

97039: Global Health, Antimicrobial Drugs and Vaccines

Module 2: The Crises of New Antibiotic Development

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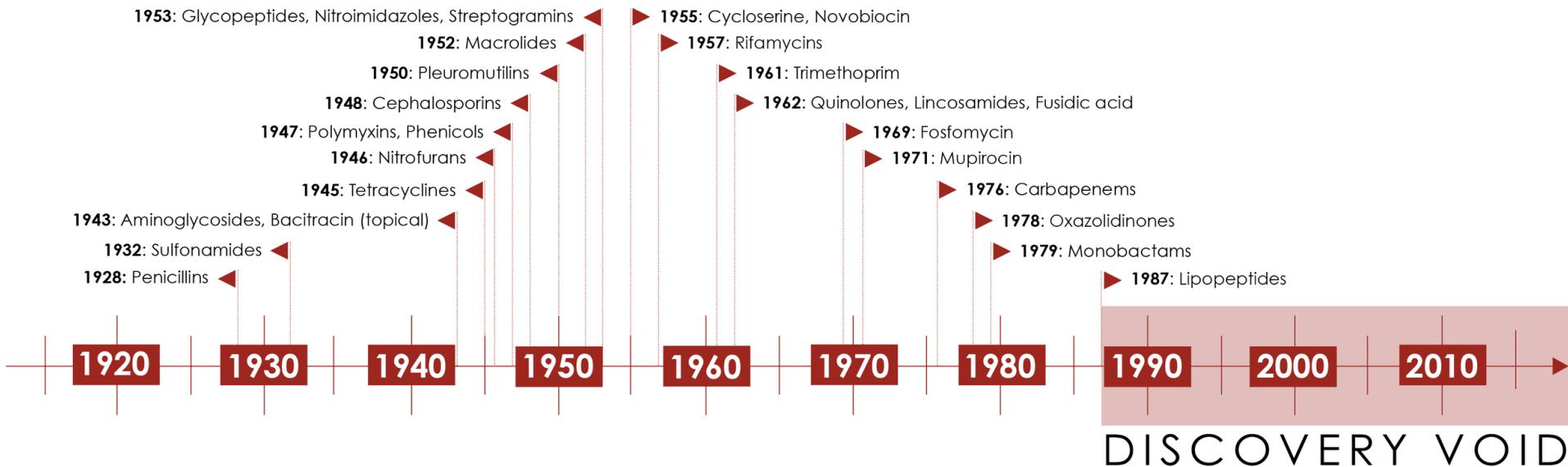


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Learning objectives

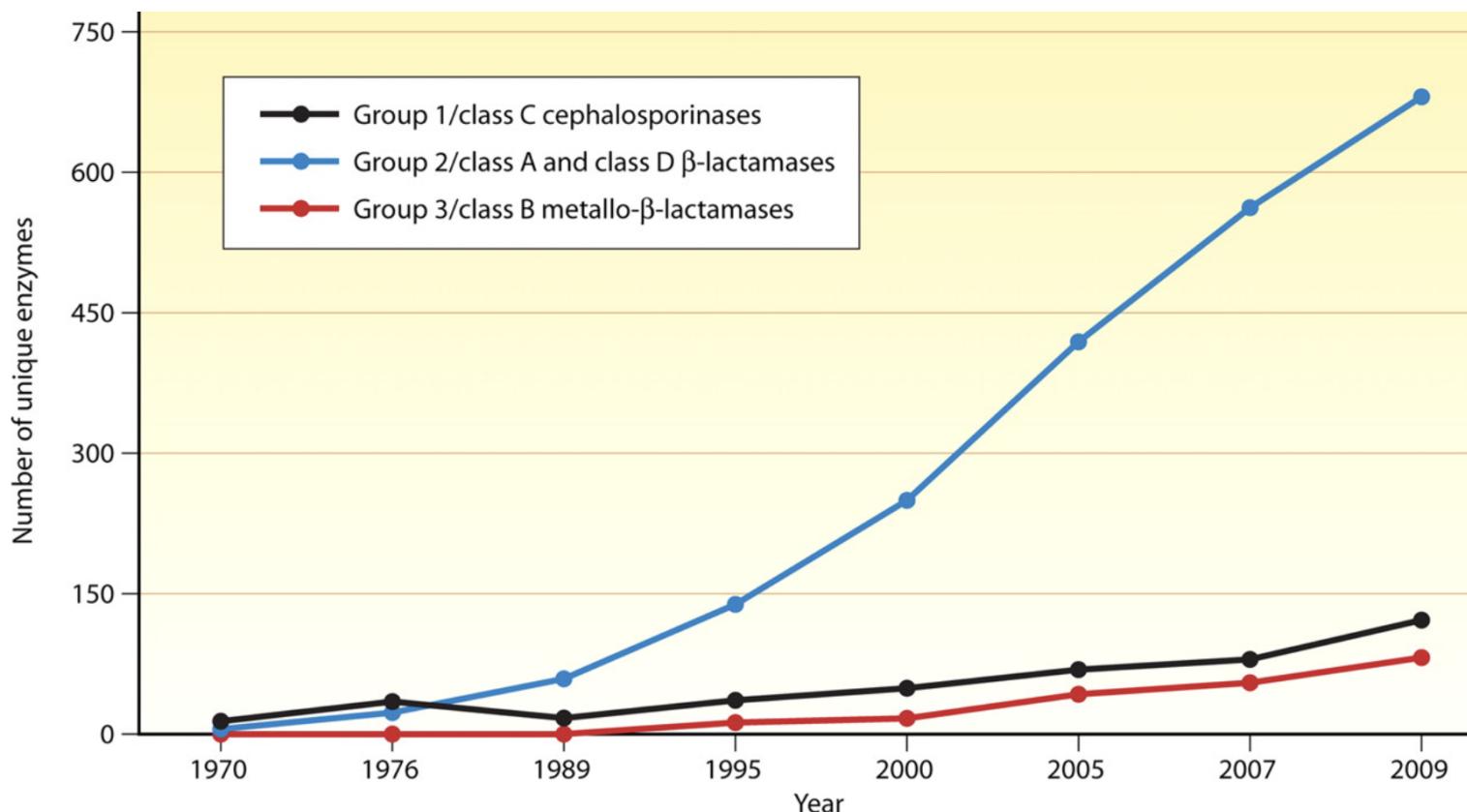
- Discuss factors contributing to the lack of antibiotic development
- Compare and contrast economic incentives proposed to enhanced antibiotic development
- Examine challenges in ensuring antibiotic access in low and middle income countries (LMICs)

Antibiotic development timeline



© ReAct Group 2015

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



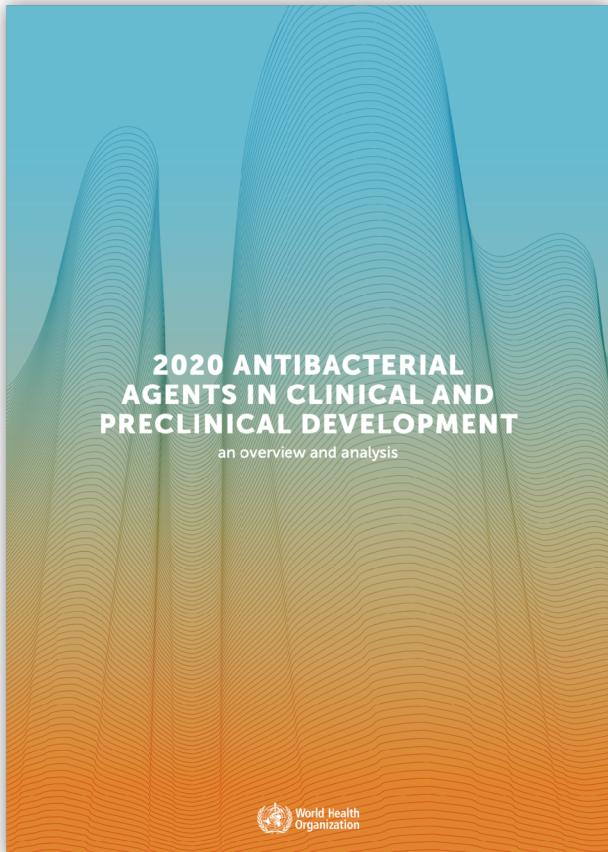
Bush, K. & Jacoby, G. A. *Antimicrobial Agents and Chemotherapy* **54**, 969–976 (2010).

