

Nuevas alianzas y estrategias enfocadas al descubrimiento de agentes antimicrobianos

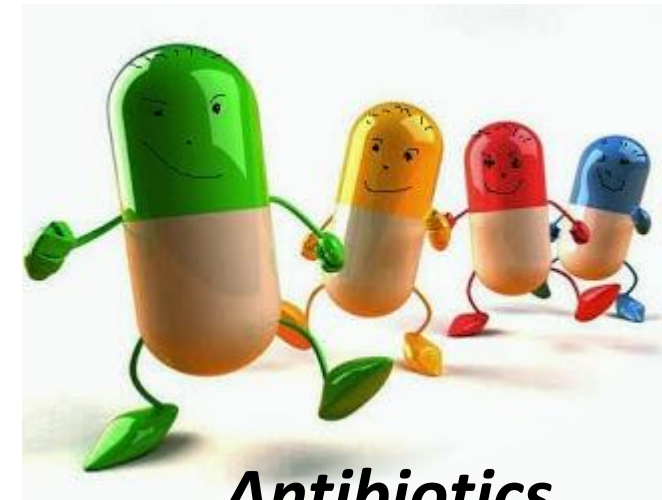
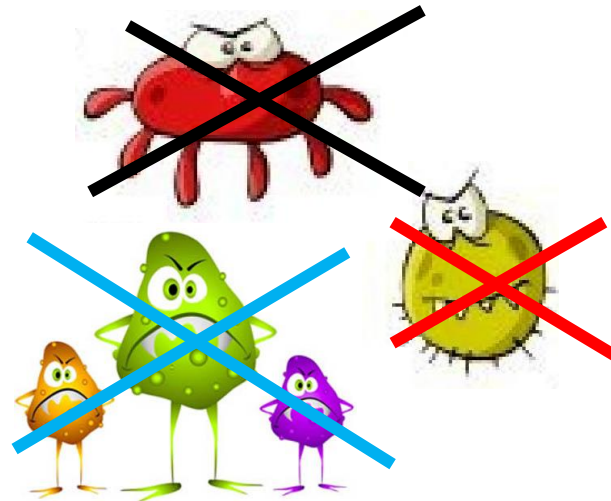
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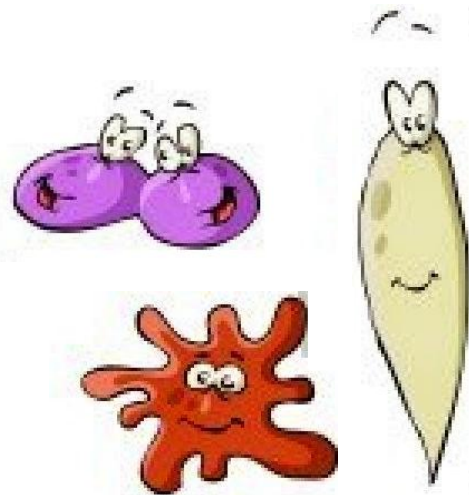
Introduction. Infectious diseases

Pathogenic organisms

.... causing epidemics with devastating consequences on humanity until the discovery of antibiotics

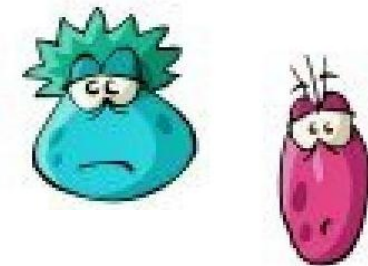


Antibiotics



Microbioma and collaborator organisms

.... important for our interests, contributing to: personal health, technological advances, social development,

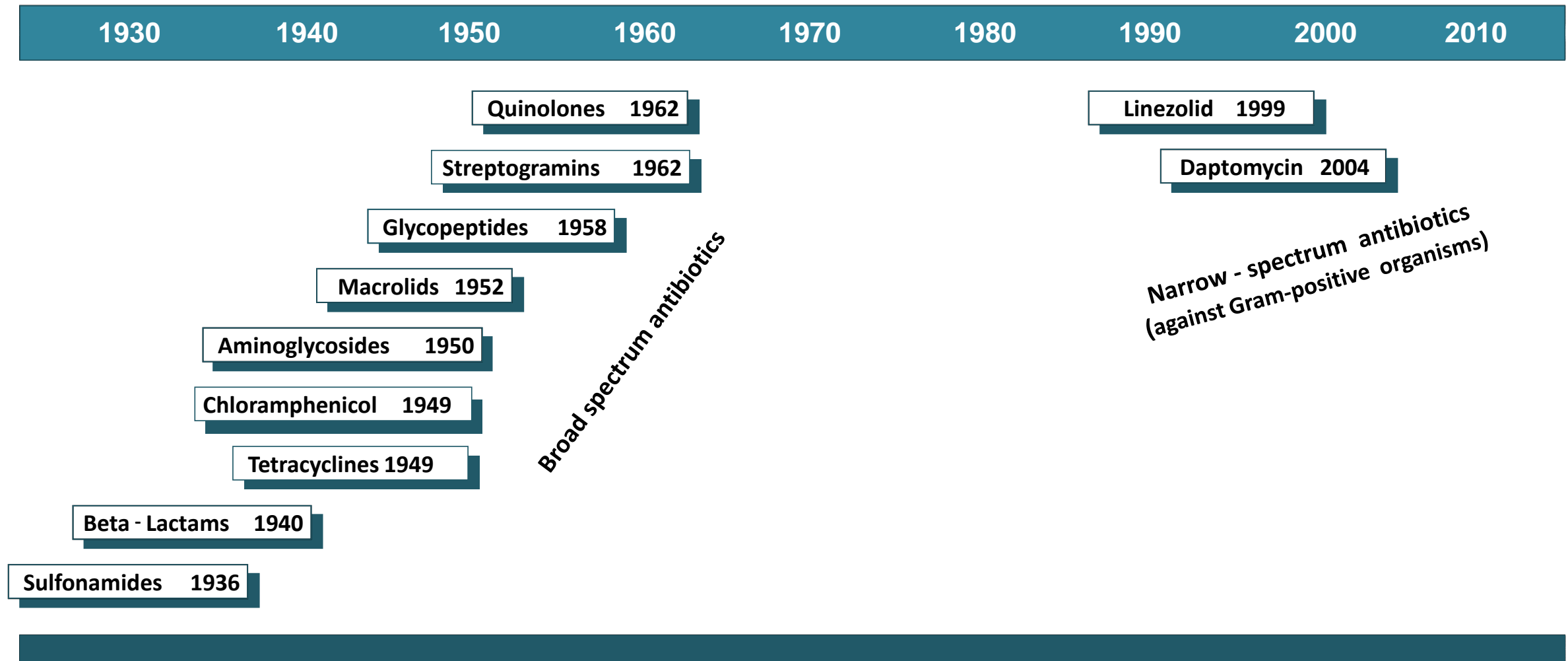


Other organisms

.... the vast majority.
We live together in a friendly way

Introduction. Infectious diseases

In the last 50 years we are losing the battle against pathogenic organisms



Many of the advances in medical treatment are dependent on the ability to fight infections with antibiotics. If that resource is lost, the possibility of protecting people's lives, and the possibility of using many of the advances of modern medicine will be lost with it.

Introduction. Infectious diseases

Two confluent conditions, exacerbated the situation dramatically

1. Alarming **increase of MDR and XDR strains**, due to a massive and inappropriate use of the same antibiotics for decades.
2. Significant **increase of patients vulnerable** to infection (Cancer chemotherapy, complex surgery, organ and bone marrow transplants, treatment of chronic diseases, dialysis, increasing elderly population)



- About 4 100 000 patients with healthcare-associated infection every year
- At least 27.000 deaths a year as a direct consequence of these infections
- At least 2 million people infected with MDR bacteria every year
- At least 23.000 deaths a year as direct results of infections

Besides, many more people die from other conditions complicated by a MDR infection

Introduction. Infectious diseases

A global health challenge for the 21st century

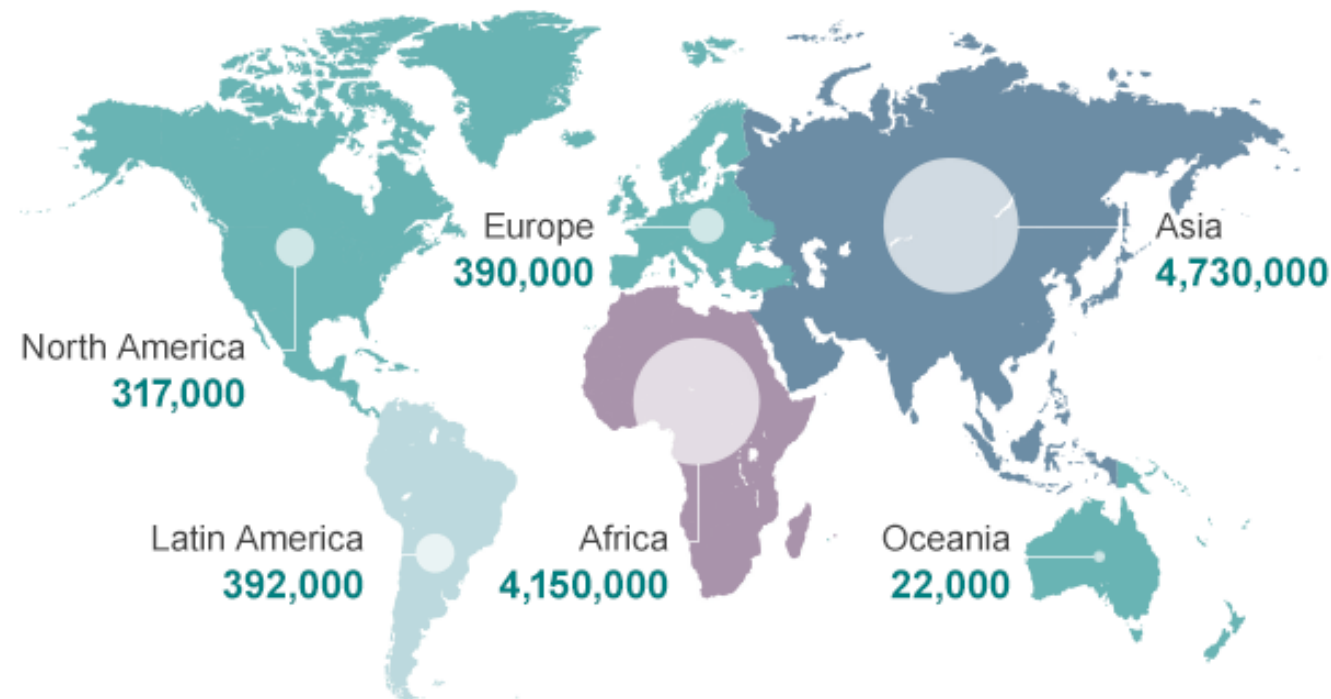


Introduction. Infectious diseases

A global health challenge for the 21st century

- **A post-antibiotic era** in which common infections and minor injuries can kill far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century
- Drug-resistant infections could claim **10 million lives annually by 2050**, with the cumulative cost in terms of global GDP reaching \$100 trillion.

