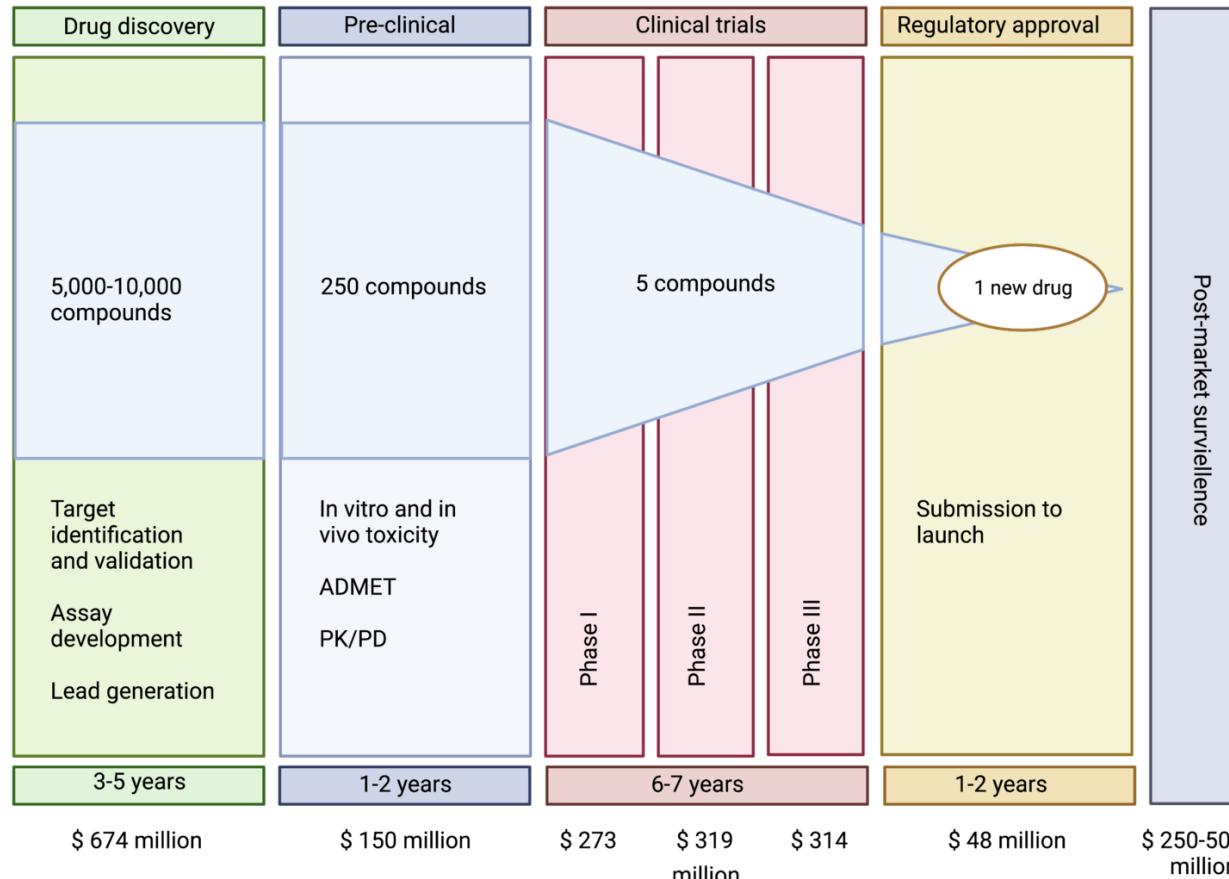


African Medicines Agency

Many other countries have their own processes for drug registration and approval

Antibiotic approval process and expected costs

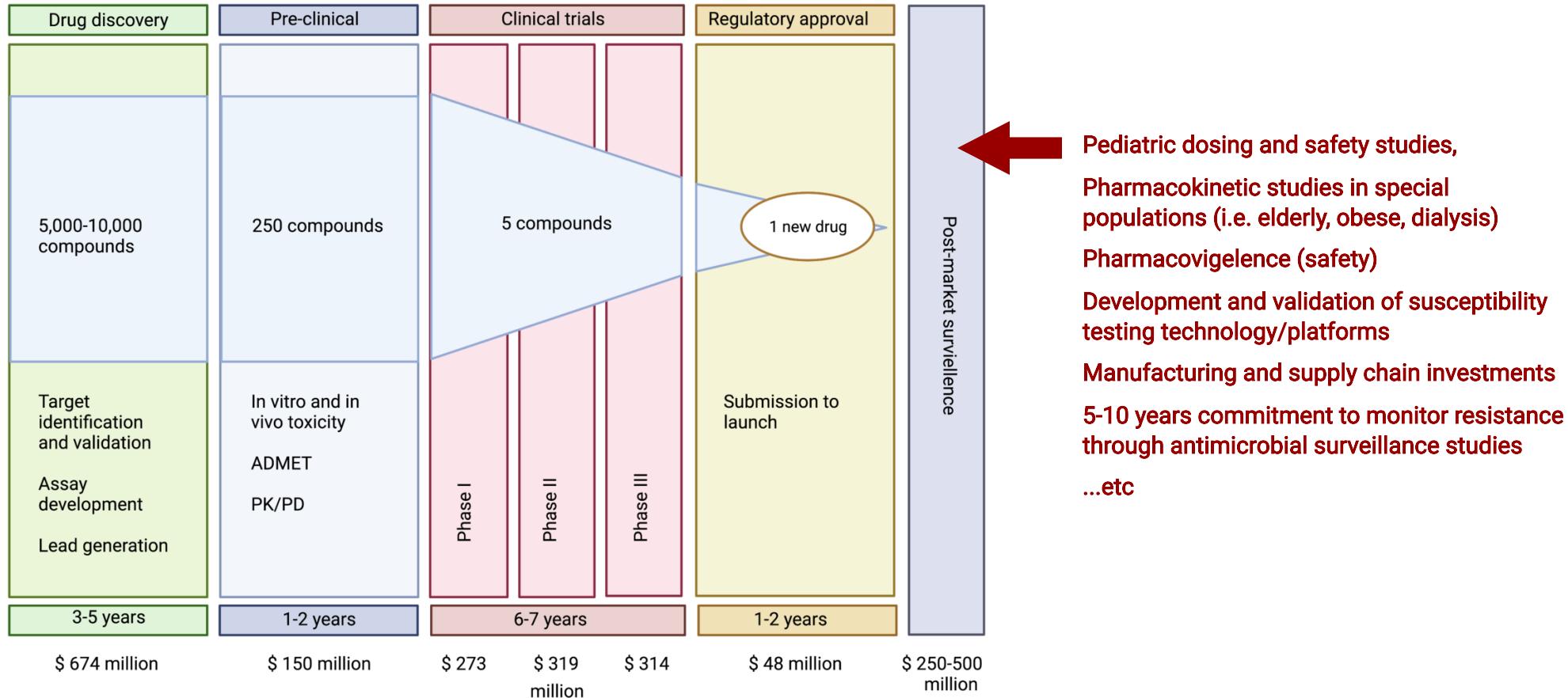
Costs on average: 1-1.5 billion US dollars



