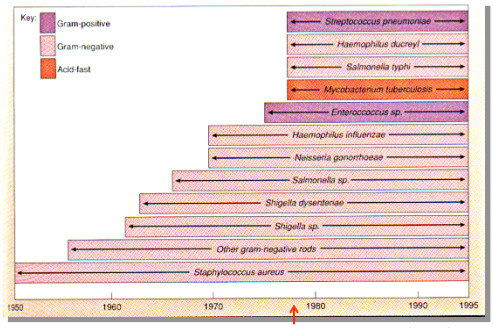
Resistência aos Antibióticos

Programa da Aula

- **Introdução**
- **Mecanismos de Resistência a Antimicrobianos**
- **Origem de Resistência a Antimicrobianos**
- **Método de Medição da Resistência Bacteriana**

Cronologia da Resistência a Antimicrobianos



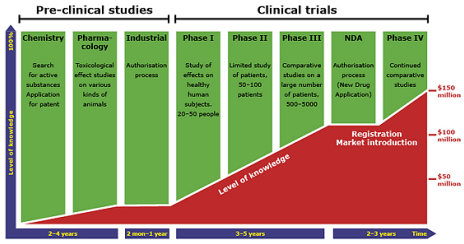
Staphylococcus aureus meticilina-resistente (MRSA)

Uso Indiscriminado de Antibióticos em Animais

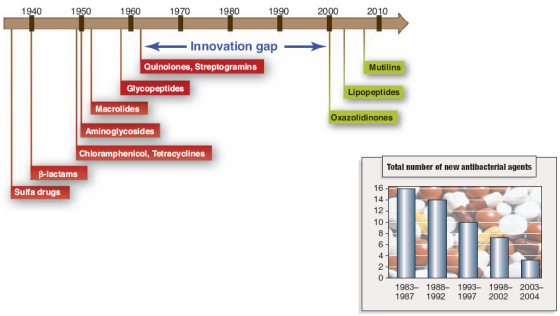
"Estudos apontam relação entre uso de antibióticos em animais e resistência a medicamentos em seres humanos"

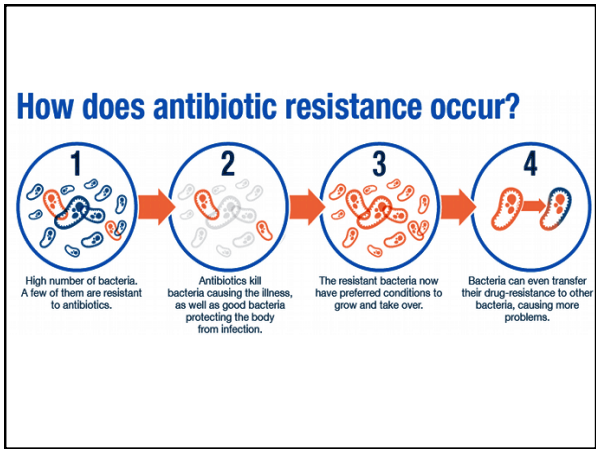
Exemplo: Animais de corte tratados com o glicopeptídeo avoparcina constituem um potencial reservatório de infecção por *Enterococcus* resistente à vancomicina (VRE) em humanos.