Deaths attributable to antimicrobial resistance every year by 2050



Increasingly, governments around the world are beginning to pay attention to a problem so serious that it threatens the achievements of modern medicine.

Introduction. Infectious diseases

A global health challenge for the 21st century



Presentación de líneas estratégicas

Para alcanzar el objetivo del Plan, se proponen **seis líneas estratégicas** comunes para la sanidad humana y veterinaria (figura 4), que se corresponden con las áreas prioritarias identificadas en los términos de referencia. Cada una de las líneas estratégicas se ha subdividido en medidas, y estas medidas en acciones concretas.

Plan estratégico y de acción para reducir el riesgo de selección y diseminación de la resistencia a los antibióticos

I. Vigilancia del consumo y de la resistencia a los antibióticos	II. Controlar las resistencias bacterianas	III. Identificar e impulsar medidas alternativas y/o complementarias de prevención y tratamiento
IV. Definir las prioridades en materia de investigación	V. Formación e información a los profesionales sanitarios	VI. Comunicación y sensibilización de la población en su conjunto y de subgrupos de población

Introduction. Infectious diseases. Unmet medical need

There is a clear demand for new agents to treat severe infections

LÍNEA ESTRATÉGICA IV

Definir prioridades
en materia de investigación

Cómo se determina la aparición de resistencias bacterianas a los antibióticos, los mecanismos de desarrollo de la resistencia y la transmisión de bacterias resistentes todavía son poco conocidos. Es necesario, por tanto, mejorar el conocimiento de los mecanismos de acción contra las bacterias, las causas y las consecuencias de la aparición y propagación de las resistencias, y alternativas específicas para el tratamiento antibiótico.

Por otro lado, el desarrollo de nuevos principios activos es complejo y quizá requiera en el futuro de iniciativas parecidas a las que se han seguido con medicamentos huérfanos y/o pediátricos. Desde hace varios años, las compañías farmacéuticas invierten poco en la búsqueda de nuevos antibióticos. Se da la paradoja de que se necesitan nuevas clases de antibióticos eficaces en especies bacterianas resistentes pero que sean de uso restringido. El resultado es una disminución de las alternativas terapéuticas disponibles.

Definir prioridades en materia de investigación

MEDIDA

IV.1

Desarrollar y promover una estrategia común
en materia de investigación

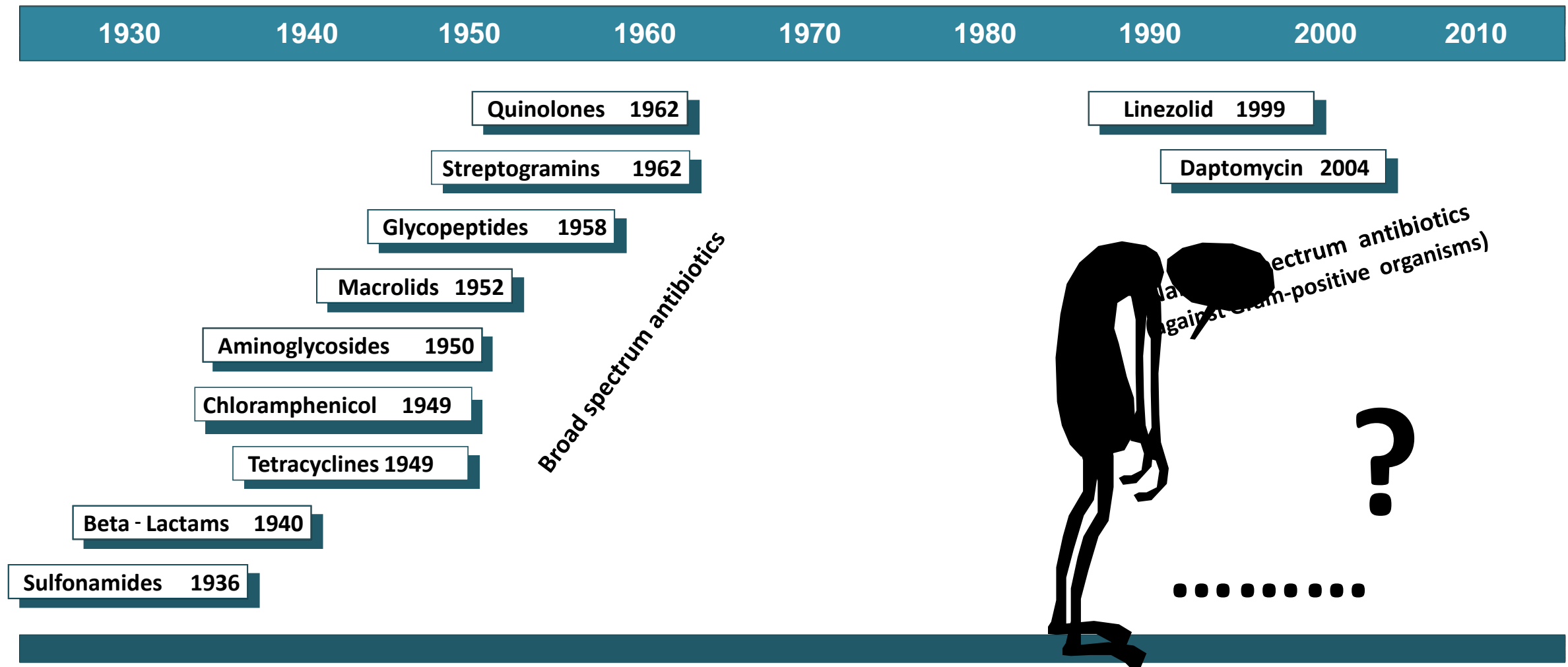
MEDIDA

IV.2

Desarrollo de la investigación epidemiológica
y socioeconómica

Introduction. Infectious diseases. Unmet medical need

There is a clear demand for new agents to treat severe infections



However, most pharmaceutical companies have left the field, and arise the return with caution arguing three main points:

1. Significant **regulatory uncertainty** concerning the approval process for novel antibacterial agents.
2. Markets may not be large enough / uncompetitive prices, to generate **return on investment**
3. The **high technical risk**, based on an unproductive experience over the last 5 decades

What can be done in order to be successful ?

Let's start by focusing the problem and doing self-criticism

3. The **high technical risk**, based on an unproductive experience over the last 5 decades

- what have we done in the last decades?:
- a) From the strategic point of view
 - b) From the technical point of view

a) From the **strategic** point of view

TPPs defined with commercial criteria , assuming a low price and return based on sales volume.
And due to the absence of suitable diagnostic techniques, the goal was:

Broad spectrum compounds for empiric treatment of uncomplicated and severe infections including community and hospital-treated patients

- Broad spectrum. Indicated for a wide range of infections (RTI, UTI, Gram+ and Gram-)
- Active against all resistant strains selected by marketed compounds (new mode of action)
- Available in both, **oral** and intravenous formulations
- Once daily dosing
- Safe and very well tolerated (due to the target population, include children)
- **Low cost** (large number of different drug classes with generic products)



What can be done in order to be successful ?

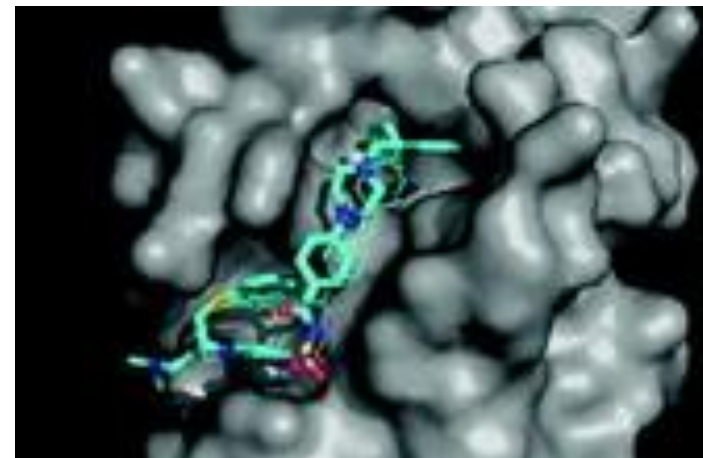
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b) From the **technical** point of view

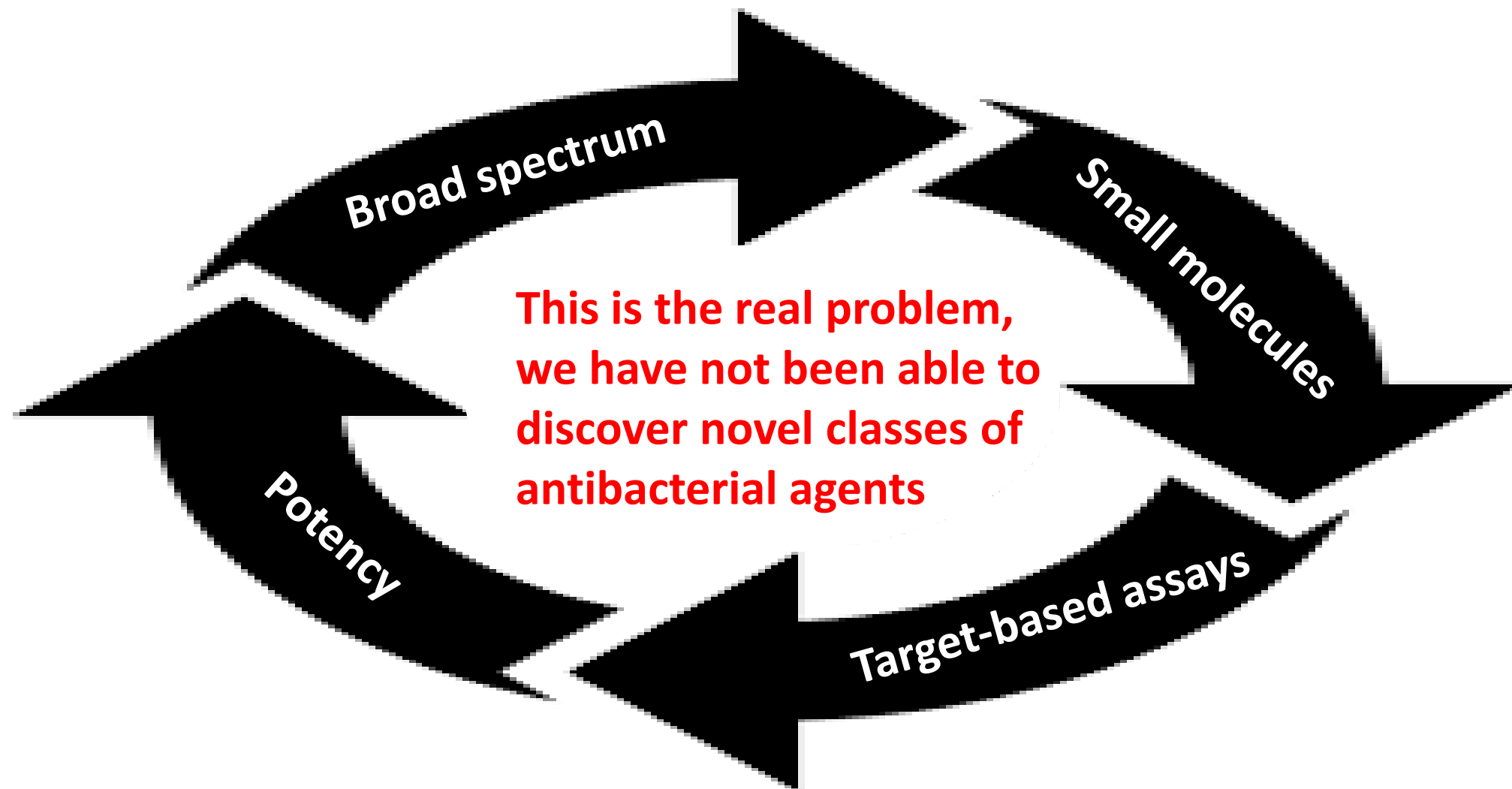
- Screening focused on small molecules, rejecting collections of natural products and extracts (due to the requirement to getting compounds by oral route and low cost)
- Target-based assays
- Prioritization and deselection of positive compounds based largely on *in vitro* activity



What can be done in order to be successful ?

