Evolution & Implications of AMR in the light of On-Health in Romania

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The material can be identified at the address :
http://www.veterinarypharmacon.com/docs/1971-2018_EFSA_CRISTINA_RT.pdf

This material is based on scientific studies of the past decade, books, expert opinions, and the author's personal experience.
Of course, as part of a continuous updating process, this (personal) point of view needs to be adapted periodically to the latest scientific knowledge gained on this topic.

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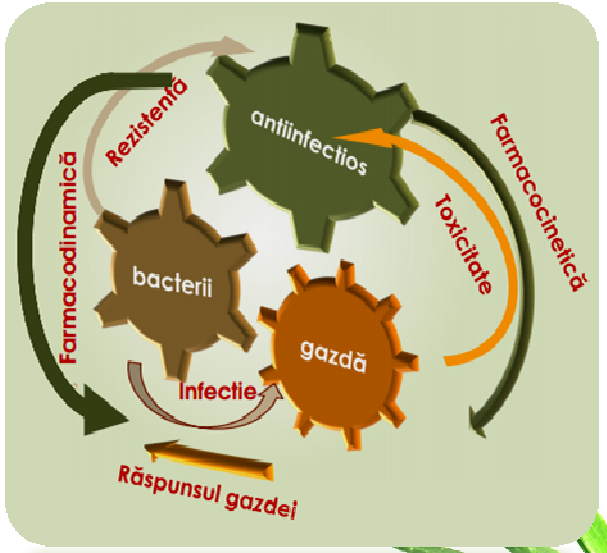
Antimicrobial resistance (AMR)

The ability of bacteria to become resistant to the effect of ***antimicrobial drugs*** *(including: antibiotics, antiviral, antifungal and antiprotozoaric drugs) to which these microorganisms have been previously susceptible.*



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*Top 5 **elements** that have stimulated the **AMR:***

1). *Increased **demand** for food.*
2). *Changes in animal production **systems**.*
3). ***Changing** trends in the animal trade.*
4). ***Increased** circulation of animals and specific products.*
5). *"**Specificity**" of livestock breeding = Lack of coherence worldwide.*

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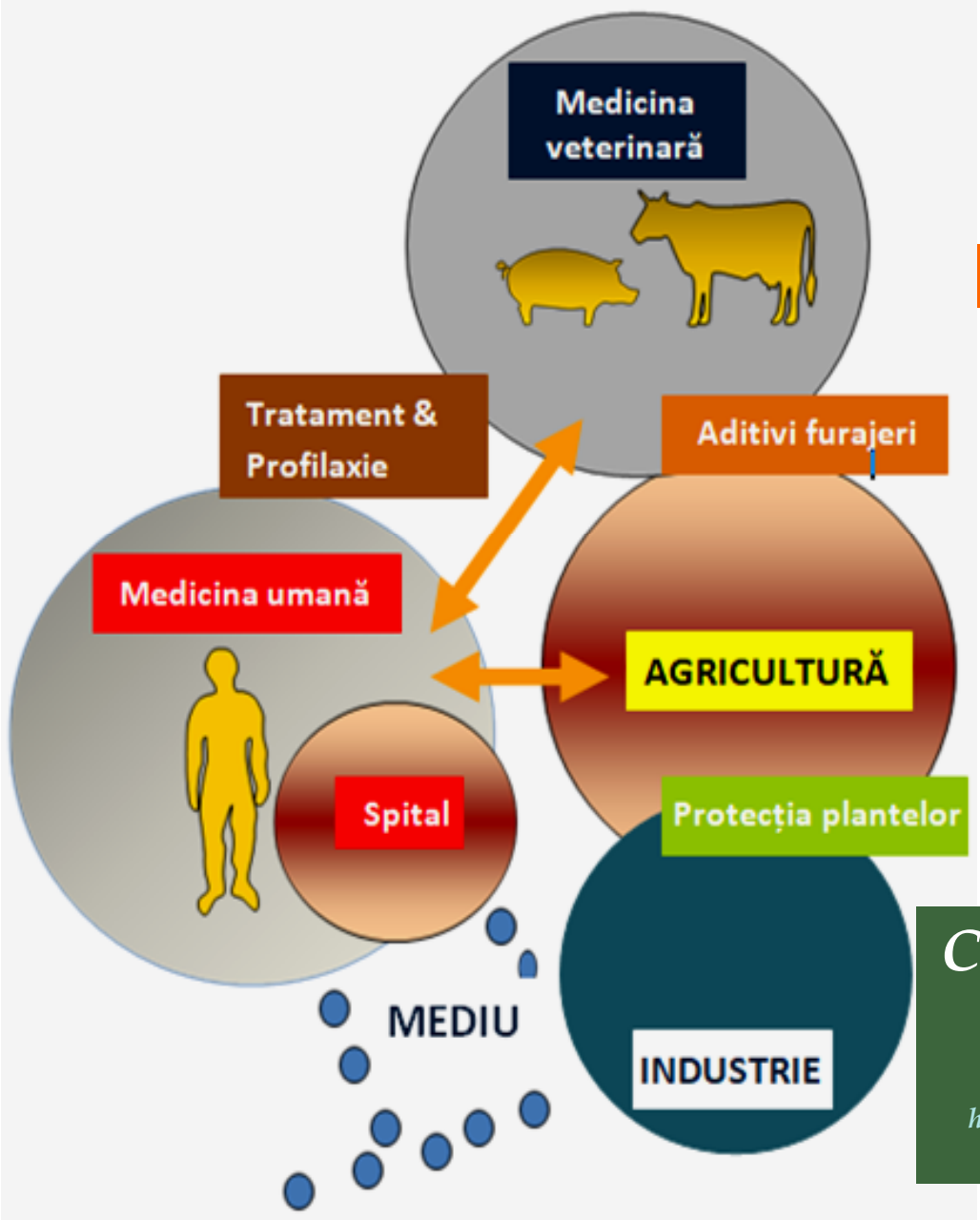

One Health MACRO

Correlations and interdependence in the emergence of resistances

Sursa: http://amrls.cvm.msu.edu/images/vph/HUMAN-HEALTH-IMPACT, prelucrat Cristina

Fact

Drug consumption in veterinary medicine ***exceeds*** *that in human medicine and it is recognized that veterinary medicine* ***contributes greatly*** *to the emergence and spread of human resistance... (OMS, 2012).*

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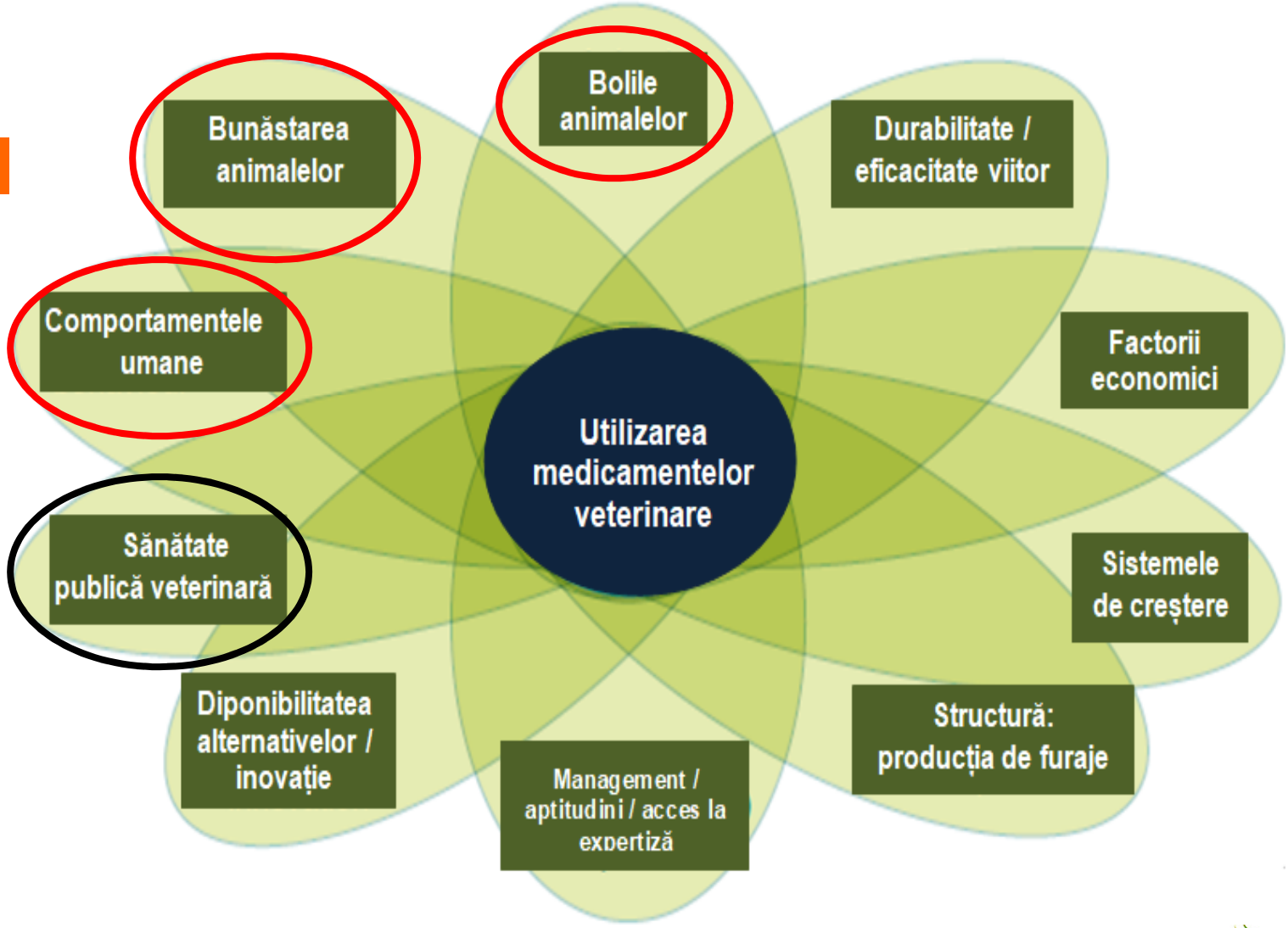
The complexity of using a.u.v. medication

Sursa: EPRUMA, 2018, (processed Cristina)



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... measures in the EU

*In **Nov. 2011 EC** through **EMA** launched the **first action plan** to address the **risks posed by AMR**.*
*The action plan is based on a holistic approach, in line with the **„One Health"** initiative.*

*The Action Plan covers **seven areas** and sets out **twelve specific measures** to be taken in the field of human and / or veterinary health.*

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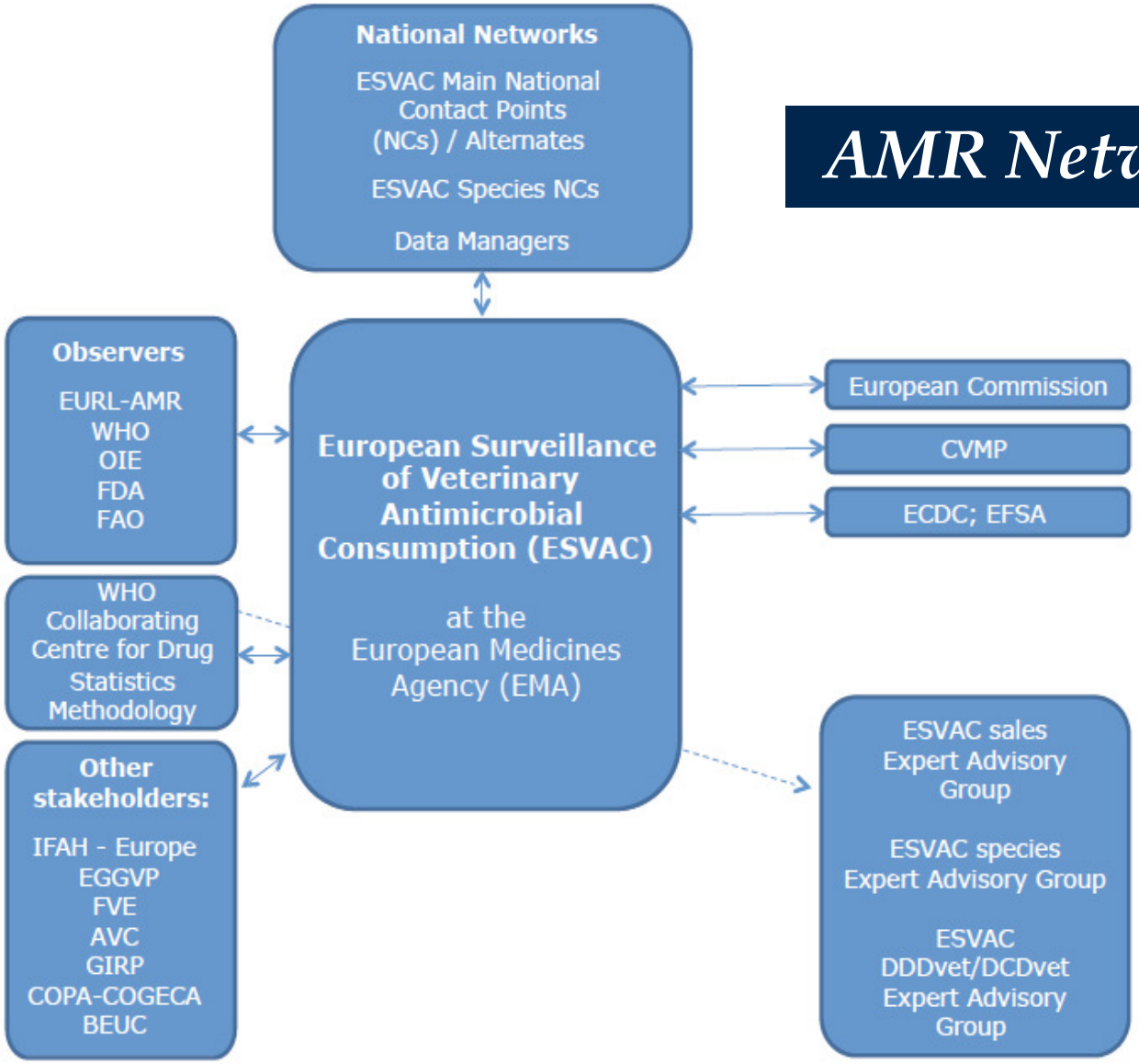
AMR Network