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



WHO Clinical Antibiotic Pipeline Report



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- 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 current clinical pipeline contains 50 antibiotics and combinations (with a new therapeutic entity) and 10 biologicals, of which 32 antibiotics are active against the WHO priority pathogens



Why is antibiotic discovery faltering?

The challenges of antibiotic discovery

The challenges of antibiotic discovery

- Ideally hit multiple targets in bacterial species (to avoid rapid resistance development) ...*but not human targets*

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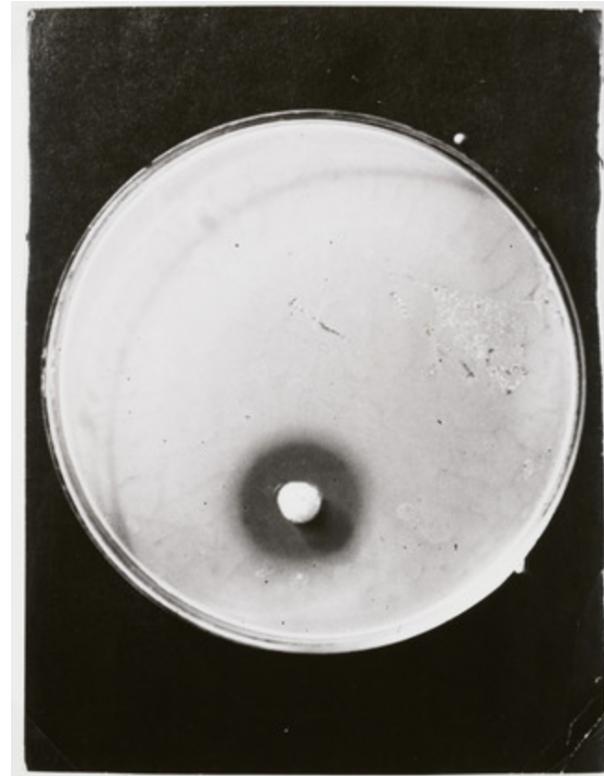
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- Must be safe...drugs are *administered grams not mg or mcg*
- Must penetrate multiple body sites
- Must be effective against future forms of resistance (i.e. predict 10 years into the future)

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

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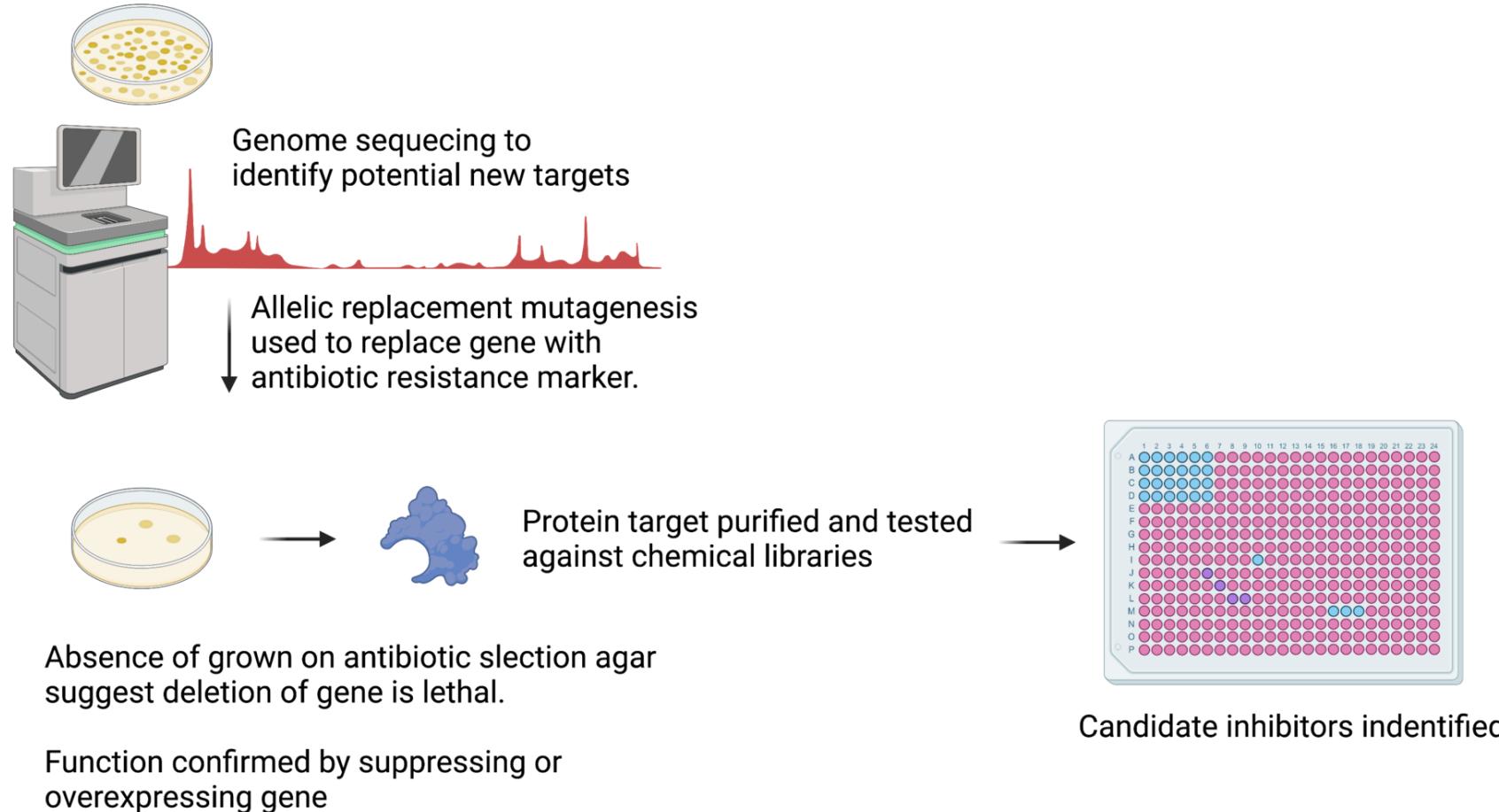
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1990s...

Genomics-driven antibiotic target identification



But few candidate antibiotics found

67 high-throughput screens, each of 260,000 –530,000...compounds tested....no drugs developed

© FOCUS ON ANTIBACTERIALS

REVIEWS

Drugs for bad bugs: confronting the challenges of antibacterial discovery

David J. Payne, Michael N. Gwynn, David J. Holmes and David L. Pompilio

Abstract | The sequencing of the first complete bacterial genome in 1995 heralded a new era of hope for antibacterial drug discoverers, who now had the tools to search entire genomes for new antibacterial targets. Several companies, including GlaxoSmithKline, moved back into the antibacterials area and embraced a genomics-derived, target-based approach to screen for new classes of drugs with novel modes of action. Here, we share our experience of evaluating more than 300 genes and 70 high-throughput screening campaigns over a period of 7 years, and look at what we learned and how that has influenced GlaxoSmithKline's antibacterials strategy going forward.

Antibiotic discovery is not very fashionable these days, and regimens and restrictions on use, particularly for children,

But few candidate antibiotics found

67 highly promising leads have been found

pathogens, including highly challenging Gram-negative pathogens, with safe drugs. Improvements in the success rate for molecular target HTS will be needed before this is a robust discovery platform for antibacterials. In the meantime, at GSK we have concentrated our effort on lead optimization of novel lead classes from alternative sources. We are mindful of other environmental factors but, from our perspective and as emphasized in this review, the scientific challenges of delivering novel mechanism antibiotics are equally difficult. The painful reality of drug discovery is that things go wrong. This is reflected in the low

GlaxoSmithKline's antibacterials strategy going forward.