Let's start by focusing the problem and doing self-criticism

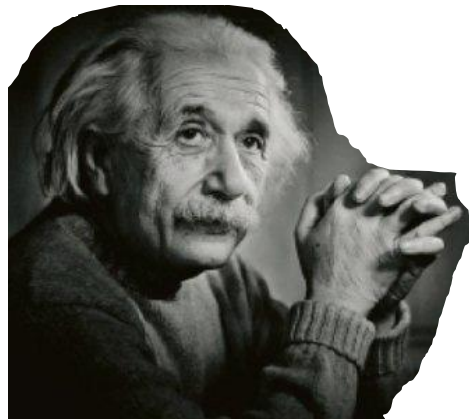
3. The **high technical risk**, based on an unproductive experience over the last 5 decades



What can be done in order to be successful ?

Assumptions to take into account. Today we have:

- More technology than ever
- More information available than ever
- More economic resources than ever
- People (scientists and managers) more deep thinkers than ever **????**



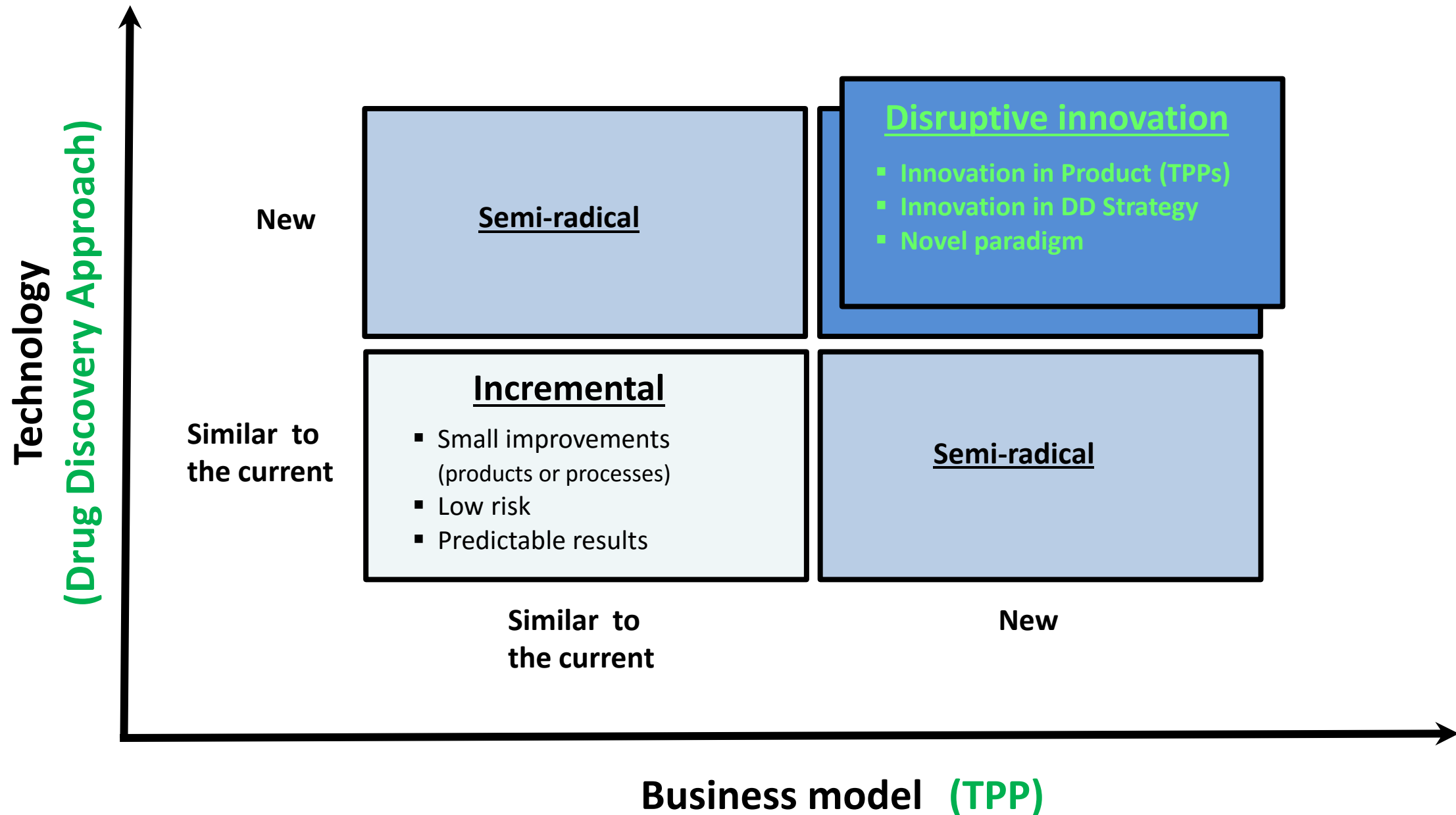
*..... doing the same thing over and over again,
expecting different results is insane*

Albert Einstein

In some circumstances, innovation is not an option it is absolutely necessary

What can be done in order to be successful ?

We have to innovate, it is imperative. Types of innovation



What can be done in order to be successful ?

Issues to consider: Broad-spectrum ?? (genetic diversity)


Diagnostics: **NO**




Empirical treatment



Treatment of Indications



Pneumonia:
Pseudomonas aeruginosa
Klebsiella pneumonia
Streptococcus pneumoniae
Haemophilus influenzae
Mycoplasma pneumoniae
Chlamydia pneumoniae
.....



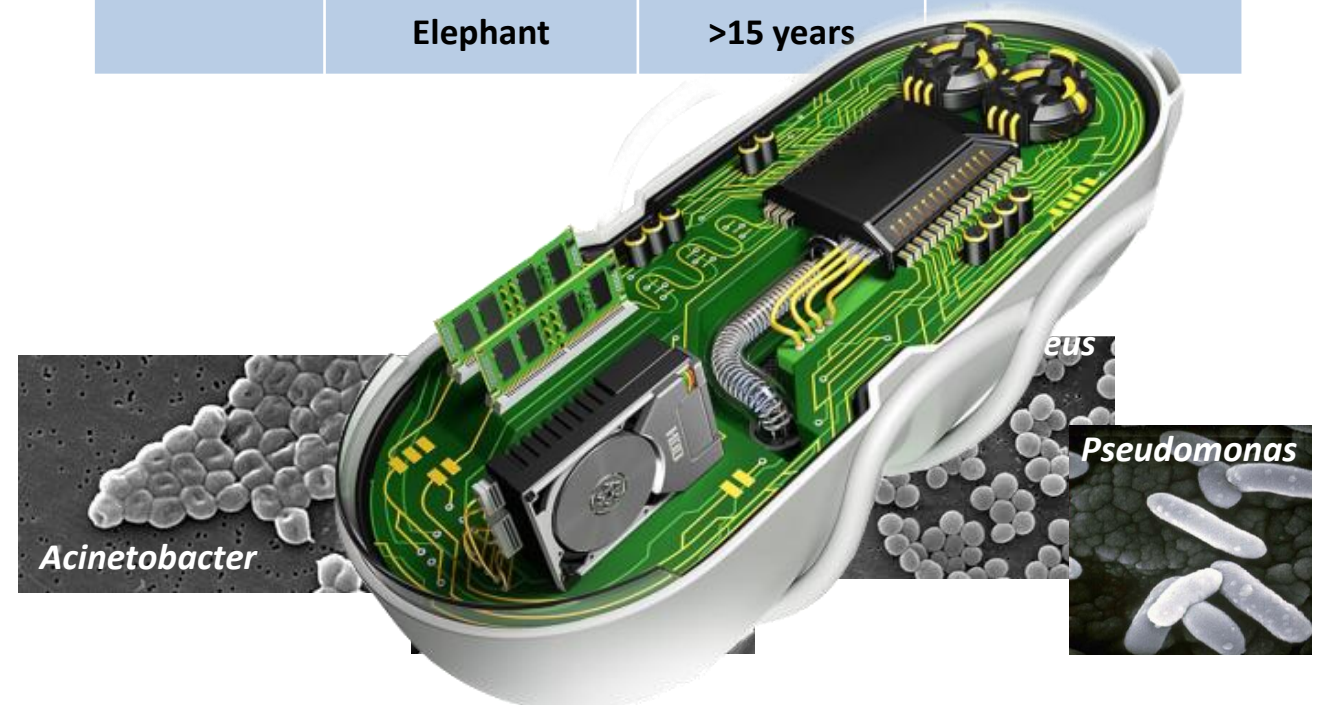
Blood infections (Sepsis):
Staphylococcus spp.
Enterococcus spp
Pseudomonas aeruginosa
Escherichia coli
Acinetobacter baumannii
Klebsiella pneumonia
.....



Broad-spectrum antibacterials



Organism		Generation time	Millions of years of existence
Mammals	Hamster	45 days	65
	Elephant	>15 years	



What can be done in order to be successful ?