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National and international agencies

involved in monitoring the resistance phenomenon

(Synthesis Cristina, 2012)

Name of the agency / organization	*Country*
National Antimicrobial Resistance Monitoring System (NARMS)	*USA*
Global Antimicrobial Resistance Surveillance System (GLASS)	*OMS*
Global Health Security Agenda (GHSA)	*USA*
Fleming Fund	*UK*
Antimicrobial Advice Ad Hoc Expert Group (AMEG)	*EU*
Global Innovation Fund	*UK/CN*
Canadian Integrated Program for Antimicrobial Resistance (CIPARS)	*Canada*
Observatoire National de Epidémiologie de la Résistance Bactérienne aux Antibiotiques (ONERBA)	*France*
The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP)	***Denmark***
Japanese Veterinary Antimicrobial Resistance Monitoring System	*Japan*
Global Salm-Surv: Salmonella surveillance program, serotyping and AMR testing throughout world	*OMS*

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...in Romania

Efforts are still being made ***to collect*** *primary data on animal resistance for* ***connection*** *to official monitoring systems of the phenomenon (already present in Europe for over* ***a decade****).*

The official presence of our country was signalled in a large-scale study of the EU in **2009***).*

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50 mg/kg bw…

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În studiul EU:

JIACRA *(Joint Interagency Antimicrobial Consumption and Resistance Analysis) Report*

EFSA Journal *2017;15(7):4872, 135 pp. doi:10.2903/j.efsa.2017.4872*

... 2013-2015, the estimated total antimicrobial consumption in mg. a.s / kg bw, was :

124 mg/kg bw *in humans =* ***media 118 mg/kg bw.***

(with variations between 50-182 mg/kg bw and

152 mg/kg bw *in farm animals =* ***media 67 mg/kg bw****.*

(variations between 3-419 mg/kg bw).

The levels of antibiotic use were lower or much lower in the animals than in humans, in 18 of the 28 countries surveyed, in ***2*** *countries it was similar, and in* ***8*** *the consumption was much higher for livestock than for humans.*

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Source:
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/580710/1101060-v1-Understanding_the_PCU_-_gov_uk_guidance.pdf

*What is **PCU** = Population Correction Unit?*

Slaughter cows	425 kg
Slaughter heifers	200 kg
Slaughter bullocks and bulls	425 kg
Slaughter calves & young cattle	140 kg
Imported/exported cattle for slaughter	425 kg
Imported/exported for fattening	140 kg
Livestock dairy cows	425 kg
Slaughter pigs	65 kg
Imported/exported pigs for slaughter	65 kg
Imported/exported pigs for fattening	25 kg
Livestock sows	240 kg
Slaughter broilers	1 kg
Slaughter turkeys	6.5 kg
Imported/exported poultry for slaughter	1 kg
Slaughter sheep & goats	20 kg
Imported/exported sheep & goats for slaughter	20 kg
Livestock sheep	75 kg
Living horses	400 kg
Slaughtered fish based on liveweight	- - kg
Slaughter rabbits	1.4 kg

Understanding the Population Correction Unit used to calculate antibiotic use in food-producing animals.

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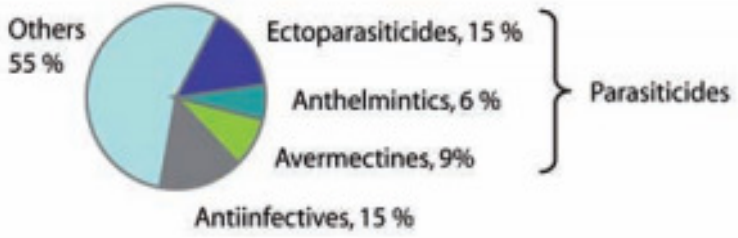
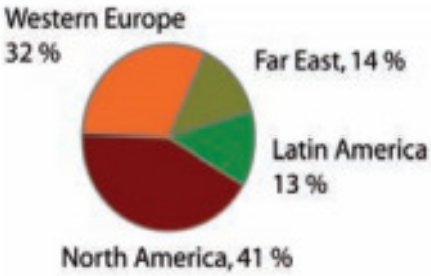
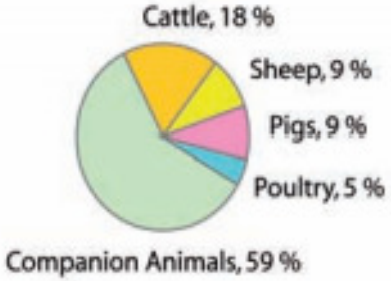
Animal Health Market: 16 Billion USD

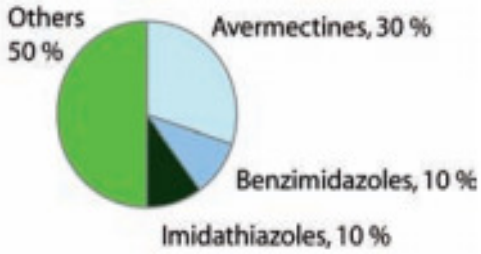


2006 !

Combined Parasiticides Market: 4.8 Billion USD

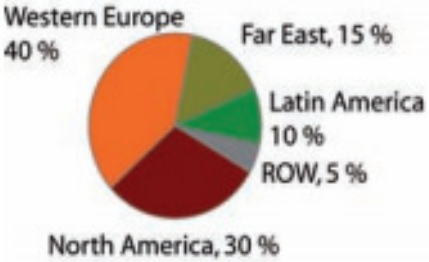


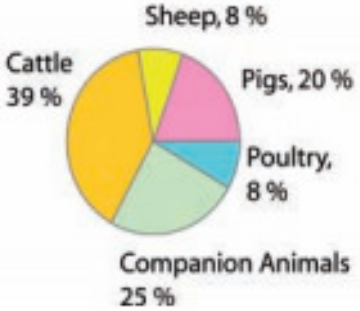


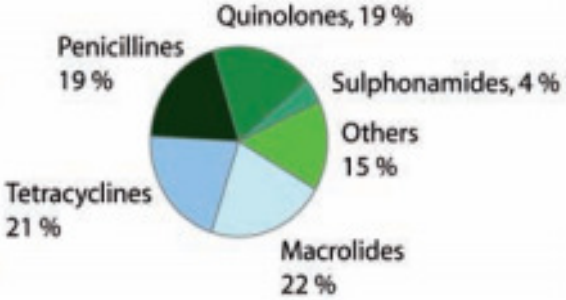


Source :
http://file.zums.ac.ir/ebook/072-Antiparasitic%20and%20Antibacterial%20Drug%20Discovery%20-%20From%20Molecular%20Targets%20to%20Drug%20Candidates%20(D.pdf

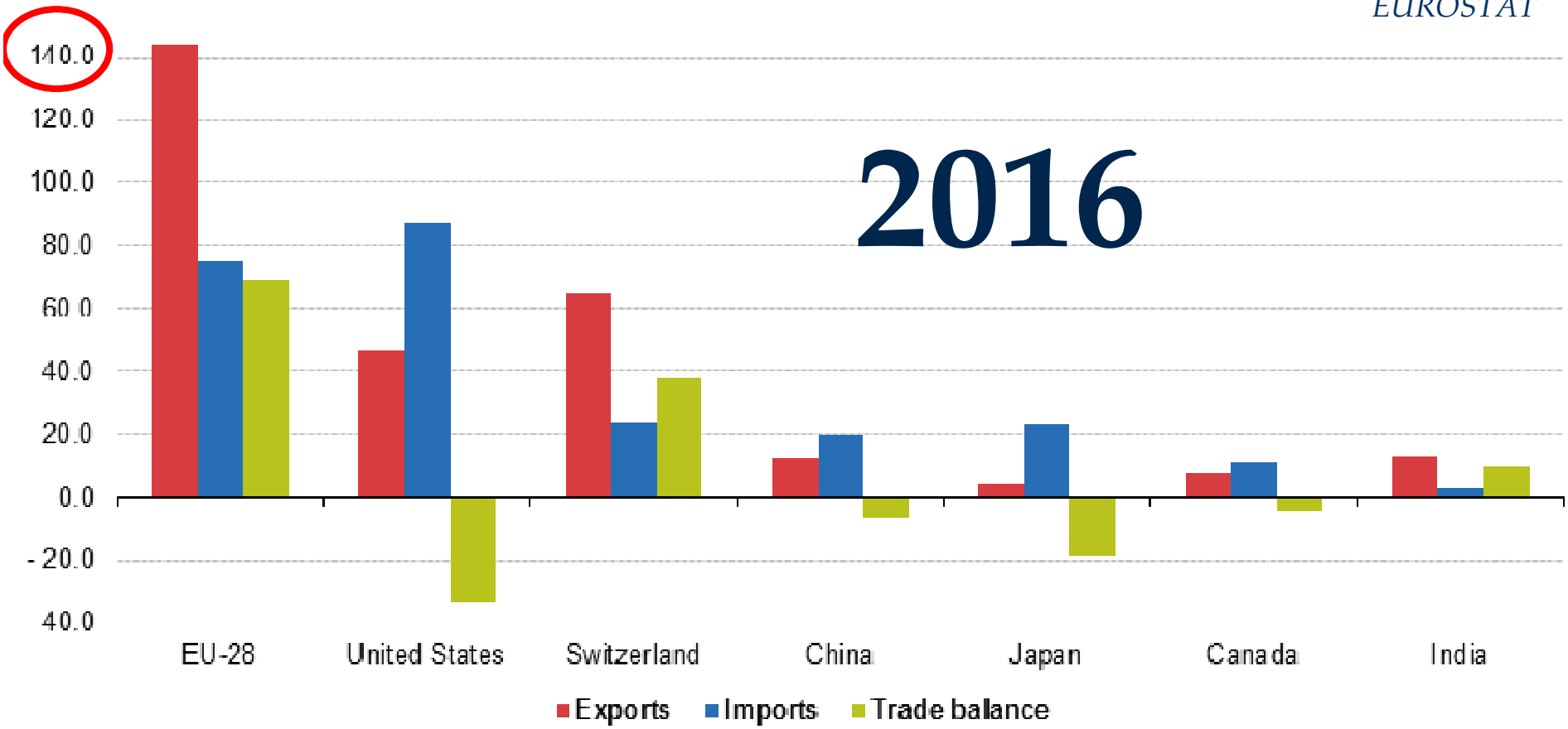
Antiinfectives Market: 2.4 Billion USD







Source :
EUROSTAT



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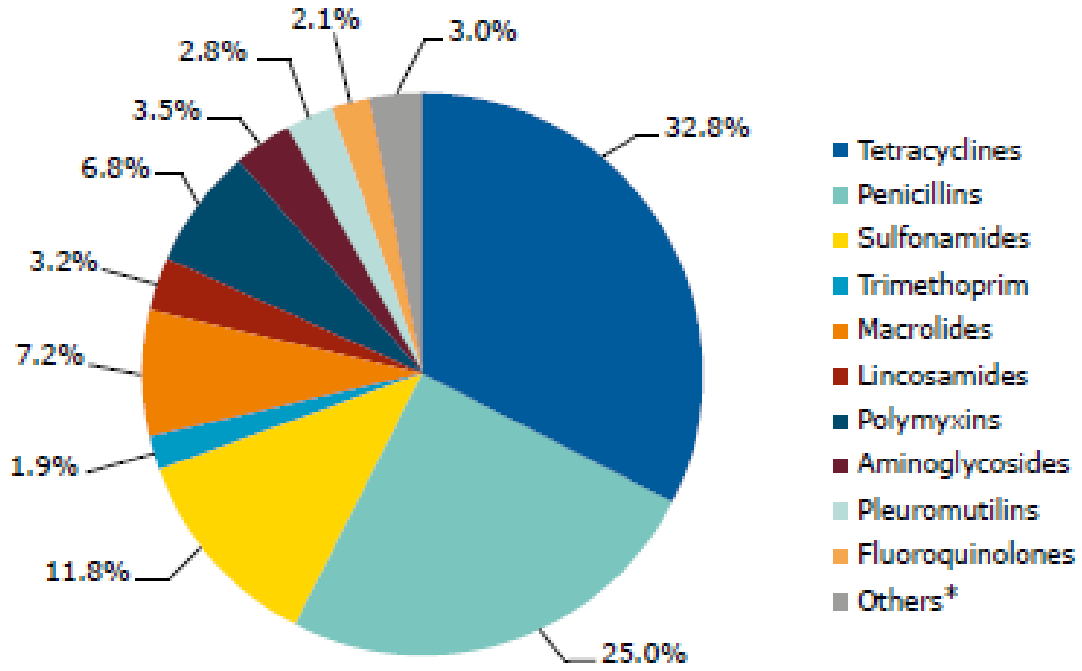
*According to the data, in **Europe**, during their short existence:*
*a **chicken** is treated with antibiotics **2.3** times and a **pig** of **5.3** times!*

Sales of antimicrobial agents by antimicrobial class as percentage of the total sales for food-producing species, in mg/PCU, aggregated by 30 European countries, for 2015



Source:
https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/antimicrobial-resistance-europe-2015.pdf