Proving efficacy in humans: The Phase III non-inferiority trial: A paradoxical problem for antibiotics

- Medical Priority: New drugs for bad bugs
 - The superiority of a NEW antibiotic is easily shown in the lab on the basis of MIC testing or in animal models of infection
- Clinical data is the problem- trials must (usually) be designed to avoid superiority
 - Instead, we must use *non-inferiority designs* showing similar activity relative to another *active agent*
 - Example: Limb-threatening infection due to MRSA....It is not ethical to randomize to methicillin vs. NEW Antibiotic, must instead compare vancomycin vs. NEW Antibiotic
- Patients cannot be enrolled if known or likely resistant to New Antibiotic or comparator

Huge costs are also incurred post-approval for antibiotics



How can a company overcome these costs?

Costs = Antibiotic price * Units sold

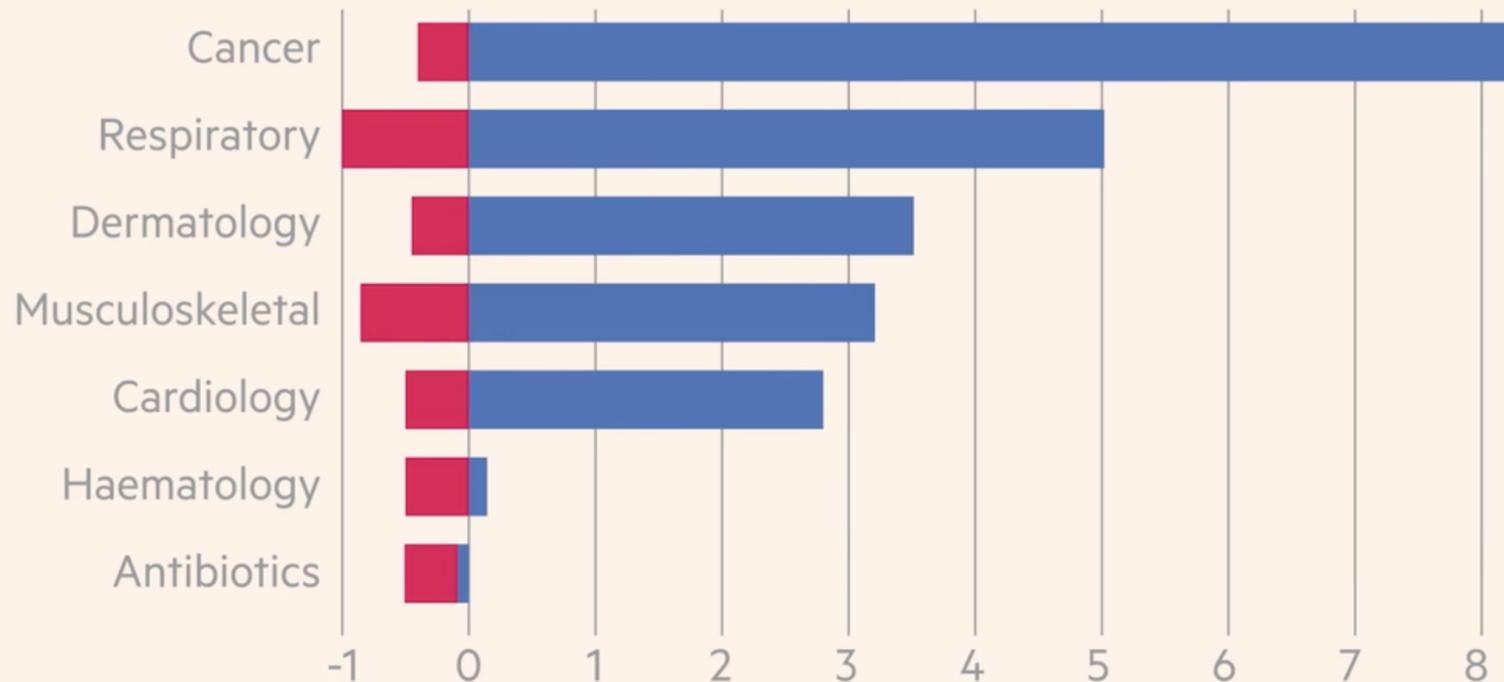


Sell lots of antibiotics (high use → drive resistance) or charge *very* high prices

Profitability of different drug types

2014-16 (\$bn)