Issues to consider: Broad-spectrum ?? . Novel TPPs

Diagnostics: **NO**



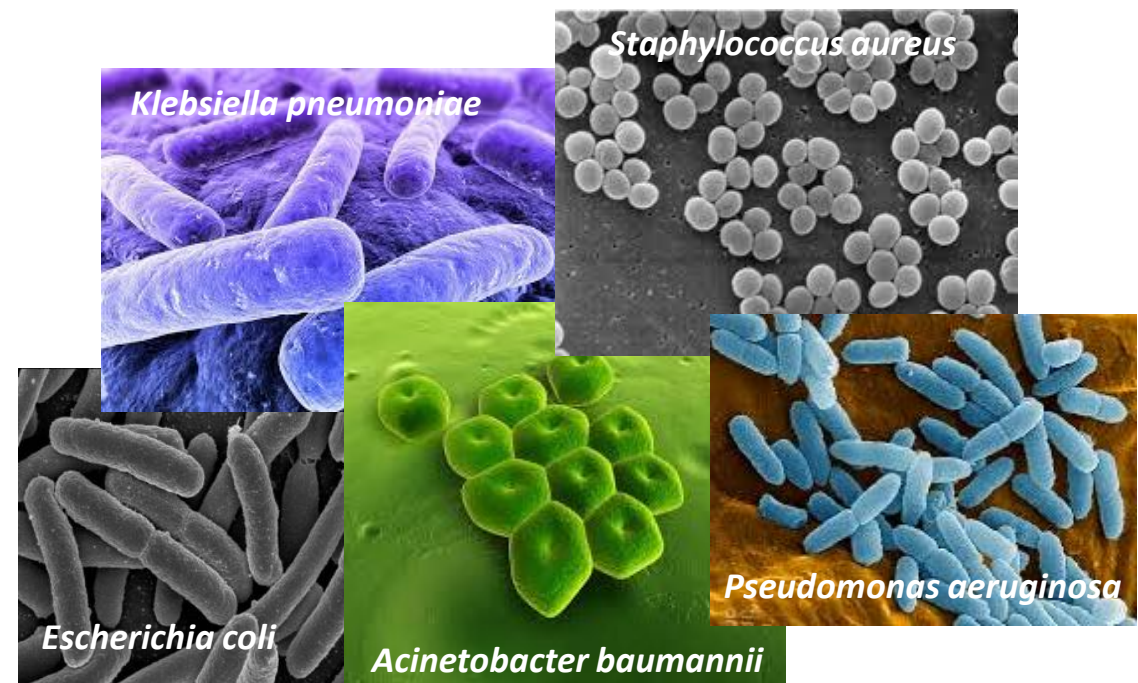
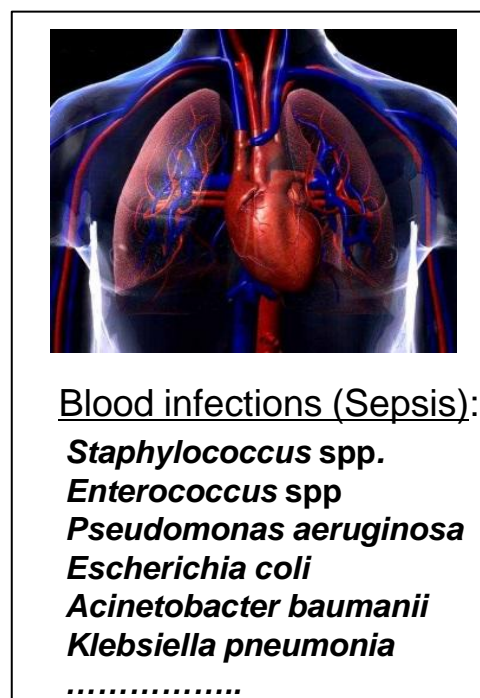
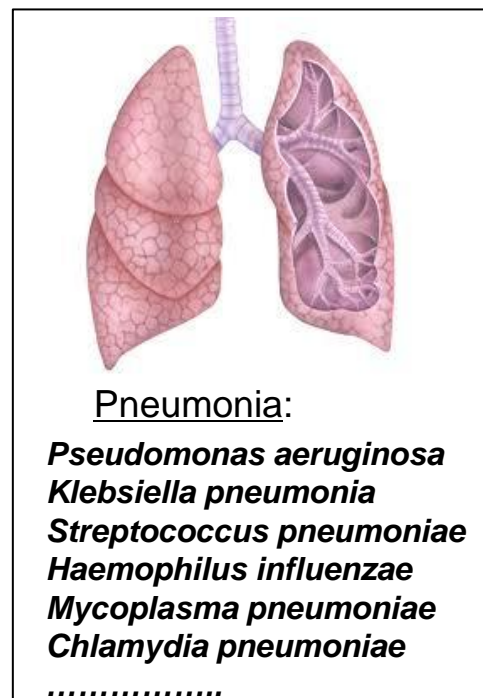
Diagnostics: **YES**

Empirical treatment

Precision medicine

Treatment of Indications

Treatment of Pathogens



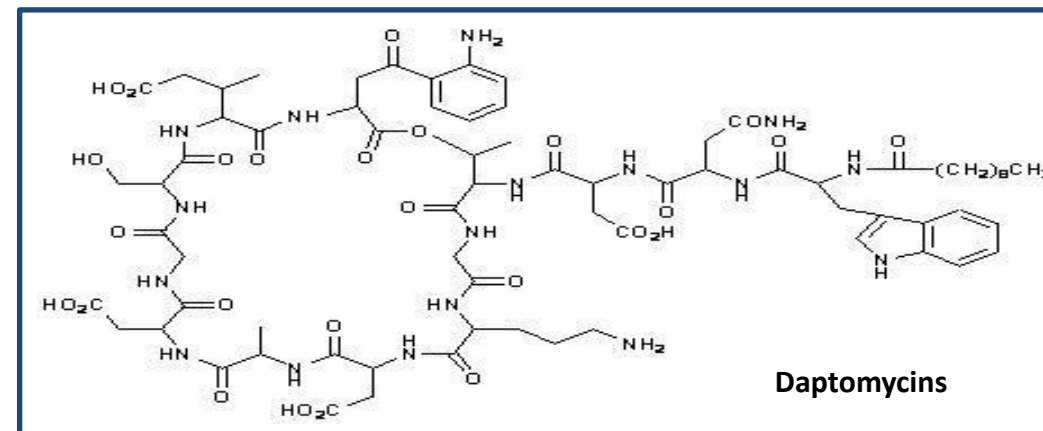
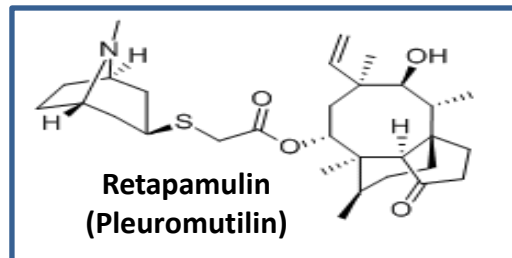
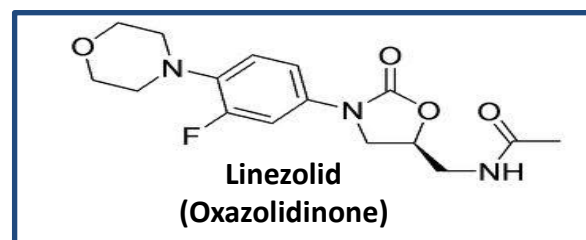
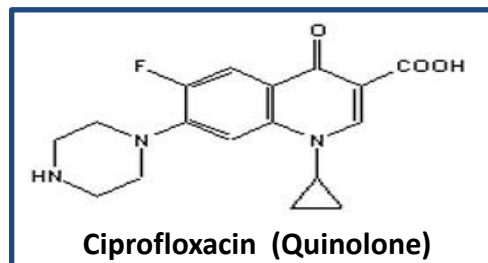
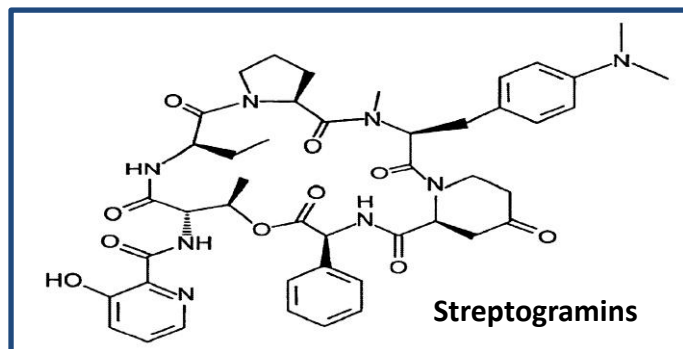
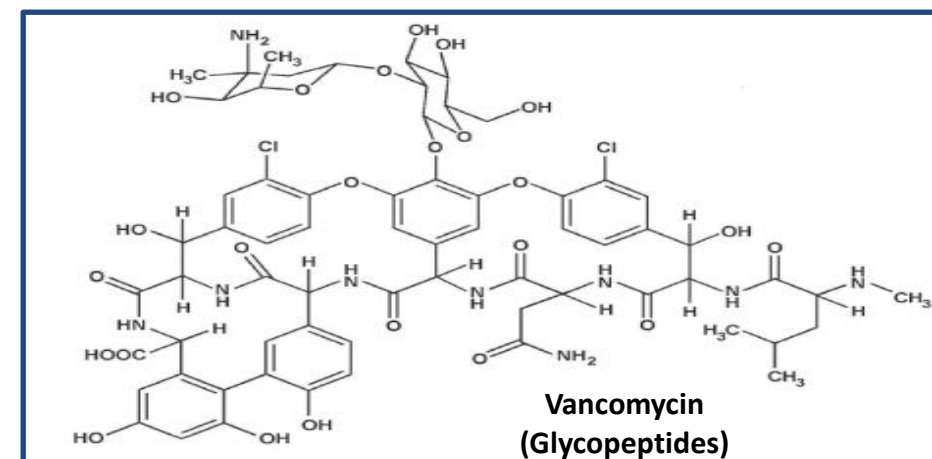
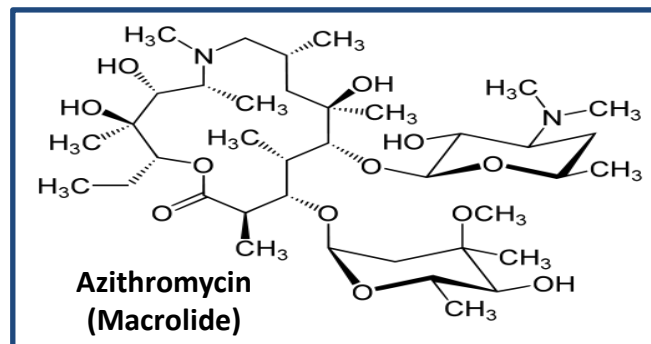
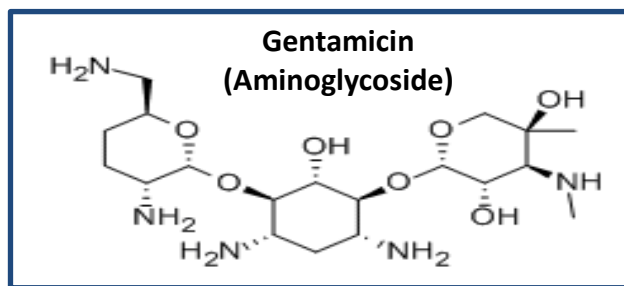
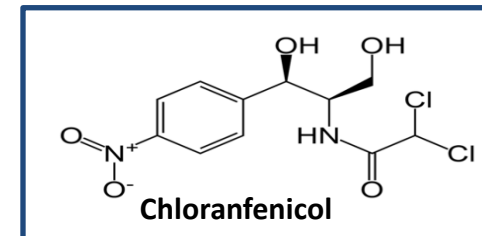
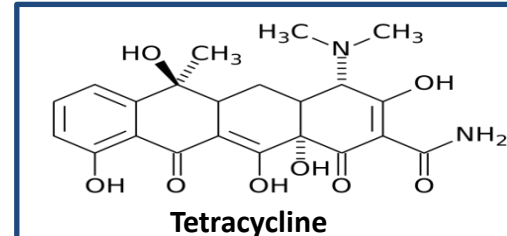
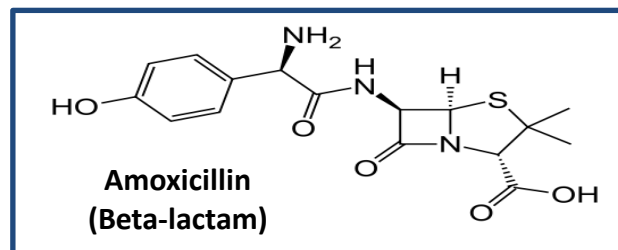
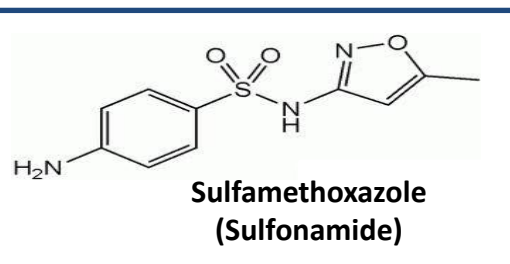
Broad-spectrum antibacterials