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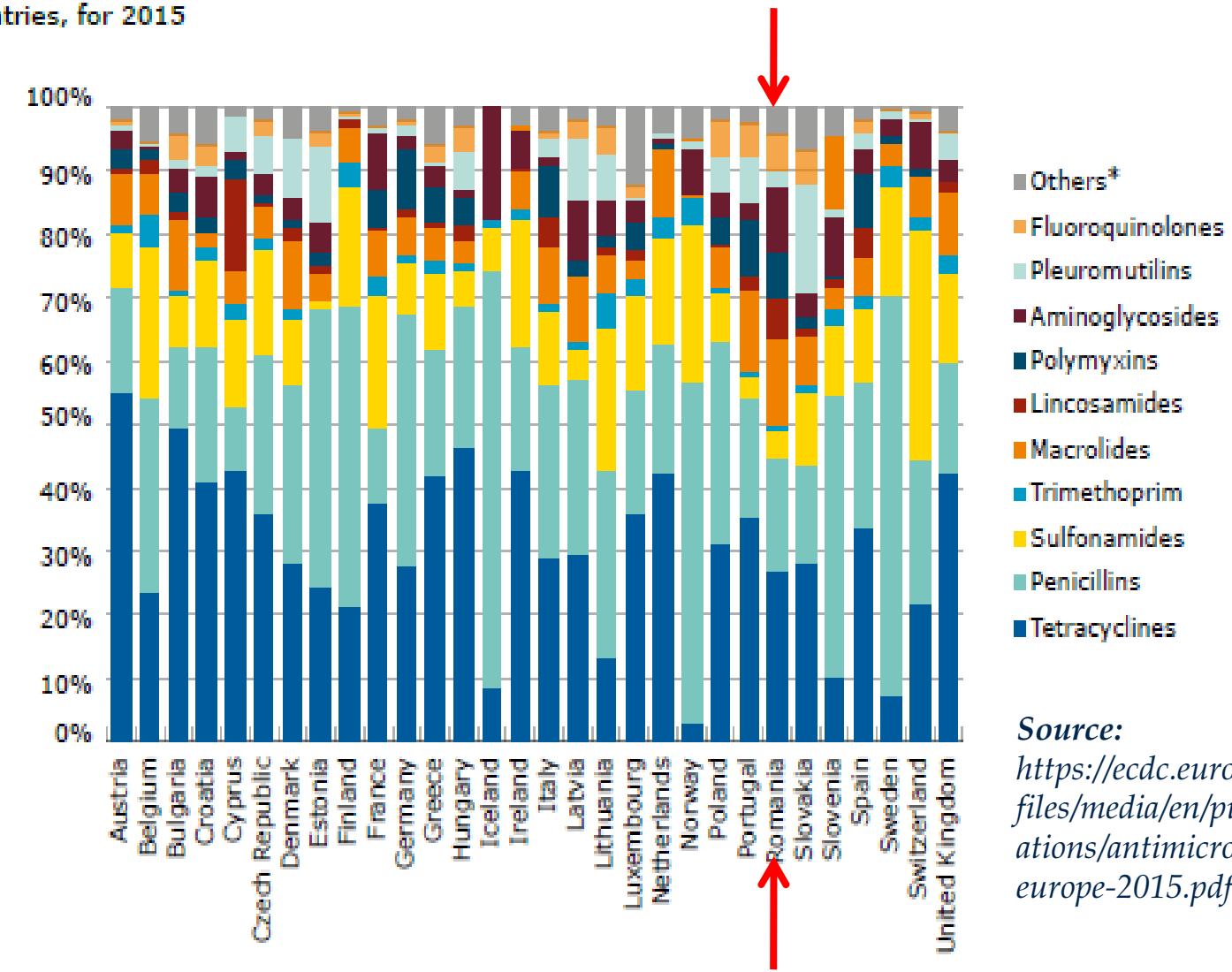
Proportion of the total sales of the different veterinary antimicrobial classes, in mg/PCU, in the 30 European countries, for 2015



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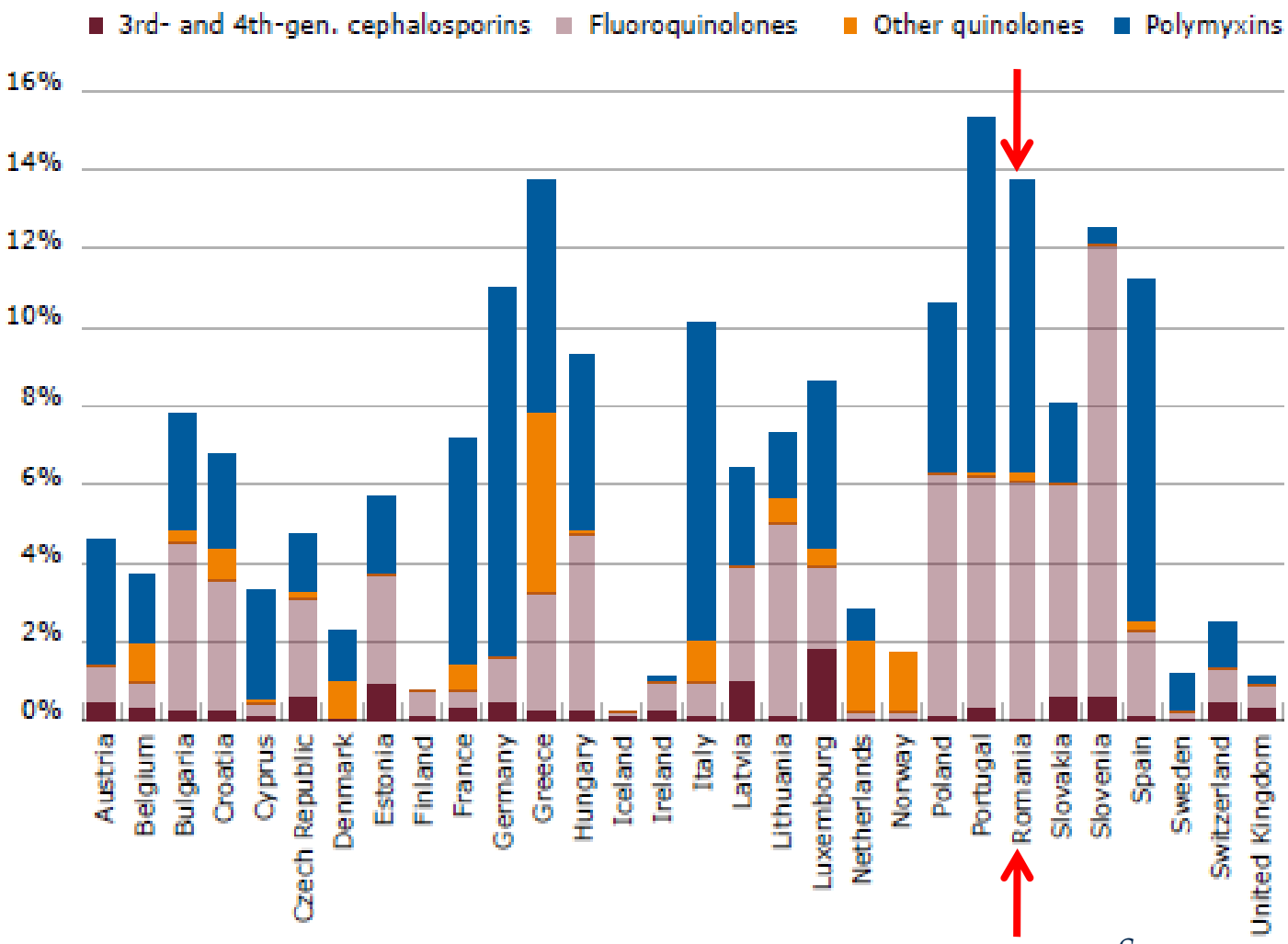

Source: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/antimicrobial-resistance-europe-2015.pdf

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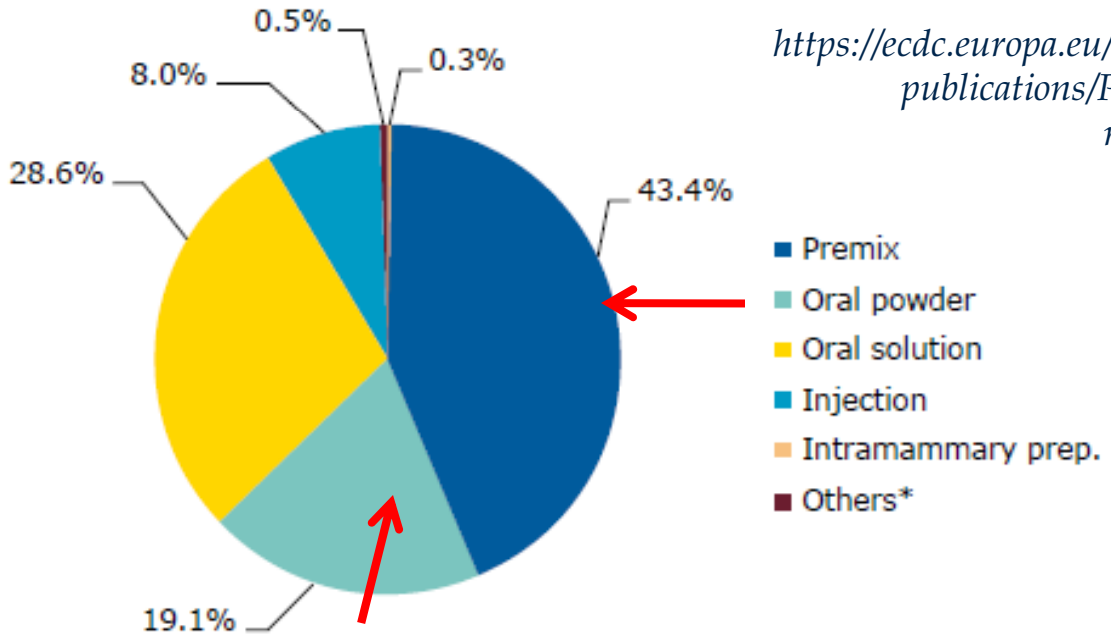
Distribution of sales, in mg/PCU, of the various pharmaceutical forms of veterinary antimicrobial agents for food-producing animals, aggregated by the 30 European countries for 2015



Source:
https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/antimicrobial-resistance-europe-2015.pdf

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Impact
of improper use of antiinfectives

... considerable and difficult to calculate!

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*Due to AMR the **huge advantage** gained in the last century, **will be lost**, on:*

infectious diseases	*cancer*	*surgical procedures,*
• *pneumonia* • *tuberculosis* • *HIV* • *malaria.*	*Antibiotics are crucial tin helping chemotherapy and implicitly against associated infections*	• *organ transplantation* • *C- section,* • *prosthesis* • *acute abdomen* • *operations on tendons*

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*After **Jim O'Neill** in: The review on antimicrobial resistance 2016 / Tackling Drug-resistant Infections Globally: Final Report and Recommendations*

Source: *https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf*

*...Over **70%** of the bacteria responsible for in-hospital infections are resistant to **at least** one antibiotic!*

*... **annually,** drug-resistant infections lead to the deaths of at least **25,000 patients in the EU** and **700,000 in the world** and generate costs of **1.5 bn €/ year only in the EU!***

*...therefore, the phenomenon of **resistance (especially antimicrobial)** has become a C.E. priority*

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*Quoting **ECDC** and **EMA**sources **in EU:***

The consequences of the phenomenon of resistance are dramatic :

- *multi-drug resistant strains : aprox.* ***400.000 strains / year;***
- *extra days of hospitalization :* ***2.500.000 days hospitalization / year;***
- *extra hospitalization costs :* ***900 millions of euro / year;***
- *productivity losses:* ***600 millions of euro / year.***
- *annually, about* ***4 million*** *patients acquire a healthcare* ***associated*** *infection.*

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Unfortunately

Approximately ***200,000 people per year die*** *due to multi-resistant antibiotic strains!*

In India, neonatal antibiotic-resistant infections are the cause of death of approx. ***60,000 newborns / year!***

Of ***40,000,000 people / year*** *treated with antibiotics for respiratory diseases only* ***13,000,000*** *confirmed the need for treatment through laboratory examinations!*

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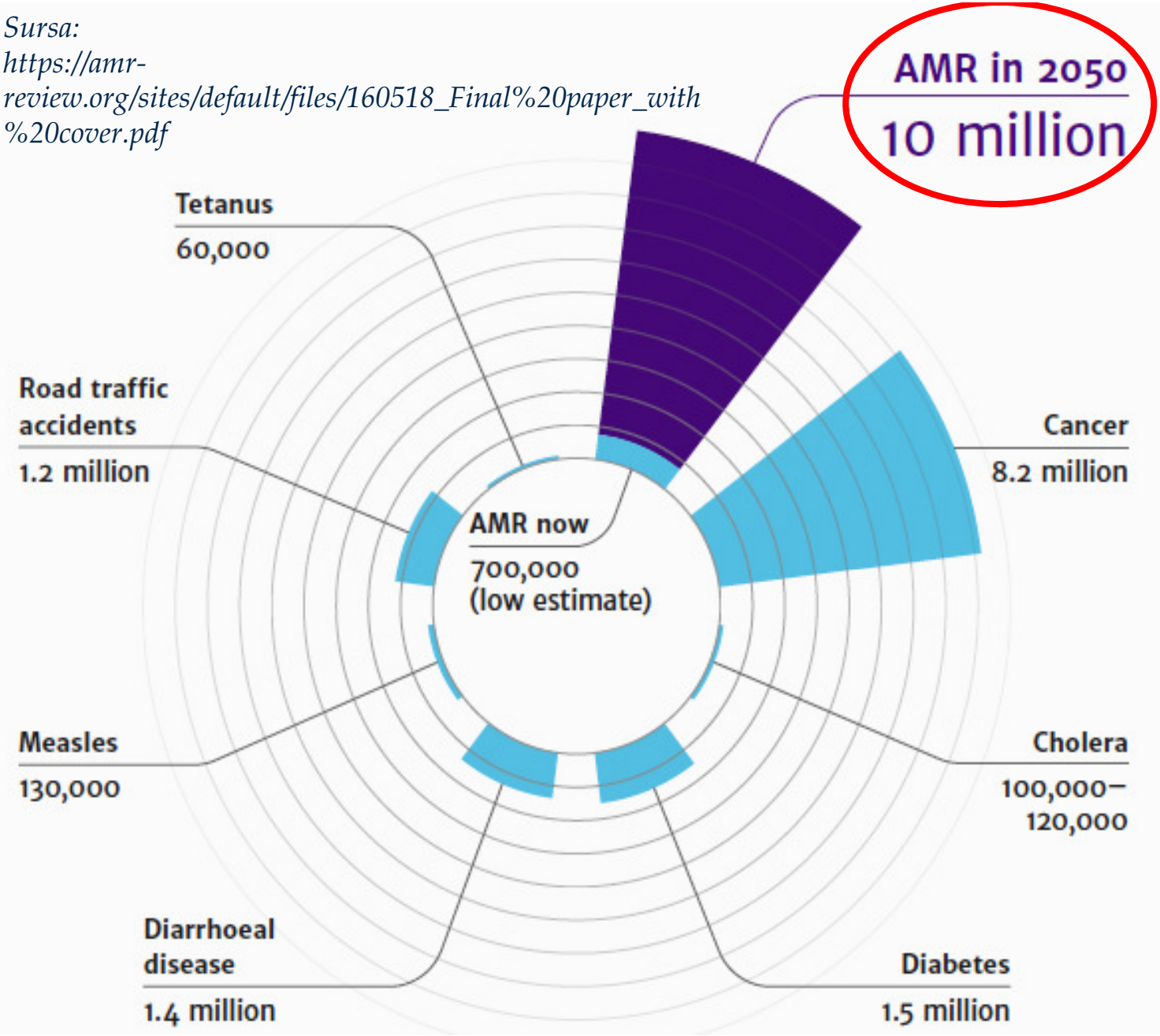
Sursa: https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf



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In Romania:

Unfortunately the circulation of a.u.v. is chaotic

Anybody can buy and administer medicines without consultation and without prescription!