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Regulatory requirements



United States Food and Drug
Administration



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA

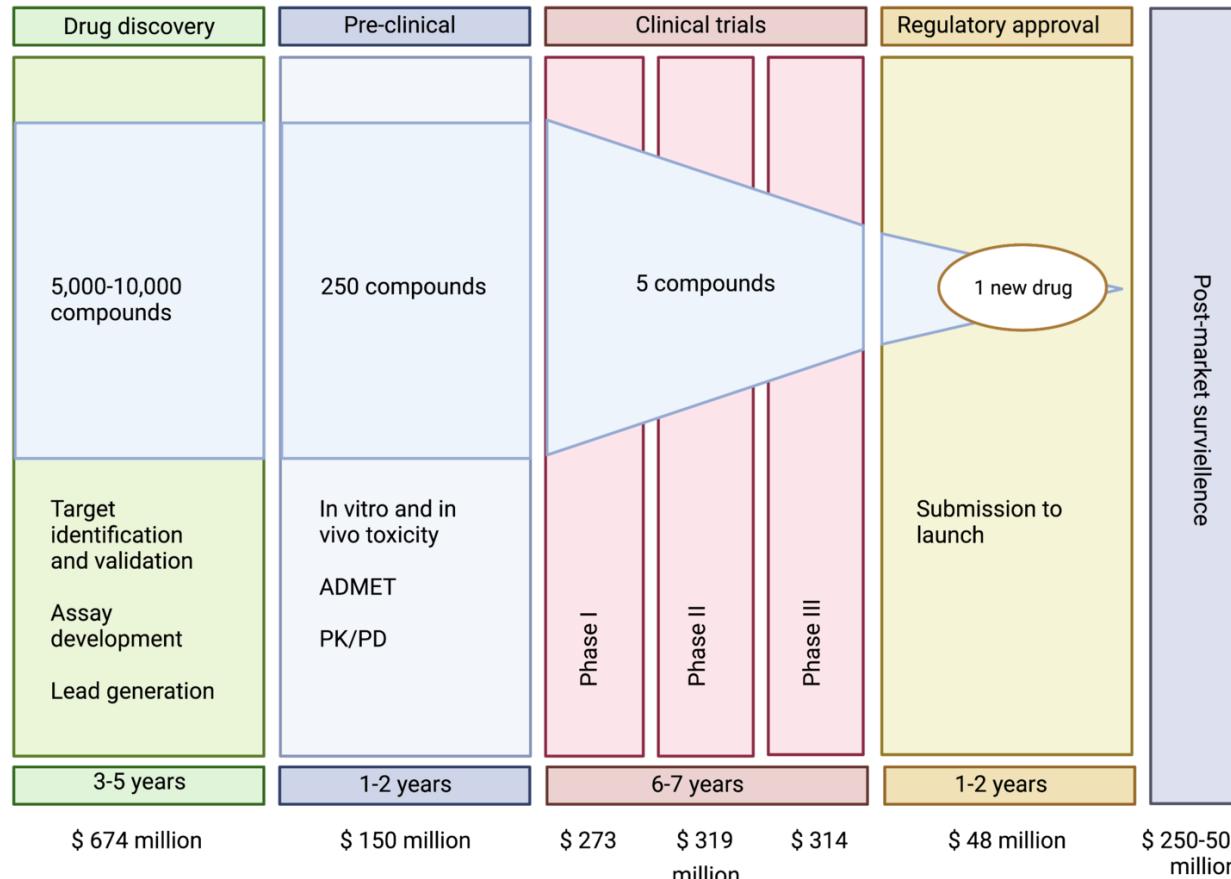


African Medicines Agency

Many LMICs have their own processes for drug registration and approval

Antibiotic approval process and expected costs

1-1.5 billion US dollars



Phase III non-inferiority trial: The paradox of antibiotics

Phase III non-inferiority trial: The paradox of antibiotics

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 - The superiority of a NEW antibiotic is easily shown in the lab on the basis of MIC testing or in animal models of infection

Phase III non-inferiority trial: The paradox of antibiotics

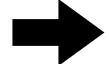
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- But asking for clinical data leads to a problem. trials must (usually) be designed to avoid superiority
 - Instead, we must use *non-inferiority designs* showing similar activity relative to another *active agent*
 - Example: Limb-threatening infection due to MRSA....It is not ethical to randomize to methicillin vs. NEW Antibiotic, must instead compare vancomycin vs. NEW Antibiotic

Phase III non-inferiority trial: The paradox of antibiotics

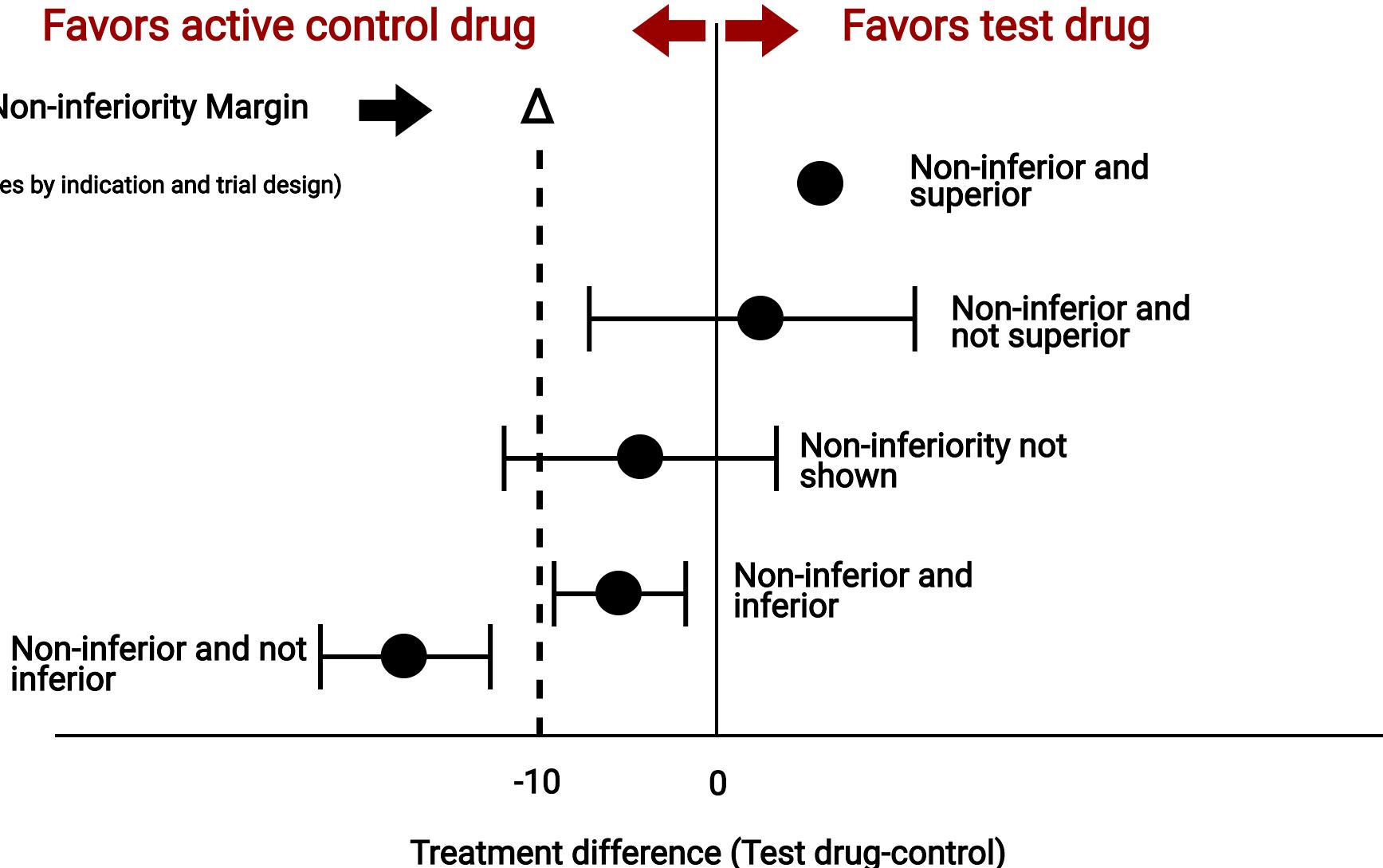
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 - Example: Limb-threatening infection due to MRSA....It is not ethical to randomize to methicillin vs. NEW Antibiotic, must instead compare vancomycin vs. NEW Antibiotic
- **Patients cannot be enrolled if known or likely resistant to New Antibiotic or comparator**