Narrow spectrum, pathogen-specific drugs

If the bacteria are very different, there should be a higher probability of discovering new pathogen-specific or narrow spectrum products, reducing the technical risk.

What can be done in order to be successful ?

Issues to consider: Small compounds ??



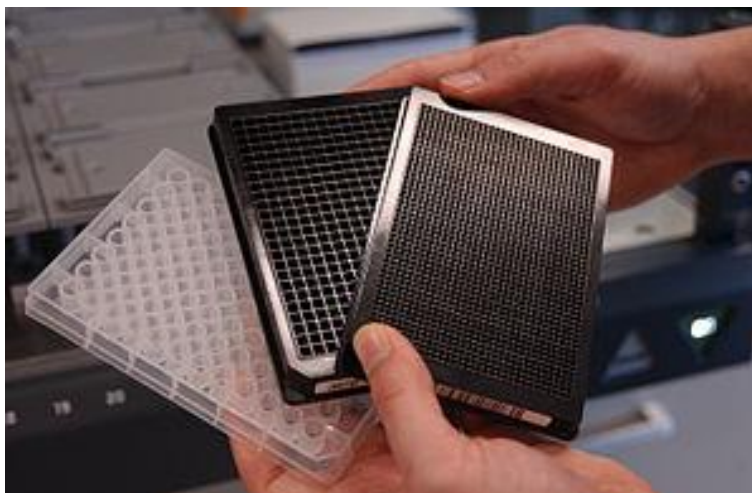
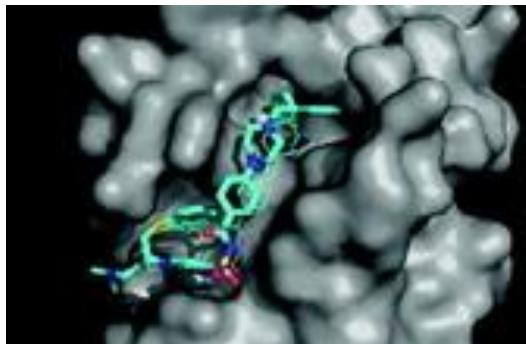
At least half of the classes of antibiotics that have reached the market are natural products. For products to treat severe infections in hospitals, IV administration is feasible, oral administration is a plus. The price of these novel compounds should be adequate to its therapeutic advantage

What can be done in order to be successful ?

Issues to consider: Targeted-based assays ??

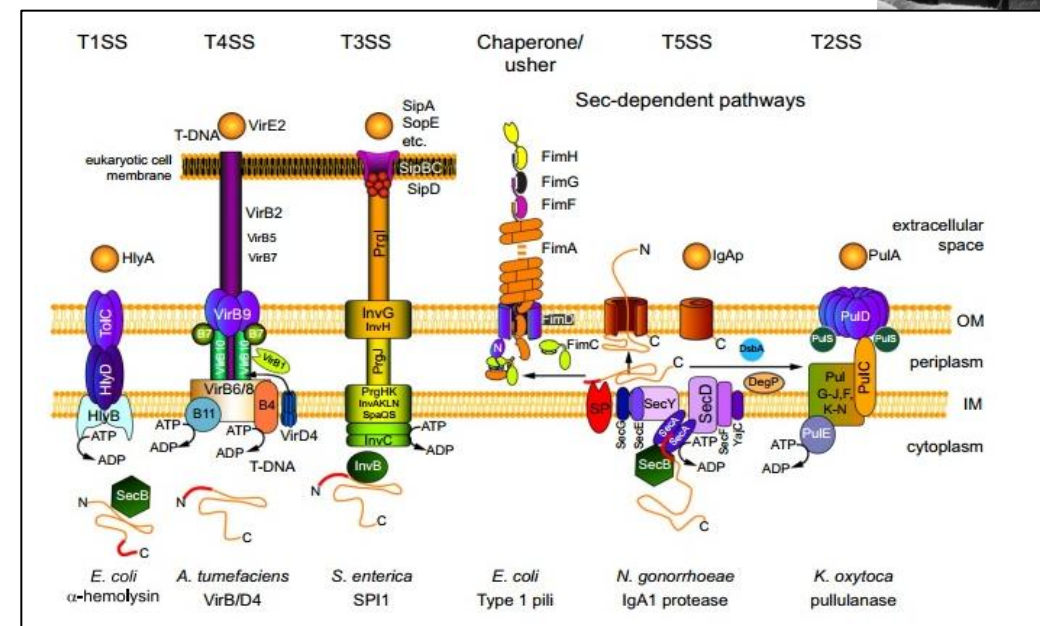
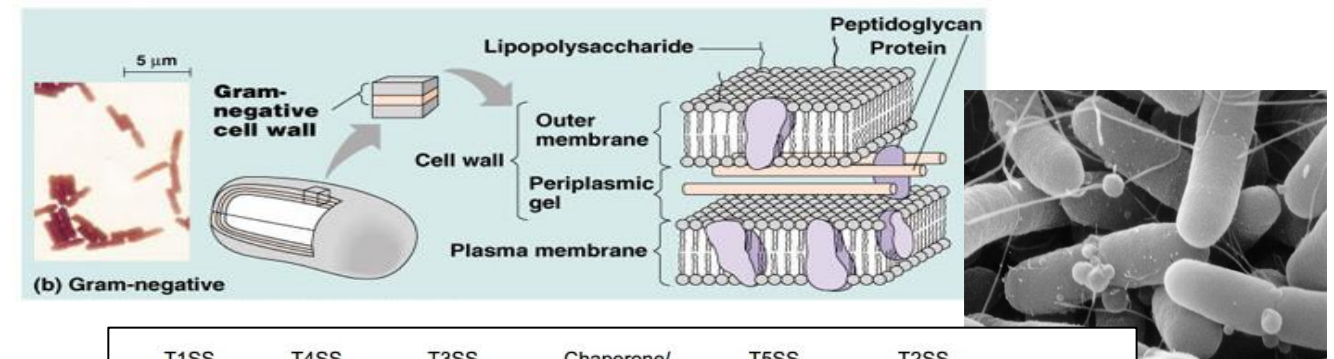
Target-based assay

- Simple
- Precise
- Easily adaptable to HTS format
- **Positives require study In whole cell**



Whole cell assay

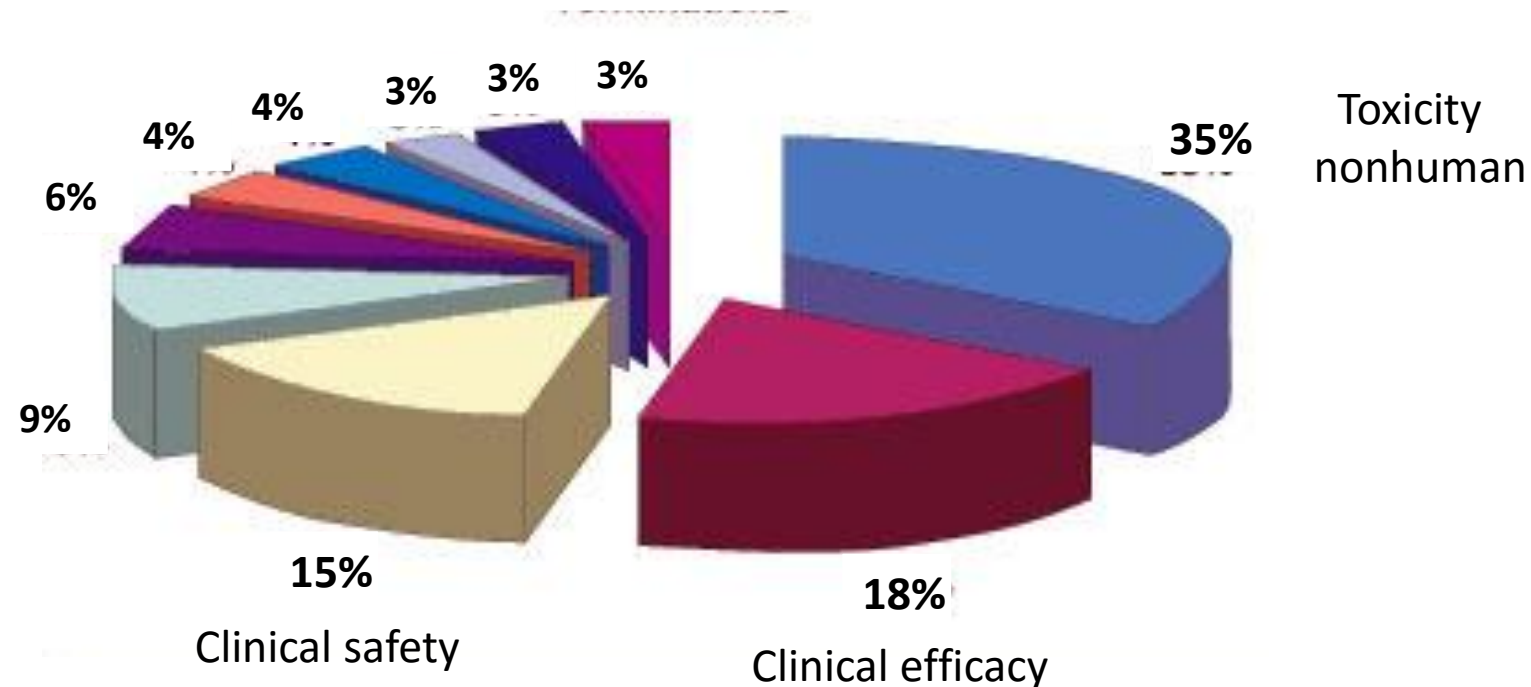
- Targets (all the existing ones) in context
- Include: membrane, cell wall,
- Include cellular metabolism
- Include transport mechanisms (pumps,..)
- **Positives require MoA characterization**



What can be done in order to be successful ?