Especially important problem in case of:
- antibiotics,
- sulfonamides,
- antiparazitics
- hormones,
with reminiscence in the animals' body, so with important consequences!

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In Romania (like in Europe...)

- *The **irresponsible** use of antibiotics in farm animals has developed resistance to animals or to the people consuming meat and by-products.*
- *Antibiotic resistance has mainly occurred through the use of antibiotics as **bio stimulators**, in the **preservation of food** of animal origin or the **most often** by administering **unrelated** antibiotics **without prescription and antibiogram!***

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In Romania (like in Europe...)

The main causes that favour the emergence of drug resistance phenomena are:

- ***under-dosing / inadequate*** *dosing of a.s.,*
- *treatment of* ***viral*** *diseases in animals with antibiotics...,*
- ***wide*** *spectrum antibiotic administration for any treatment, while a narrow spectrum antibiotic would be sufficient.*

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AT / AMR link

has already been demonstrated statistically ***(p<0,05)*** *for:*

- ***fluoroquinolone*** */ E. coli in humans and animals,*
- ***cephalosporins*** *3rd & 4th G in E. coli in humans,*
- ***tetracyclines*** *and* ***polymyxins*** *in E. coli in animals.*
- ***carbapenems*** *&* ***polymyxins*** */ K. pneumoniae in humans*
- ***macrolides*** *in animals have been associated with cross-resistance to Campylobacter spp. in animals and humans.*
- ***Cephalosporins*** *of 3rd & 4th G = cross-resistance to fluoroquinolone / E. coli in humans,*
- ***fluoroquinolone*** */ Salmonella spp. & Campylobacter spp. in humans was linked to AT with fluoroquinolone in animals.*

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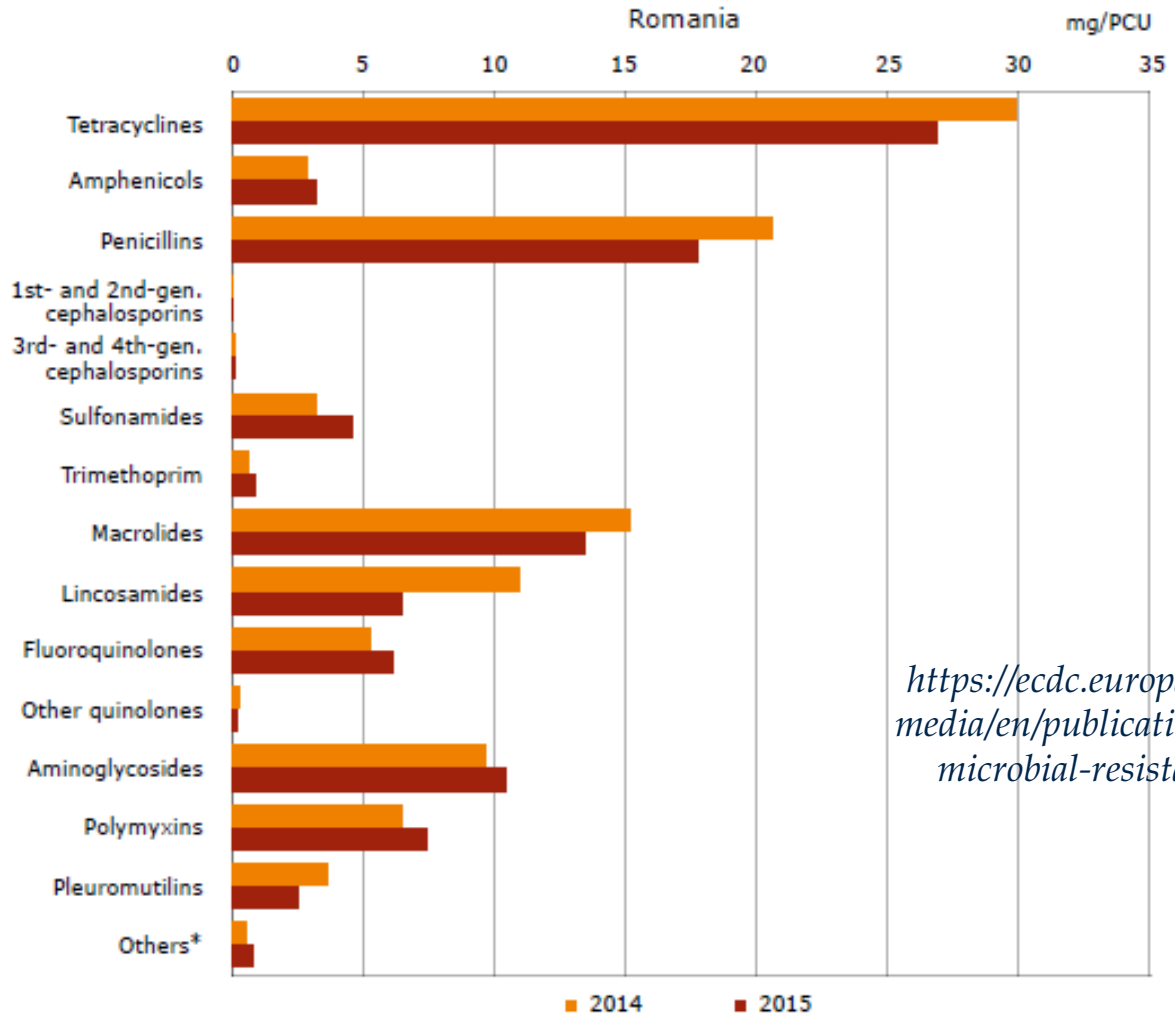
Romania

Sales (mg/PCU) by antimicrobial class in Romania, from 2014 to 2015



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https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/antimicrobial-resistance-europe-2015.pdf

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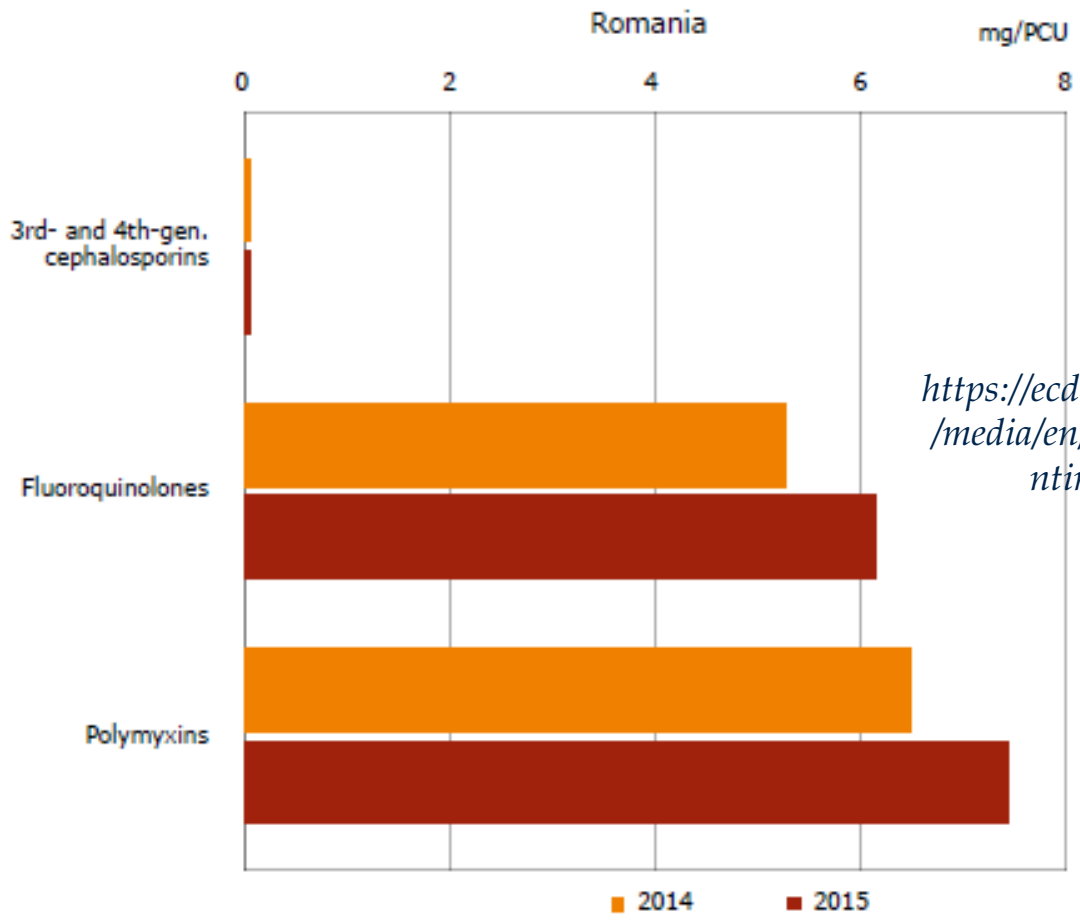
Sales (mg/PCU) of 3rd- and 4th-generation cephalosporins, fluoroquinolones and polymyxins in Romania, from 2014 to 2015



Source:
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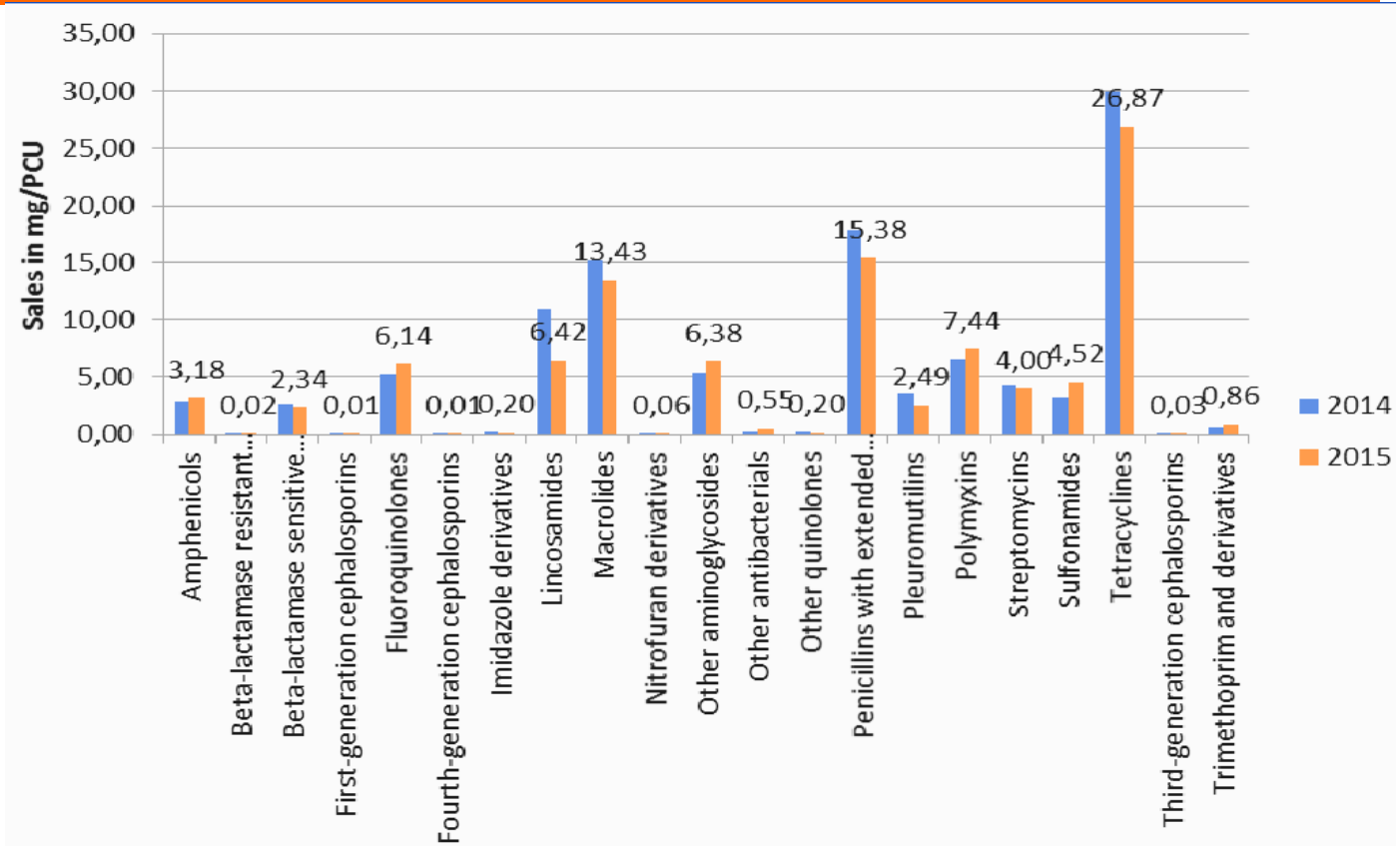
Romania (comparison 2014 / 2015)