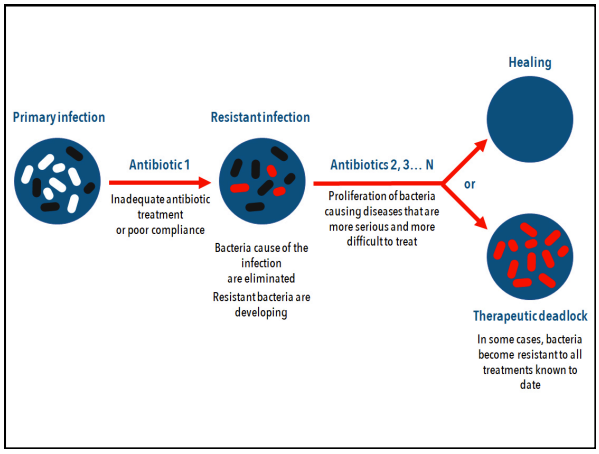
Desenvolvimento de Novas Drogas

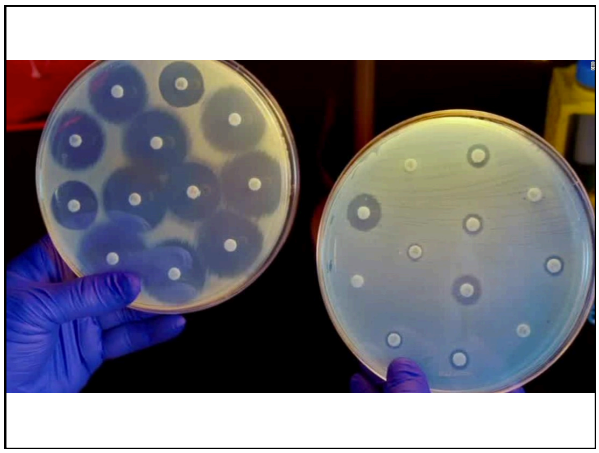


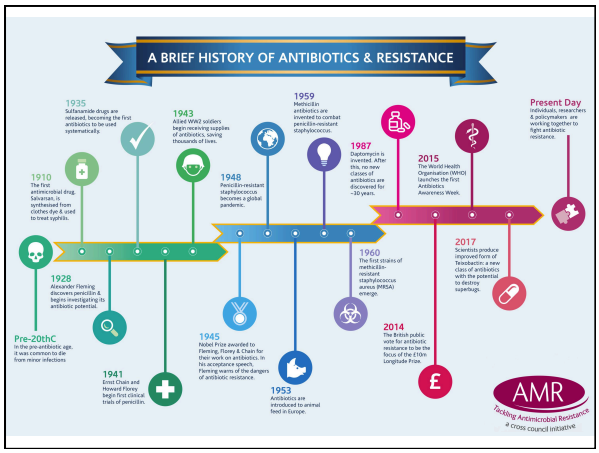
Desenvolvimento de Novas Drogas

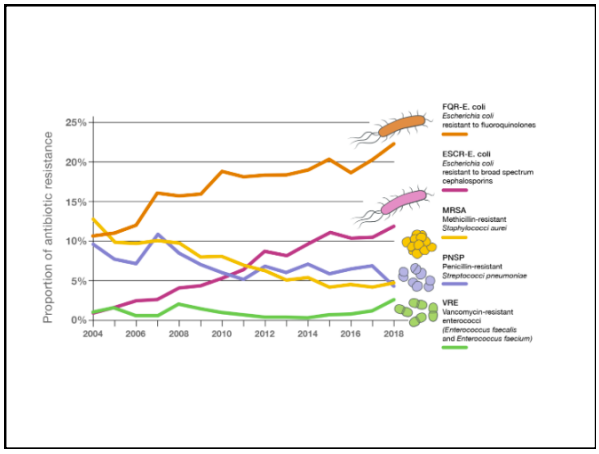



How does antibiotic resistance occur?
1
2
3
4
High number of bacteria. A few of them are resistant to antibiotics.
Antibiotics kill bacteria causing the illness, as well as good bacteria protecting the body from infection.
The resistant bacteria now have preferred conditions to grow and take over.
Bacteria can even transfer their drug-resistance to other bacteria, causing more problems.


Primary infection
Antibiotic 1
Inadequate antibiotic treatment or poor compliance
Resistant infection
Bacteria cause of the infection are eliminated
Resistant bacteria are developing
Antibiotics 2, 3… N
Proliferation of bacteria causing diseases that are more serious and more difficult to treat
Healing
or
Therapeutic deadlock
In some cases, bacteria become resistant to all treatments known to date




A BRIEF HISTORY OF ANTIBIOTICS & RESISTANCE
Pre-20thC
1910
1928
1935
1941
1943
1945
1948
1953
1959
1960
1987
2014
2015
2017
Present Day
AMR


Proportion of antibiotic resistance
25%
20%
15%
10%
5%
0%
2004
2006
2008
2010
2012
2014
2016
2018
FQR-E. coli
Escherichia coli
resistant to fluoroquinolones
ESCR-E. coli
Escherichia coli
resistant to broad spectrum
cephalosporins
MRSA
Methicillin-resistant
Staphylococci aurei
PNSP
Penicillin-resistant
Streptococci pneumoniae
VRE
Vancomycin-resistant
enterococci
(Enterococcus faecalis
and Enterococcus faecium)