Issues to consider: in vitro activity vs toxicity

The two more prevalent causes of termination are: lack of efficacy and toxicity

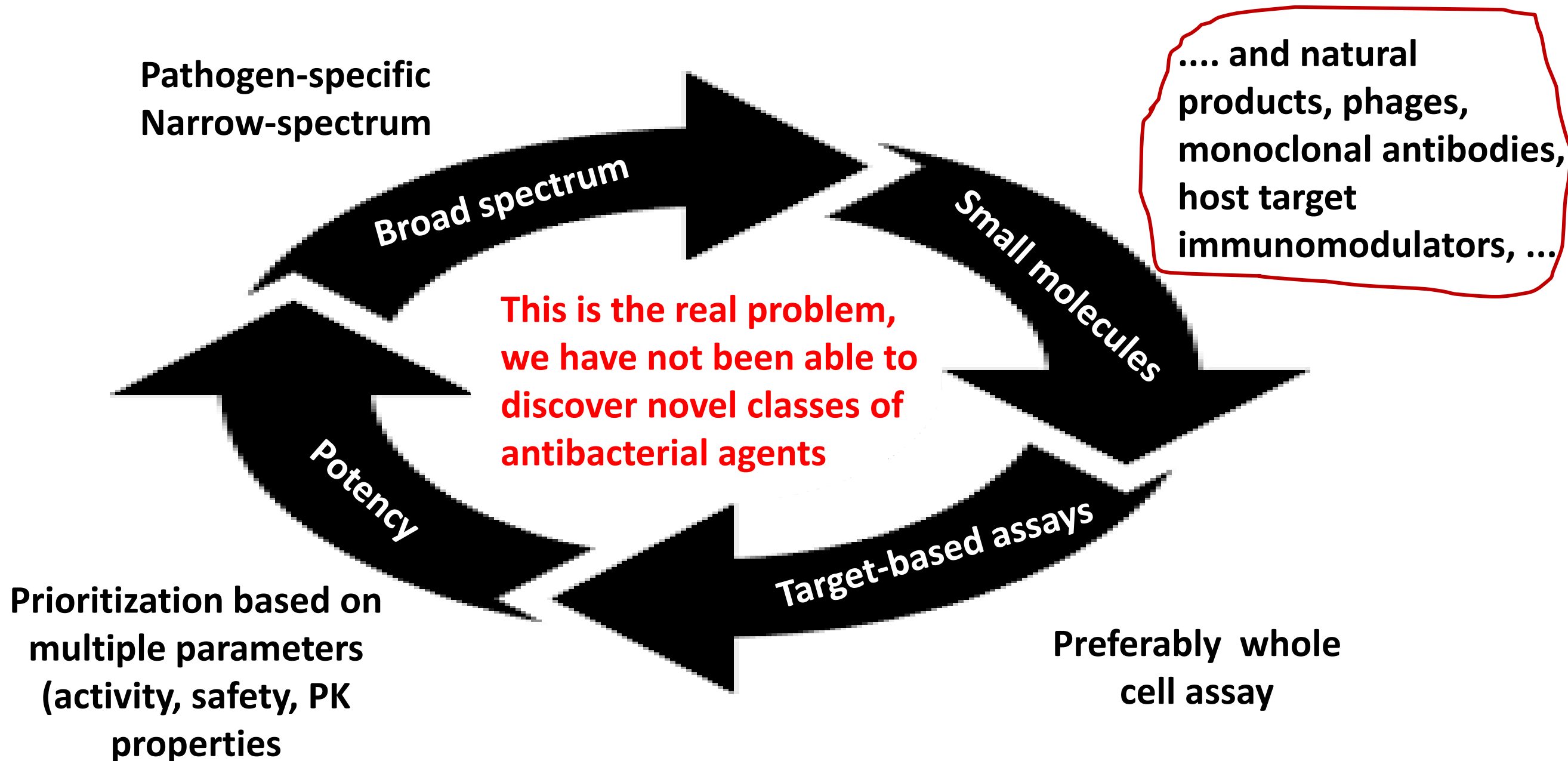


- ***For antimicrobial drugs, the main problem is toxicity, due to the high doses of product used (grams / day, for several days)***
- ***In general, animal models to assess the therapeutic efficacy of antimicrobial agents are quite predictive.***

New paradigm

Disruptive innovation: novel TPPs, novel DD approaches

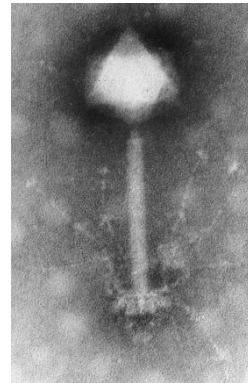
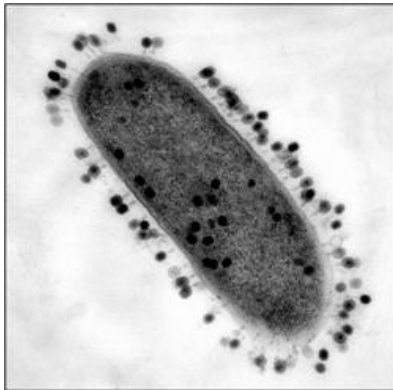
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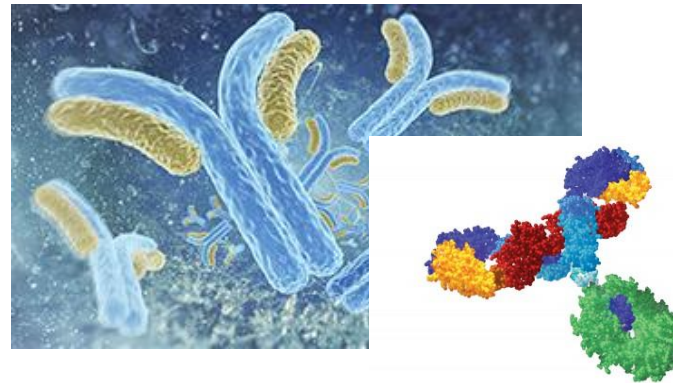
New paradigm

