Antibiotic

Resistance

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Overview

- **ANTIBIOTICS**
- Role of **VETERINARY** medicine
- **ANTIBIOTIC RESISTANCE**

  definition, origin, evolution, causes and consequences
- **MECHANISMS** of resistance

  strategies that bacteria use to resist antibiotics
- **TRANSFER** of resistant bacteria and genes

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What is antibiotic?

Anti = “against” and bios = “life”


antibiosis – life is used to destroy another life


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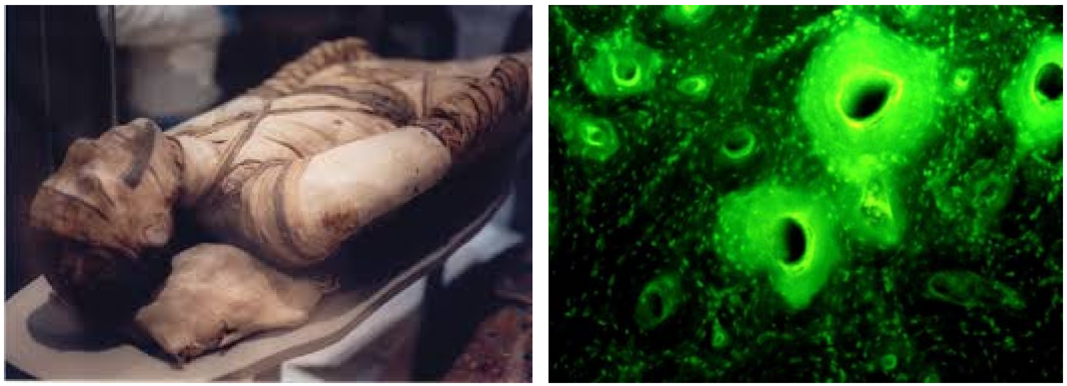
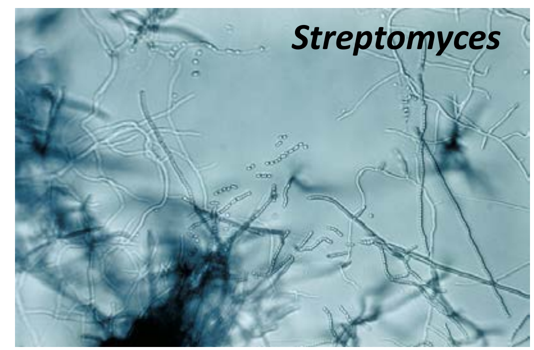
History of antibiotics

"Natural, synthetic/semisynthetic compound that can inhibit or kill sensitive microbes"



Antibiotics and egyptian mummies
(1980, tetracycline, Nubia 550 years B.C.)

"beer" with Streptomycetes and tetracycline



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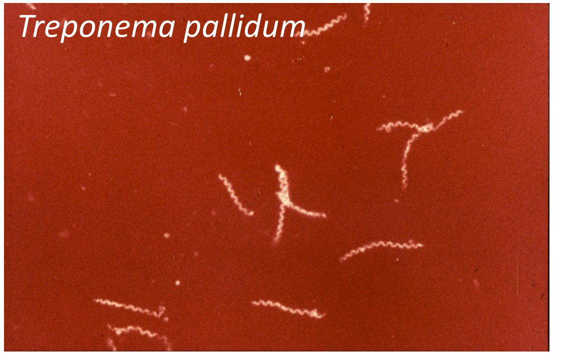
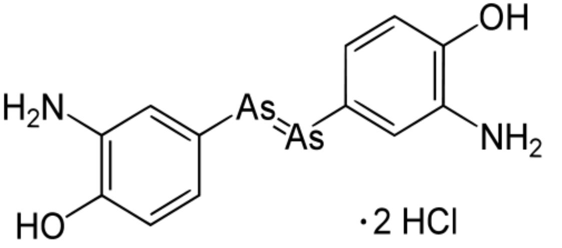
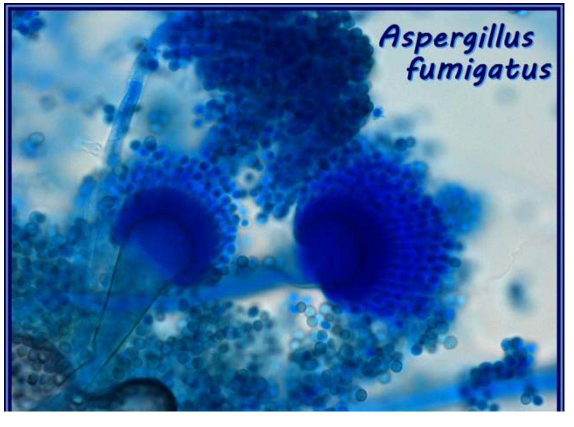
History of antibiotics

Bacillus pyocyaneus
(*Pseudomonas aeruginosa*)
Charin a Gugnard (1889)
„pyocyanase“





Ehrlich (1909)
Salvarsan



- Vaudremer (1913)

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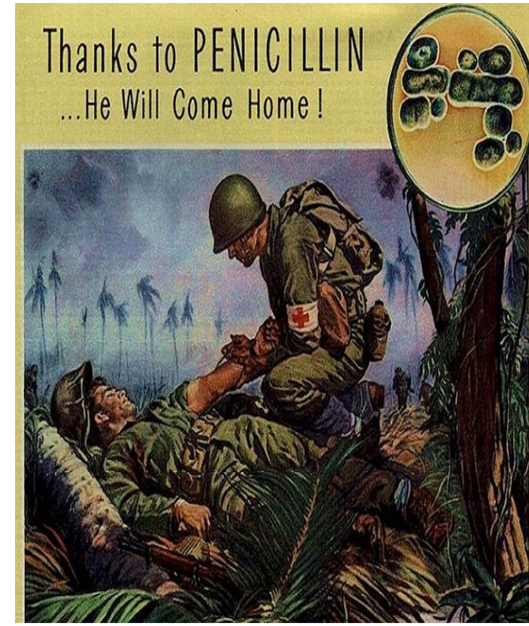
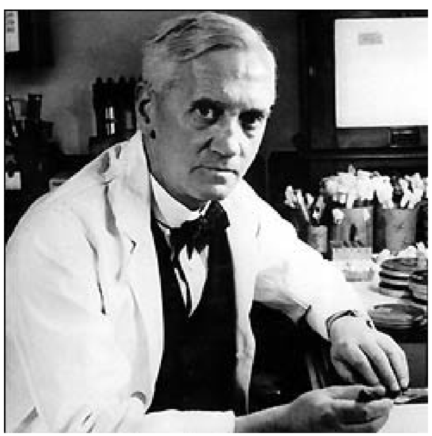
History of antibiotics

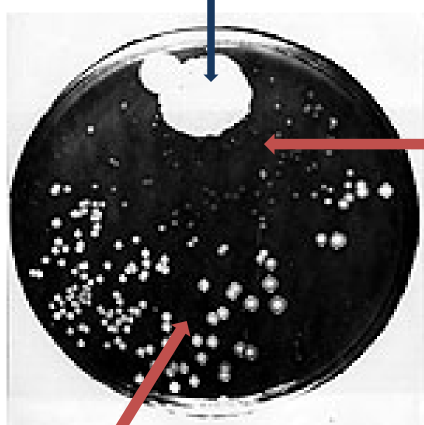
- Penicillin in 1929 - Alexander Fleming
- 2nd World War
- Golden era of antibiotics
- 150 types used today





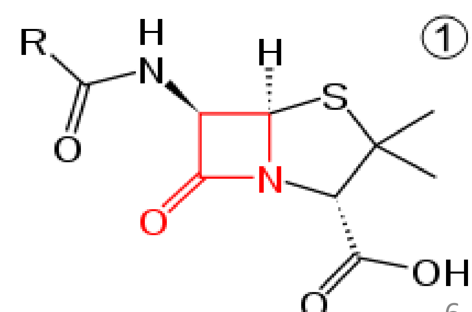
Alexander Fleming
(1881-1955)

Penicillium notatum



Inhibited colonies of *Staphylococcus aureus*

Staphylococcus aureus



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Antibiotics and resistance – Timeline

1935
sulfonamides

1941
β-lactams

1944
aminoglycosides

1947
nitrofurantoin

1949
chloramphenicol

1950
tetracyclines

1956
glycopeptides

1962
quinolones

1968
trimethoprim

1980
carbapenems

2003
lipopeptides

1930 | 1940 | 1950 | 1960 | 1970 | 1980 | 1990 | 2000 | 2010

1940
Penicilinase
1942
Resistance
to sulphonamides
1942
Resistance
to streptomycin

1953
Resistance
to macrolides

1961
MRSA
1966
Resistance
to quinolones
1968
Resistance
to tetracyclines
1969
Resistance
to aminoglycosides

1981
AmpC β-laktamases
1983
ESBL
1986
VRE

1990
Resistance
to fluoroquinolones
1997
VISA

1996
Resistance
to carbapenems

2002
Resistance
to linezolide and
daptomycin
2002
VRSA

http://www.pharmazie.uni-duesseldorf.de

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Antibiotic resistance

Resistance to antibiotics is the ability of bacteria and other microorganisms to resist the effects of an antibiotic to which they were once sensitive

- Worldwide problem
- Misuse and overuse of antibiotics
- Threatens effective prevention and treatment of infectious diseases
- Increased mortality and morbidity
- Persistence of infections and increased risk of transfer to other individuals
- Economic costs
- Threat for modern society