■ Development cost ■ Profit



Sources: BCG Analysis, EvaluatePharma

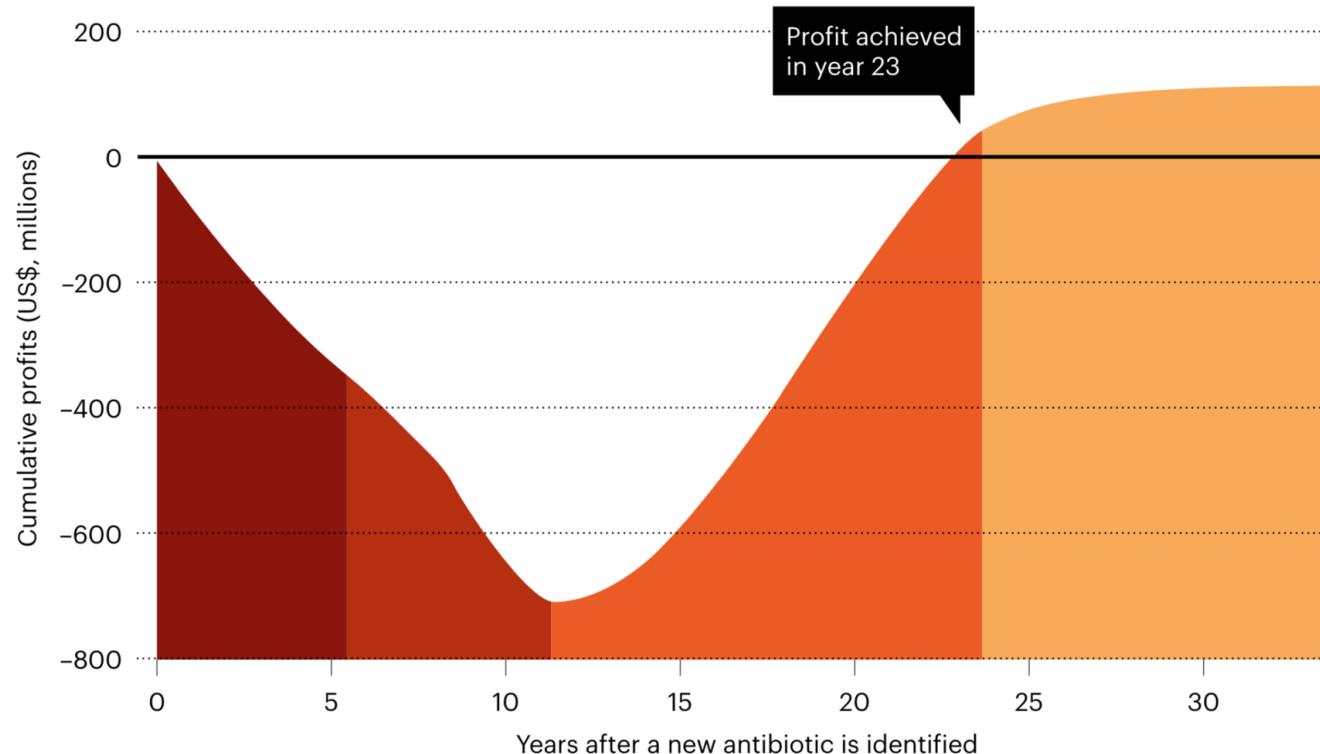
Source: Financial Times

LONG PATH TO PROFITABILITY

Estimates suggest that it takes more than 20 years to see any profit from a newly developed antibiotic. Once a drug goes off patent, increasing that profit becomes much more difficult.

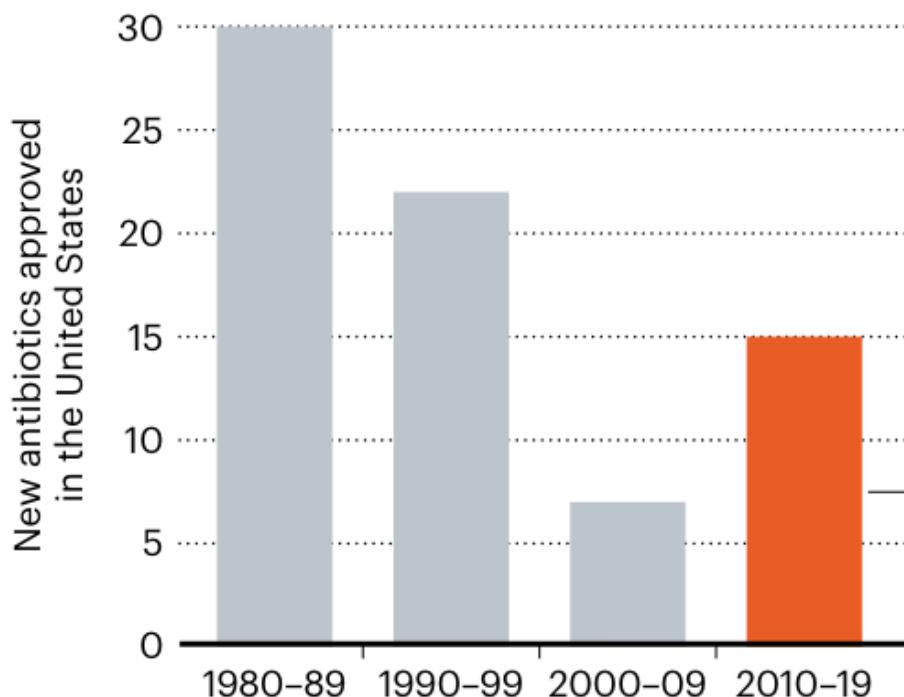
Typical patent life: 20 years from discovery

■ Preclinical research ■ Clinical research ■ On-patent sales ■ Off-patent sales

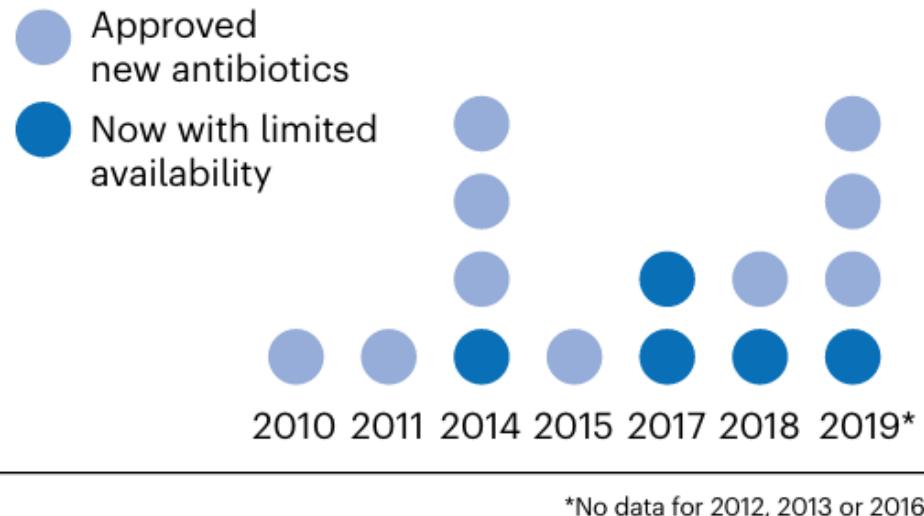


TRIMMING A THINNING HERD

Over the past several decades, the number of new antibiotics approved for use in the United States has been declining, as it has elsewhere in the world.