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Mechanisms & Consequences

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AMR = *consequence:* ***evolution, natural selection and genetic mutation!***

The massive use of drugs, especially anti-infectives, exerts a ***major selection pressure*** *followed by the emergence of resistant microorganisms in human and animal populations.*

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*The **conditions** that lead to the emergence of antibiotic resistance*

*By selection the bacterial genome has become **1000 times smaller** than the animal / human genome!*
*This is due to: "**rationalization of the genome**".*
*There is **fierce competition** for resources among the bacteria.*
*In order to maintain and reproduce the genome, the bacterium needs: **energy + resources**.*
*A large genome requires **more energy** to be kept in function and duplication.*

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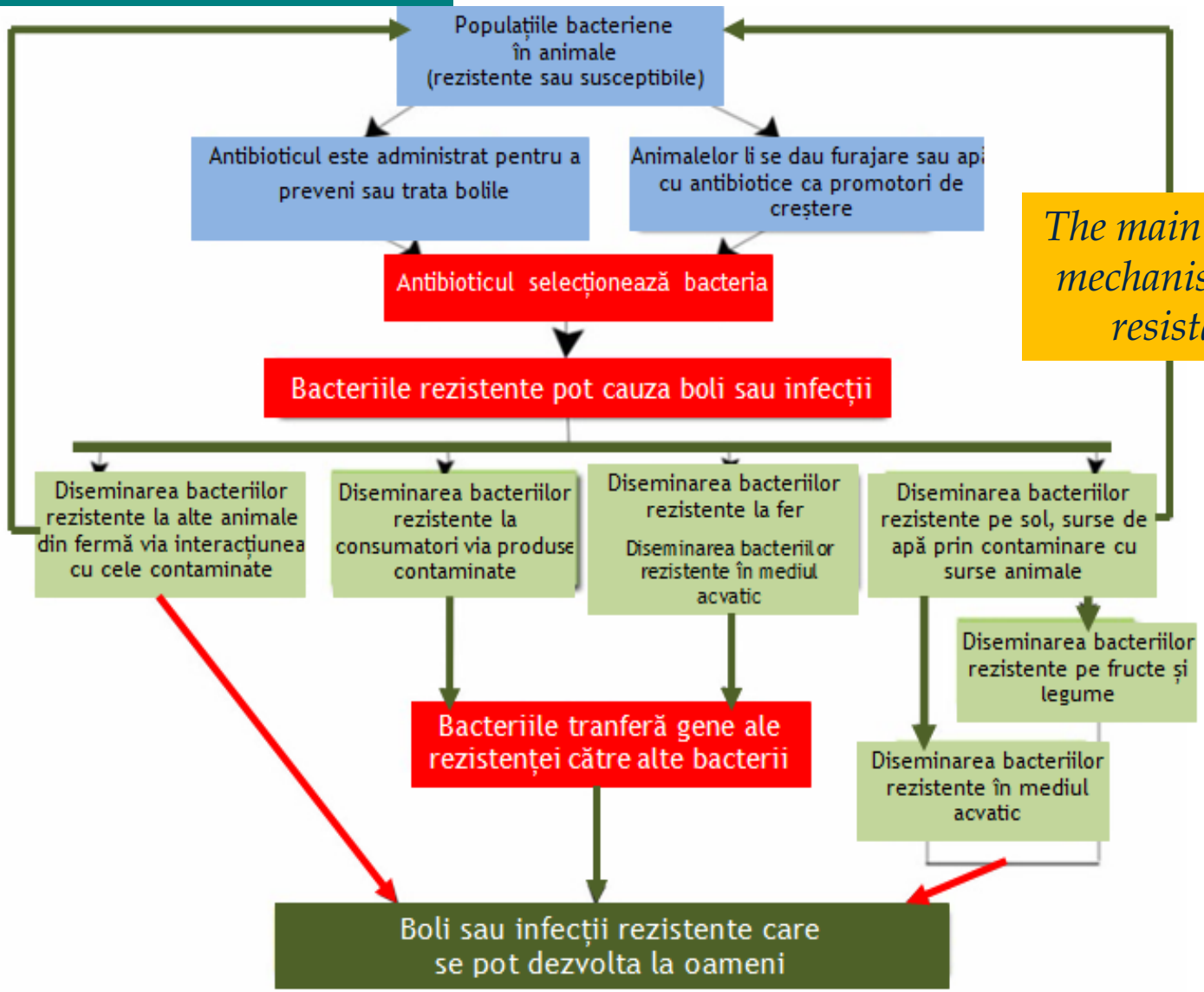

The main interactions in the mechanism of anti-bacterial resistance (Cristina 2018)

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Unfortunately

*Genomic screening techniques **have not yet been able** to deliver their promise of "**revolution**" in the discovery of new antibiotics!*

*This has led in time to the emergence of the "**superbugs**" = bacteria that is resistant to most of the used antibiotics.*

Classic examples :

- *Methicillin-resistant S. aureus (MRSA),*
- *M. tuberculosis super-resistant to antibiotics.*

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Evolution of drugs to ***" Superbug Era"***

Source:
http://amrls.cvm.msu.edu/images/pharm/timeline_01.jpg

Before 1930

Penicllin discovered (1928)

1930-1939

Sulfonamides discovered (1932)
Gramicidin discovered (1939)

1940-1949

Penicillin introduced (1942)
Streptomycin discovered (1943)
Bacitracin discovered (1943)
Cephalosporins discovered (1945)
Chloramphenicol discovered (1947)
Chlortetracycline discovered (1947)
Neomycin discovered (1949)

1950-1959

Oxytetracycline discovered (1950)
Erythromycin dicovered (1952)
vancomycin discovered (1956)
Kanamycin discovered (1957)

1960-1969

Methicillin introduced (1960)
Ampicillin introduced (1961)
Spectinomycin reported (1961)
Gentmicin discovered (1963)
Cephalosporins introduced (1964)
Vancomycin introduced (1964)
Doxycycline introduced (1966)
Clindamycin reported (1967)

1970-1979

Rifampicin introduced (1971)
Tobramycin discovered (1971)
Cephamycins discovered (1972)
Minocycline introduced (1972)
Cotrimoxazole introduced (1974)
Amikacin introduced (1976)

1980-1989

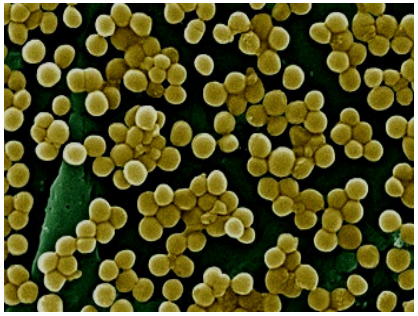
Amoxicillin-clavulanate introduced (1984)
Imipinem/cilastin introduced (1987)
Ciprofloxacin introduced (1987)

1990-1999

Azithromycin introduced (1993)
Quinupristin/dalfopristin introduced (1999)

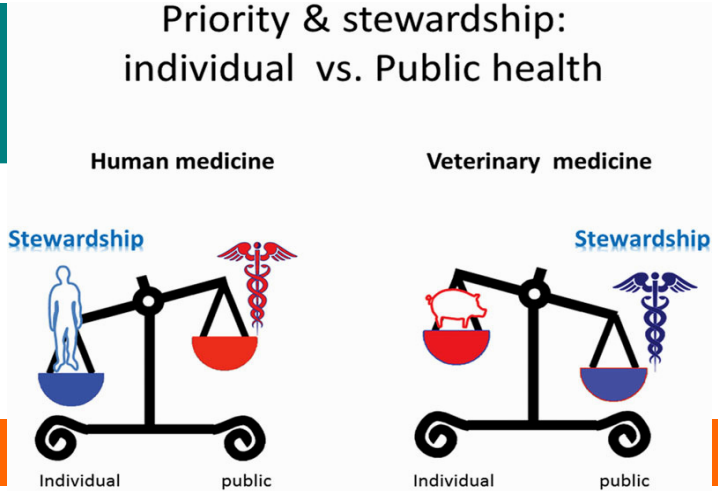
2000 onwards

Linezolid introduced (2000)
Cefditoren introduced (2002)
Daptomycin introduced (2003)
Telithromycin introduced (2004)
Tigecycline introduced (2005)



Sursa:
http://img.timeinc.net/time/daily/2007/0706/a_lantibiotics_0618.jpg

Fact !



Source: *https://www.frontiersin.org/files/Articles/206029/fmicb-07-01196-HTML/image_m/fmicb-07-01196-g003.jpg*

The spread and transmission of the resistance genes is ***crossed*** *and* ***has been demonstrated*** *as possible between:*

- ***humans - animals,***
- ***animals - humans****, and between*
- ***animals - environment.***

In this regard, it is essential to note that: ***in respect of One Health,*** *a lasting antimicrobial veterinary treatment must be* ***related to the public health*** *and* ***not to the*** *animal health problems!*

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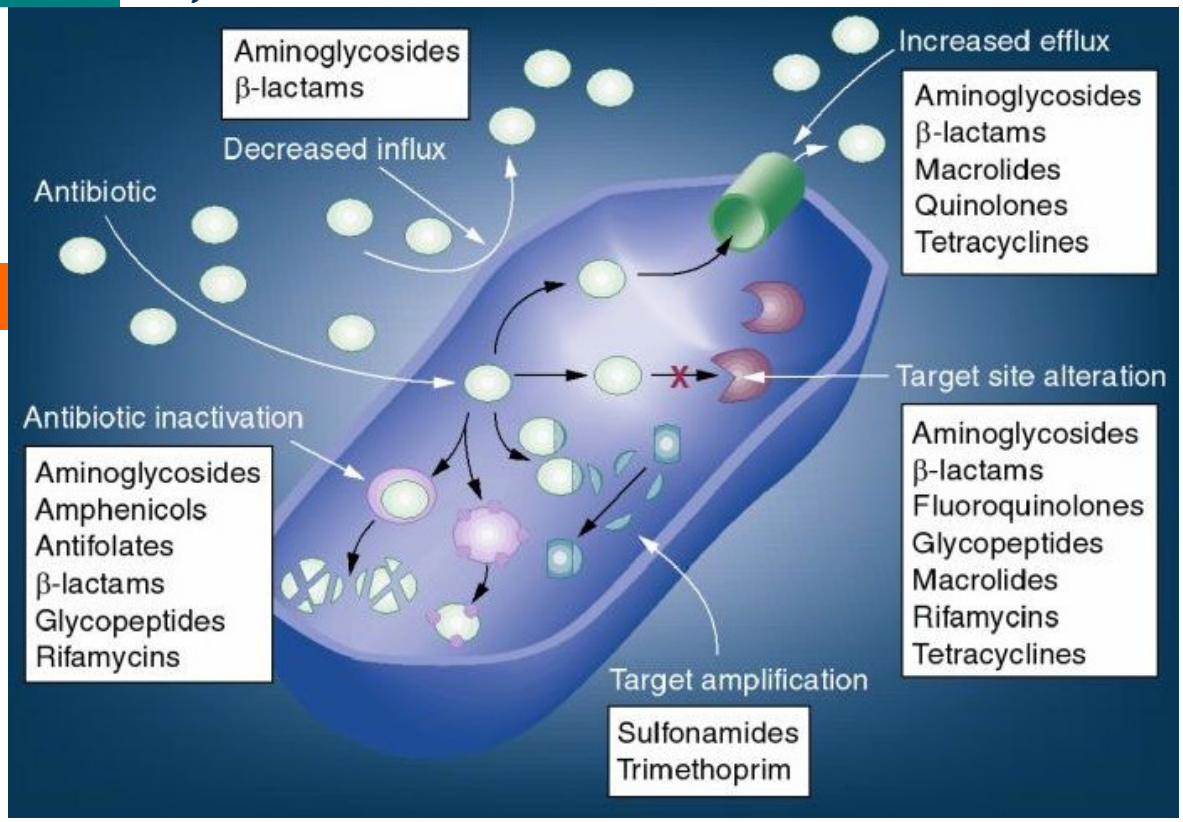
Specific antibiotic resistance interactions (after EMA)



Source: http://images.forbes.com/media/magazines/forbes/2006/0619/Forbes_0619_p70_f1.gif

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Excessive antibiotic prescribing is not the only source of antibiotics that pollutes the environment!