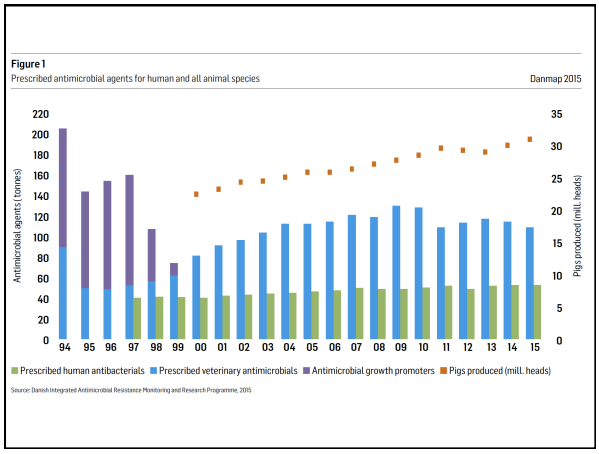
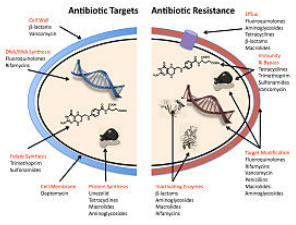
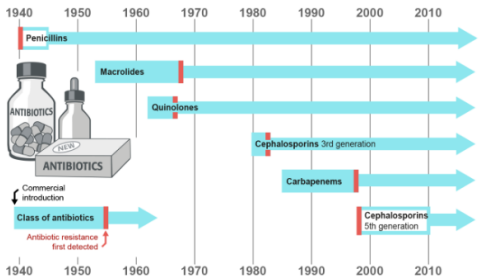
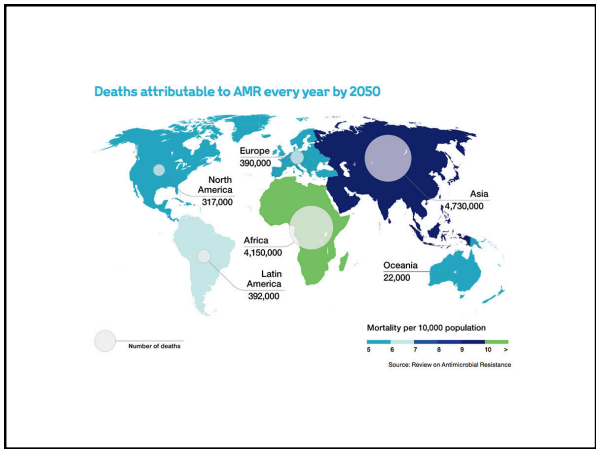
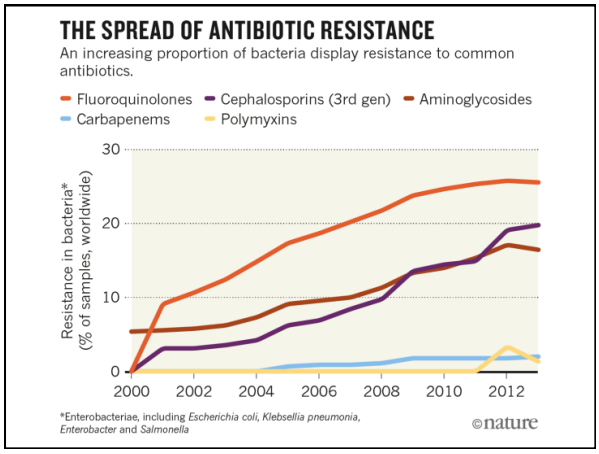


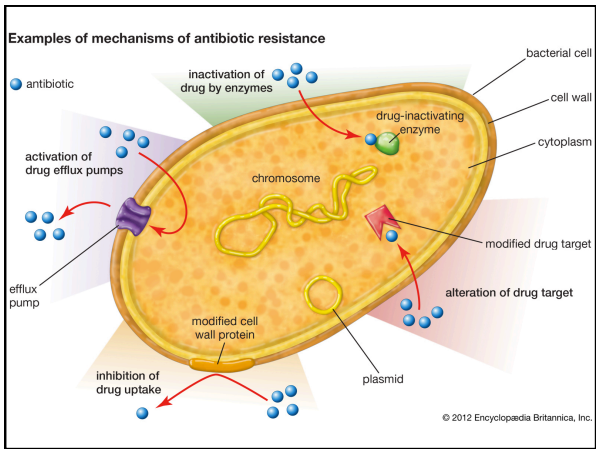
Figure 1
Prescribed antimicrobial agents for human and all animal species
Danmap 2015
Antimicrobial agents (tonnes)
Pigs produced (mill. heads)
220
200
180
160
140
120
100
80
60
40
20
0
35
30
25
20
15
10
5
0
94 95 96 97 98 99 00 01 02 03 04 05 06 07 08 09 10 11 12 13 14 15
Prescribed human antibacterials
Prescribed veterinary antimicrobials
Antimicrobial growth promoters
Pigs produced (mill. heads)
Source: Danish Integrated Antimicrobial Resistance Monitoring and Research Programme, 2015


Antibiotic Targets
Antibiotic Resistance


1940
1950
1960
1970
1980
1990
2000
2010
Penicillins
Macrolides
Quinolones
Cephalosporins 3rd generation
Carbapenems
Cephalosporins 5th generation
ANTIBIOTICS
NEW!
ANTIBIOTICS
Commercial introduction
Class of antibiotics
Antibiotic resistance first detected


Deaths attributable to AMR every year by 2050
Europe
390,000
North America
317,000
Asia
4,730,000
Africa
4,150,000
Latin America
392,000
Oceania
22,000
Number of deaths
Mortality per 10,000 population
5 6 7 8 9 10 >
Source: Review on Antimicrobial Resistance


THE SPREAD OF ANTIBIOTIC RESISTANCE
An increasing proportion of bacteria display resistance to common antibiotics.
Fluoroquinolones
Cephalosporins (3rd gen)
Aminoglycosides
Carbapenems
Polymyxins
Resistance in bacteria* (% of samples, worldwide)
30
20
10
0
2000
2002
2004
2006
2008
2010
2012
*Enterobacteriae, including Escherichia coli, Klebsellia pneumonia, Enterobacter and Salmonella
©nature