Of the 15 new antibiotics that earned US Food and Drug Administration approval in the past decade, 5 have been essentially shelved as the companies that created them filed for bankruptcy or were sold off.



*No data for 2012, 2013 or 2016.

The Achaogen story (developer of plazomicin)

DEADLY GERMS, LOST CURES

Crisis Looms in Antibiotics as Drug Makers Go Bankrupt

First Big Pharma fled the field, and now start-ups are going belly up, threatening to stifle the development of new drugs.

f s t e g m 1275



Dr. Ryan Cirz, a microbiologist and a co-founder of Achaogen, a company whose drug, Zemdri, showed promise in treating U.T.I.s. Brian L. Frank for The New York Times

NY Times December 25, 2019

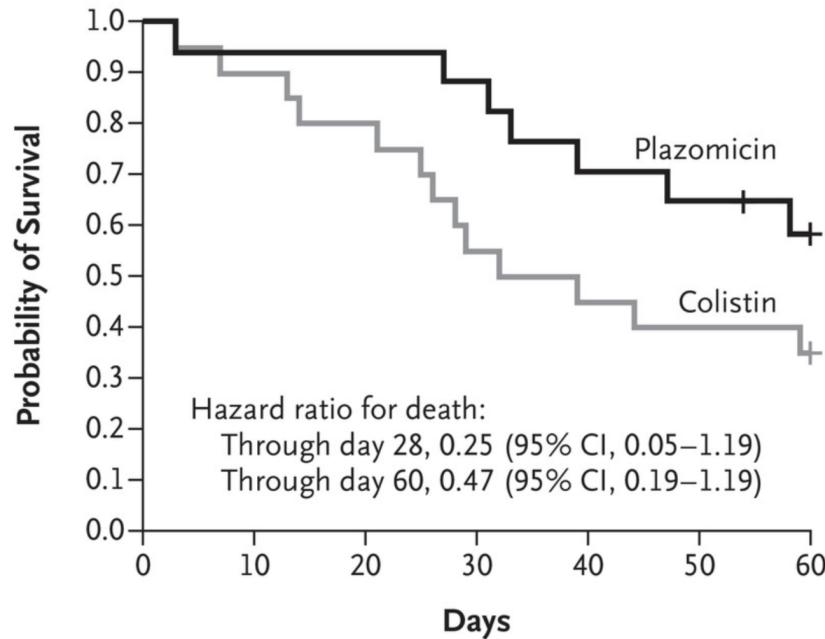
The Achaogen story...

- A phase 3 complicated UTI trial was completed in Dec 2016 demonstrated impressive activity vs. meropenem (EPIC trial)

The Achaogen story cont.