Favors active control drug ← → Favors test drug

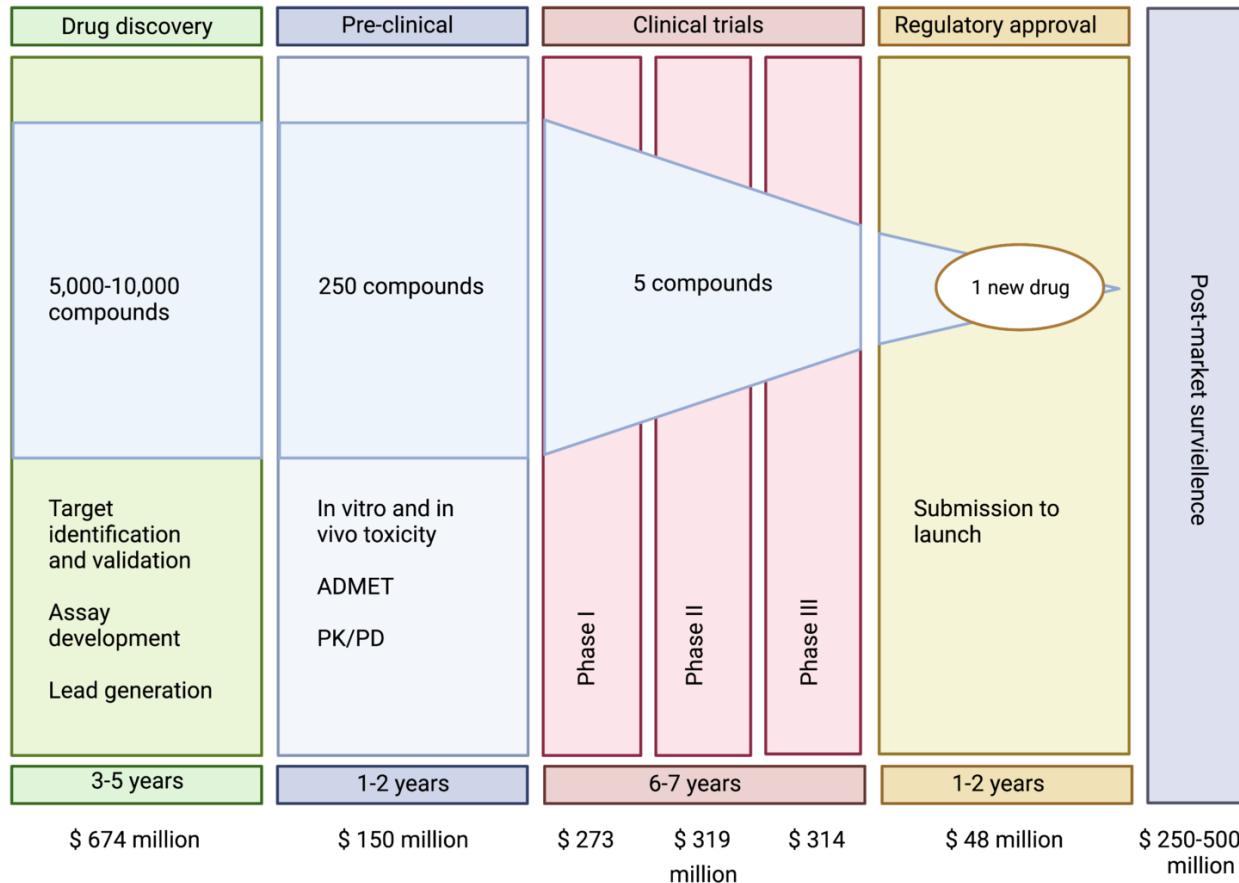
Non-inferiority Margin



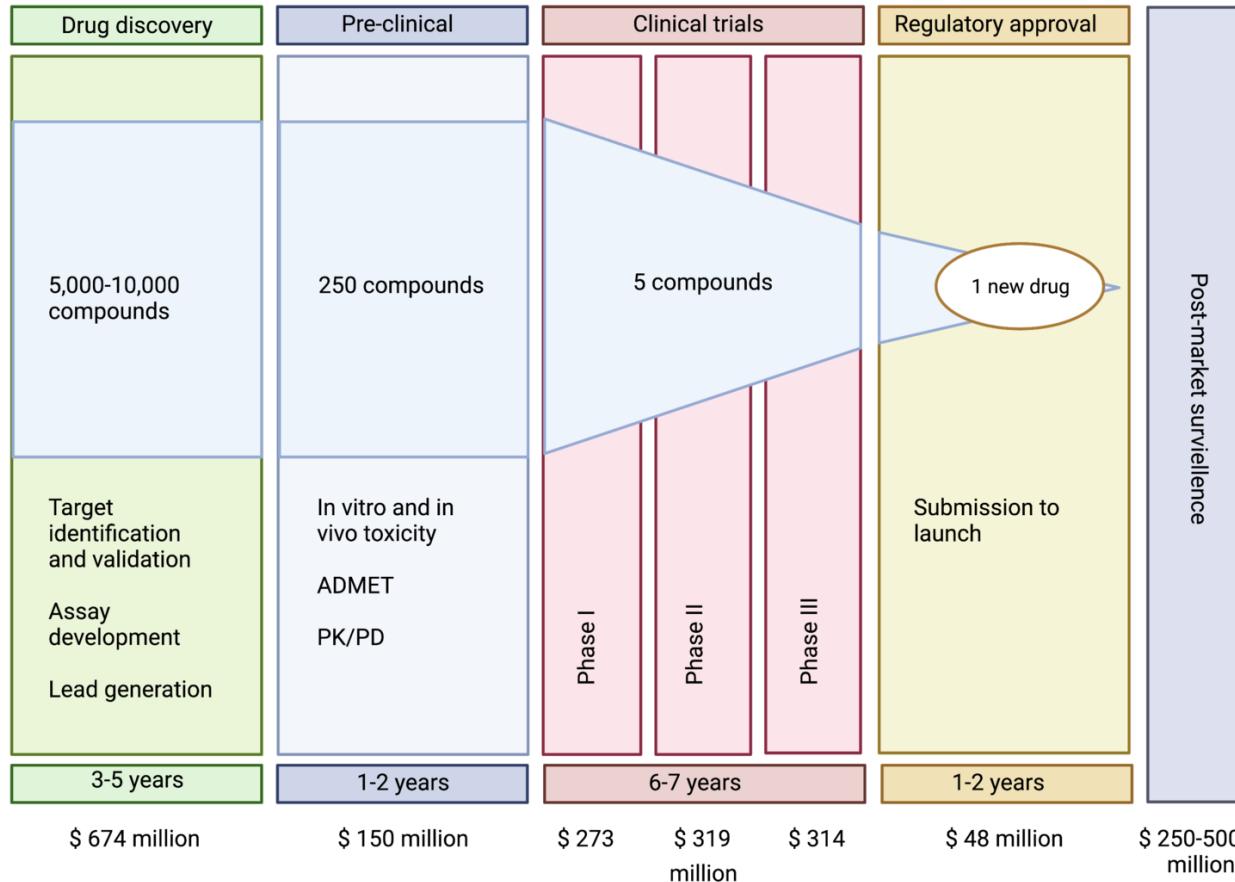
(varies by indication and trial design)



Huge costs are also incurred post-approval for antibiotics



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Pediatric dosing and safety studies,

Pharmacokinetic studies in special populations (i.e. elderly, obese, dialysis)

Pharmacovigilance (safety)