*As early as the **1970s**, antibiotics could be found in the meat of cattle, pigs, and birds, and the **same antibiotics (!)** were later identified in the municipal and ground water systems or in the soil, with its dramatic consequences!*

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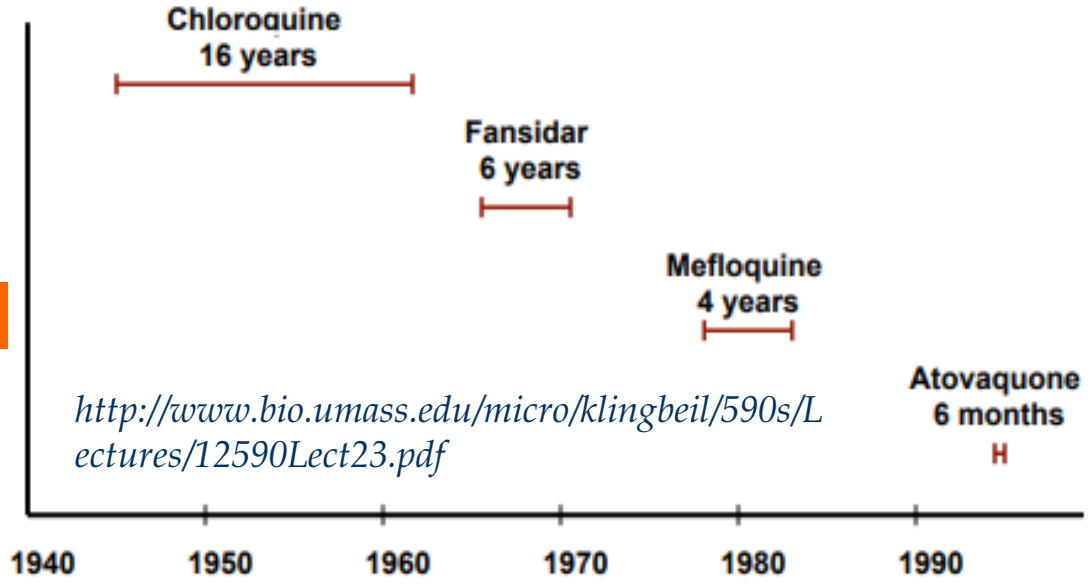
For example :



http://www.bio.umass.edu/micro/klingbeil/590s/Lectures/12590Lect23.pdf

The emergence of fluorochinolone resistance after commonplace infections with Campylobacter and E. coli in humans is clear following their use in animal feed with the transmission of human-resistant bacteria ***through meat and animal products!***

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Fact !

Most reports refer to the trend of increasing use of antimicrobial substances used in ***sub-therapeutic*** *doses in chickens and birds.*

Both molecular and epidemiological evidence indicates that the prevalence of antibiotic resistance among humans was triggered by the introduction of ***enrofloxacin*** *in bird feed, which led the FDA in 2011 to* ***ban*** *the use of this drug in poultry.*

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Fact !

An increase in the frequency of resistance to ***quinolones*** *among human and animal strains has already been demonstrated for Salmonella enteritidis and Campylobacter spp.*

A ***multiple*** *resistance of Salmonella typhimurium to:* ***ampicillin, chloramphenicol, streptomycin, sulfonamides and tetracycline (ACSSuT),*** *was also reported*

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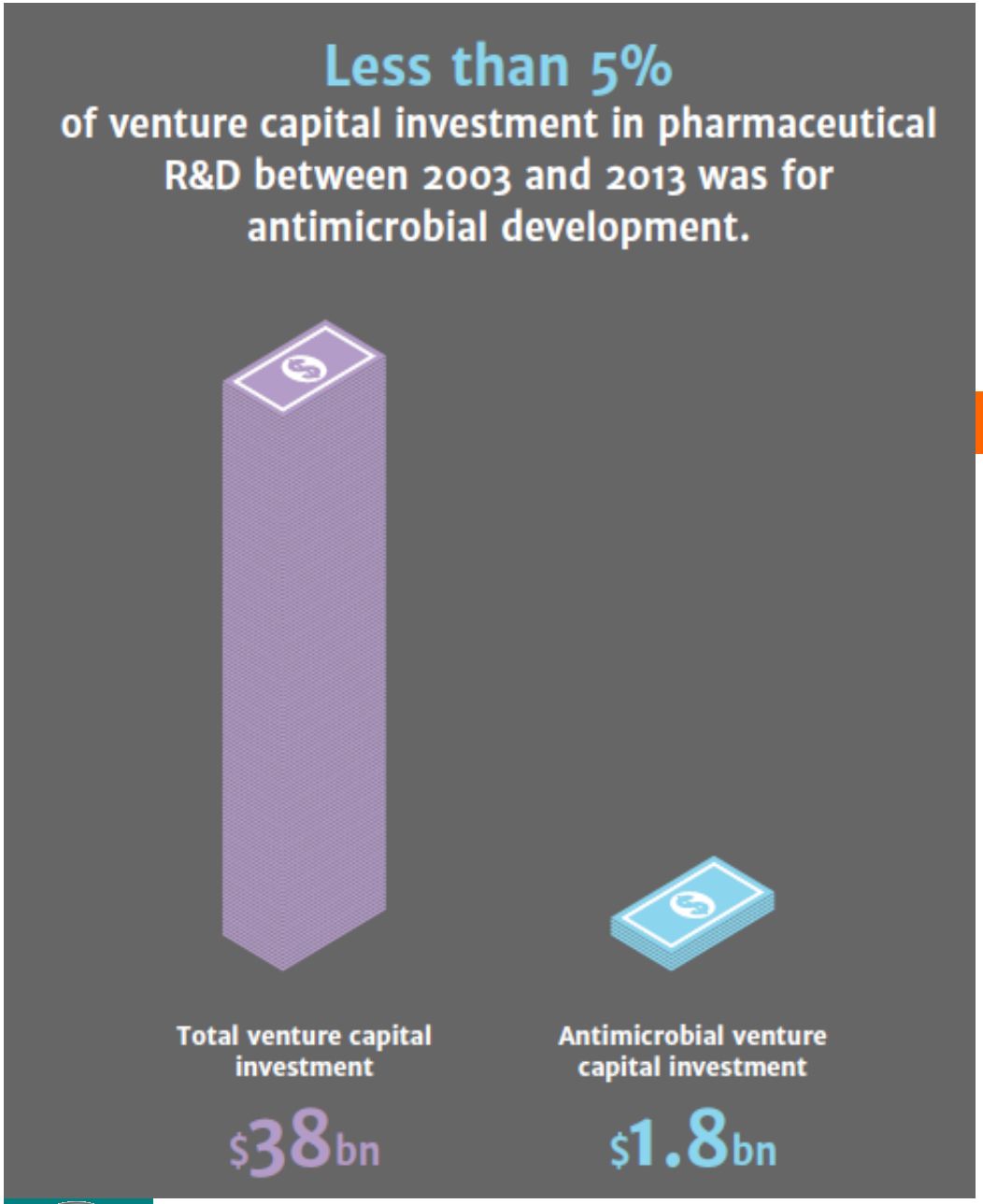

Source:
https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf

Major threats

!

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*AMR is **not** a problem that can be solved **by any one country**, or even any one region... Our broad estimate for the cost of taking global action on AMR is up to **40 billion USD** over a **10-year period** (Jim O'Neil, 2016)*

!

2014 **800** *(oncogenes)*

50 *(antibiotics)*

prophylaxis

4.5 / an

60

U S N I H

1.2% antibio

18,6% onco

UK: ***Swine flu* = 1.9** *billions USD / year*

SUA: ***Ebola* = 5.4** *billions USD / year*

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*Of the **40,000,000** Americans who take antibiotics for respiratory problems / year*

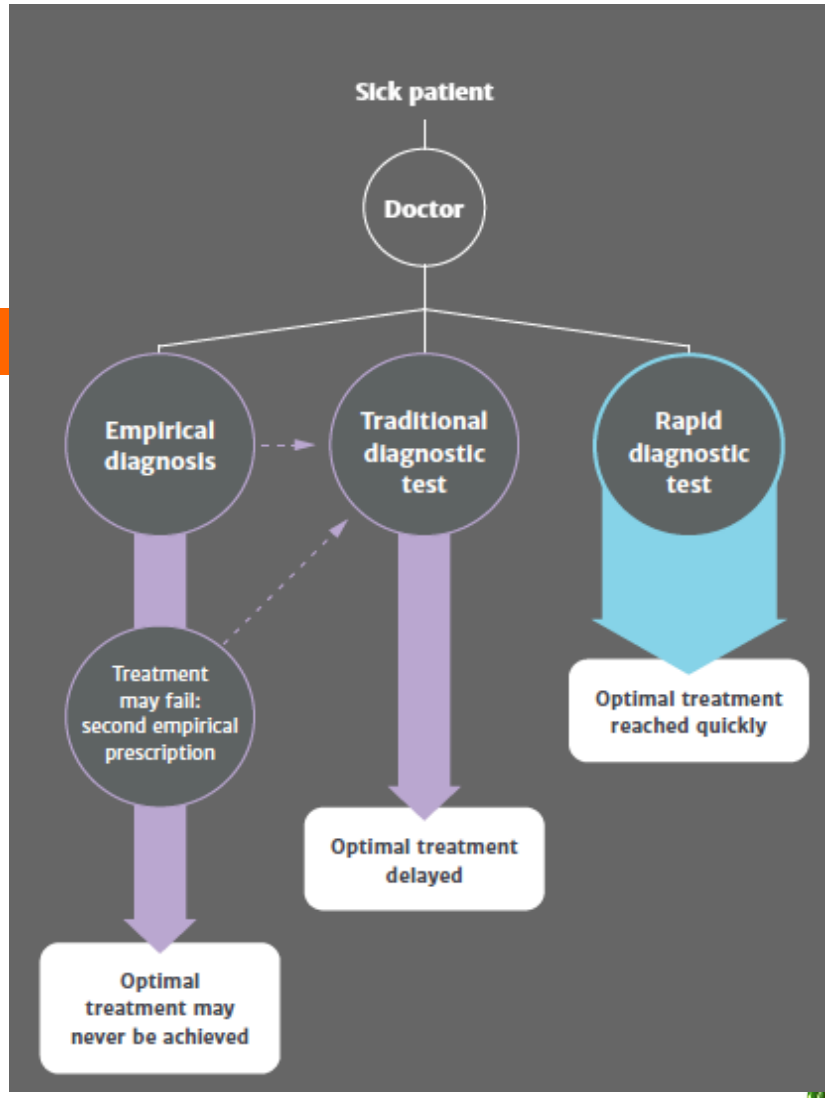
***27,000,000** take them for nothing!*

Today, antibiotics are rarely prescribed based on a definitive diagnosis.

Diagnostic tests can show whether or not an antibiotic is actually needed, and which one.

Dr Margaret Chan,

Director General of the WHO



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!

30.000-70.000 tones

10-20%

200 factories

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Fact!

Organ / țesut	Cal	Câine	Capră	Vacă	Om
Sânge	8,60	-	4,70	7,80	-
Creier	0,21	0,51	0,29	0,06	2,00
Cord	0,66	0,82	0,48	0,37	0,47
Pulmon	0,89	0,89	0,88	0,71	1,40
Ficat	1,30	2,32	0,95	1,22	2,60
Splină	1,11	0,26	0,25	0,16	0,26
Rinichi	0,36	0,61	0,35	0,24	0,44
Intestine	5,80	3,90	6,40	3,80	1,70
Continut intestinal	12,30	0,72	13,90	18,40	1,40
Piele	7,45	9,30	9,20	8,30	3,70
Mușchi	40,10	54,50	45,50	38,50	40,00
Oase	14,60	8,70	6,30	12,70	14,00
Tendoane	1,71	-	-	-	2,00
Tesut adipos	5,10	-	-	18,09	18,10
Greutate medie	380,0	16,0	39,0	620,0	70,0

Proporția distribuției în diferite organe și tesuturi (Sinteză, Cristina, 2000)

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Fact!

Antibiotics given to animals ***are not completely*** *absorbed by them!*

Depending on the antibiotic, ***between 30 and 90%*** *of the antibiotic may be excreted in the urine or faeces in the* ***bioactive*** *state, even intact or in the form of antibiotic metabolites, which* ***may retain*** *their antimicrobial activity. Antibiotics administered to animals often reach* ***soil*** *and* ***water*** *through medical waste and improperly disposed medicines or dust from industrial growth units.*

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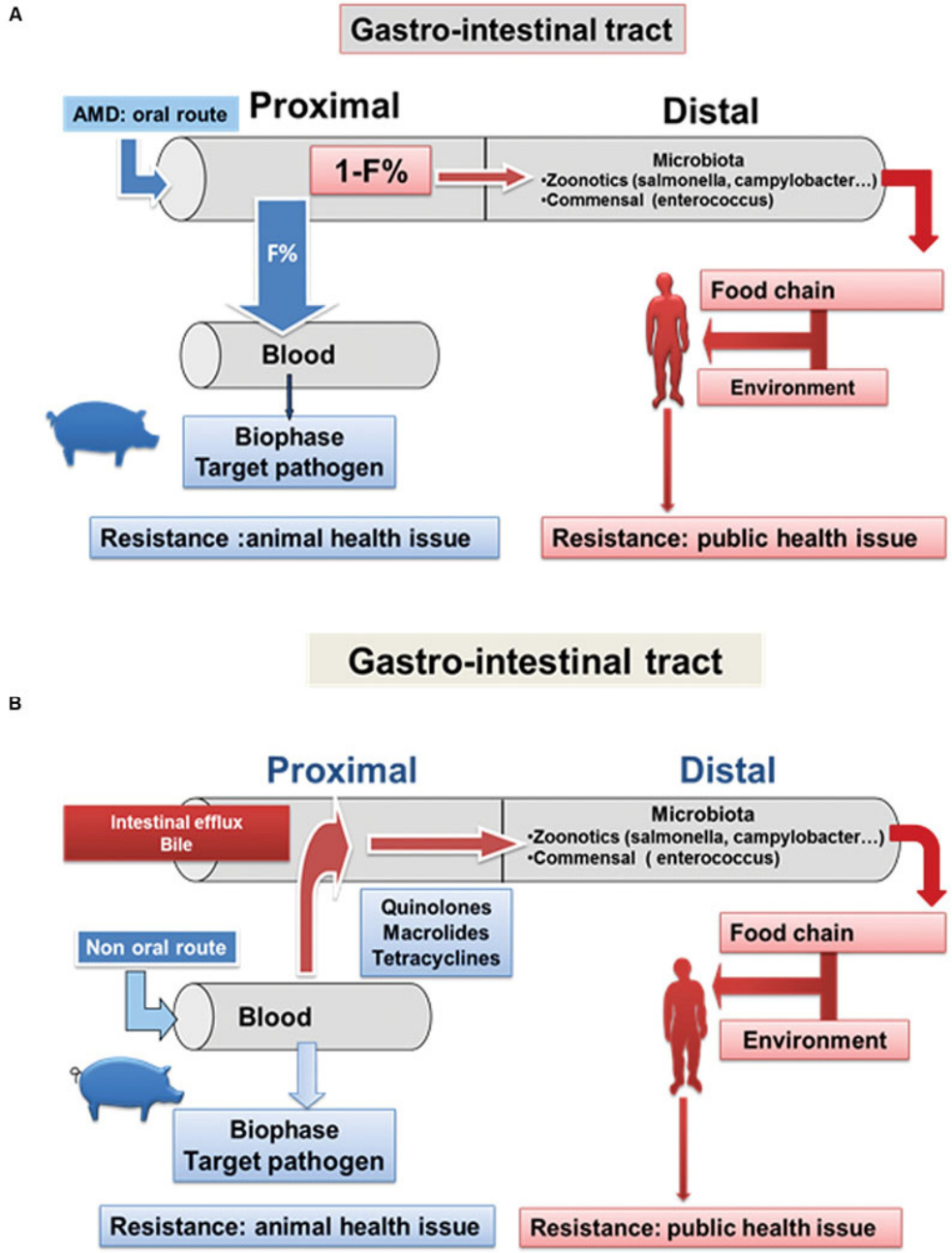
Impact of antibiotic administration

Source:
https://www.frontiersin.org/articles/10.3389/fmicb.2016.01196/full



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*After **oral** administration*

The distal intestinal microbiota includes zoonotic pathogens and commensal flora.