Plazomicin- a major advance, but rarely used for CRE infections

A Cumulative Probability of Survival



No. at Risk

Plazomicin	17	16	16	15	12	11	9
Colistin	20	18	16	11	9	8	7

Patients receiving plazomicin developed less nephrotoxicity:
16.7% vs. 50%

HEALTHCARE & PHARMA DECEMBER 27, 2019 / 4:59 PM / UPDATED 2 YEARS AGO

Antibiotics maker Melinta files for Chapter 11 bankruptcy

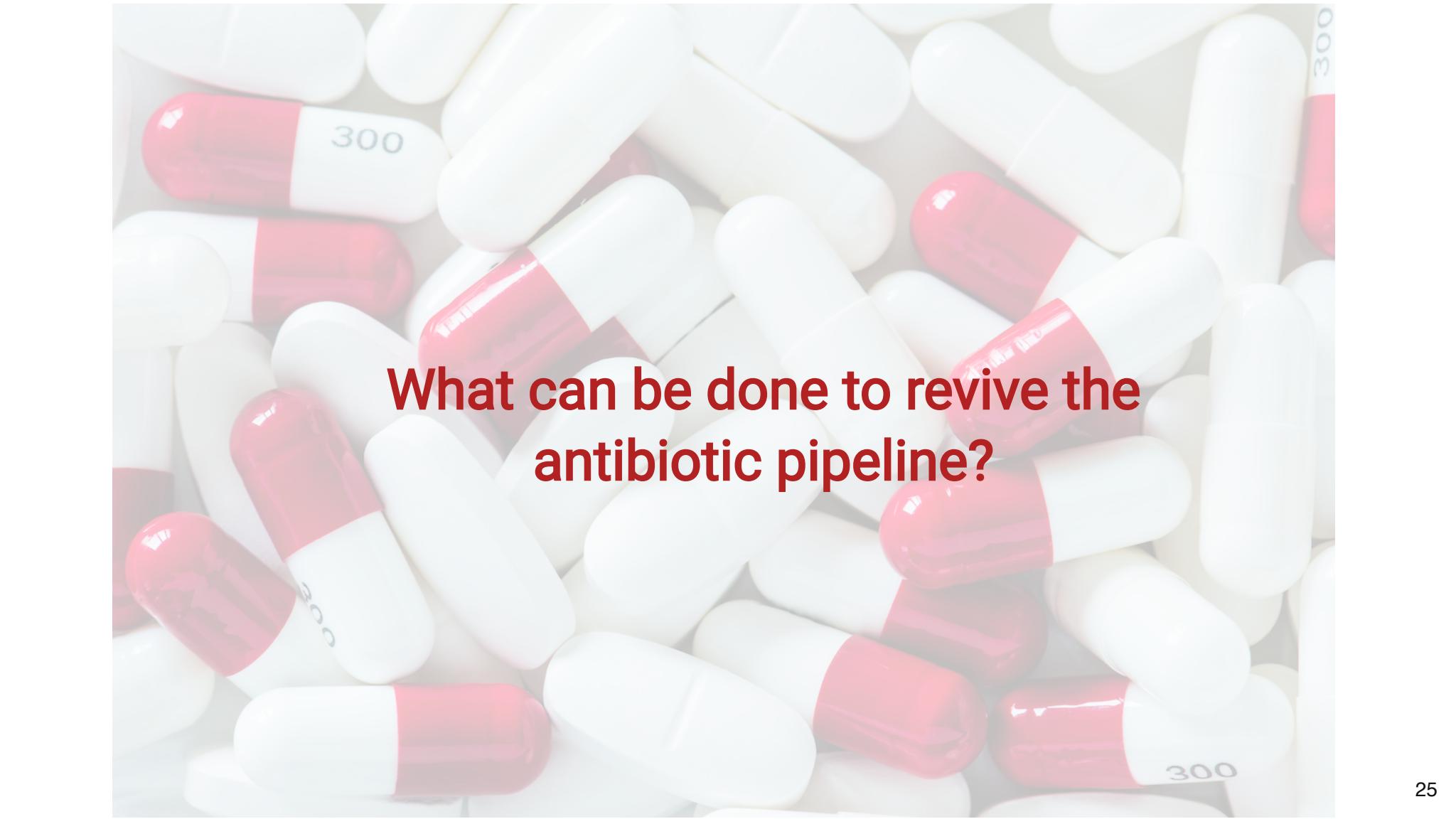
By Reuters Staff

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.

Manufacturer of meropenem-vaborbactam



What can be done to revive the antibiotic pipeline?

"Push incentives"

- Early stage funding
- Occur before regulatory approval by regulatory agency
- Supports many projects, including many that fail before approval

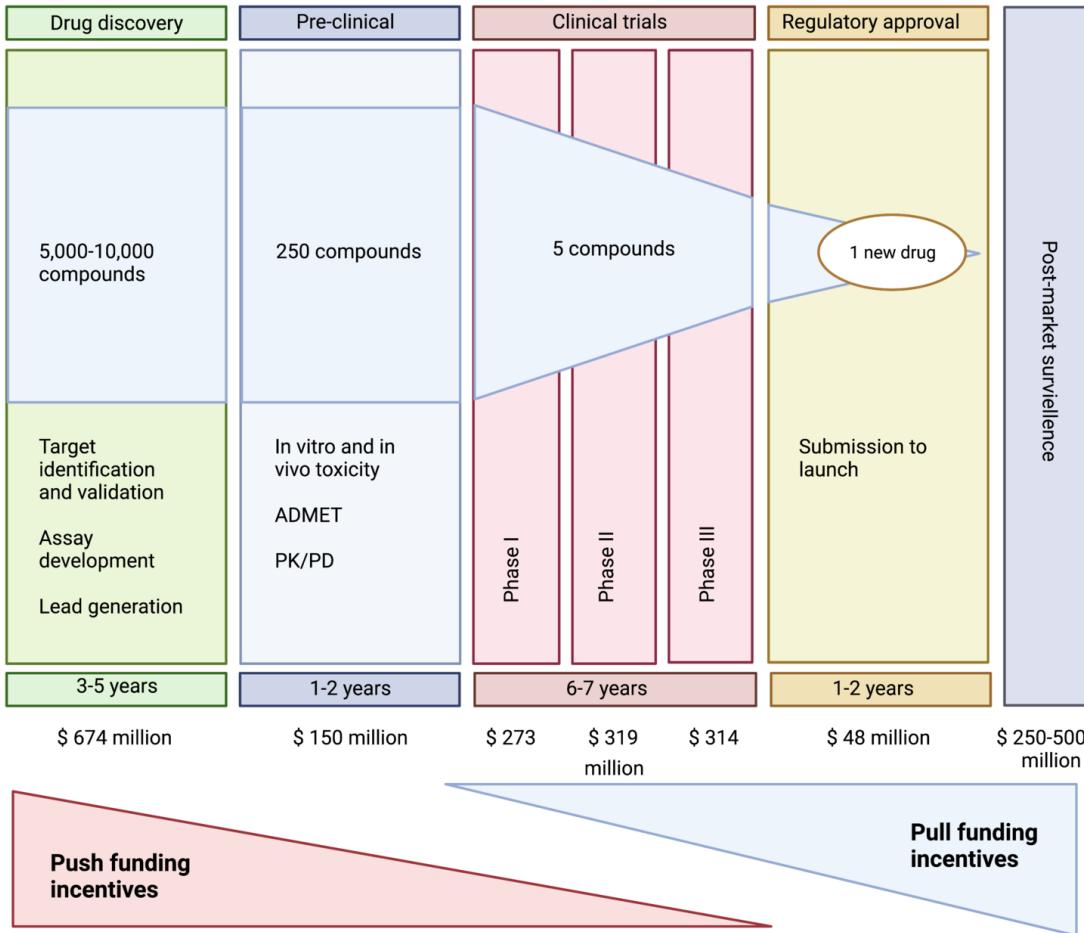
Examples of Push Incentives

- US Biomedical Advanced Research and Development Authority BARDA (1.2 billion dollars to support Phase 2/3 antibiotic development against 21st century threats including drug-resistant bacteria, supports CARB-X)
- CARB-X (550 million, Hits to lead Phase 1 product development of therapeutics, diagnostics and preventatives against WHO and CDC priority drug-resistant bacteria)
- The Global Antibiotic Research and Development Partnership -GARDP (Produce discovery from discovery to delivery including novel therapeutics, optimizing antibiotics, developing combinations. Focused on WHO priority list).
- The European Gram Negative AntiBacterial Engine-ENABLE
- Novo Holdings REPAIR Impact Fund (165 million investment in 165 million investment in lead optimization to Phase I development of therapeutics and diagnostics against WHO priority drug-resistant bacteria)
- Joint Programming Initiative on Antimicrobial Resistance -JPIAMR (novel therapeutics, diagnostics, surveillance, prevention, stewardship, WHO priority pathogens)

Examples of Push Incentives, cont.