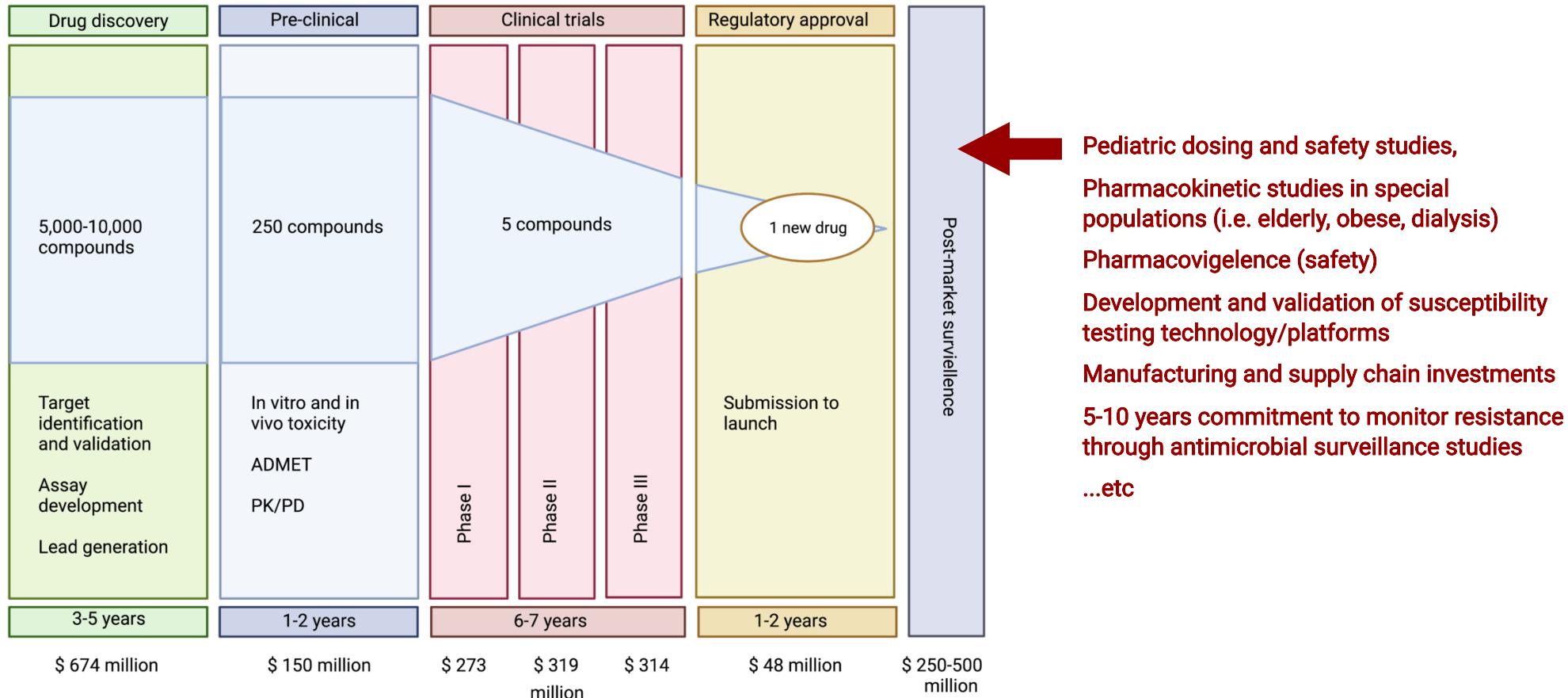
Development and validation of susceptibility testing technology/platforms

Manufacturing and supply chain investments

5-10 years commitment to monitor resistance through antimicrobial surveillance studies

...etc

Huge costs are also incurred post-approval for antibiotics



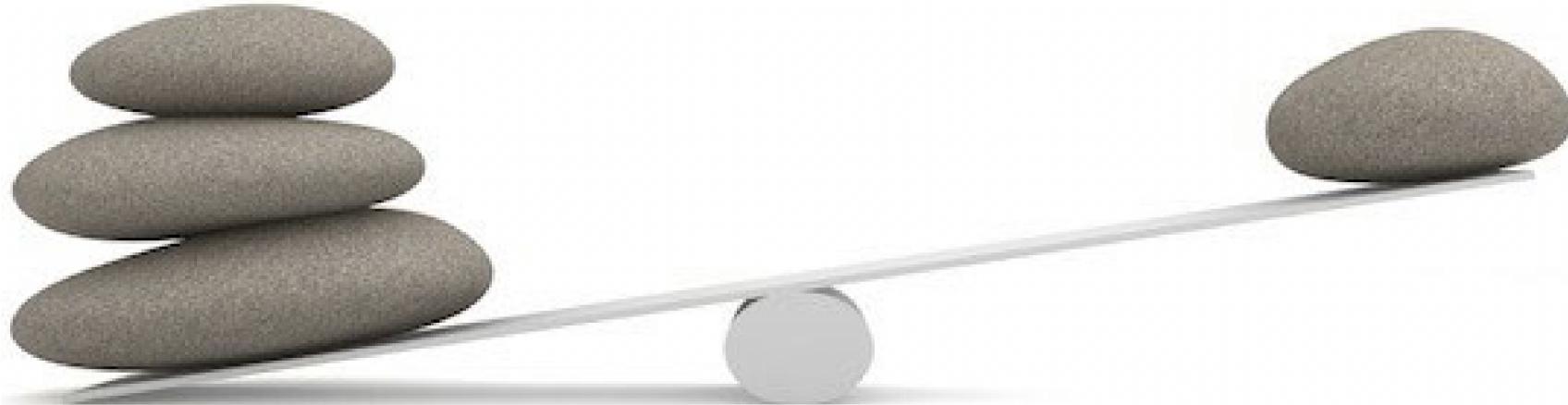
How can a company overcome these costs?

Costs >>> Antibiotic price * Units sold



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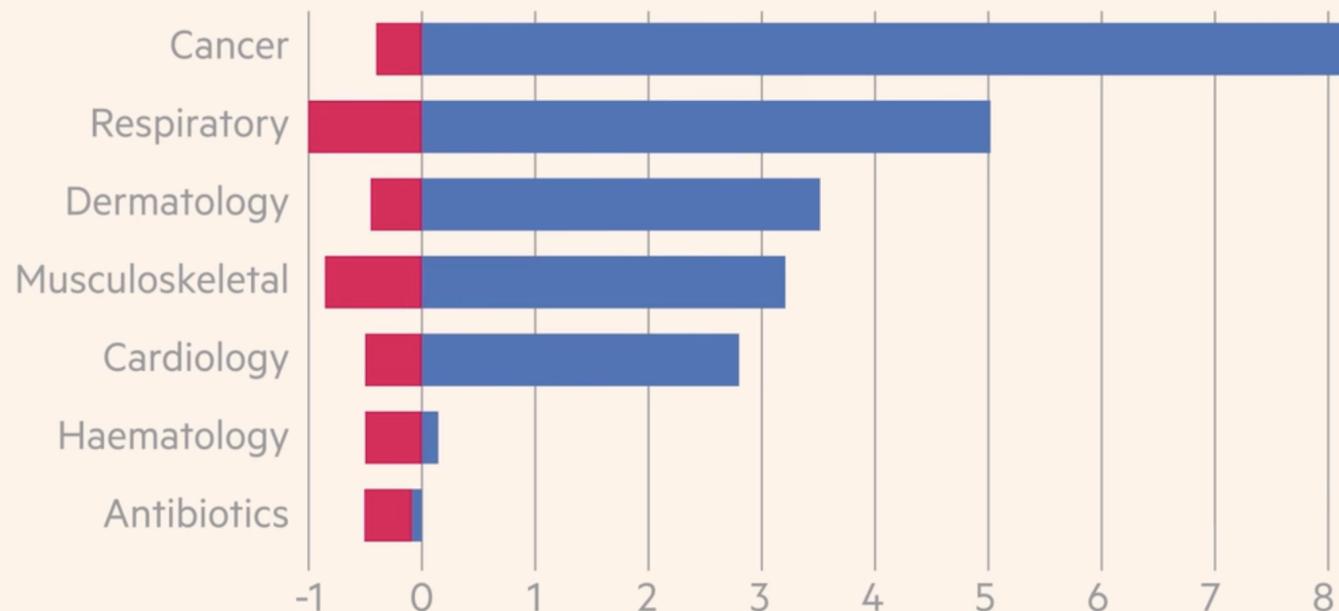


Sell lots of antibiotics (high use → drive resistance)
or charge very high prices

Profitability of different drug types

2014-16 (\$bn)