EUROPE

25 000 death/year from MDR hospital infections

€1.5 billion / year - costs of extra health-care costs and productivity losses

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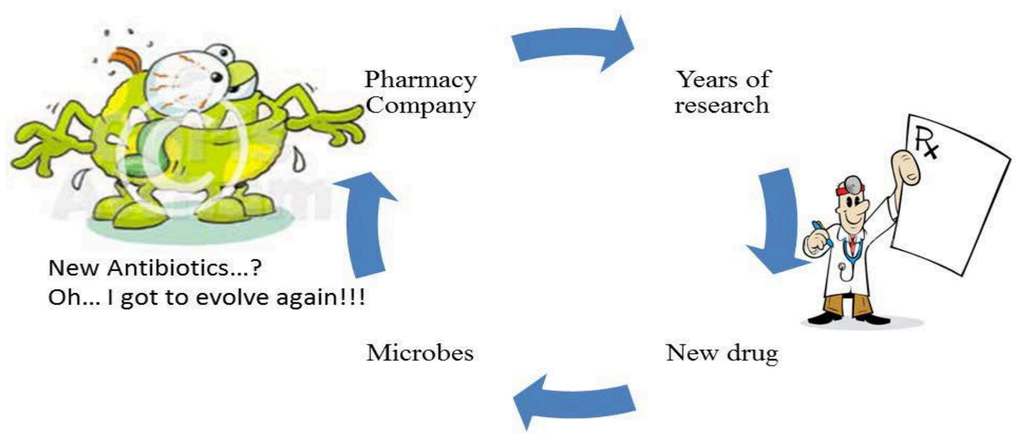
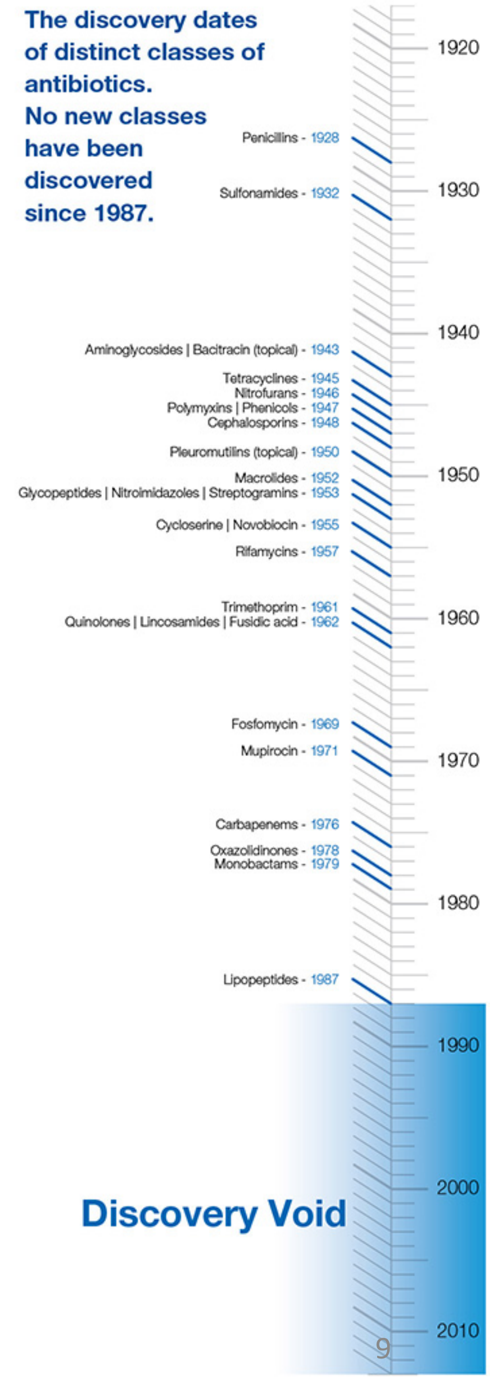
Antibiotic resistance

- Increasing, multiresistance, novel mechanisms
- Absence of effective antibiotics and limited development of novel drugs

  call from the Infectious Diseases Society of America (IDSA) to introduce 10 new systemic antibacterial drugs by 2020

- Predictions of a medical catastrophe and return to pre-antibiotic era





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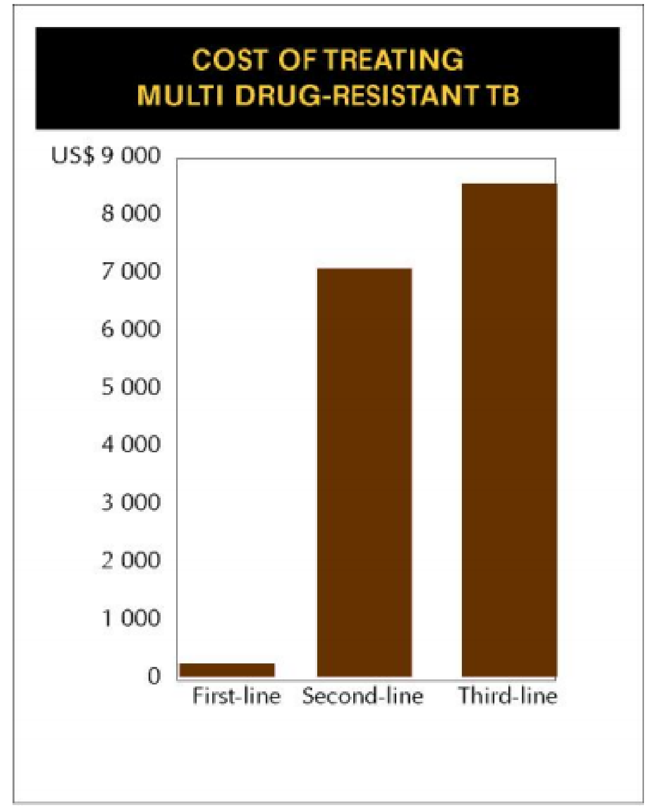
Antibiotic resistance - economic burden

Multiresistant *Mycobacterium tuberculosis*

penicilin $0.24
linezolid $86.90
360 x as much



Source: Farmer et al. The Global Impact of Drug Resistant Tuberculosis, Harvard Medical School and Open Society Institute: pp. 168, 1999

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World Health Organization

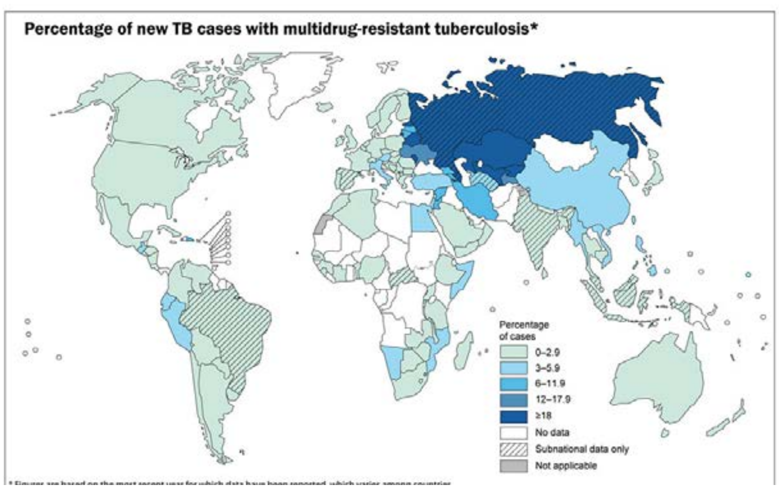
"Hot issues":

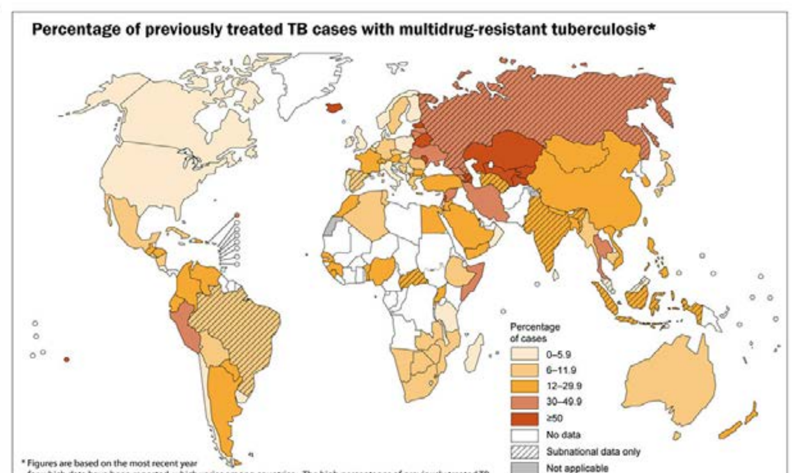
Bacteria → *Klebsiella pneumoniae*, *Escherichia coli*, *Staphylococcus aureus*, *Neisseria gonorrhoeae*, *Clostridium difficile*, *Mycobacterium tuberculosis*

HIV

Malaria

Influenza





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Antibiotics in veterinary medicine

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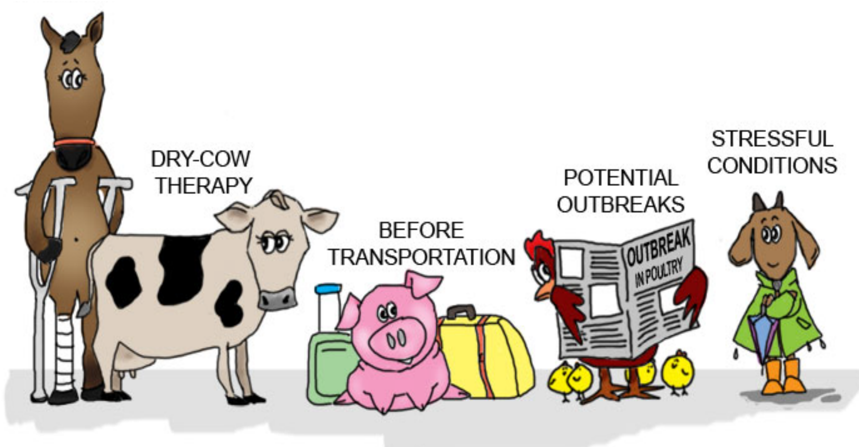
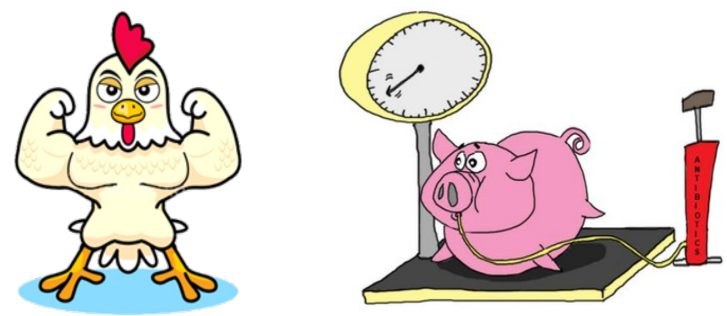
Antibiotics in veterinary medicine

All veterinary antibiotics have they analogues in human medicine – cross-resistance!