Disruptive innovation: novel TPPs, novel DD approaches

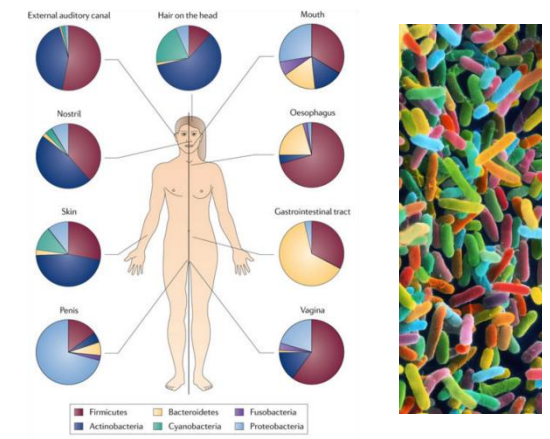
▪ Phages



▪ Monoclonal antibodies

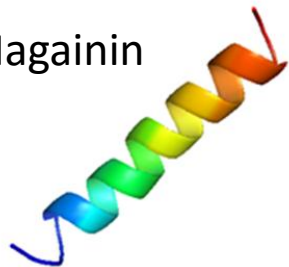


▪ Microbiome modulators



▪ Peptides

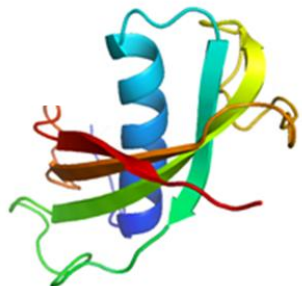
Magainin



Indolicidin



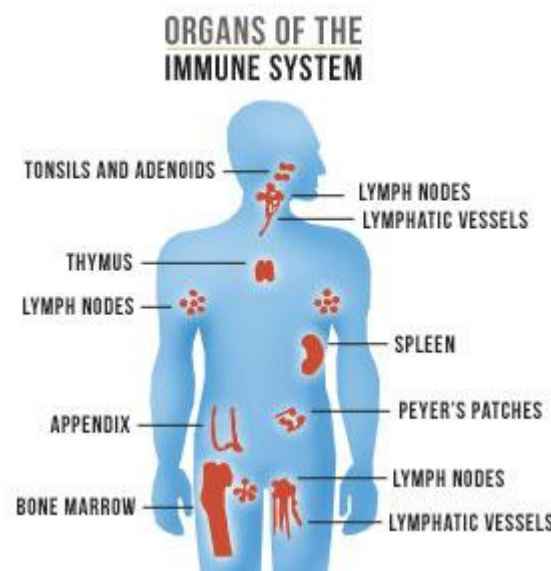
Protegrin-1



Defensin-human



▪ Host target immunomodulators



▪ Vaccines



New paradigm

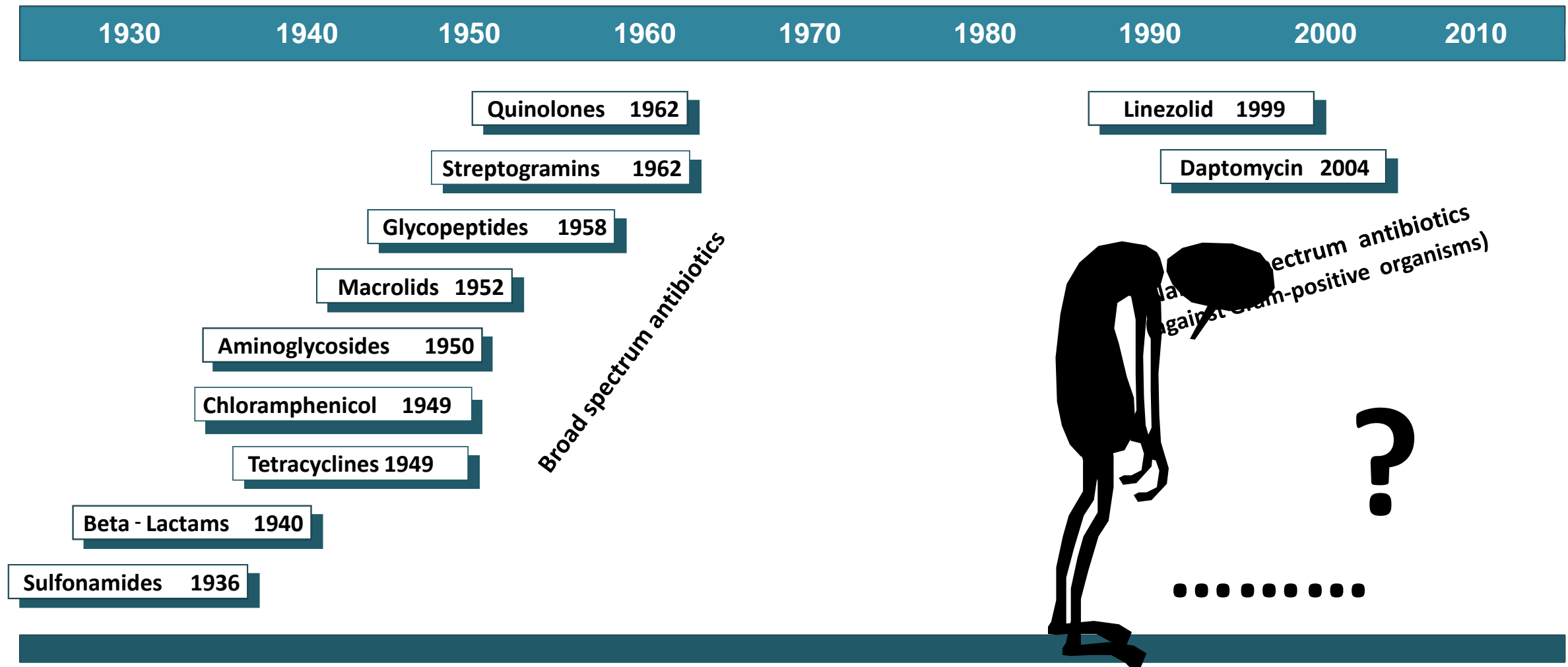
Empirical treatment with Broad-Spectrum antibacterials. Collateral effects



- Elimination of the normal microbiota (flora). Most physiological and immunological parameters are affected by the normal microbiota in the body (1 to 1.5 kg of body weight), being the host resistance to infection one of the most important factors (preventing secondary infections).
- Selection of resistant bacteria. Particular organisms present in the bowel, but also in nature, through antibiotics excreted in urine and feces in active form.
- In addition, broad-spectrum antibacterials are used in animal husbandry, fish farms and plant production.

Introduction. Infectious diseases. Unmet medical need

There is a clear demand for new agents to treat severe infections

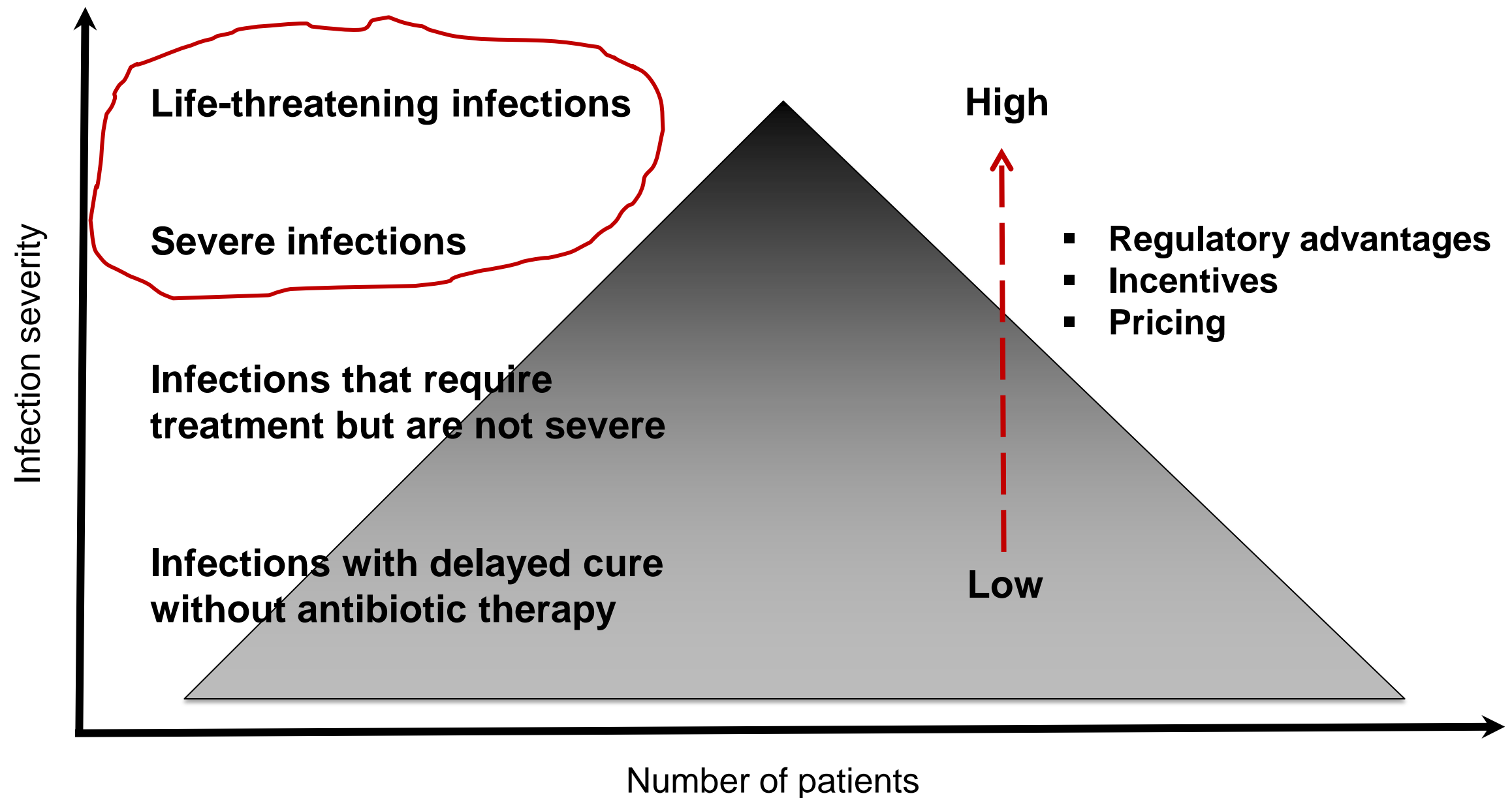


However, most pharmaceutical companies have left the field, and arise the return with caution arguing three main points:

1. Significant **regulatory uncertainty** concerning the approval process for novel antibacterial agents.
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New paradigm

There is a clear demand for new agents to treat severe infections



New paradigm

Let's start by focusing the problem and doing self-criticism

2. Markets may not be large enough / uncompetitive prices, to generate **return on investment**

From **VOLUME** model

(Driven by business)



To **VALUE** model

(Driven by medical need)



Generic
≈ 50 USD/Day



Cubicin (Daptomycin)
Launched 2005
Gram Positive
171 USD/Day



Avycaz (ceftazidime-avibactam)
Launched 2015
Gram Negative
855 USD/Day

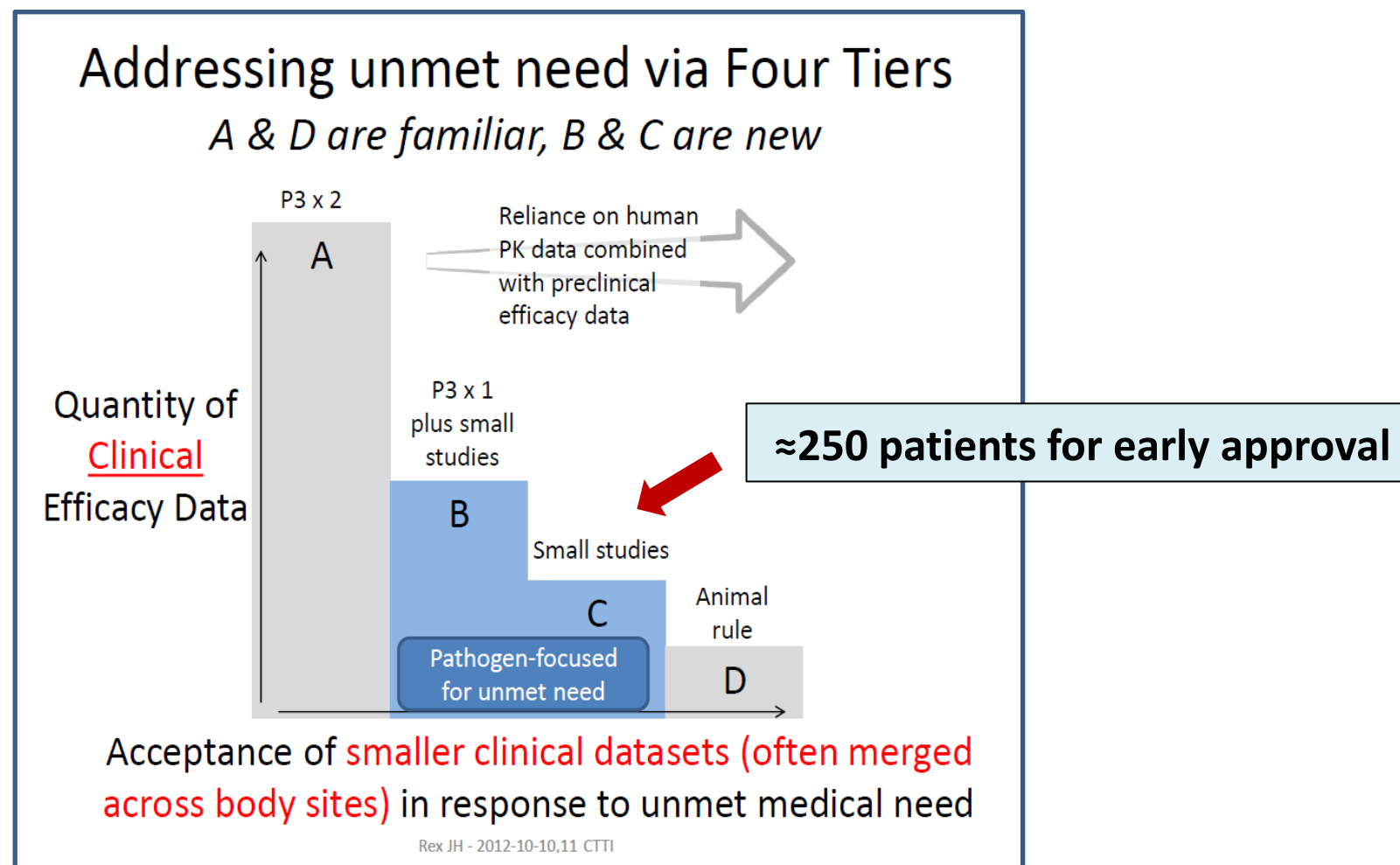
Pricing and return of investment is an important point in constant discussion, but products effective against MDR strains, should get a more competitive price