■ Development cost ■ Profit

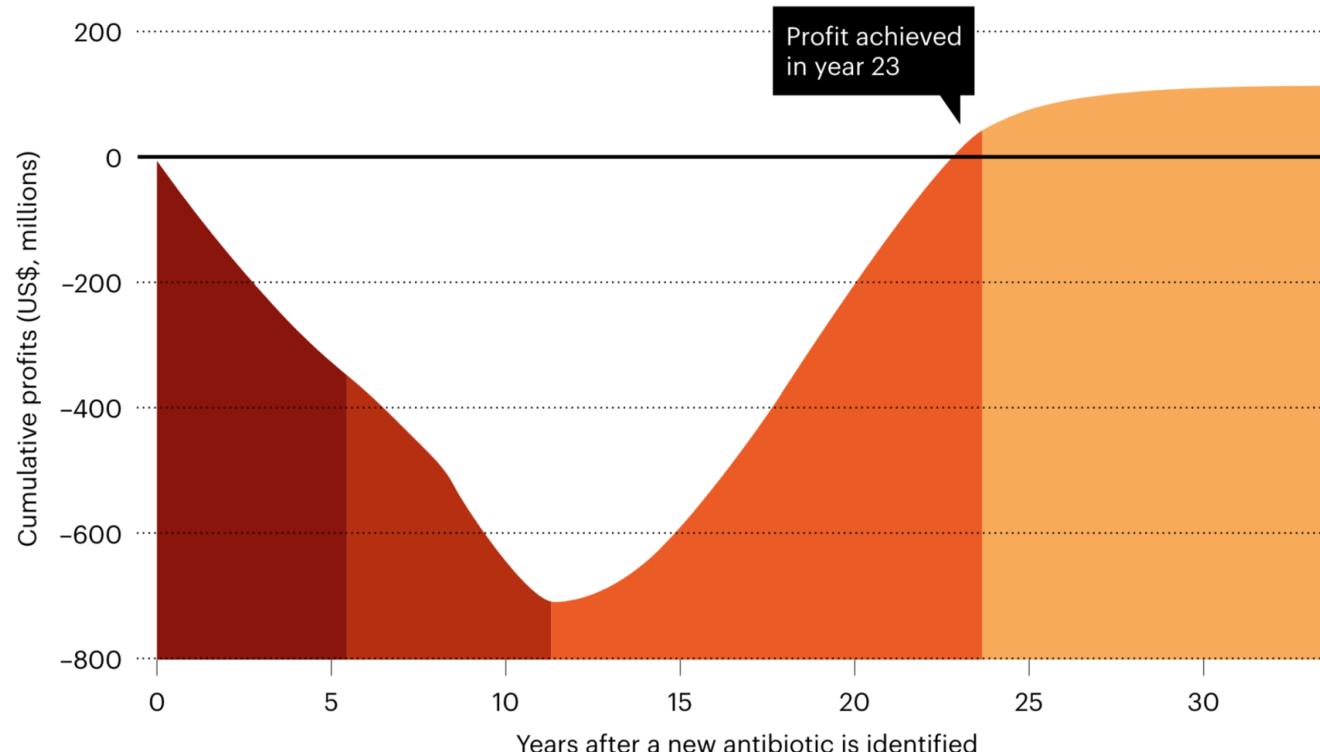


Sources: BCG Analysis, EvaluatePharma

LONG PATH TO PROFITABILITY

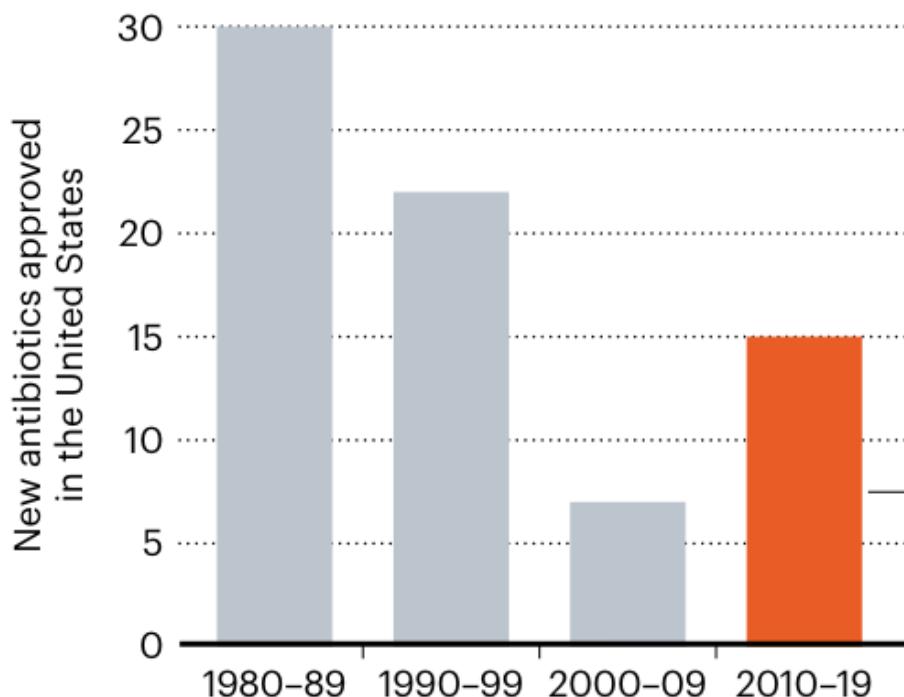
Estimates suggest that it takes more than 20 years to see any profit from a newly developed antibiotic. Once a drug goes off patent, increasing that profit becomes much more difficult.

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

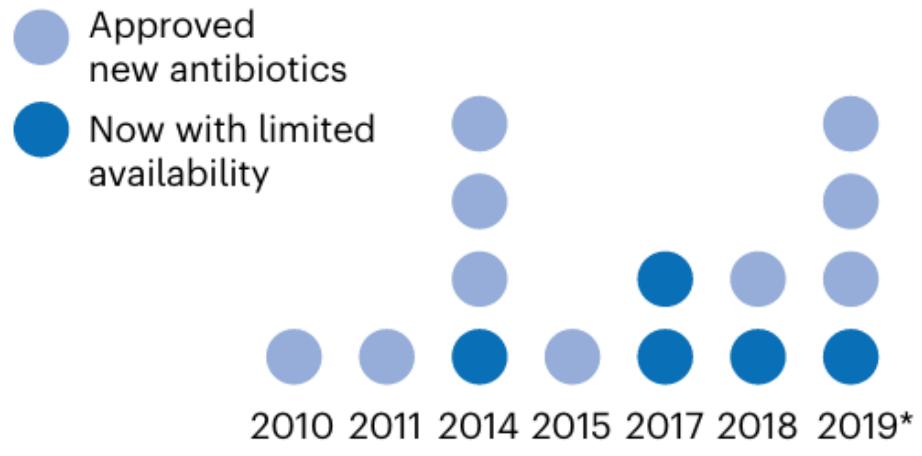


TRIMMING A THINNING HERD

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 Archaeogen 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 a b 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

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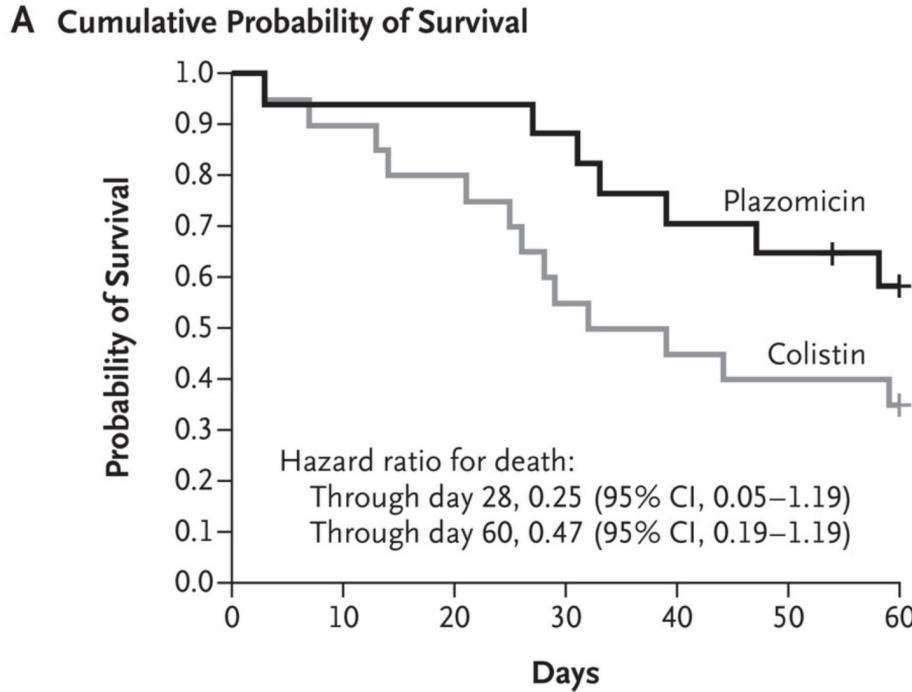
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- Plazomicin was launched in the U.S. in July 2018
- Archaogen filed for Chapter 11 bankruptcy in April 2019

The idea of "non-inferiority" is confusing as for infection: superiority = something bad *but preventable* has happened



No. at Risk	Plazomicin	17	16	16	15	12	11	9
No. at Risk	Colistin	20	18	16	11	9	8	7

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- Archaogen assumed meropenem-vabobactam and plazomicin would displace ceftazidime-avibactam and accelerate a decline in polymyxin use.
- Instead, polymyxin use is stable while meropenem-vaborbactam and plazomicin are essentially not used at all.