Therapeutic – prophylactic - metaphylactic



Growth promoters



1st January 2006 – no antibiotics as growth promoters in EU

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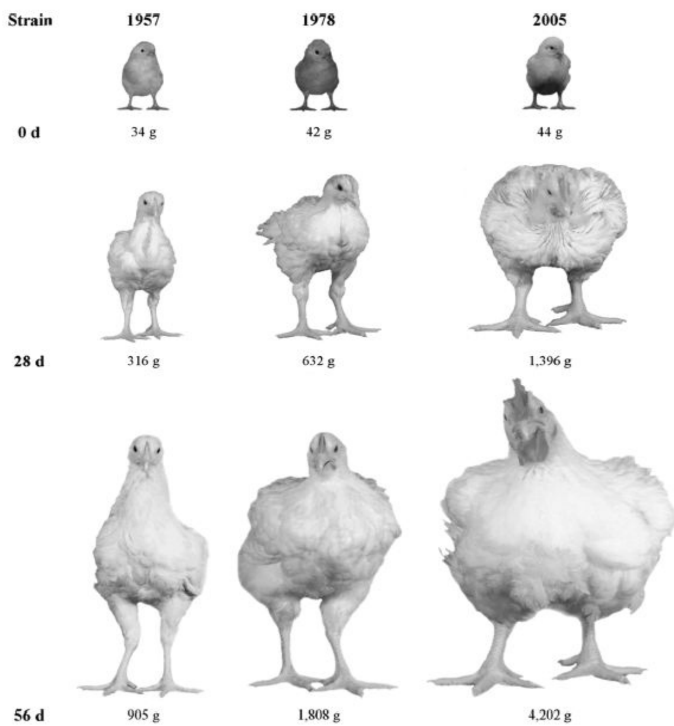
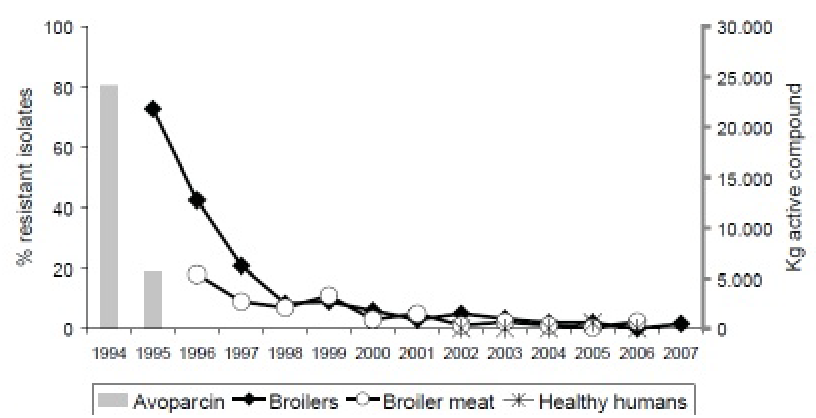
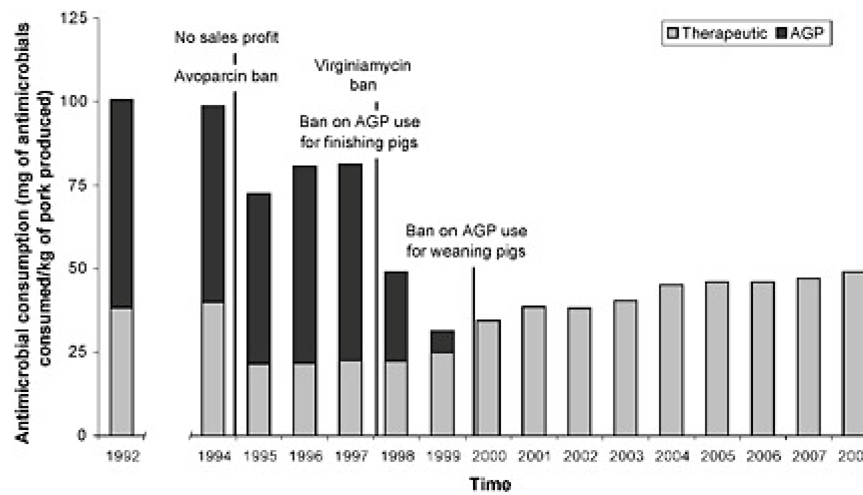




Glycopeptide resistance of *Enterococcus faecium* in Denmark

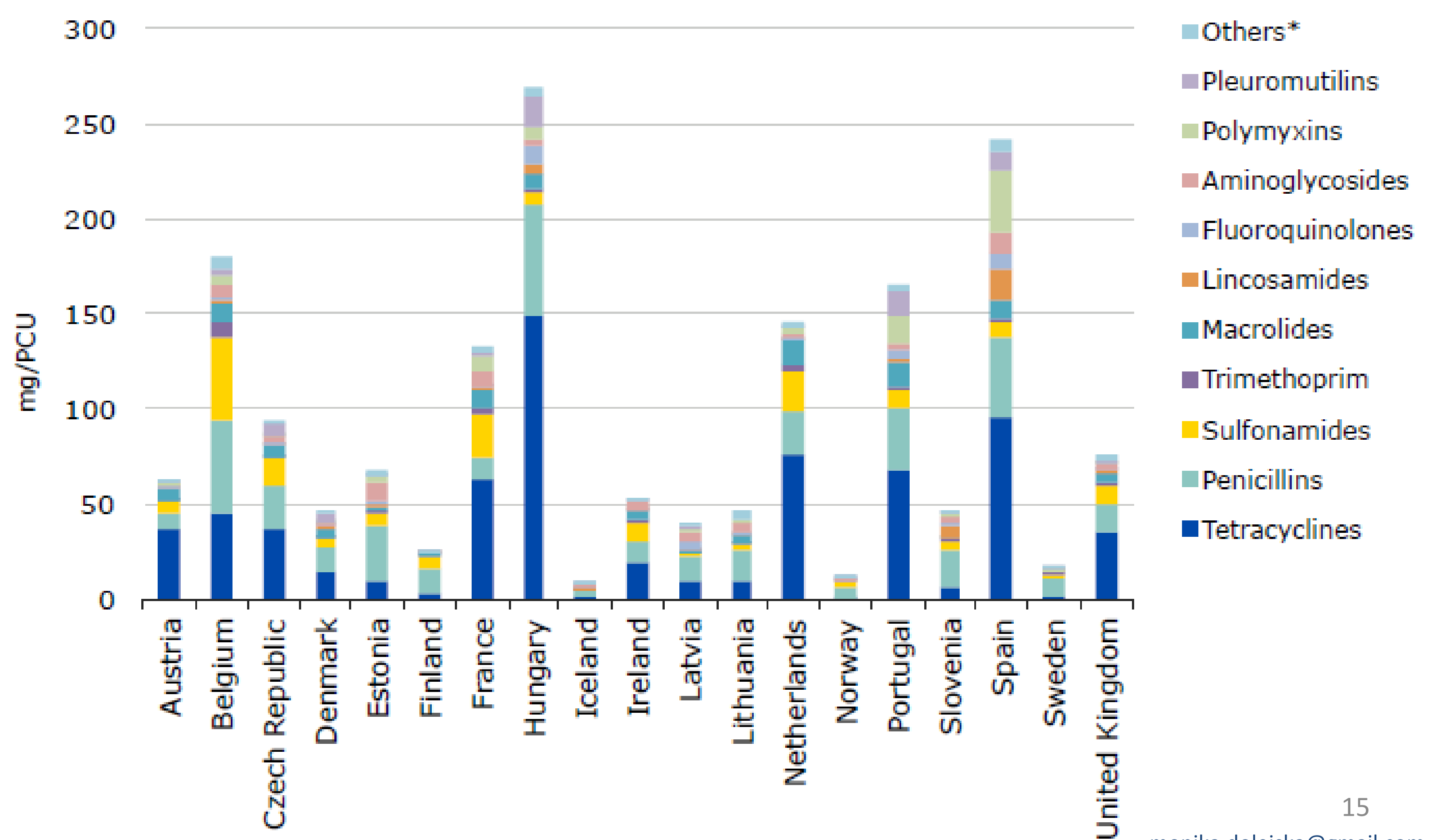
Hammerum A. Emerging Infectious Diseases 2007, 13.



Ban of antibiotic growth promoters and the impact on therapeutic use of antibiotics *Hammerum A. Emerging Infectious Diseases 2007,13.*

Antibiotics in veterinary medicine

Figure 7. Sales for food-producing species, including horses, in mg/PCU, of the various veterinary antimicrobial classes, by country[1], for 2010



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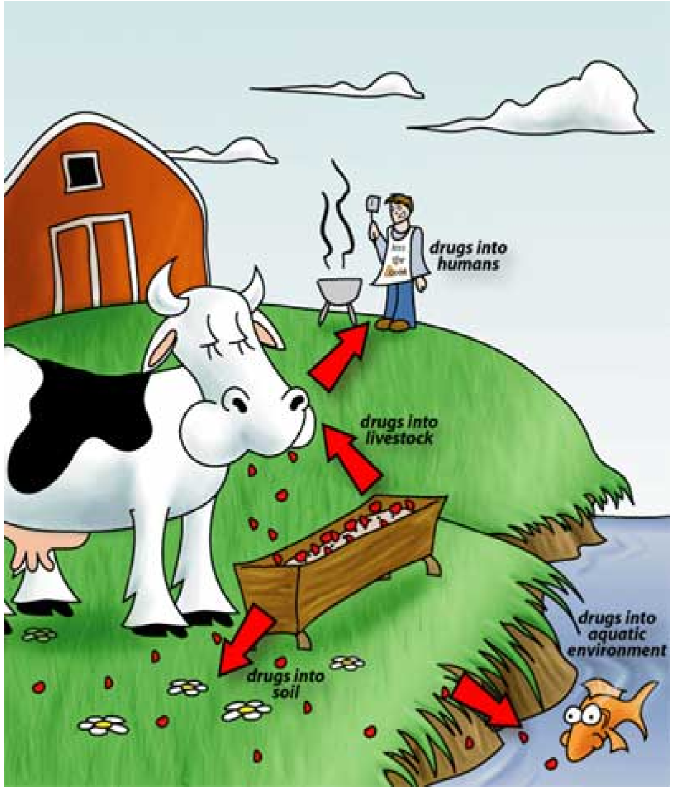
Antibiotics in veterinary medicine – risk for humans