New paradigm

Let's start by focusing the problem and doing self-criticism

1. Significant **regulatory uncertainty** concerning the approval process for novel anti-bacterial agents.

- Fast Track Status
- Exclusivity. 5 years of exclusivity for a NCE
- Priority Review. Qualifies for priority review, 8 months



New paradigm

Assumptions to take into account. “fight against I like”:

- The industry like to invest in projects of low risk (**easy** to make)
- ... and projects that provide short-term results (**fast**)
- Health insurance and public health institutions, like **cheap** products

The perfect combination: easy, fast, and cheap

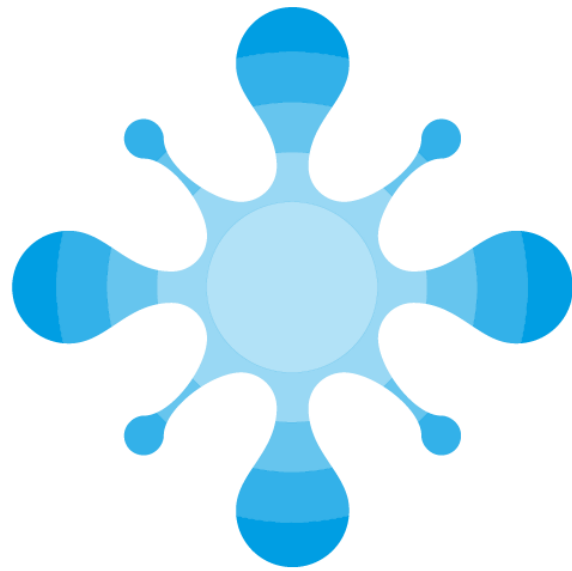


.....the way that goes nowhere

Important and complex problems do not have easy solutions

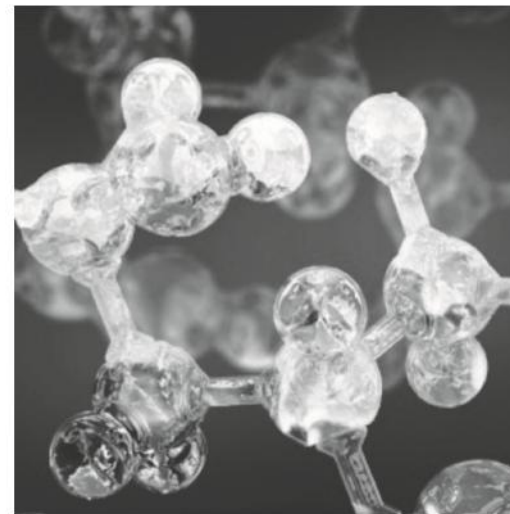
A global health challenge for the 21st century

Solutions to complex problems requires multidisciplinary teamwork and coordination



AD-ES ●●●

*Asociación para el Descubrimiento
de Nuevos Antibióticos en España*



A global health challenge for the 21st century

Solutions to complex problems requires multidisciplinary teamwork and coordination

Los fines de la asociación AD-ES son los siguientes:

- Promover el descubrimiento y desarrollo de nuevos agentes antibacterianos para combatir el fenómeno de la resistencia antimicrobiana, considerado uno de los mayores retos para la salud pública global en las próximas décadas
- Servir de nexo entre personas, grupos y entidades interesadas en el tratamiento y manejo de las enfermedades infecciosas, especialmente en la lucha contra los patógenos multi-resistentes, independientemente del campo científico en el que trabajen, para fomentar la difusión y el intercambio de ideas
- Facilitar la formación de profesionales, impulsar la investigación en este campo y favorecer la comunicación entre la administración, la industria, la comunidad científica y la sociedad
- Representar a España en los foros y alianzas europeas e internacionales que estén alineadas con los fines de la AD-ES

A global health challenge for the 21st century

Solutions to complex problems requires multidisciplinary teamwork and coordination

Para el cumplimiento de fines de AD-ES se realizarán las siguientes actividades:

- Rediseñar y promover la creación de infraestructuras, como base de conocimiento y formación, necesaria para el descubrimiento de nuevos antibióticos a nivel nacional
- Impulsar el interés en la industria, por el descubrimiento y desarrollo de nuevos antibióticos
- Potenciar sinergias y promocionar el diálogo entre industria, científicos, legisladores, y sociedad tanto a nivel nacional como internacional
- Aumentar la proyección a nivel internacional, integrándose y representando a España en las iniciativas europeas que se están creando, o se creen en el futuro, en esta área terapéutica
- Colaborar con la administración para combatir el problema social de los patógenos multi-resistentes

A global health challenge for the 21st century

Solutions to complex problems requires multidisciplinary teamwork and coordination



BEAM Alliance

**Biotechs from Europe
innovating
in Anti-Microbial Resistance**

<http://beam-alliance.eu/>

The Challenge

The emergence of multi-drug resistant bacteria presents a global public health crisis which demands the development of new antibiotics, preventive or alternative strategies, yet the R&D investment from pharmaceutical companies is on the wane due to lack of attractiveness of investment in this therapeutic area.

Innovation is thus largely driven by biotech companies, and European nations need to engage more extensively in supporting this innovation via new policies and R&D stimulating incentives.

The Alliance of 34 Biotechs in 10 European Countries



If you are a European biotech interested in joining the Alliance, please contact: Maria SAUMIER, Da Volterra - maria.sauhier@da-volterra.com

Our Mission

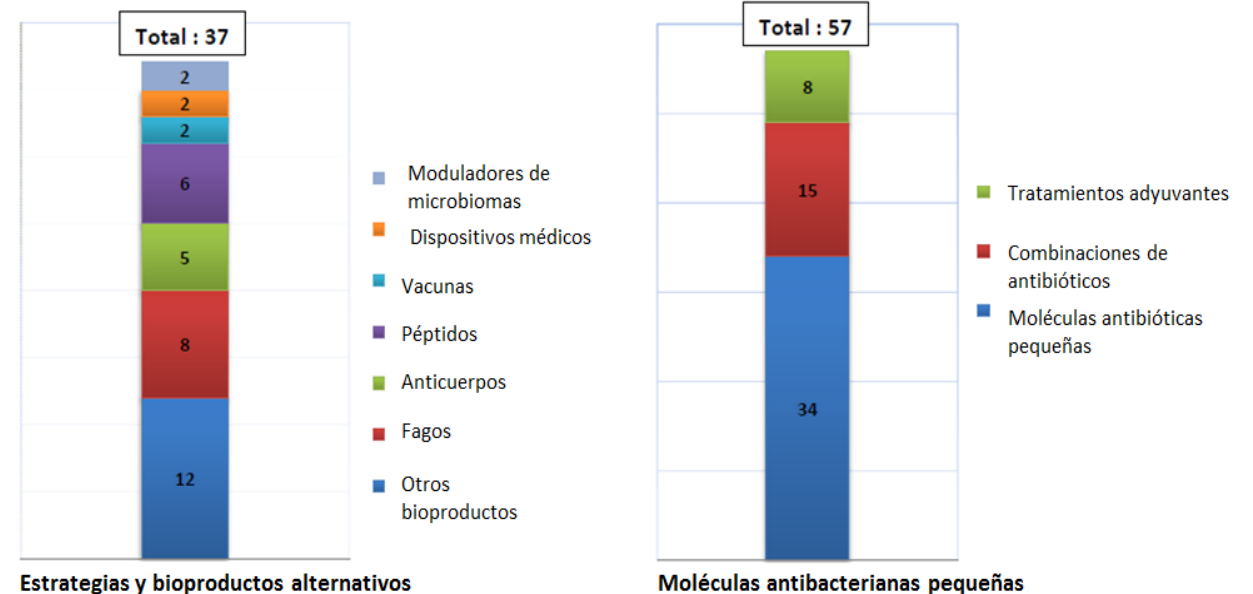
- Representing European biotech companies involved in developing innovative products to tackle antimicrobial resistance
- Collaborating with the existing community of stakeholders dedicated to implementing tangible solutions

- Giving Members a unique voice to propose and support policies and incentives to identified issues in Europe
- Recommending Supportive incentives that warrant action by policymakers to stimulate innovation by biotech companies

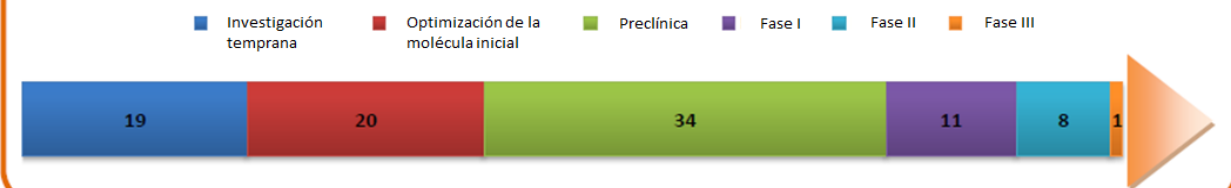
94 productos antibacterianos en desarrollo:

- El 82% son novedosos tratamientos curativos
- Más de 50 tienen un mecanismo de acción innovador
- El 18% son nuevos enfoques preventivos
- Casi 40 corresponden a enfoques innovadores, alternativos a los antibióticos

Tipo de producto



Fases de desarrollo del producto



A global health challenge for the 21st century

Disruptive innovation and private public partnership



BEAM
Alliance

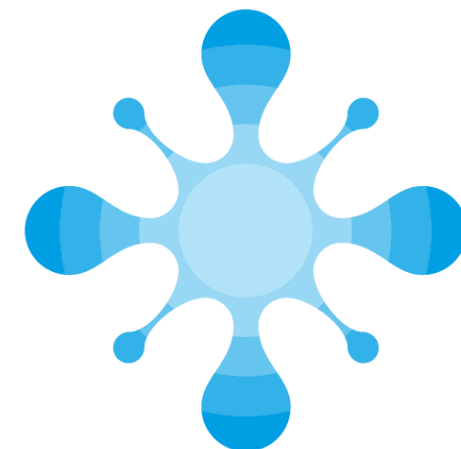
Biotechs from Europe
innovating
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AD-ES ...

*Asociación para el Descubrimiento
de Nuevos Antibióticos en España*

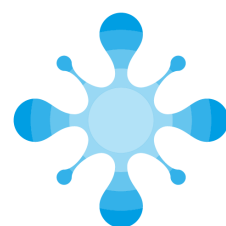
Administration

Industry



Scientific
community

Society



AD-ES ●●●
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de Nuevos Antibióticos en España*



**Biotechs from Europe
innovating
in Anti-Microbial Resistance**

Muchas gracias !!

Nuevas alianzas y estrategias enfocadas al descubrimiento de agentes antimicrobianos

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dgargallo@abactherapeutics.com



**Plan Nacional
Resistencia
Antibióticos**

**Día Europeo
para el Uso Prudente
de los Antibióticos**



Una iniciativa europea para la salud 



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agencia española de
medicamentos y
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