Examples of mechanisms of antibiotic resistance
antibiotic
inactivation of drug by enzymes
bacterial cell
cell wall
drug-inactivating enzyme
cytoplasm
activation of drug efflux pumps
chromosome
modified drug target
efflux pump
alteration of drug target
modified cell wall protein
plasmid
inhibition of drug uptake
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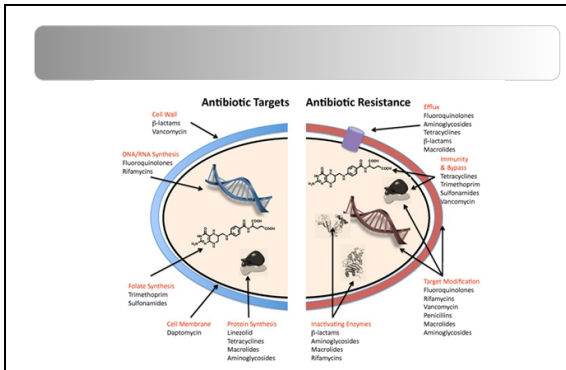
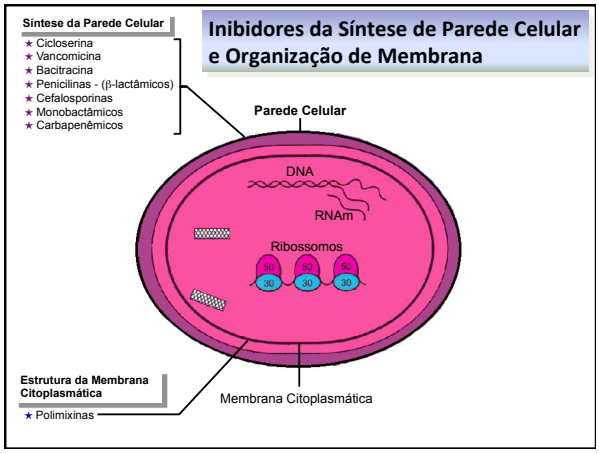
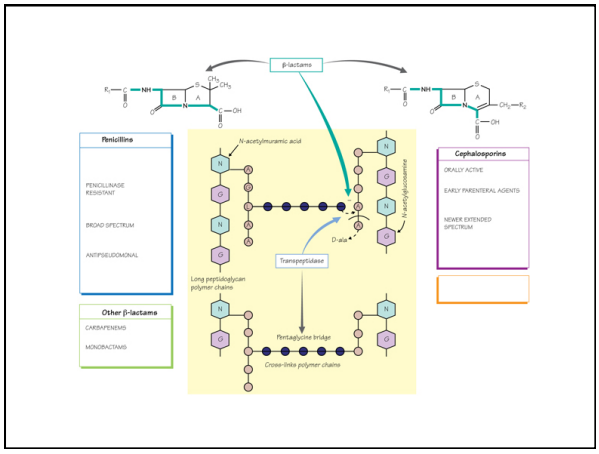
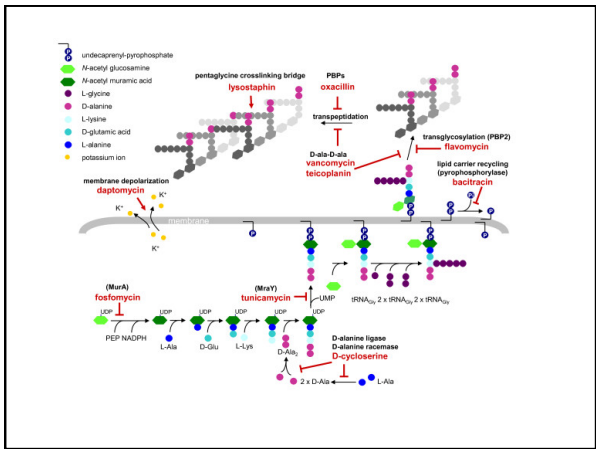
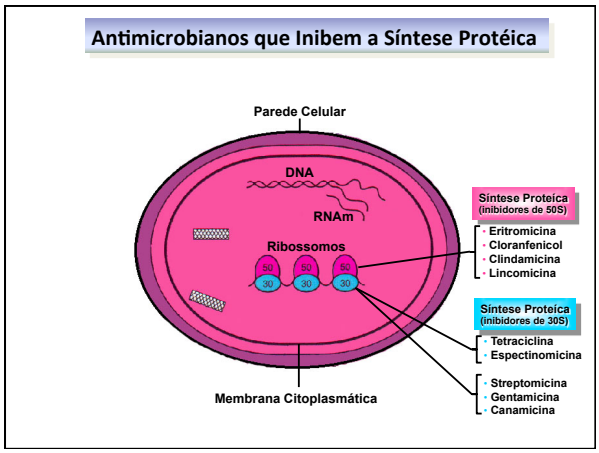
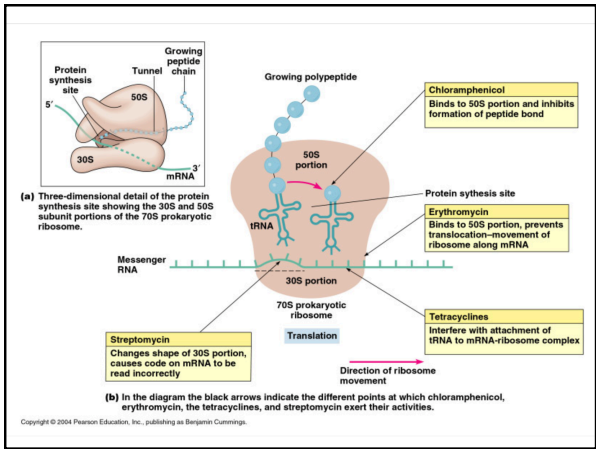