*It will be exposed to the fraction of unabsorbed drug in the proximal digestive segment = **local selective pressure increases** = **increases the density of bacteria** and therefore **the frequency of resistance genes!***

*Resistant bacteria + resistance genes are released into the environment **via faecal excretion**.*

*These organisms and genes can reach humans, in several ways and finally, they will have access to the human GIT microbiota through the **main metabolic pathway = food chain.***

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after ***systemic*** *administration*

Most a.u.v. are eliminated, and get to GIT, either by ***biliary secretion*** *or by* intestinal ***clearance*** *= emergence of drug* ***concentrates*** *capable of selecting resistant organisms = negative effects*

In addition, the impact of antibiotics on the animal TGI microbe is not limited to the ***aerobic fraction*** *- 1-2% of the total microbe; (usually Escherichia coli și E. faeciens - considered sentinel bacteria) - can also generate a negative impact on the* ***anaerobic population*** *(which is a much larger sequence)!*

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Dr Keiji Fukuda,
the Director General's
Special Representative for Antimicrobial Resistance
at the World Health Organization (WHO)

The basics of public health – clean water, good sanitation and hygiene, infection prevention and control and surveillance – are as critical for reducing the impact of antimicrobial resistance as they are for infectious disease control…

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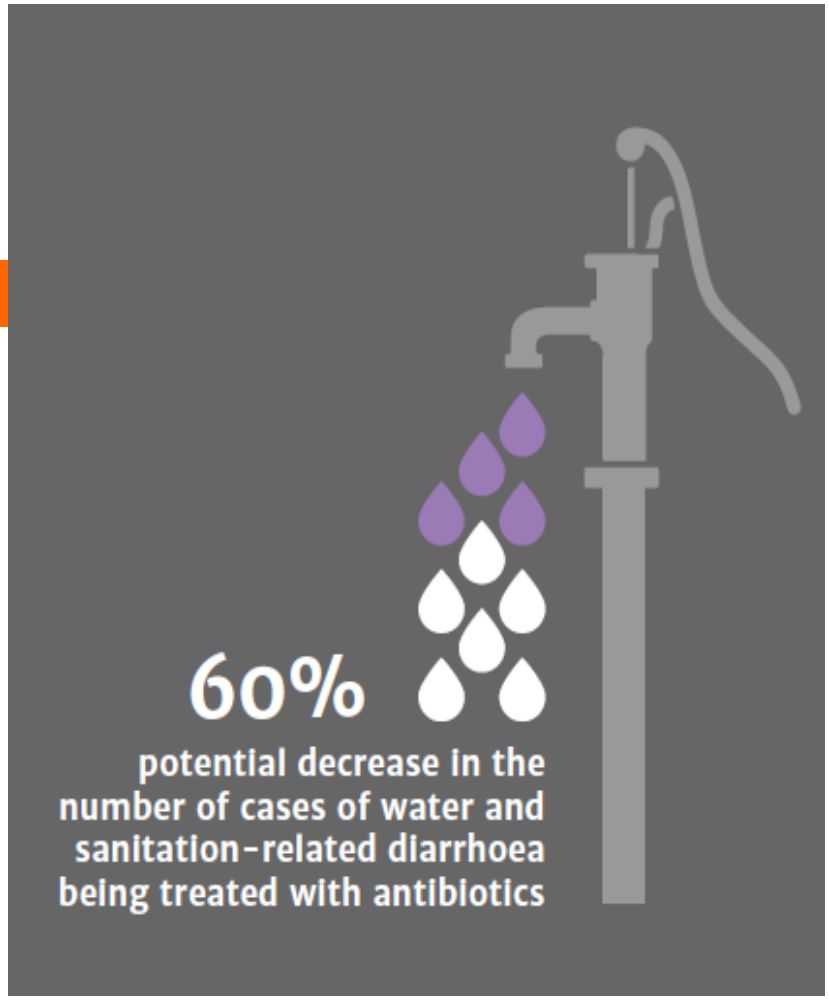
Fact!

Antibiotics that have been identified in surface waters have often included :

- *macrolides,*
- *sulphonamides*
- *tetracyclines,*
- *chloramphenicol,*
- *chlortetracycline,*
- *sulfamethazine*
- *lincomycin*
- *trimethoprim,*
- *sulfadimethoxin*
- *sulfamethazine.*



Source:
https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf

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One World, One Health and "One Resistome"....

*Given that the countries of the **G20** account for **80%** of total world meat production…, a large part of antibiotic consumption in livestock and the likelihood of generating drug resistance, currently rests with them.*

(Jim O'Neil, 2016)

What to do?

10-year targets to reduce unnecessary antibiotic use in agriculture, introduced in 2018….

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Medication limitations today :

- *unsatisfactory bioavailability*
- *limited effect*
- *cytotoxicity*
- *long and frequent treatments*

In this context, new specific features that may reduce morbidity and mortality are needed!

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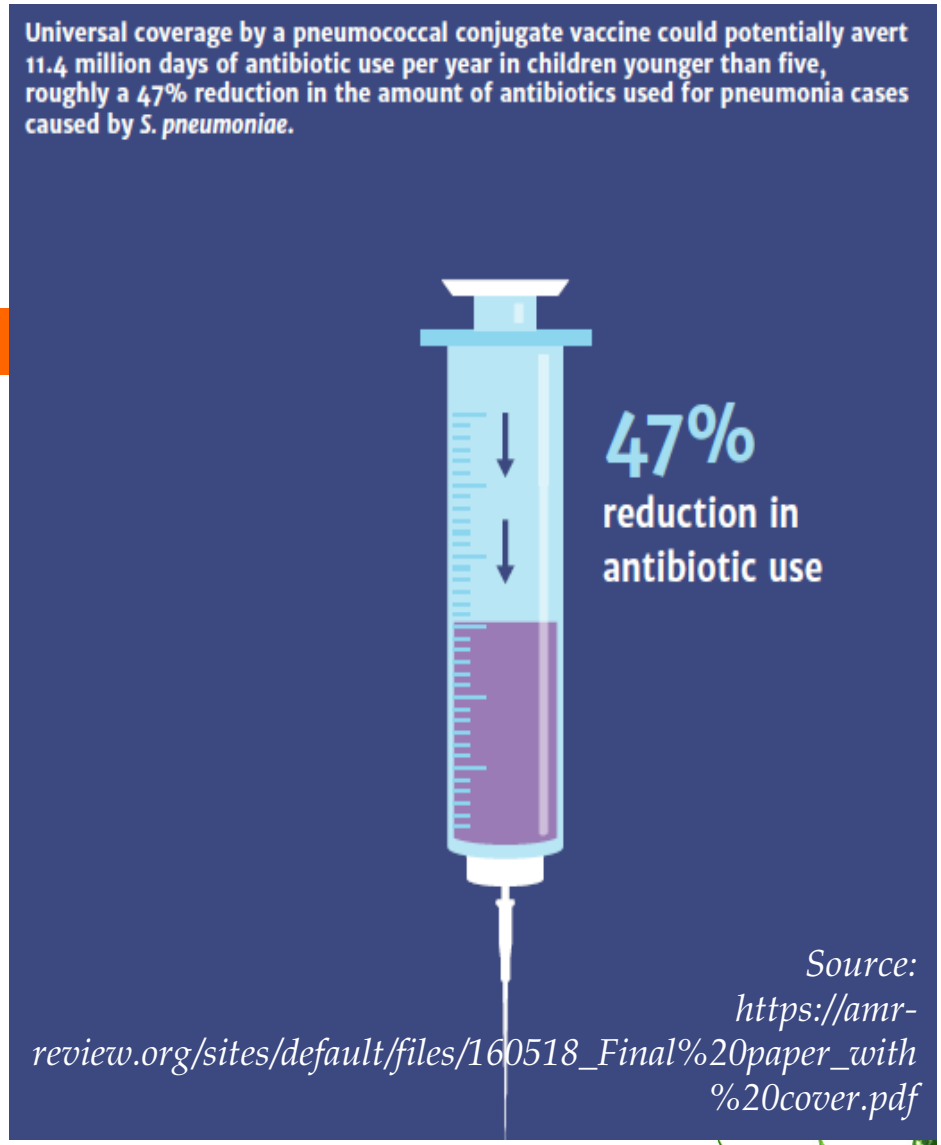
Sally Davies,

Chief Medical Officer for England

*Tackling antimicrobial resistance requires a **wide range of approaches and developing alternatives** to antibiotics, in humans and animals, is critical to the fight. Vaccines have a vital role to play in combating drug resistance, by preventing infections in the first place.*



Source: https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf

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*Attractive **alternatives** to vaccines could be:*

- ***pathogen pecific antibodies,***
- ***immunomodulatory agents,,***
- ***bacteriophages,***
- ***antimicrobial peptides and***
- ***pro, pre- or symbiotic products.***

***Examples** of antibiotic use reduction:*

- *an effective vaccine for the prevention of furunculosis in Norway (Midtlyng et al., 2011).*
- *the use of a vaccine to prevent enteritis caused by Lawsonia intracellularis in pigs.*

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A selection of alternative products that are under development, which could be used for prevention or therapy.

Phage therapy

Natural or engineered viruses that attack and kill bacteria

Lysins

Enzymes that directly and quickly act on bacteria

Antibodies

Bind to particular bacteria or their products, restricting their ability to cause disease

Probiotics

Prevent pathogenic bacteria colonising the gut

Immune stimulation

Boosts the patient's natural immune system

Peptides

Non-mammalian animals' natural defences against infection

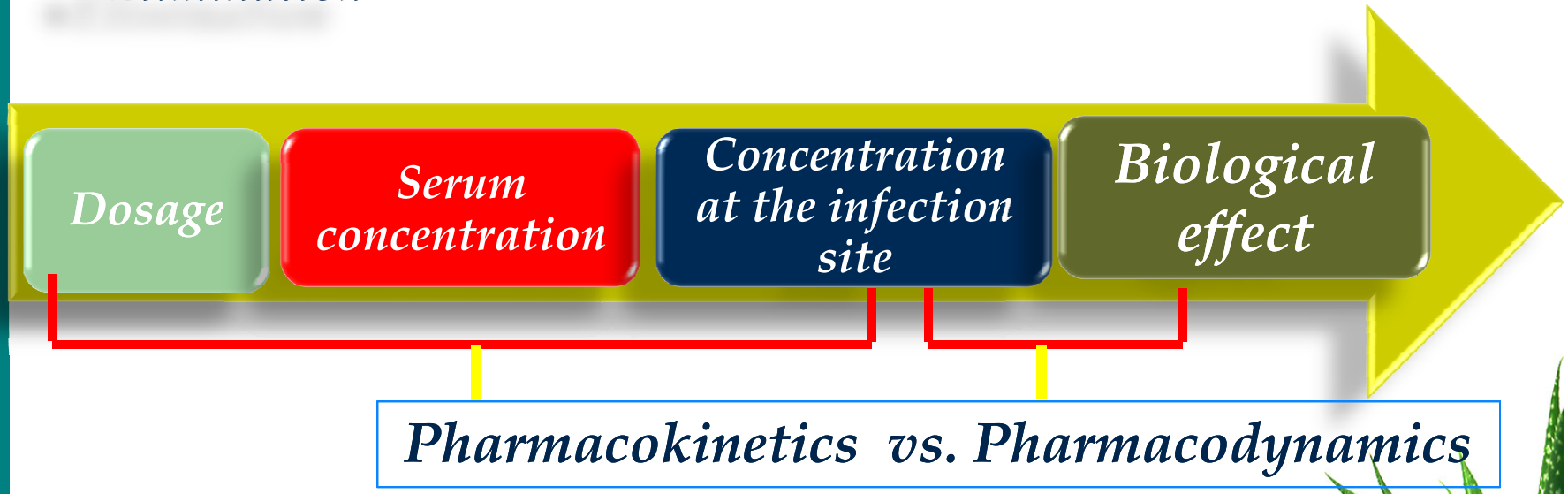
Source: *https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf*

Pharmacokinetics vs. Pharmacodynamics

- *Absorbtion*
- *Distribution*
- *Metabolism*
- *Elimination*

Effect on pathogens

Source:
Cristina RT; http://www.veterinarypharmacon.com/docs/899-Curs-4-5.S.II.pdf