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HEALTHCARE & PHARMA

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

Antibiotics maker Melinta files for Chapter 11 bankruptcy

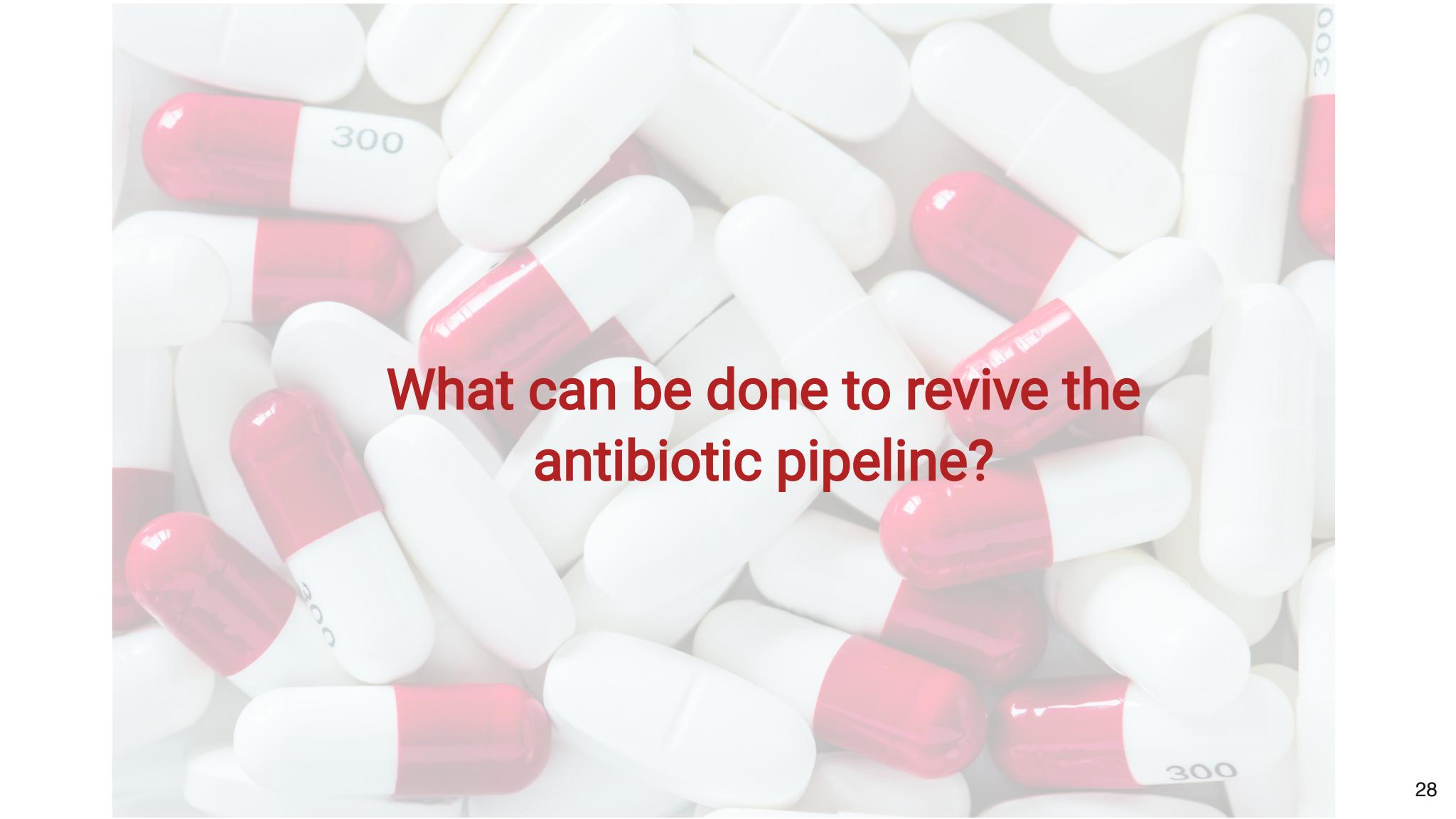
By Reuters Staff

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

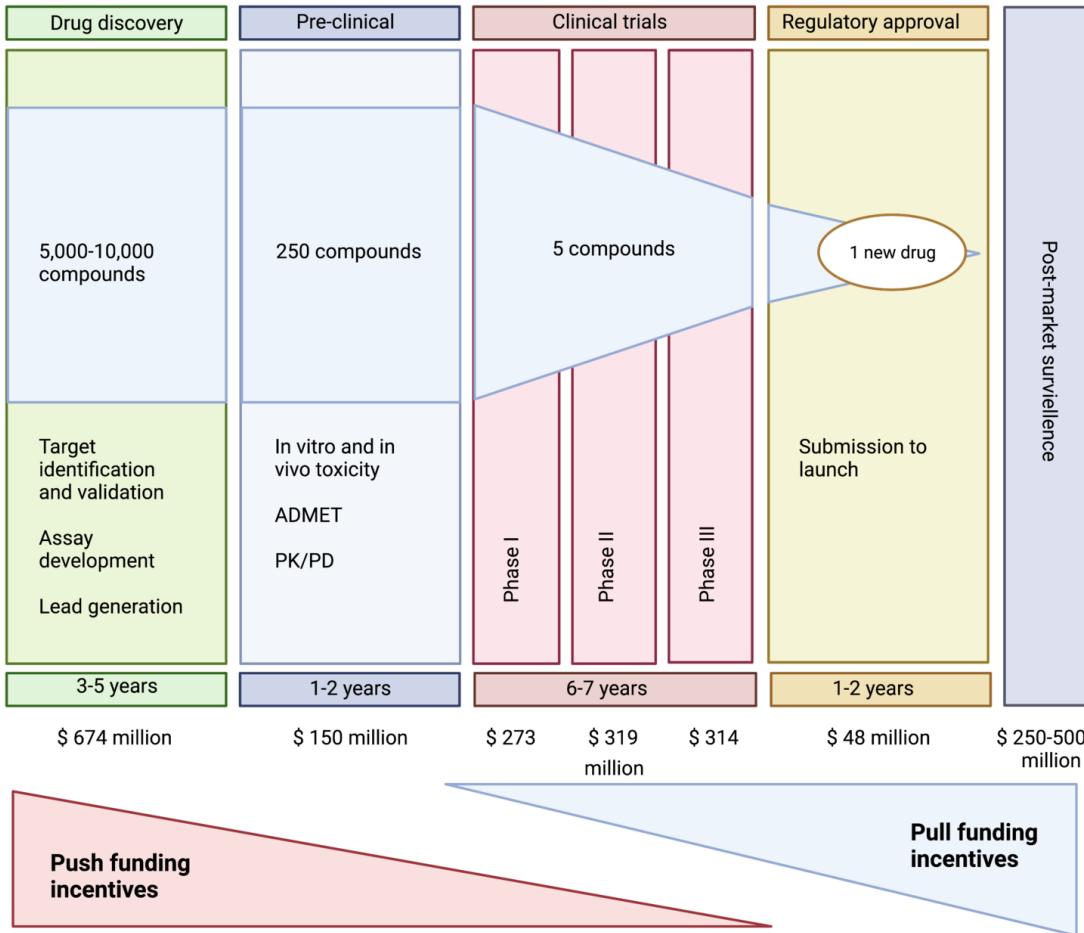
Examples of Push Incentives

- 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 paid only after regulatory approval and hence only successful products are supported

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Antibiotic benefits go beyond simple use

- **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

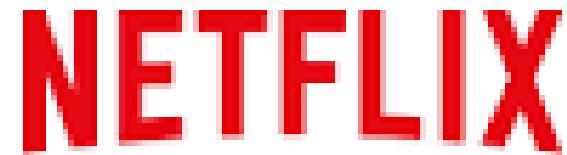
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A fire fighter uses a hose to subdue flames engulfing a home while a physician uses antibiotics to stop an infection in your body. We need to be prepared for fires – the flame kind and the medical kind

Pull incentives: the NETFLIX Model

A large, bold, red "NETFLIX" logo centered on the slide.

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?