Antibiotic Targets
Antibiotic Resistance

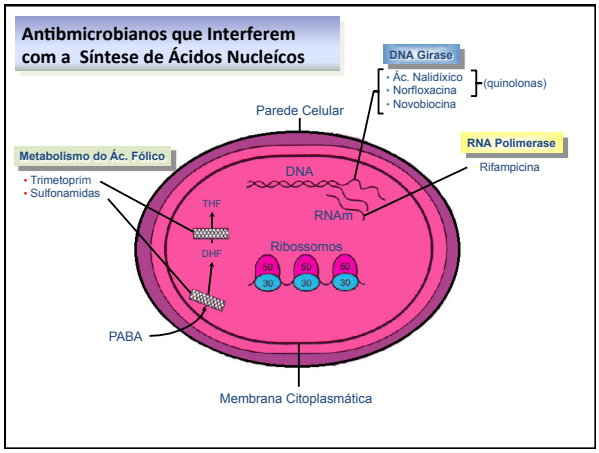

Síntese da Parede Celular
★ Cicloserina
★ Vancomicina
★ Bacitracina
★ Penicilinas - (β-lactâmicos)
★ Cefalosporinas
★ Monobactâmicos
★ Carbapenêmicos
Inibidores da Síntese de Parede Celular e Organização de Membrana
Parede Celular
DNA
RNAm
Ribossomos
50
30
Estrutura da Membrana Citoplasmática
★ Polimixinas
Membrana Citoplasmática


β-lactams
Penicillins
Cephalosporins
Other β-lactams
N-acetylmuramic acid
N-acetylglucosamine
D-ala
Transpeptidase
Long peptidoglycan polymer chains
Pentaglycine bridge
Cross-links polymer chains

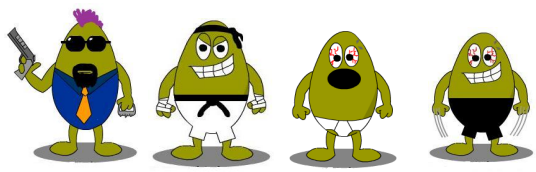

undecaprenyl-pyrophosphate
N-acetyl glucosamine
N-acetyl muramic acid
L-glycine
D-alanine
L-lysine
D-glutamic acid
L-alanine
potassium ion
pentaglycine crosslinking bridge
lysostaphin
PBPs
oxacillin
transpeptidation
transglycosylation (PBP2)
flavomycin
D-ala-D-ala
vancomycin
teicoplanin
lipid carrier recycling (pyrophosphorylase)
bacitracin
membrane depolarization
daptomycin
membrane
(MurA)
fosfomycin
(MraY)
tunicamycin
UMP
PEP NADPH
L-Ala
D-Glu
L-Lys
D-Ala
D-alanine ligase
D-alanine racemase
D-cycloserine
2 x D-Ala
L-Ala


Antimicrobianos que Inibem a Síntese Protéica
Parede Celular
DNA
RNAm
Ribossomos
50
30
Membrana Citoplasmática
Síntese Proteica (inibidores de 50S)
· Eritromicina
· Cloranfenicol
· Clindamicina
· Lincomicina
Síntese Proteica (inibidores de 30S)
· Tetraciclina
· Espectinomicina
· Streptomicina
· Gentamicina
· Canamicina





Mecanismos de Resistência a Antimicrobianos



Mecanismos de Resistência a Antimicrobianos

- **Alteração do alvo**
- **Enzimas inativadoras ou modificadoras**
- **Bombas de efluxo**
- **Impermeabilidade do envoltório celular**

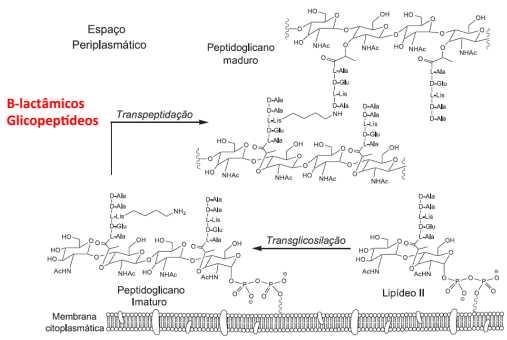
1 – Alteração do alvo

- Por alteração da sequência de aminoácidos da proteína alvo;
- Por modificação química do alvo mediada por enzimas.