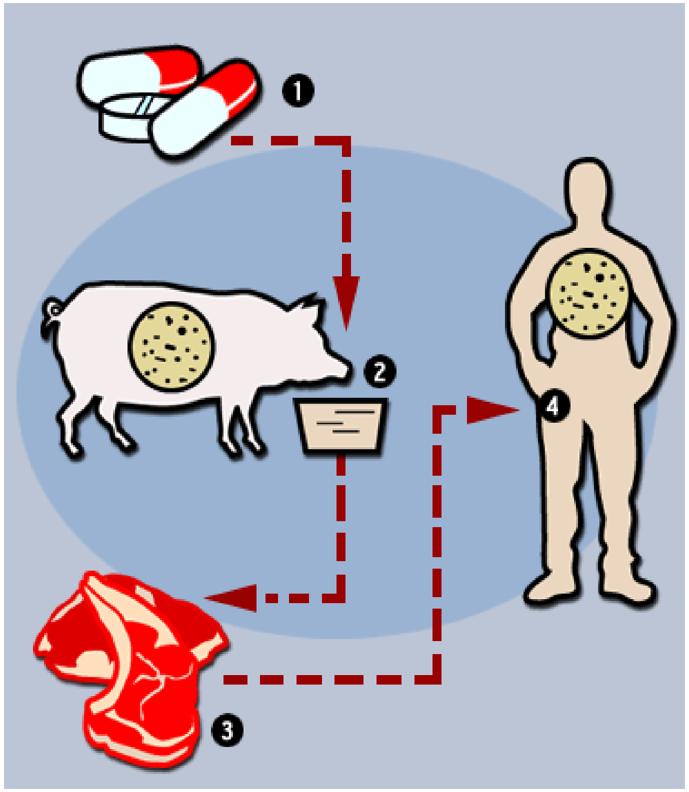
Risk antibiotic groups

fluoroquinolones

cephalosporins of 3rd and 4th generation

aminoglycosides





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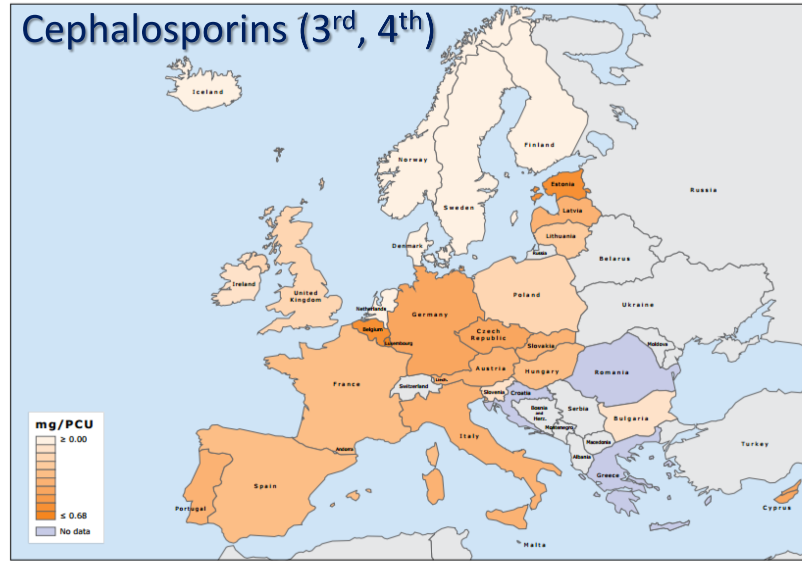
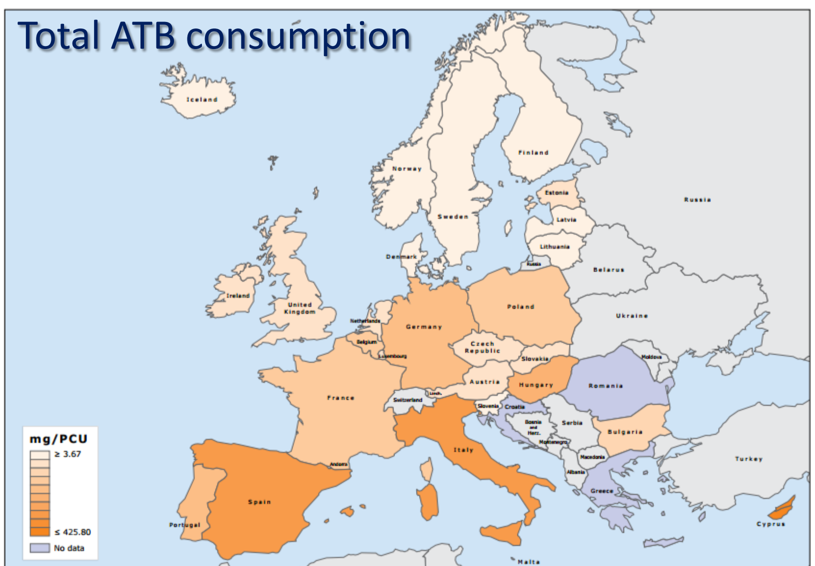
Antibiotics in veterinary medicine

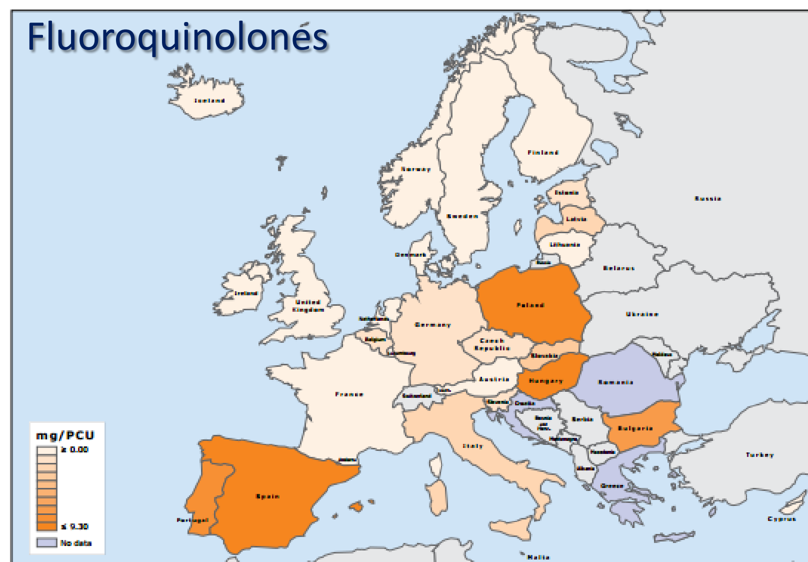
Risk group of antibiotics:

- fluoroquinolones
- 3rd and 4th generation of cephalosporins
- aminoglycosides

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH







European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) – Report 2013

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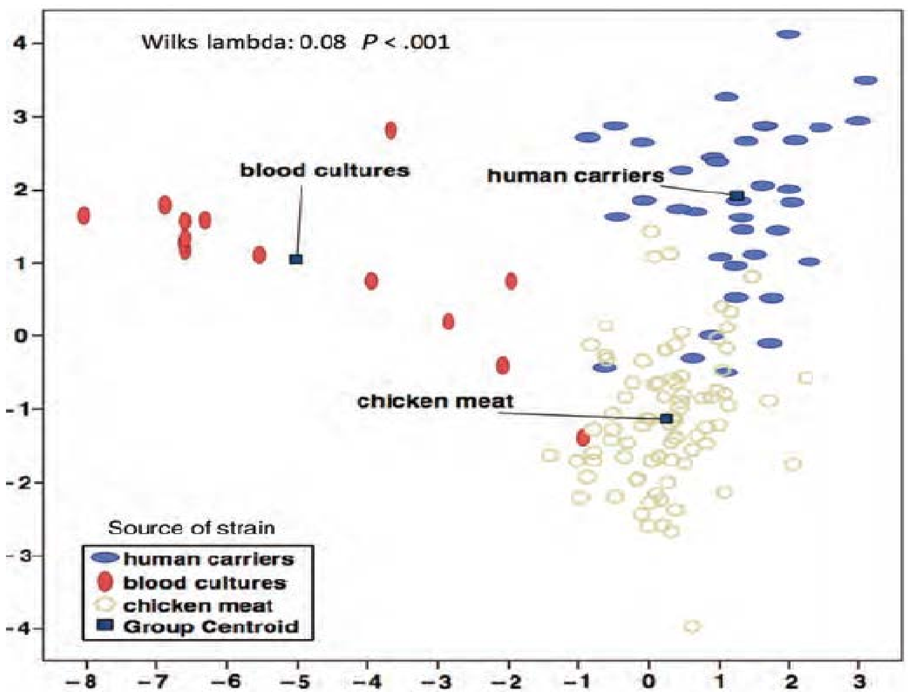
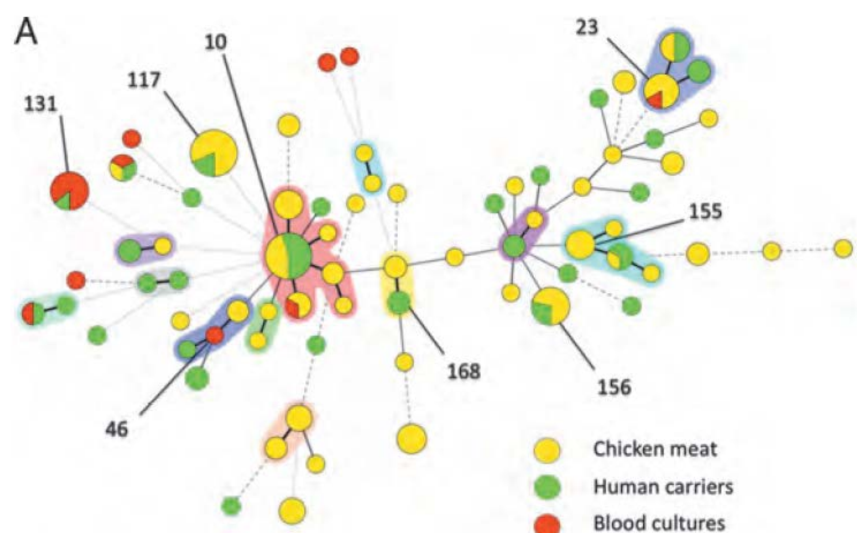
Antibiotics in veterinary medicine – risk for humans

Extended-Spectrum β-Lactamase–Producing *Escherichia coli* From Retail Chicken Meat and Humans: Comparison of Strains, Plasmids, Resistance Genes, and Virulence Factors

Jan A. J. W. Kluytmans,[1,2,3] Ilse T. M. A. Overdevest,[1,2] Ina Willemsen,[1] Marjolein F. Q. Kluytmans-van den Bergh,[1] Kim van der Zwaluw,[4] Max Heck,[4] Martine Rijnsburger,[3] Christina M. J. E. Vandenbroucke-Grauls,[3] Paul H. M. Savelkoul,[3] Brian D. Johnston,[5] David Gordon,[6] and James R. Johnson[5]





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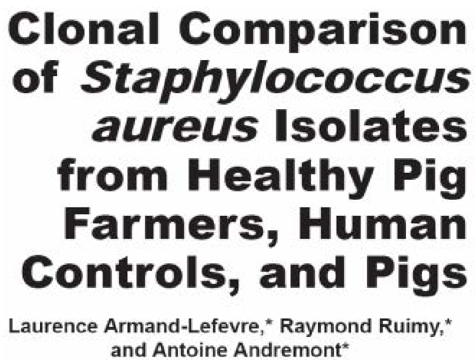
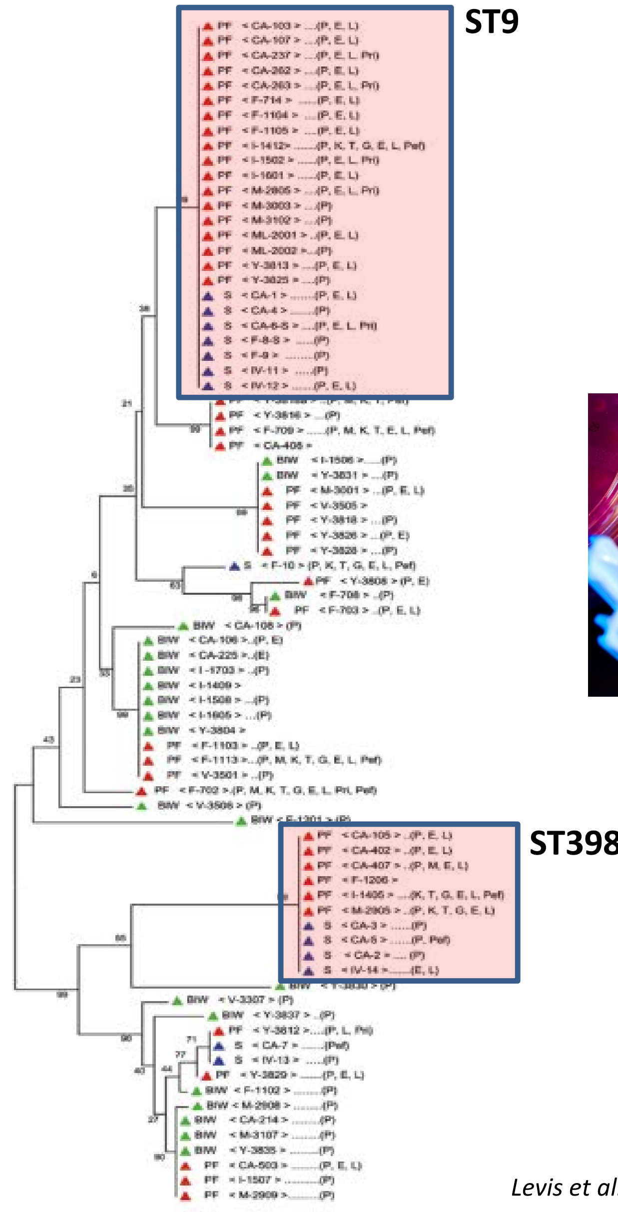
Antibiotics in veterinary medicine – risk for humans


Clonal Comparison of *Staphylococcus aureus* Isolates from Healthy Pig Farmers, Human Controls, and Pigs