- [Wellcome Trust](#) (175 million drug-resistant infections focused on policy, strengthening evidence for action, clinical trial capabilities and innovative product development including CARB-X)
- [Innovative Medicines Initiative](#)
- [AMR Action Fund](#). WHO, European Investment Bank, and Wellcome Trust
- [UK AID](#) (315 million pounds funded through the Global AMR innovation fund and the Fleming Fund to help LMICs tackle AMR).
- The [German Federal Ministry of Education and Research](#) support of national research programs as well as contributions to international initiatives like CARB-X, GARDP, and JPIAMR.
- [Bill & Melinda Gates Foundation](#)(124 million targeting drug-resistant infections in low-middle income countries (LMICs), disease surveillance, vaccine development, economic modeling, and CARB-X)
- [U.S. National Institutes of Health](#) (1.4 billion dollars funding basic research, academic industry startup partnerships, and other research and development against bacterial threats, for vaccines, therapeutics and diagnostics)

Pull incentives



Pull incentives are primarily *after regulatory approval* and hence only successful products are supported

Antibiotic benefits go beyond simple use: rethinking the economics

- **Enabling value:** Many surgical and medical procedures rely on prophylaxis with effective antibiotics.
- **Option or insurance value:** We may want to have an antibiotic in reserve before we really need it, so it's ready if resistance arises or worsens.
- **Diversity value:** Having multiple antibiotics may reduce selection pressure and delay resistance

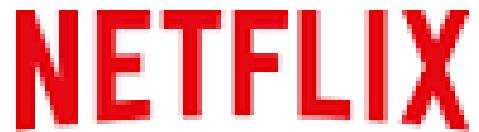
Antibiotics are the "fire extinguishers" of medicine



- Nobody wishes to put out a fire
- Firefighters perform regular maintenance and training to ensure they are ready 24/7 as a precaution to fight fires
- We pay firefighters to be available and prepared so they can come to our rescue when we need them

A fire fighter uses a hose to subdue flames engulfing a home while a physician uses antibiotics to stop an infection in your body. We need to be prepared for fires – the flame kind and the medical kind

Pull incentives: the NETFLIX Model



Netflix is a **subscription-based** streaming service that allows our members to watch TV shows and movies without commercials on an internet-connected device.

You pay a monthly fee whether or not you watch movies.

How would a Netflix-like pull incentive work for antibiotics?

- National Institute for Health and Care Excellence (NICE) performs a cost-effectiveness analysis, then computes a fair "subscription price"

How would a Netflix-like pull incentive work for antibiotics?

- This maximum annual fee is based on a calculation what approximately England's "fair share" would be of the proposed US \$2–4 billion financial incentive needed, per new antimicrobial, globally, to revitalise the antimicrobial pipeline

More detail on antibiotic pull incentives being considered by different countries...

Health Policy 125 (2021) 296–306



Contents lists available at [ScienceDirect](#)

Health Policy

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journal homepage: www.elsevier.com/locate/healthpol



Reimbursement models to tackle market failures for antimicrobials:
Approaches taken in France, Germany, Sweden, the United Kingdom,
and the United States



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More on pull incentives...see online handout!

<https://www.ft.com/video/adada10f-5747-4976-a3e0-958b0165e0ef>

A man in a white lab coat stands in a aisle between two rows of shelves filled with boxes. The shelves are stacked high with various items, creating a repetitive pattern. The man is looking towards the camera.

Lack of antibiotic availability due to supply chain problems

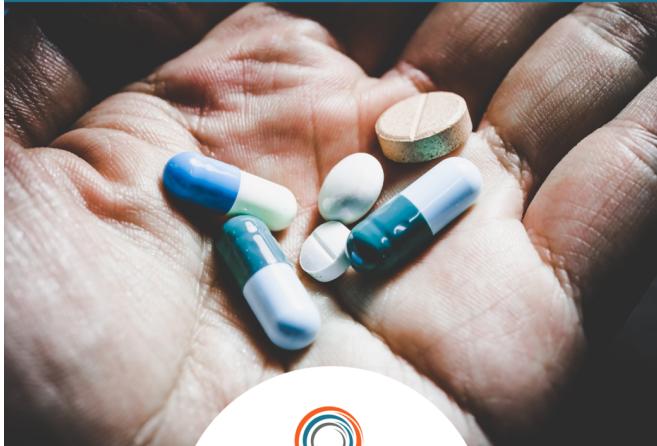
Increasing frequency of shortages for injectable generic antibiotics contributes to antimicrobial resistance



Inefficient, fragmented supply chains	Poorly functioning systems for drug pricing	Issues related to policy and regulatory processes
Single source or gaps in active pharmaceutical ingredients and other essential materials	Lack of commercial incentives and market	Regulatory challenges e.g.,: No systematic strategy for (registering and ensuring availability) on the Essential Medicines List
Limited and unequally distributed quality manufacturing of source materials	Low net present value	Inadequate government regulation to ensure access to quality-assured medicines
Complex and inefficient procurement processes	High prices of new antimicrobials creating imbalances in supply and demand	Inadequate recognition of right of access to essential medicines in national constitutions
Unavailable or inefficient forecasting systems		