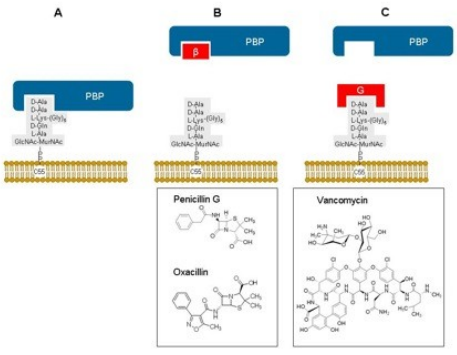
★ Exemplos:

- ✦ β-lactâmicos
- ✦ Glicopeptídeos
- ✦ Sulfonamidas
- ✦ Rifampicina
- ✦ Quinolonas
- ✦ Aminoglicosídeos

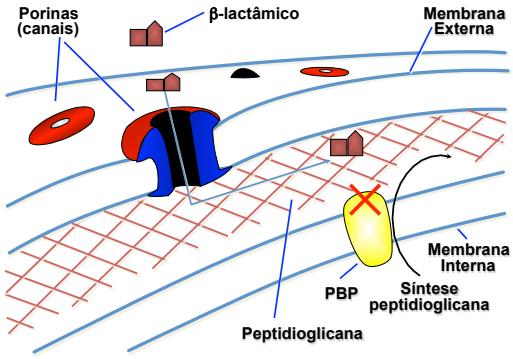
Formação do Peptideoglicano e Ação de Antimicrobianos que Agem na Parede Celular



Formação do Peptideoglicano e Ação de Antibióticos que Agem na Parede Celular

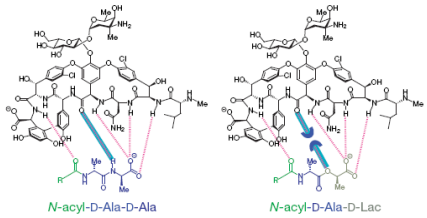


Resistência Mediada por Alteração de Alvo



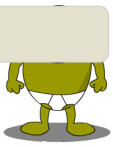
Resistência Mediada por Alteração de Alvo

Glicopeptídeo: Vancomicina



- *Enterococcus* resistente à vancomicina (VRE)

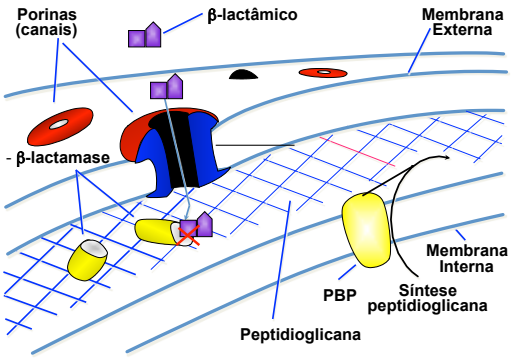
2 – Enzimas inativadoras



★ Exemplos:

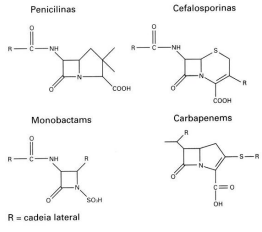
- ✦ β-lactâmicos
- ✦ Aminoglicosídeos
- ✦ Clorafenicol

Resistência Mediada por β-lactamases



Resistência Mediada por Enzimas Inativadoras (hidrólise)

β-lactâmicos



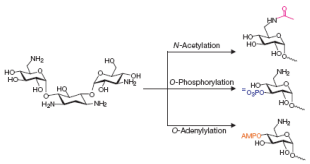
β-lactamases

- Classe A ou grupo II: hidrolisam penicilinas e cefalosporinas
- Classe B ou grupo III: hidrolisam carbapenêmicos
- Classe C ou grupo I: hidrolisam cefalosporinas
- Classe D: hidrolisam penicilinas e cloxacilina
- Grupo IV: hidrolisam penicilina

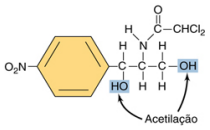
IMPORTANTE: β-lactamases de amplo espectro ou espectro estendido (ESBL – Extended Spectrum β-lactamases)

Resistência Mediada por Enzimas Inativadoras

Aminoglicosídeos



Clorafenicol



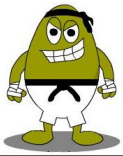
3 – alteração na permeabilidade da membrana

★ Exemplos:

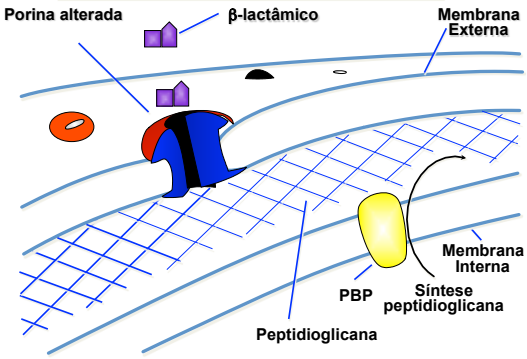
β-lactâmicos

Aminoglicosídeos

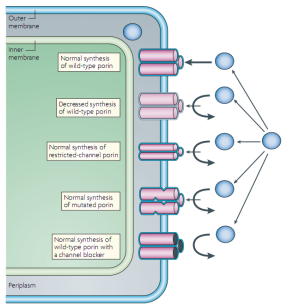
Quinolonas



Resistência mediada por alteração de permeabilidade



Resistência mediada por alteração de permeabilidade



Diminuição da expressão de OmpF leva a resistência a:

quinolonas

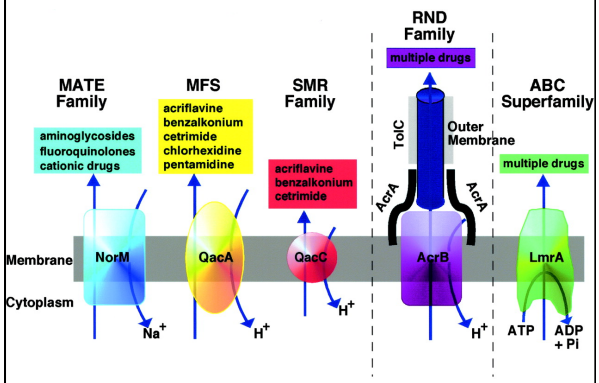
tetraciclinas

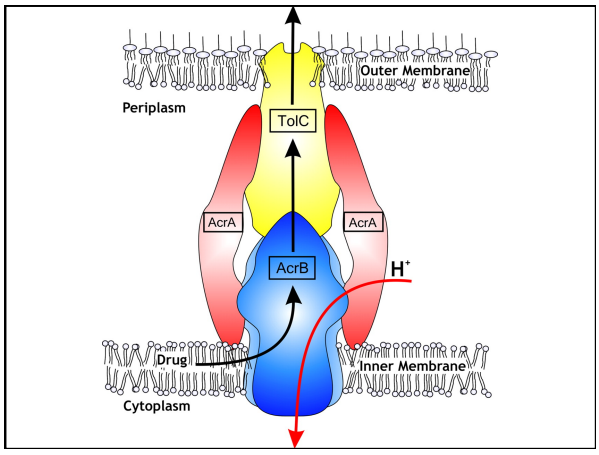
clorafenicol

β-lactâmicos

4 . Efluxo

★ Exemplos:
- ✦ Tetraciclina
- ✦ β-lactâmicos
- ✦ Cloranfenicol
- ✦ Quinolonas





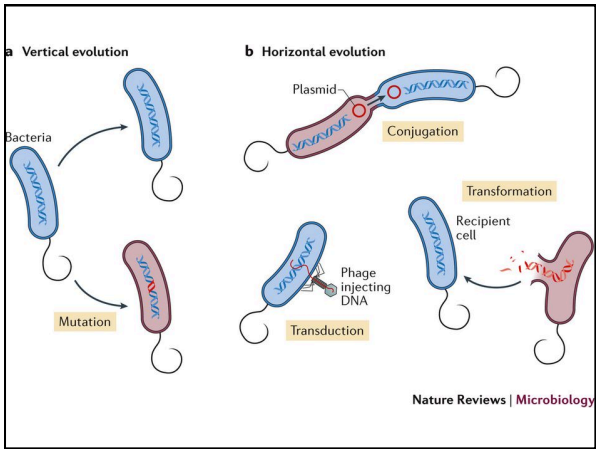
Origem da Resistência a Antimicrobianos

Aspectos relacionados à resistência aos antimicrobianos em bactérias

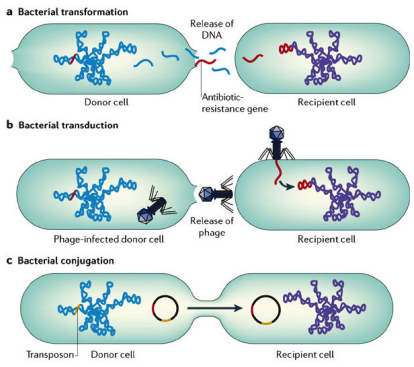
★ **Origem da Resistência**
- ✦ resistência cromossomal
- ✦ resistência extracromossomal

★ **Mecanismos de transmissão**
- ✦ transmissão vertical
- ✦ transmissão horizontal

➢ Resistência Intrínseca e Extrínseca

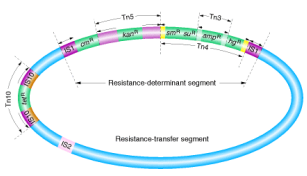


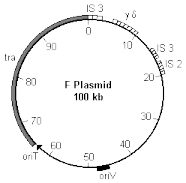
Transmissão Horizontal



Plamídeos de Resistência

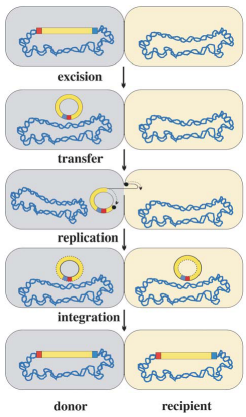
- Carregam genes de resistência
- Podem conter transposons e/ou integrons
- Podem ser transferidos (geralmente através de conjugação), mas também por transformação ou transdução