Laurence Armand-Lefevre,* Raymond Ruimy,* and Antoine Andremont*



- insurance company workers (green triangle)
- pig farm workers (red triangle)
- pigs (blue triangle)

Levis et al. 2005, 2008 Emerging Infectious Diseases

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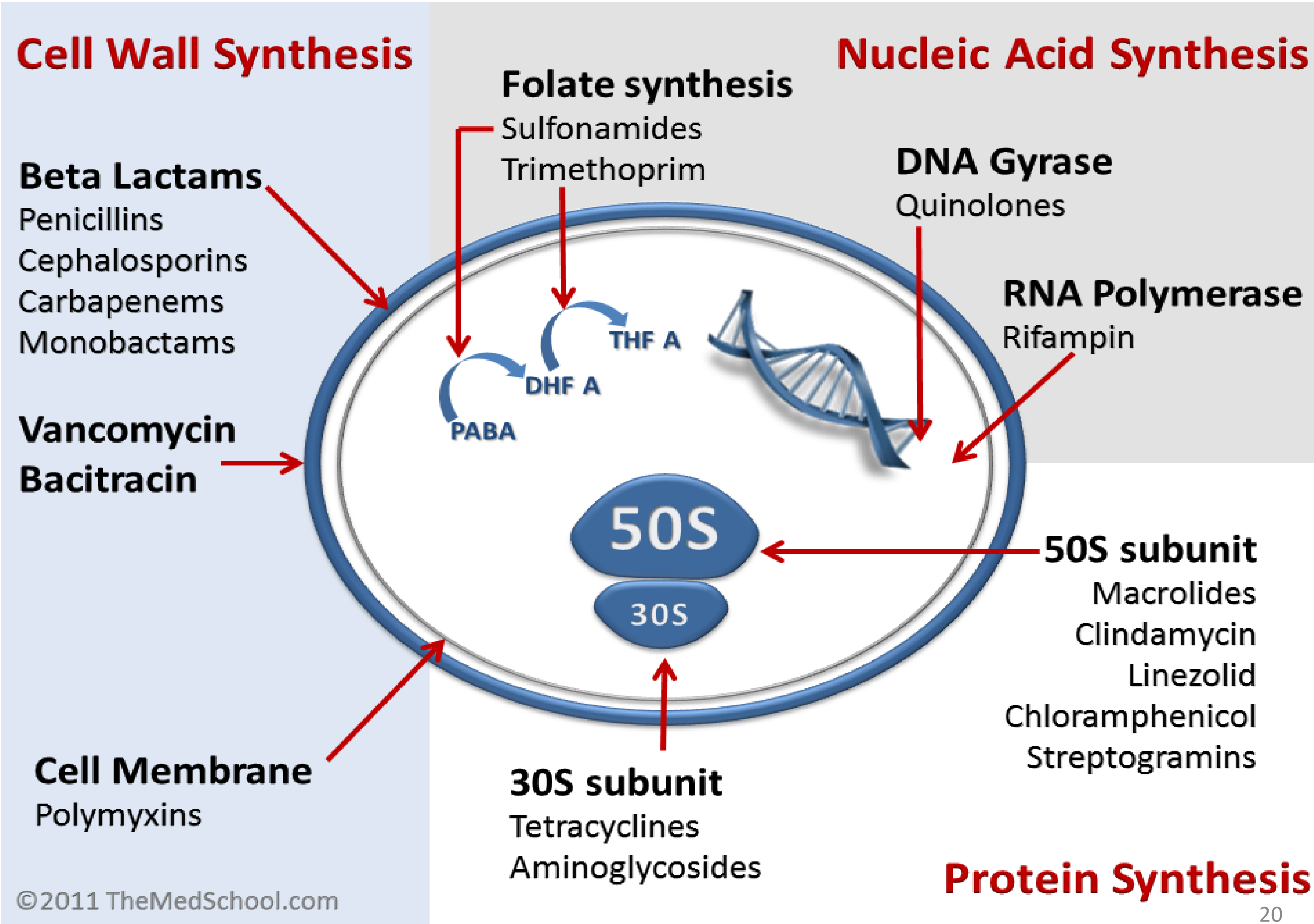
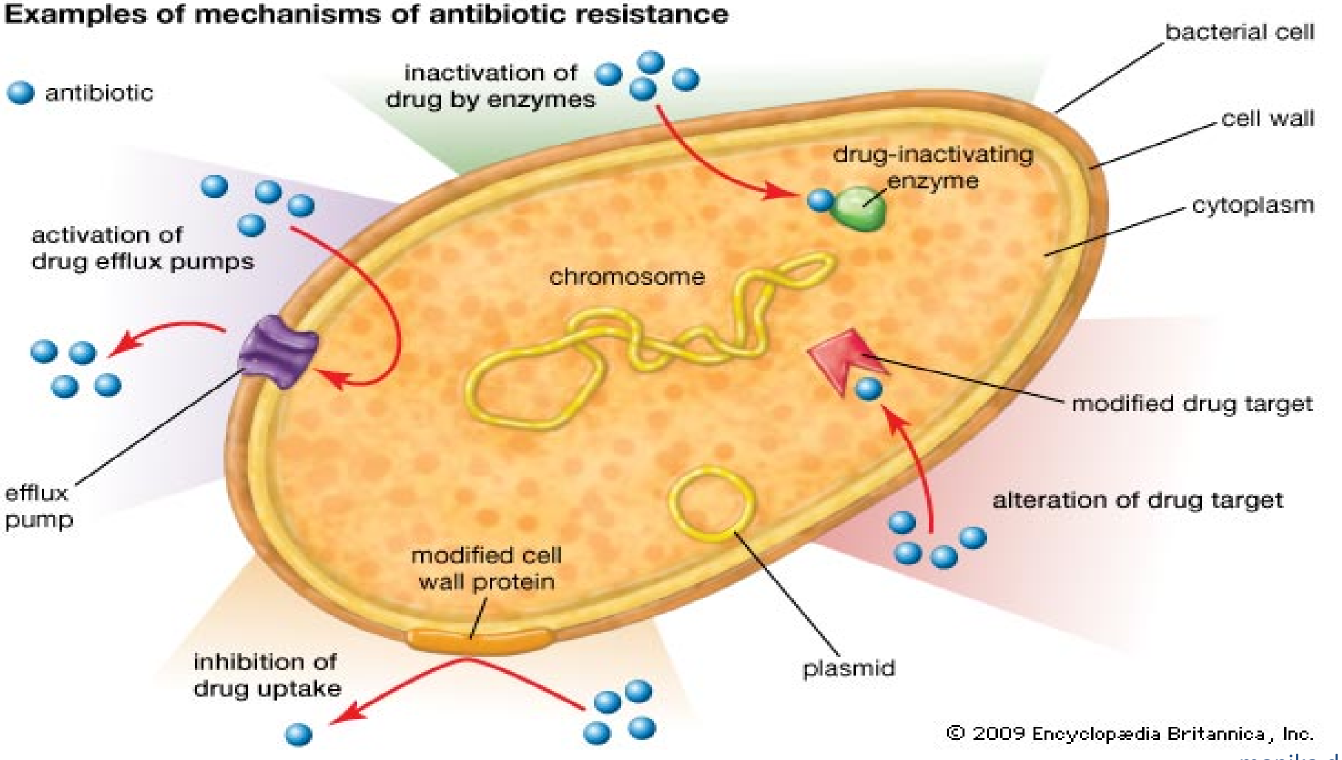
Antibiotics – mode of action



Antibiotic resistance mechanisms

1. Inhibition of drug uptake
2. Efflux pumps
3. Inactivation of antimicrobial agents
4. Modification of the antimicrobial target



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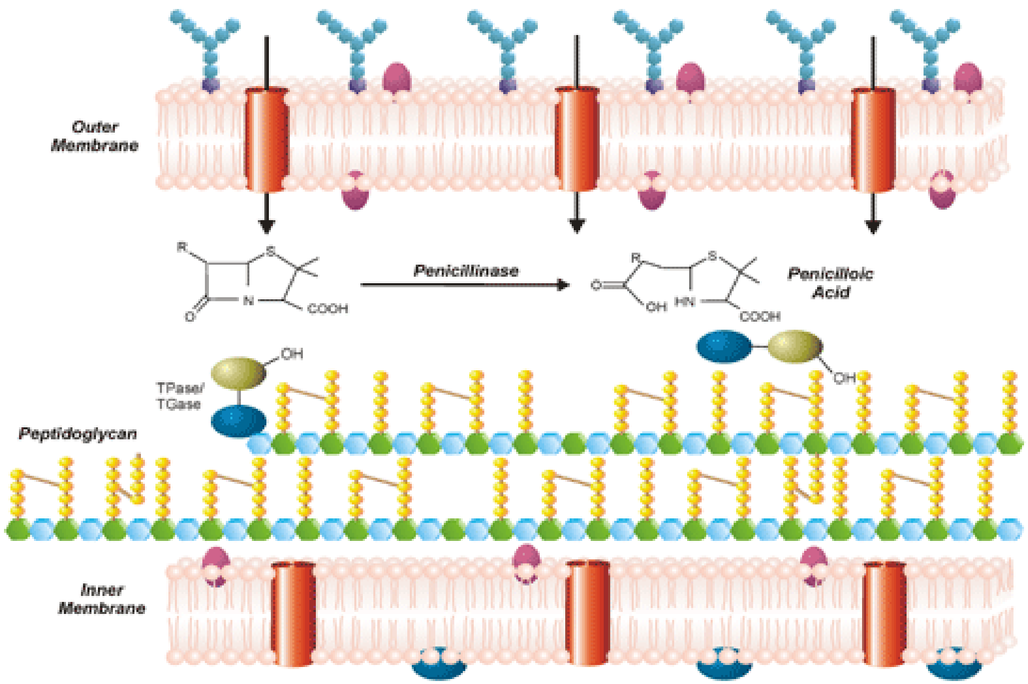
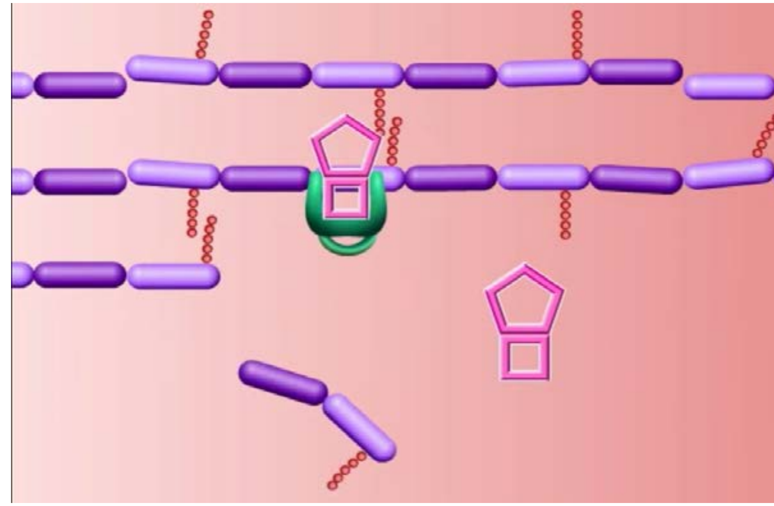
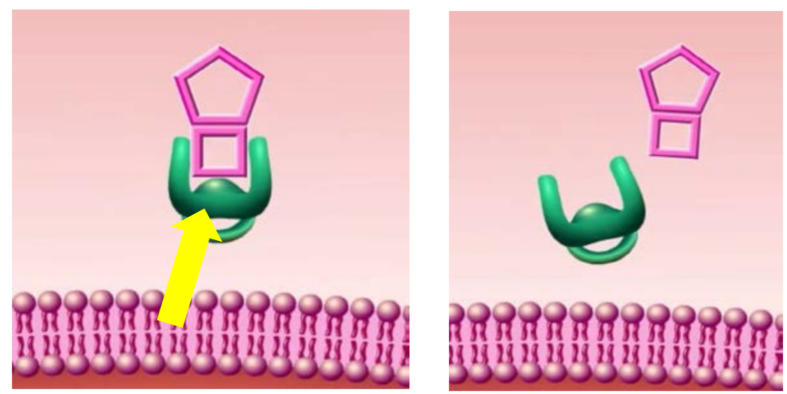
Resistance mechanisms – example on beta-lactams