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- **UK Example:** Two antibiotics from a pool of candidates are selected- must be an antimicrobial approved in the last 1.5–3 years, and the other will be a late-stage pipeline product expected to be approved by the end of 2020

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

- **UK Example:** Two antibiotics from a pool of candidates are selected- must be an antimicrobial approved in the last 1.5–3 years, and the other will be a late-stage pipeline product expected to be approved by the end of 2020
- Any company to be considered for the model must have a demonstrated commitment to relevant environmental and access standards as described in the [AMR Benchmark](#)

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- Any company to be considered for the model must have a demonstrated commitment to relevant environmental and access standards as described in the [AMR Benchmark](#)
- National Institute for Health and Care Excellence (NICE) performs a cost-effectiveness analysis, then computes a fair "subscription price"

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- National Health Service (NHS) England then enters into commercial negotiations with the proprietors of the two selected products to agree on payments, which will take the form of an annual fixed fee of up to £10 million per product

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- 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

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



Dzintars Gotham^{a,*}, Lorenzo Moja^c, Maarten van der Heijden^b, Sarah Paulin^b,
Ingrid Smith^d, Peter Beyer^b

^a Independent Researcher, London, UK

^b Department of Coordination and Partnership on AMR, AMR Division, World Health Organization, 20 Avenue Appia, 1211, Geneva, Switzerland

^c Department of Health Products Policy and Standards, World Health Organization, 20 Avenue Appia, 1211, Geneva, Switzerland

^d Research and Development Department, Haukeland University Hospital, Bergen, Norway

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-a contributor to AMR



Inefficient, fragmented supply chains

Single source or gaps in active pharmaceutical ingredients and other essential materials

Limited and unequally distributed quality manufacturing of source materials

Complex and inefficient procurement processes

Unavailable or inefficient forecasting systems

Poorly functioning systems for drug pricing

Lack of commercial incentives and market

Low net present value

High prices of new antimicrobials creating imbalances in supply and demand

Issues related to policy and regulatory processes

Regulatory challenges e.g.,:
No systematic strategy for (registering and ensuring availability) on the Essential Medicines List

Inadequate government regulation to ensure access to quality-assured medicines

Inadequate recognition of right of access to essential medicines in national constitutions

Changes in prescribing practices

Access Barriers to Antibiotics



Antibiotic access in low-middle income countries

The challenges in many LMICs

The challenges in many LMICs

- Limited access to basic sanitation or health care increases the risk and spread of antimicrobial resistance

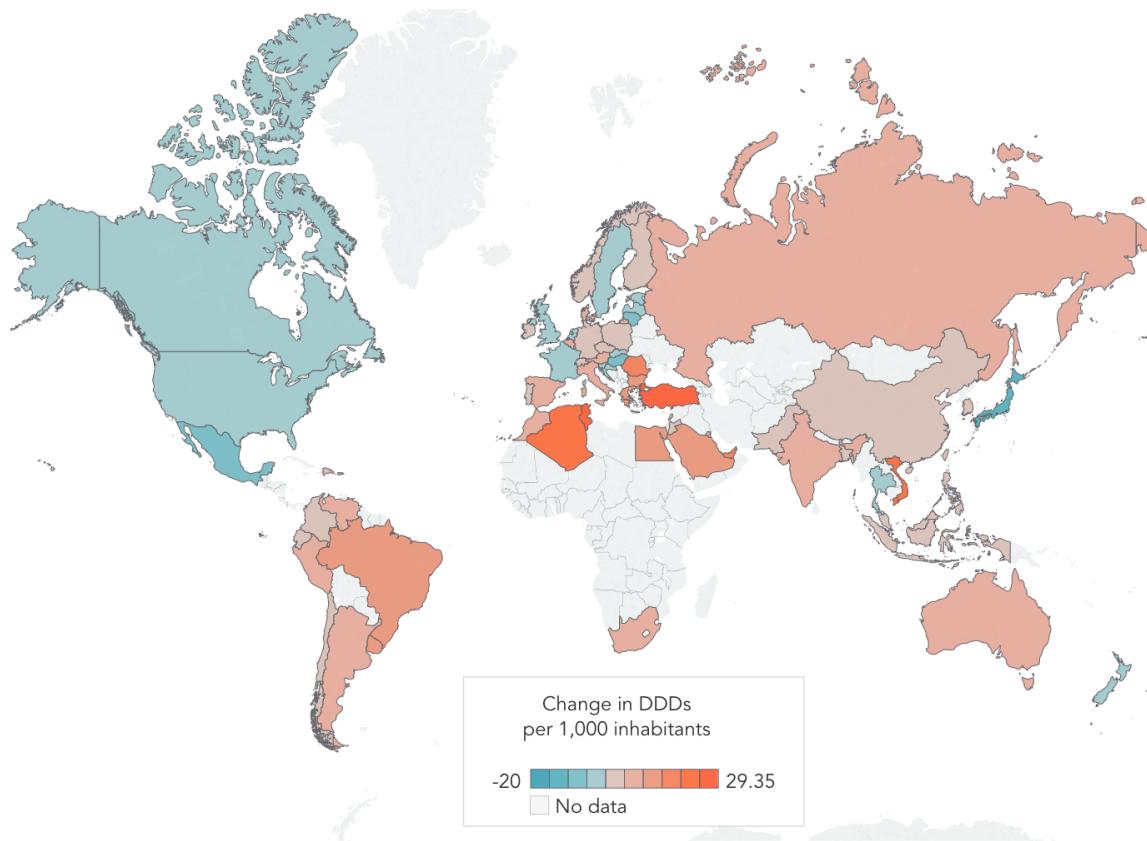
The challenges in many LMICs

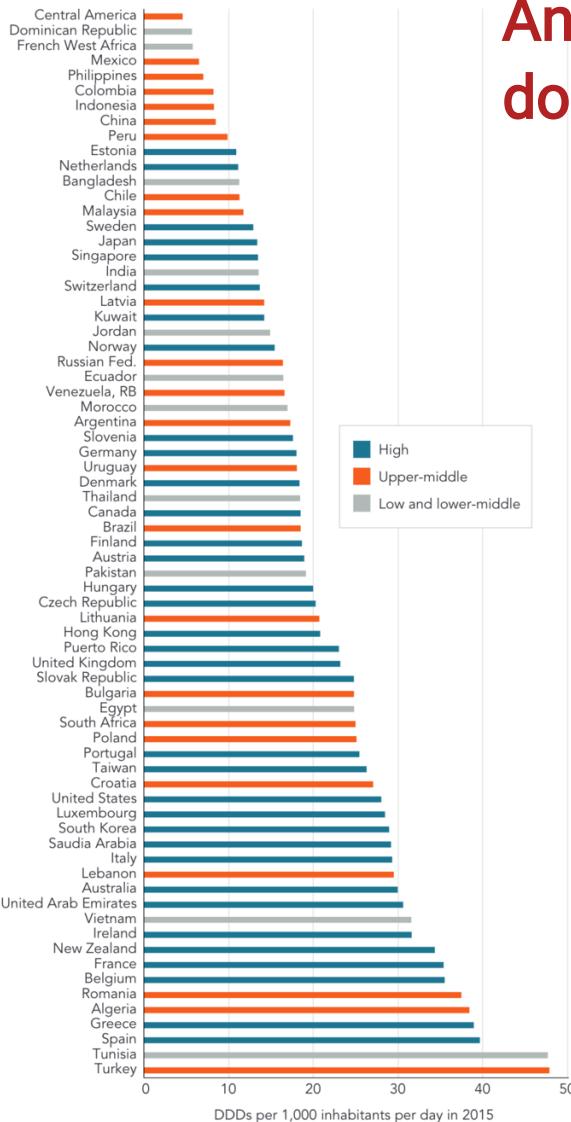
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- Antibiotics, often available without prescription, are often used for substitutes of clean food, water and access to vaccines or diagnostics

The challenges in many LMICs

- Limited access to basic sanitation or health care increases the risk and spread of antimicrobial resistance
- Antibiotics, often available without prescription, are often 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

DDD is a statistical measure of drug consumption, defined by the World Health Organization, and is used to standardize the comparison of drug usage between different drugs or between different health care environments

Barrier 1: Irrational selection and use of antibiotics

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- 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

	CDDEP Recommendation	Stakeholders	Rationale
1	Encourage R&D of new or improved antibiotics, diagnostic tests, vaccines, alternatives to antibiotics for bacterial infections	Countries, regional collaboratos, 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.

	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.

Progress in regulation and rationale use



African Antibiotic Treatment Guidelines for Common Bacterial Infections and Syndromes



First Edition
2021



STRENGTHENING
REGULATORY SYSTEMS

African Medicines Agency



The African Medicines Agency:
towards a unified continental
regulatory framework



A group of diverse healthcare professionals, including a woman in a patterned dress holding a child, a man in a blue uniform, and another man in a light-colored shirt, are gathered together, smiling.

	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

Summary

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- Both scientific and economic challenges for developing new antibiotics 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

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

	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.

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

and strengthen pharmaceutical regulatory capacity	regulators, countries, pharmaceutical suppliers and manufacturers	<p>national and regional regulators could collaborate to support quality assurance and avoid duplication of effort across countries;</p> <p>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>
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	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.