Changes in prescribing practices

Access Barriers to Antibiotics

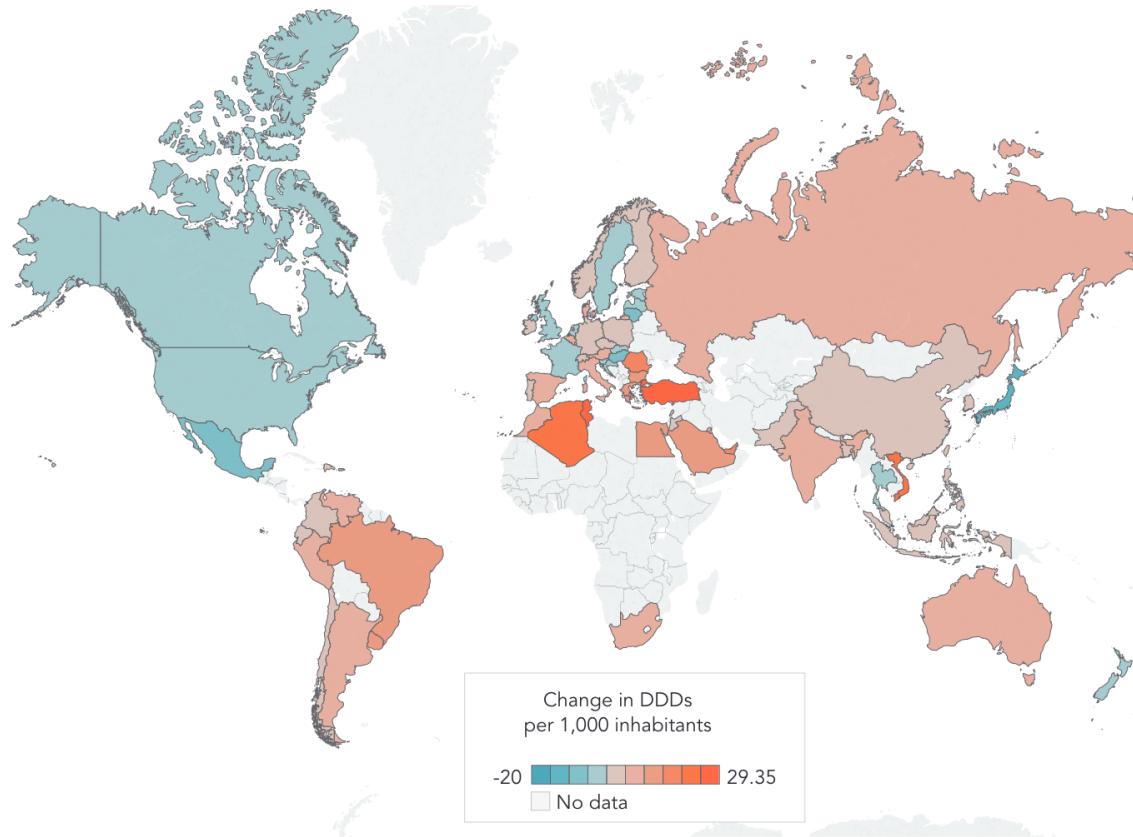


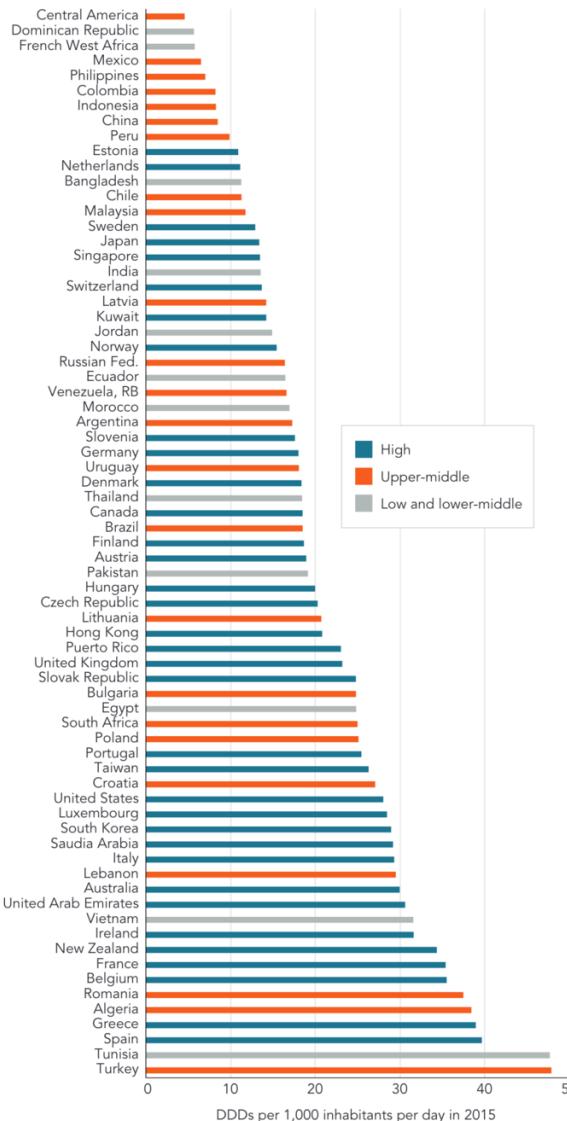
Antibiotic access in low-middle income countries

The challenges in many LMICs

- Antibiotics, often available without prescription, may be used for substitutes of clean food, water and access to vaccines or diagnostics
- Antibiotic access and resistance cannot be addressed effectively without addressing contributing factors

Global antibiotic consumption (2000 to 2015). Change in antibiotic consumption rate per 1,000 inhabitants per day.





Antibiotic consumption rate in defined daily doses (DDDs) per 1,000 inhabitants per day by country in 2015

Defined daily dose (DDD) is a standardised index of drug consumption, defined by the WHO, used to antibiotic use between different drug classes and dosage forms.

DDD is calculated by multiplying the quantity field by the DDD conversion factor field. In this example, the strength of one tablet is 500 mg and the ATC/DDD is 1 g for ciprofloxacin. Each 500 mg tablet is equivalent to 0.5 DDD.