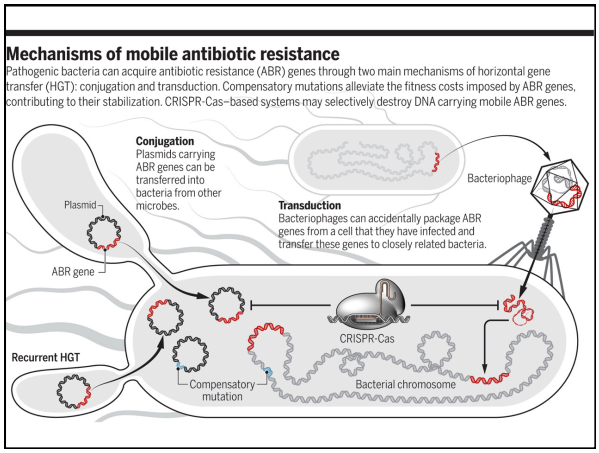


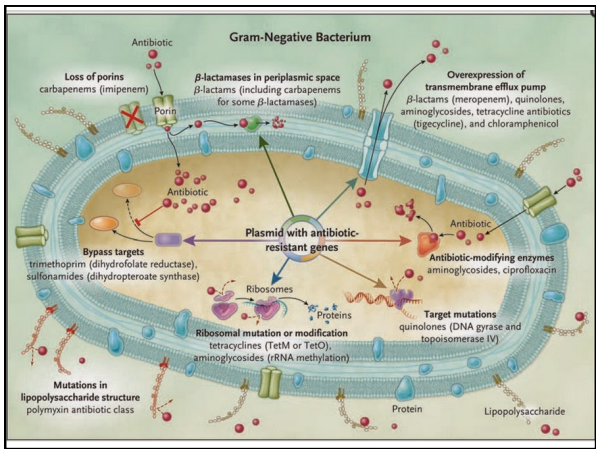


Transposons Conjugativos

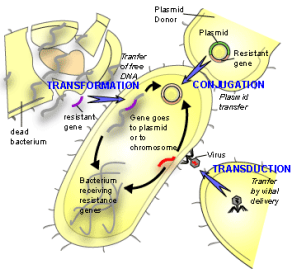
Mecanismo de transferência





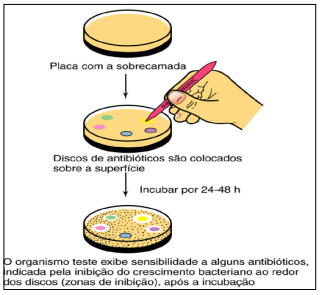


Transmissão horizontal da resistência bacteriana



Método de Medição da Resistência Bacteriana

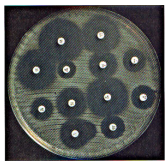
Métodos de Medição de Resistência



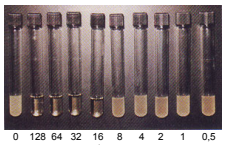
Métodos de Medição de Resistência

- **Método qualitativo**: Método de difusão com discos de Kirby-Bauer
- **Método quantitativo**: Macrodiluição.

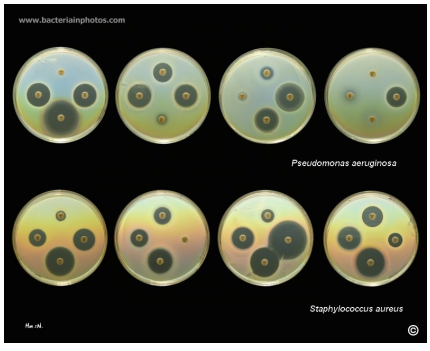
Antibiograma



Macrodiluição



Teste de difusão em disco de ágar



Plano de iniciativas para vencer a resistência

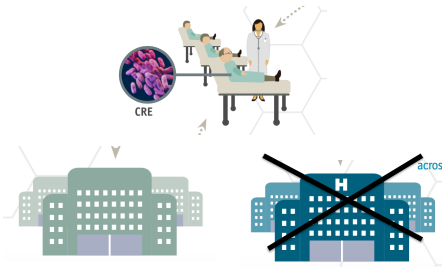
Problema:

2.049.442 doenças

2.023.000 mortes

Plano de iniciativas para vencer a resistência

- **Estabelecimento de Programas de Prevenção, grupos dedicados à educação em saúde, prevenir infecções**



Plano de iniciativas para vencer a resistência

- Detectar e responder rapidamente para reduzir a MDR em gonorréia;
- Identificar intervenções críticas contra *M. tuberculosis* multi-resistentes, expandir avaliação de imigrantes e refugiados;

Plano de iniciativas para vencer a resistência

Avaliar impacto dos antibióticos no microbioma e avaliar como usar os microrganismos para controle