Inhibition of transpeptidases by beta-lactam antibiotic



Alternation of transpeptidase → low afinity to beta-lactam antibiotic

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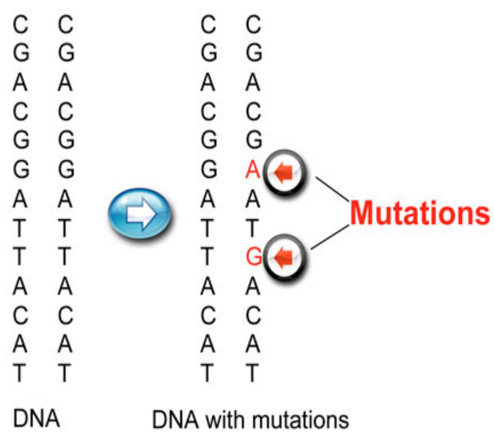
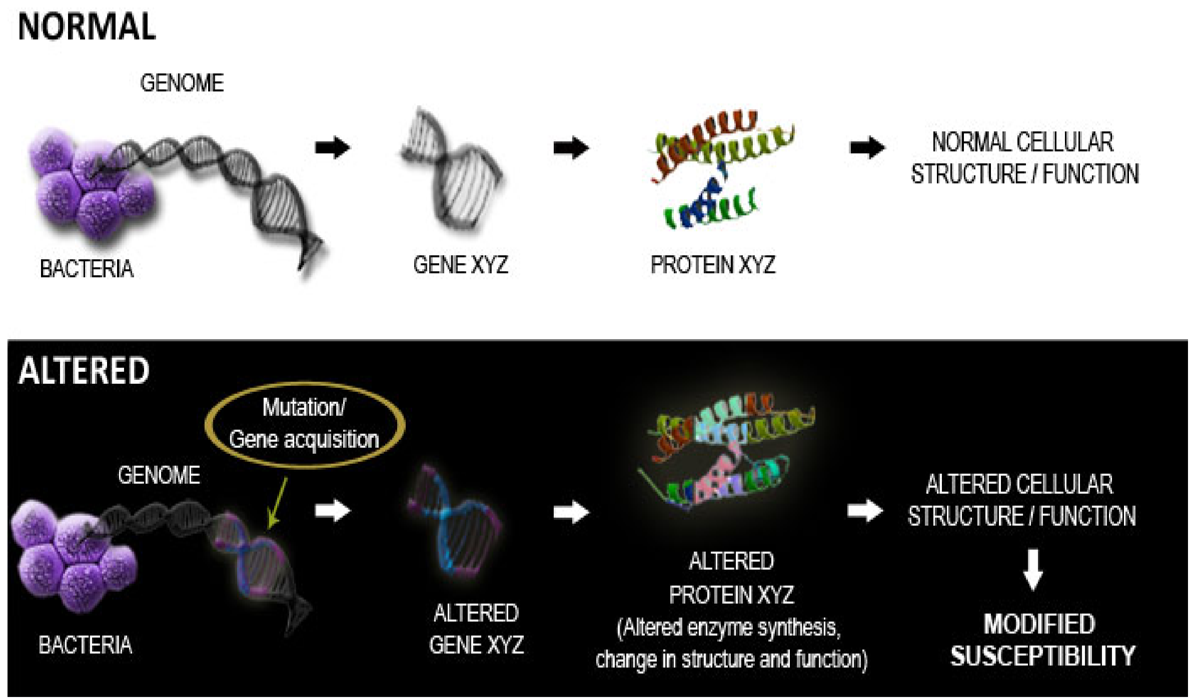
Molecular basis of antibiotic resistance





Point mutations and resistance to quinolones:

	MIC (mg/l)		**Substitution in amino acids**		
Strain	**Ciprofloxacin**	**Nalidixic acid**		**GyrA**	
A	0.007	2	Ser-83	Ala-84	Asp-87
B	2	512	**Leu-83**	Ala-84	Asp-87
C	128	>2000	**Leu-83**	Ala-84	**Tyr-87**

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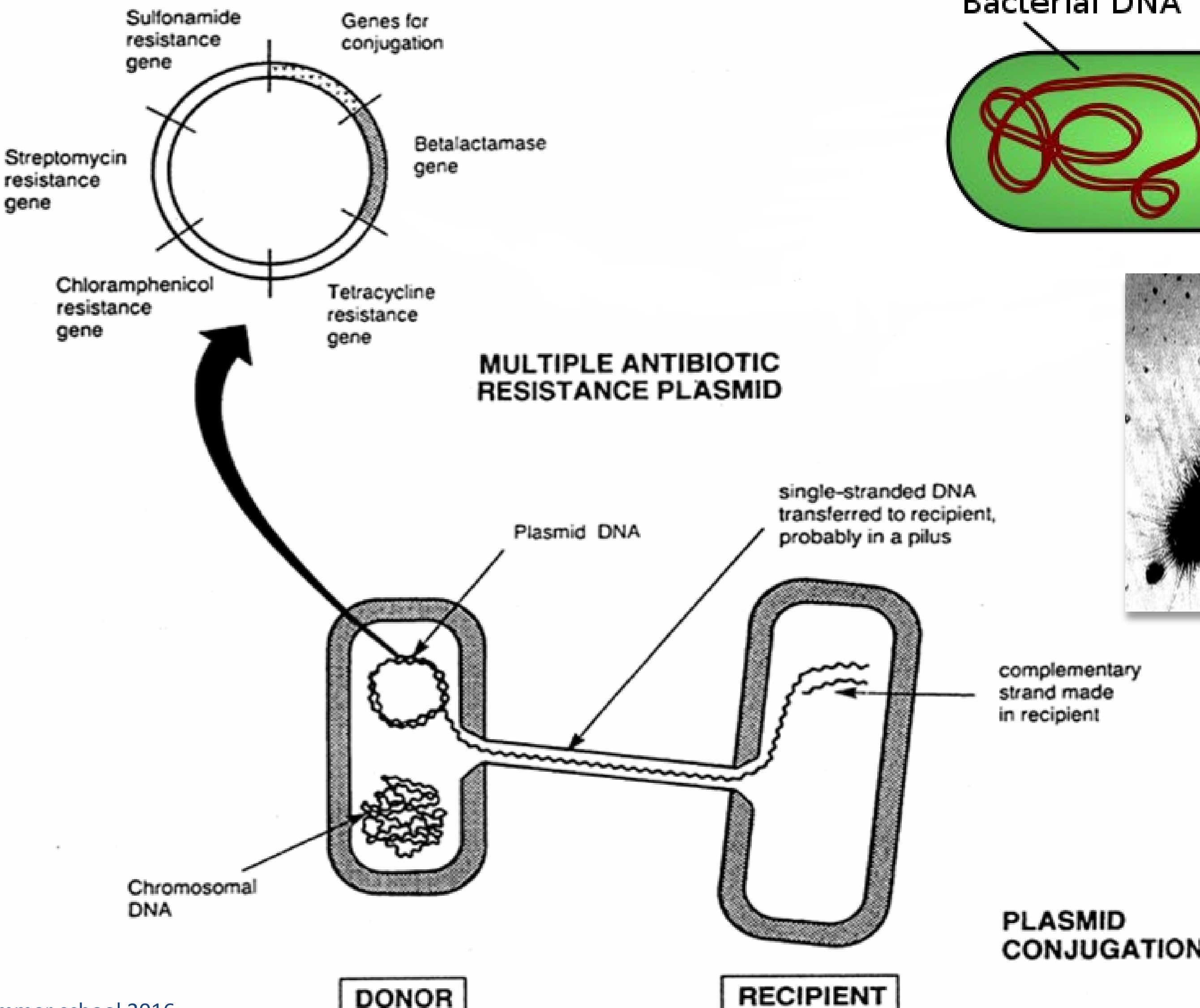
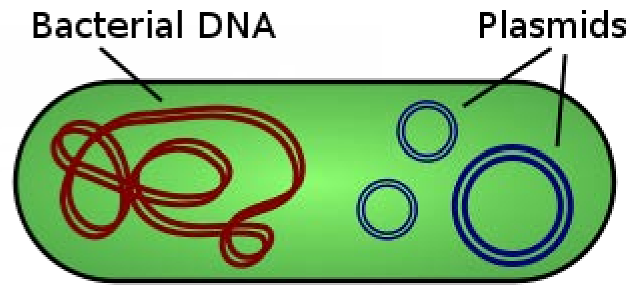
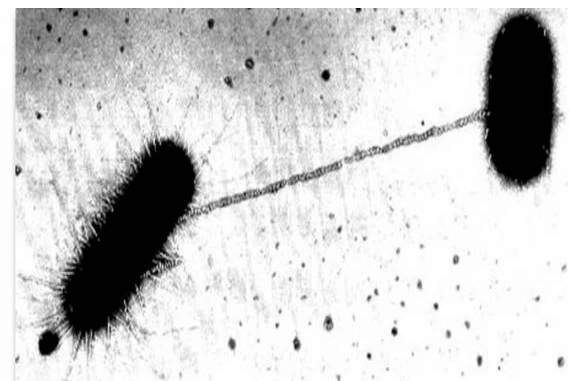
Molecular basis of antibiotic resistance

Chromosomal x extrachromosomal







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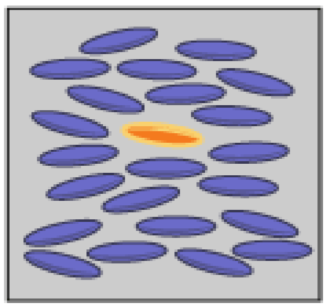
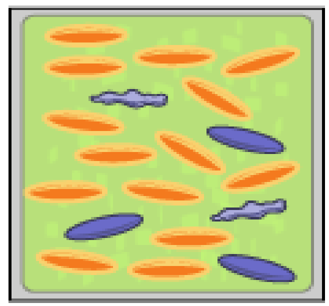
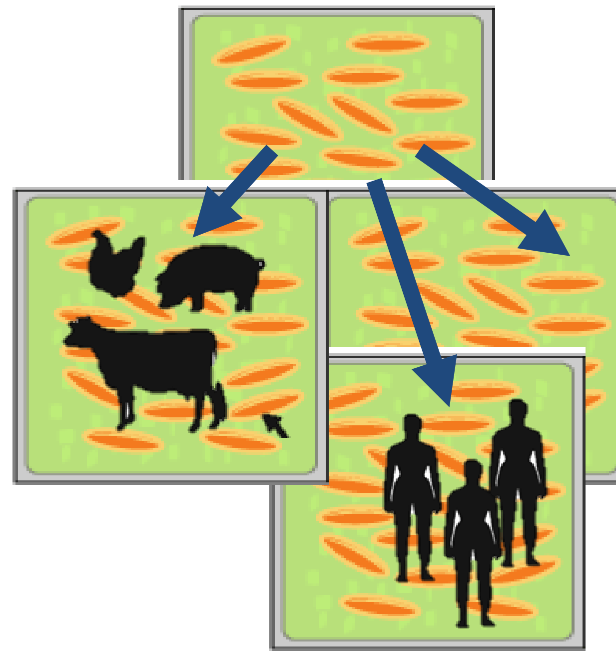
3 Steps in antibiotic resistance