Antibiotic access in LMICs:

Barrier 1: Irrational selection and use of antibiotics

- Incentives for sale and inappropriate use of antibiotics- i.e. conflict of interest common such as payments linked to antibiotic prescribed
- Over the counter antibiotic sales
- Frequent prescribing by non-professionals
- Multiple different regulatory agencies- difficult cost justification for registration in many LMICs

Access Barriers
to Antibiotics



CDDEP

	CDDEP Recommendation	Stakeholders	Rationale
1	Encourage R&D of new or improved antibiotics, diagnostic tests, vaccines, alternatives to antibiotics for bacterial infections	Countries, regional collaborators, WHO and other international bodies, pharmaceutical industry, academia	At a global scale, higher investment in novel antibiotics, temperature-stable formulations, and rapid diagnostic tests
2	Support the registration of antibiotics in more countries according to clinical need	WHO and other international bodies, national governments, policymakers, regulators, pharmaceutical industry	<p>Efforts at the national, regional, and global levels to support drug registration could reduce the upfront cost of accessing less attractive markets and benefit patients by making life-saving drugs available.</p> <p>Newer drugs coming to market are likely to be introduced by small and medium-size enterprises that may not have the expertise or resources to register in multiple countries.</p> <p>However, this cost should not be a barrier.</p>
		Regulators and policymakers	In many instances, regulations and requirements could be aligned across countries and simplified to reduce costs
		Pharmaceutical companies	Plans for registration should be part of the development process.

Access Barriers
to Antibiotics



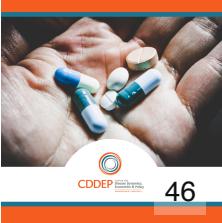
	CDDEP Recommendation	Stakeholders	Rationale
3	Establish standards of practice and national treatment guidelines.	WHO, countries, experts and their professional associations, hospitals and community care facilities	The WHO should issue a call to action for all professional associations and councils involved in prescribing practices to develop clinical guidelines for treating infectious diseases at all levels of healthcare.
4	Generate awareness and educate patients and prescribers.	Non governmental organizations (NGOs), advocacy groups, professional bodies, WHO offices at all levels, health ministries, and local institutions (hospitals, clinics, schools, churches, etc.)	Information about the price and quality of antibiotics approved for use in a country will support rational prescribing and use, as will surveillance data on local antibiotic resistance profiles. NGOs, professional bodies, and advocacy groups can use existing communications channels to educate patients and prescribers about drug quality and rational antibiotic use. Such information will empower consumers who purchase drugs out-of-pocket to demand quality antibiotics while increasing price competition among suppliers and removing poor-quality suppliers from the market.

Access Barriers
to Antibiotics



	CDDEP Recommendation	Stakeholders	Rationale
5	Reduce conflict of interest and incentives that lead to inappropriate antibiotic use.	Regulators, NGOs, doctors, and patients	Conflicts of interest between prescribers and the vendors of pharmaceuticals can be addressed by regulating gifts from drug companies and promoting the enforced or voluntary declaration of such gifts

Access Barriers
to Antibiotics



Progress in regulation and rationale use



African Antibiotic Treatment Guidelines for Common Bacterial Infections and Syndromes



First Edition
2021



The graphic features a teal header with a diamond pattern. On the left is a white ribbon award icon. To its right, the text "STRENGTHENING REGULATORY SYSTEMS" is written in bold, uppercase letters, with "REGULATORY SYSTEMS" in a smaller font below "STRENGTHENING". Below this, "African Medicines Agency" is written in a smaller, sans-serif font. The main body of the graphic is a light grey area containing the text "The African Medicines Agency: towards a unified continental regulatory framework". To the right of this text is a photograph of a diverse group of healthcare professionals and patients, including a woman holding a child, a man, and several medical staff members, all smiling.

STRENGTHENING
REGULATORY SYSTEMS

African Medicines Agency

The African Medicines Agency:
towards a unified continental
regulatory framework

Barrier 2: Antibiotics are not affordable for many in LMICs and government funding for health is low

- Less than 10% of public spending in many LMICs goes to healthcare
- Less than half of essential medicines are available in many countries

Access Barriers
to Antibiotics



CDDEP
Centre for
Development
and Economic
Policy Research

	CDDEP Recommendation	Stakeholders	Rationale
6	Explore innovative funding of essential antibiotics	UNICEF, WHO, national governments, pharmaceutical manufacturers	Countries with less purchasing power could pool their resources for procurement under arrangements similar to Gavi (the vaccine alliance) or the Global Fund. UNICEF/WHO might coordinate procurement and distribution. Besides helping LMICs increase their purchasing power, such an arrangement would support quality manufacturers while driving out substandard suppliers.

Access Barriers
to Antibiotics



We will focus on this topic more in Module 3

Barrier 3: Weak health systems, unreliable supply chains and poor quality control fail to deliver antibiotics to patients in need

- Out-of-pocket payments for antibiotics either limit access or push people further into poverty
- In remote areas, transportation costs and accompanying relatives may be unaffordable
- Antibiotics are often not available or may be of poor quality

Access Barriers
to Antibiotics



CDDEP
Centre for
Development
and Evaluation
of Policies
and Programmes

	CDDEP Recommendation	Stakeholders	Rationale
7	Ensure the quality of antibiotics, and strengthen pharmaceutical regulatory capacity	WHO, national and regional regulators, countries, pharmaceutical suppliers and manufacturers	<p>WHO support and coordination, national and regional regulators could collaborate to support quality assurance and avoid duplication of effort across countries; Rapid information exchange for pharmacovigilance, information on poor-quality suppliers, and sharing of best practices and innovation will help drive substandard and falsified antibiotics from the market.</p> <p>An international entity, such as the WHO, could provide surveillance, monitoring, and compliance testing for antibiotic quality. Such work would support LMICs' regulatory authorities and also ensure the integrity of the supply chain from the dominant suppliers in India and China. It could also establish standards for generic antibiotics and fixed-dose combinations, which are commonly used in LMICs, and support the industry in self-regulation.</p>

	CDDEP Recommendation	Stakeholders	Rationale
8	Encourage local manufacturing for cost-effective antibiotics.	Countries, regional collaborations, pharmaceutical industry, including drug R&D and manufacturers	Development and diversification of local manufacturers can help ensure the steady supply of essential, quality-assured antibiotics so that countries can meet their own needs. This should be supported through regional collaborations of countries such as the African Union.



Summary

- Both scientific and economic challenges has caused many companies abandon development of new antibiotics
- The depleted antibiotic pipeline and increasing resistance has major public health implications for medicine in both high-income and low-income countries
- While antibiotic overuse is the major concern in high-income countries, access to effective and affordable antibiotics in many LMICs is inadequate but increasing with less infrastructure to support rationale use