Emergence of resistant bacteria → **Selection** → **Dissemination**







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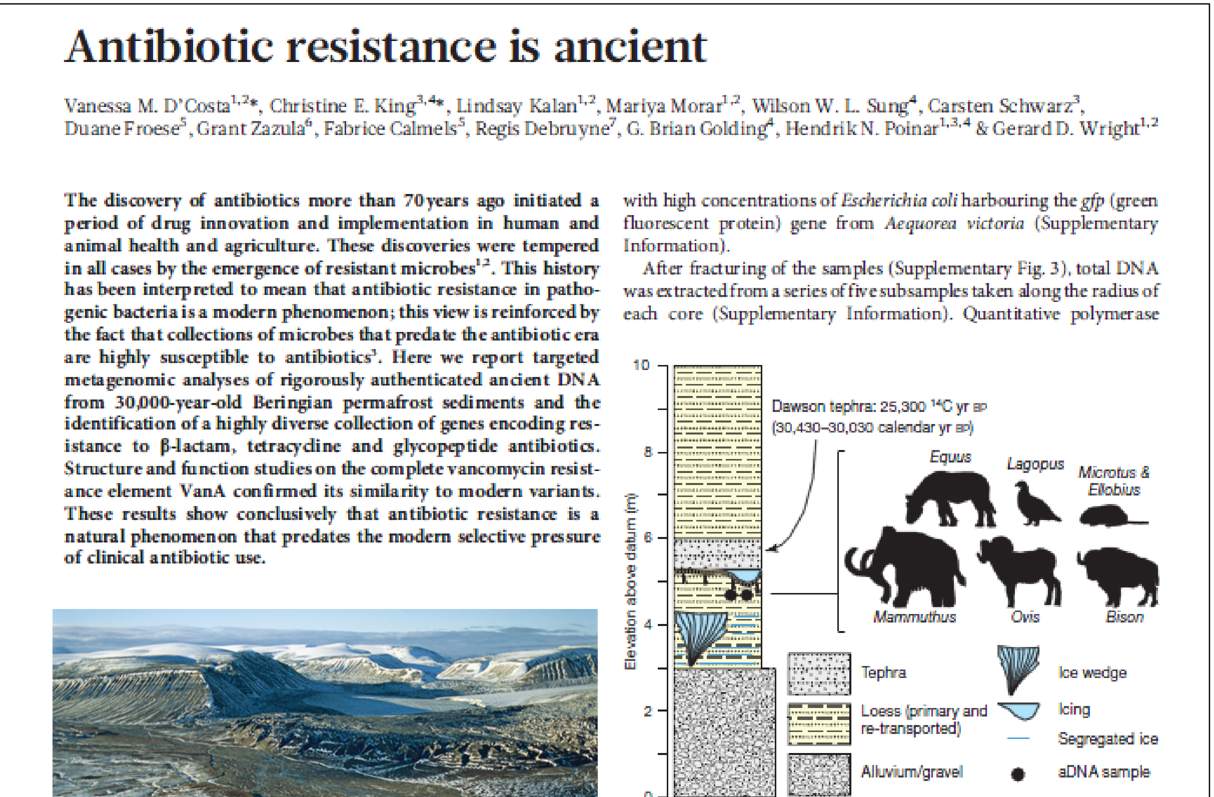
Origin of resistant bacteria



Antibiotic resistance is ancient

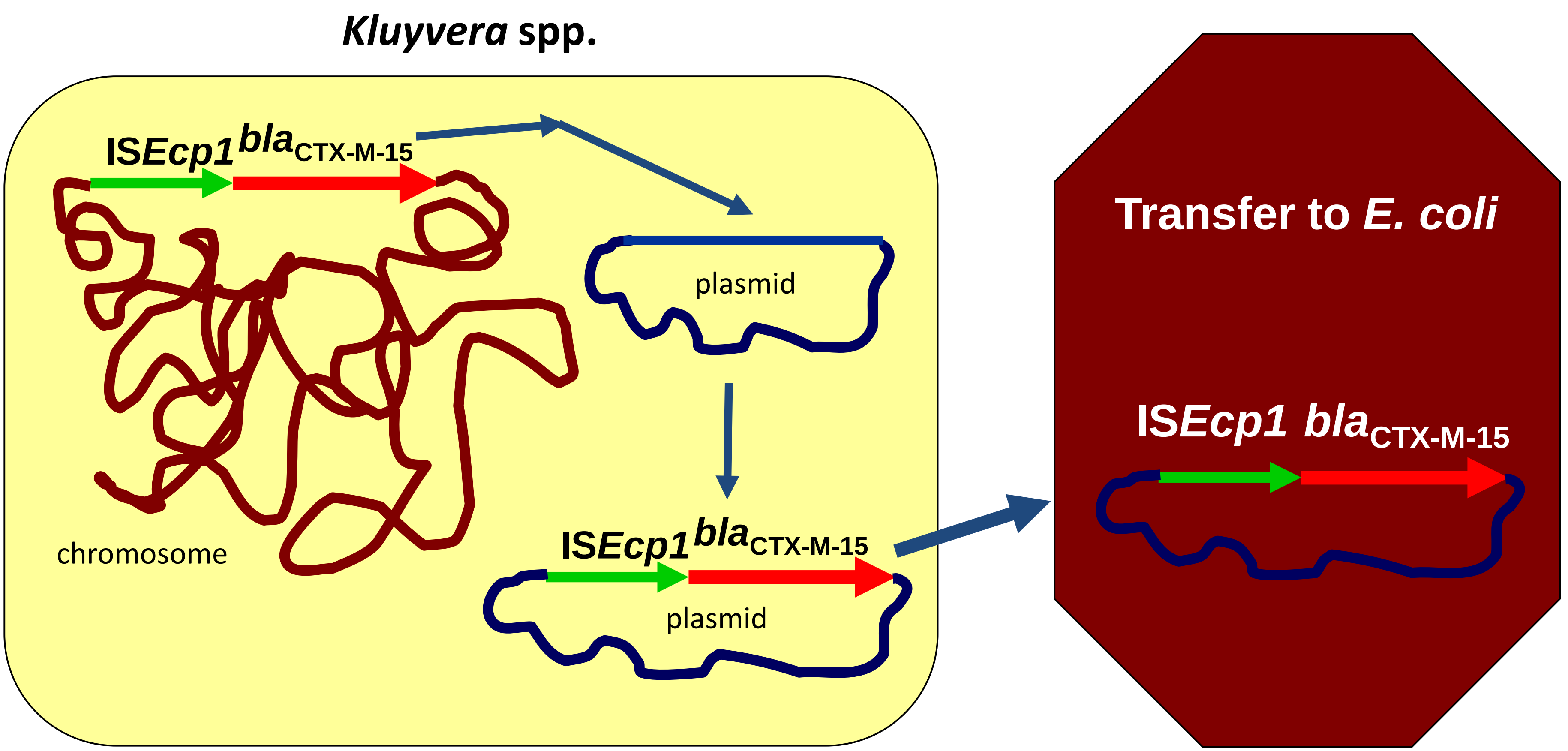
Vanessa M. D'Costa[1,2]*, Christine E. King[3,4]*, Lindsay Kalan[1,2], Mariya Morar[1,2], Wilson W. L. Sung[4], Carsten Schwarz[3], Duane Froese[5], Grant Zazula[6], Fabrice Calmels[5], Regis Debruyne[7], G. Brian Golding[4], Hendrik N. Poinar[1,3,4] & Gerard D. Wright[1,2]

The discovery of antibiotics more than 70 years ago initiated a period of drug innovation and implementation in human and animal health and agriculture. These discoveries were tempered in all cases by the emergence of resistant microbes[1,2]. This history has been interpreted to mean that antibiotic resistance in pathogenic bacteria is a modern phenomenon; this view is reinforced by the fact that collections of microbes that predate the antibiotic era are highly susceptible to antibiotics[3]. Here we report targeted metagenomic analyses of rigorously authenticated ancient DNA from 30,000-year-old Beringian permafrost sediments and the identification of a highly diverse collection of genes encoding resistance to β-lactam, tetracycline and glycopeptide antibiotics. Structure and function studies on the complete vancomycin resistance element VanA confirmed its similarity to modern variants. These results show conclusively that antibiotic resistance is a natural phenomenon that predates the modern selective pressure of clinical antibiotic use.

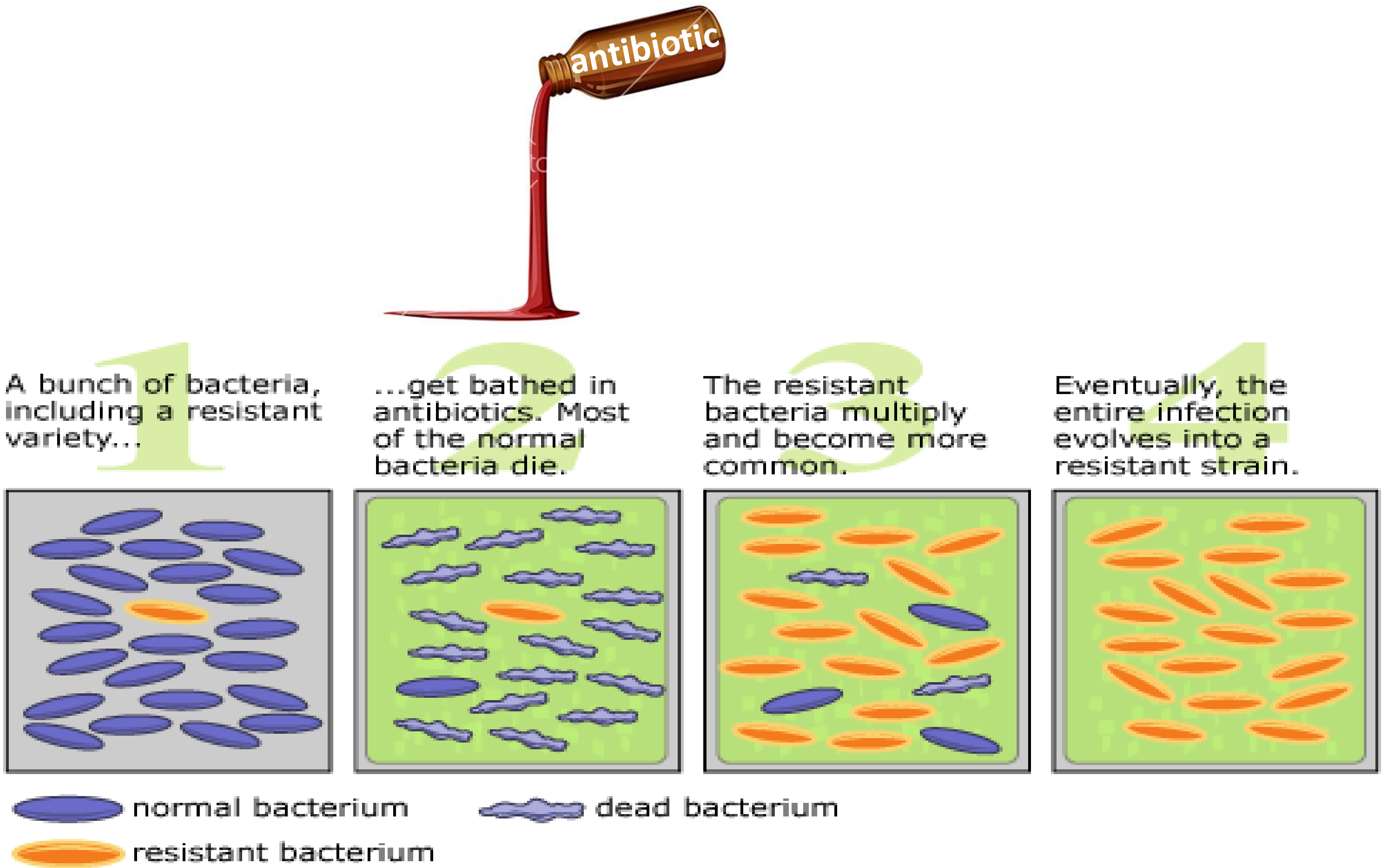
with high concentrations of *Escherichia coli* harbouring the *gfp* (green fluorescent protein) gene from *Aequorea victoria* (Supplementary Information).

After fracturing of the samples (Supplementary Fig. 3), total DNA was extracted from a series of five subsamples taken along the radius of each core (Supplementary Information). Quantitative polymerase

1. Emergence of resistant bacteria

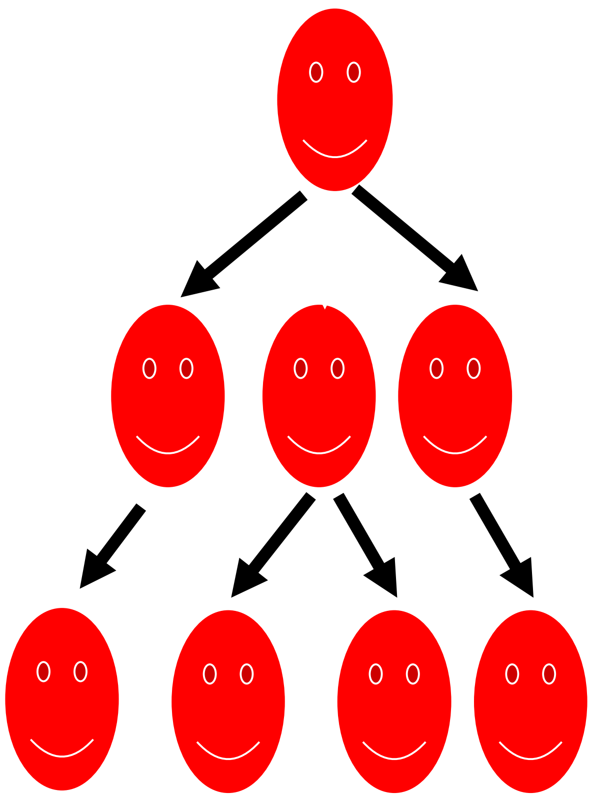


2. Selection of resistant bacteria



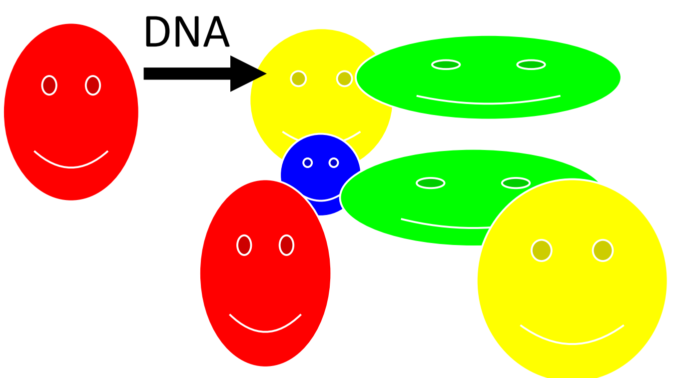
3. Dissemination of resistant bacteria

Clonal dissemination



→ Successful bacterial lineages

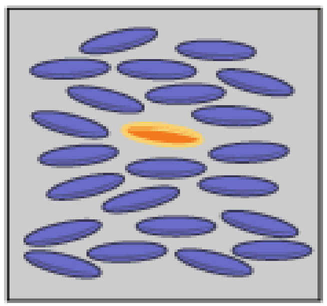
Horizontal transfer of genetic information

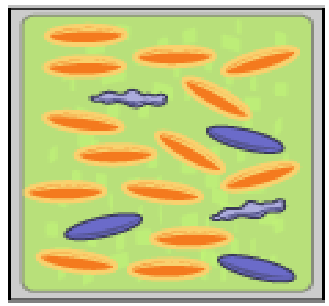


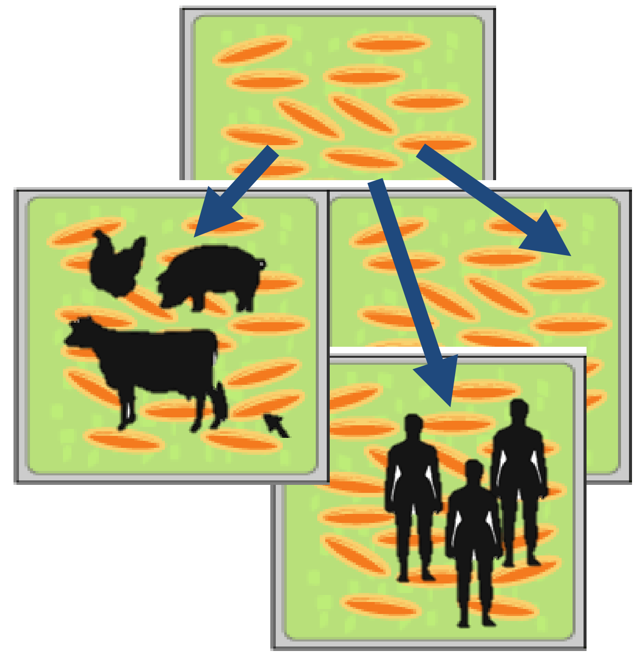
→ Successful resistance genes

3 Steps in antibiotic resistance

Emergence of resistant bacteria → **Selection** → **Dissemination**







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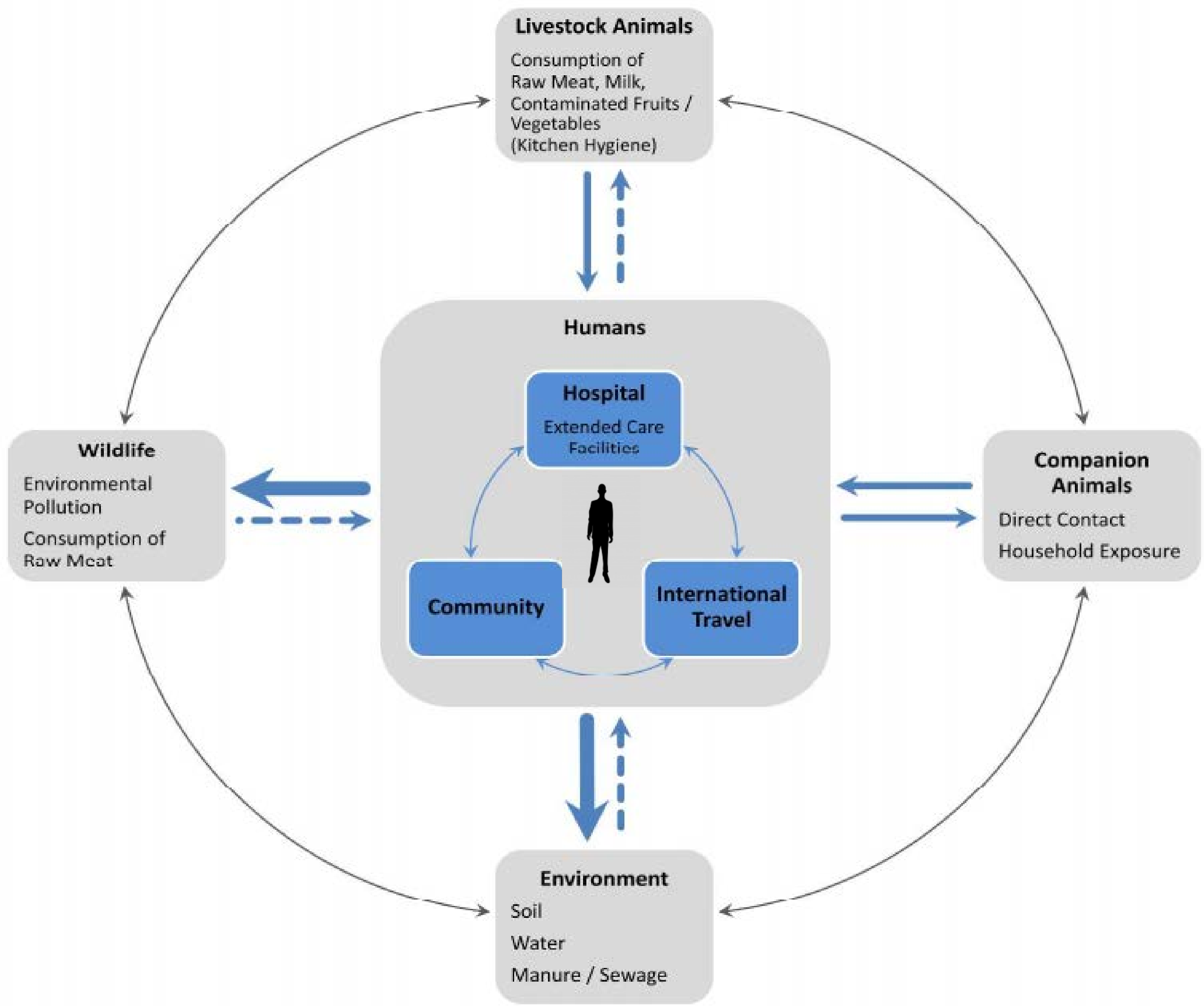
Transfer of resistant bacteria



To conclude…

- Misuse, overuse, under/ inadequate use of antimicrobials
- Costs money and lives
- Threat to global stability and national security
- Antibiotic resistant bacteria are found everywhere
- Increasing resistance and multiresistance
- Emergence and worldwide transmission of multiresistant clones
- Dissemination accelerated by gene transfer

To conclude…

- Monitoring of resistance
- Antibiotic policy
- National and international programs to combat resistance
- Hygiene and infection control strategies
- Novel antibiotics
- Alternative treatment methods