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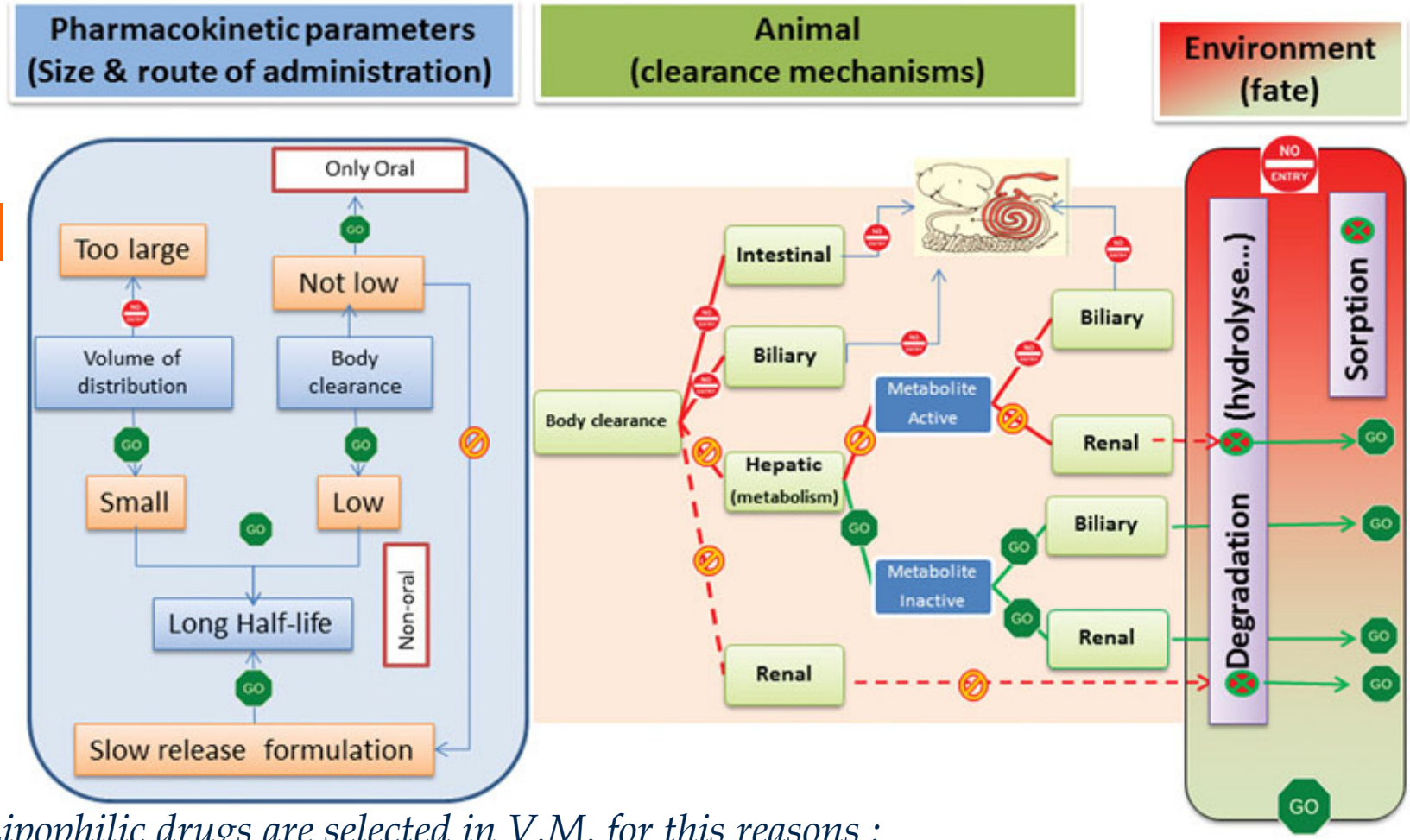
Eco-green drugs…



Lipophilic drugs are selected in V.M. for this reasons :

- the need for ***retardation*** *and* ***correlation with t 1/2.***

- the development of new and eco-green drugs: ***ceftaroline, telavancin and dalbavancin.***

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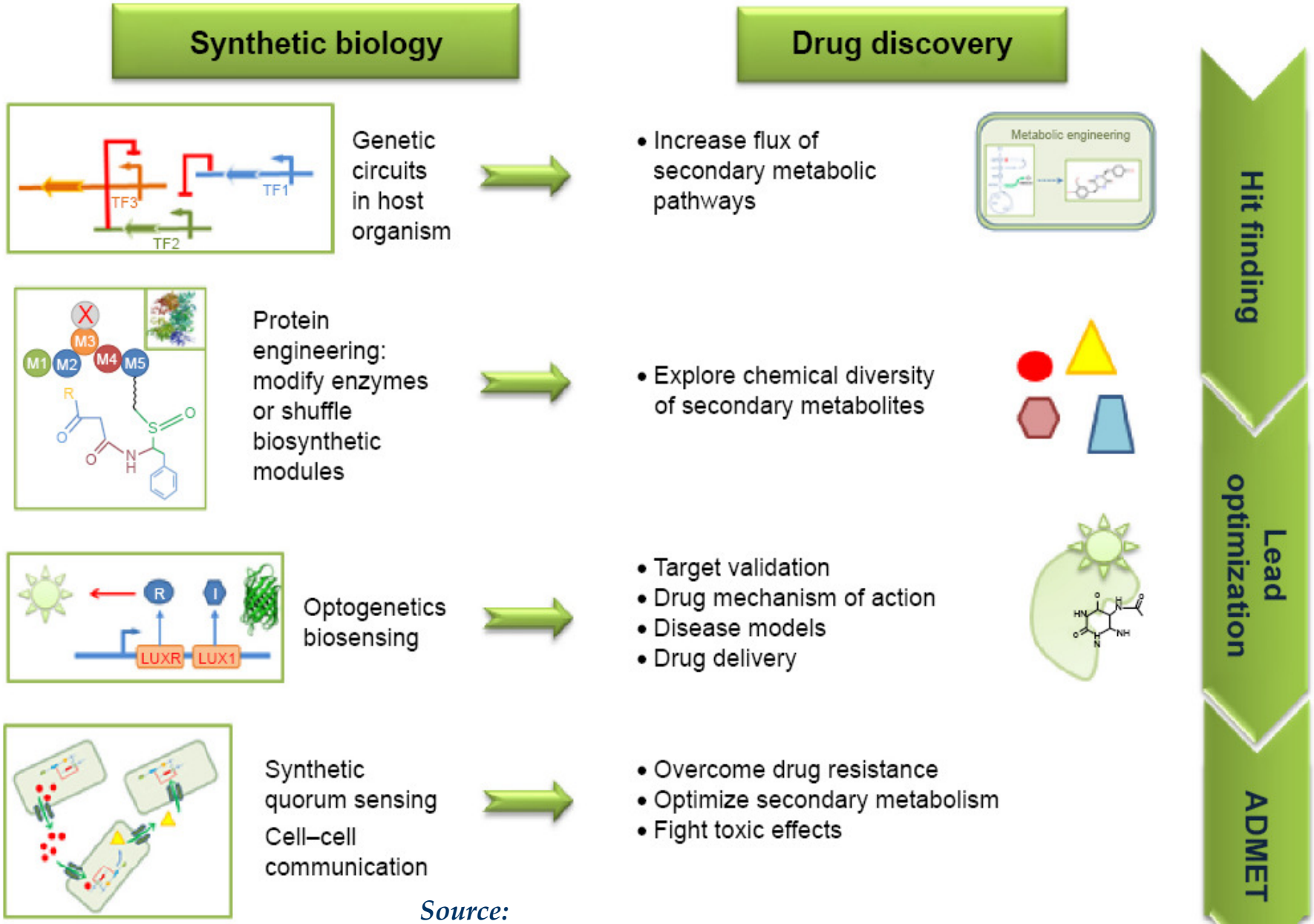

Source:
https://www.dovepress.com/synthetic-biology-for-pharmaceutical-drug-discovery-peer-reviewed-fulltext-article-DDDT

Figure 2 Synthetic biology tools in various steps of drug discovery.
Abbreviations: ADMET, absorption, distribution, metabolism, excretion, and toxicity; TF, transcription factor.

Other viable alternatives

Nanobiotechnology

a) minimal invasive therapy
b) high density functions
c) concentrations in very small volumes

Nano-devices

- *maximizes therapeutic activity*
- *minimizes secondary toxic effects*
- *target specific cells and not tissues*

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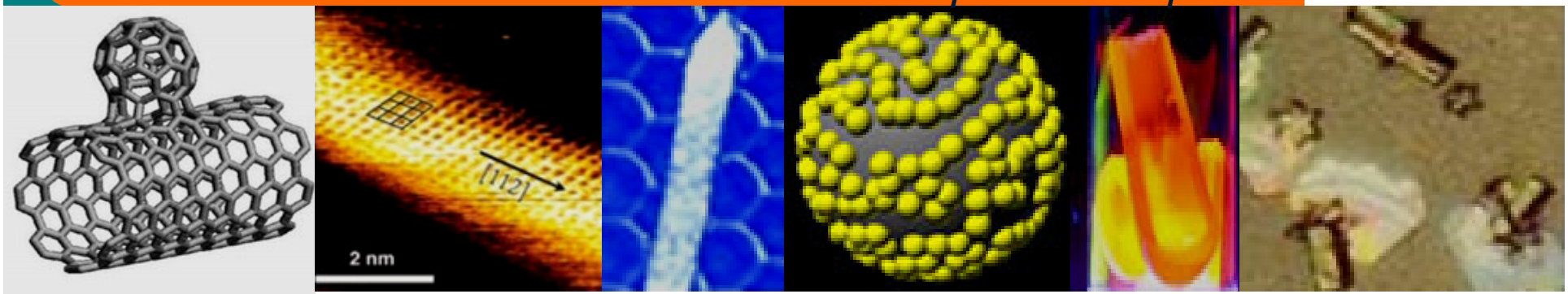
Nano-devices

Nanotubes *Nanowires* *Nanostructures* *Nanospheres* *Nanopores* *Fullerenes*



They are increasingly sophisticated due to molecular studies this allowing them to :

1. *target,*
2. *identify,*
3. *specifically release the active substance,*
4. *monitor real-time therapeutic efficacy.*

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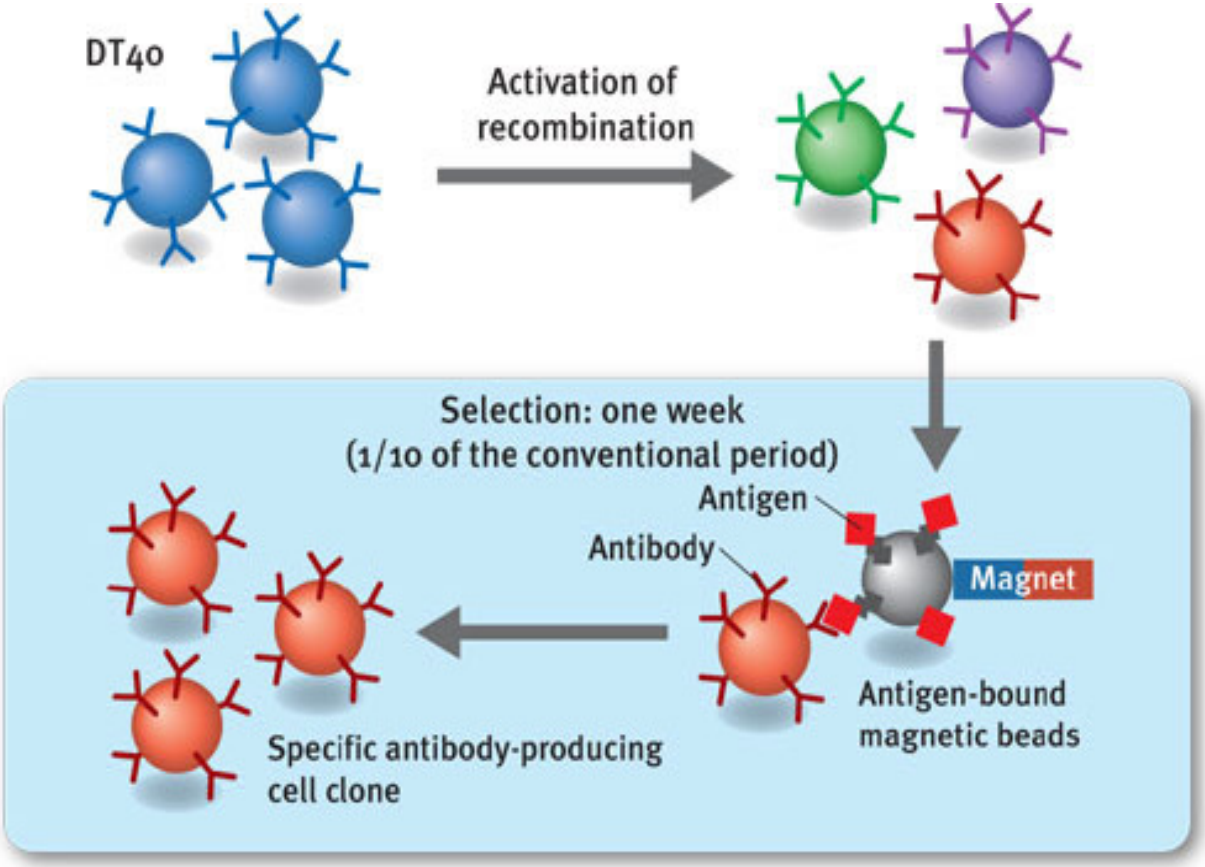
ADLib

New way** to produce antibodies! It opens the way for applications in the field of diagnostic products for **customized treatments.



Source: *www.rikenresearch.riken.jpg*

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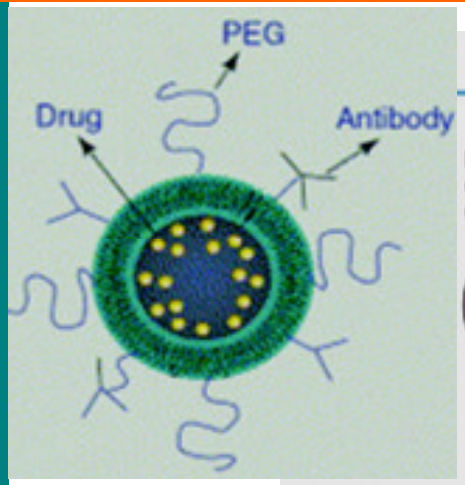
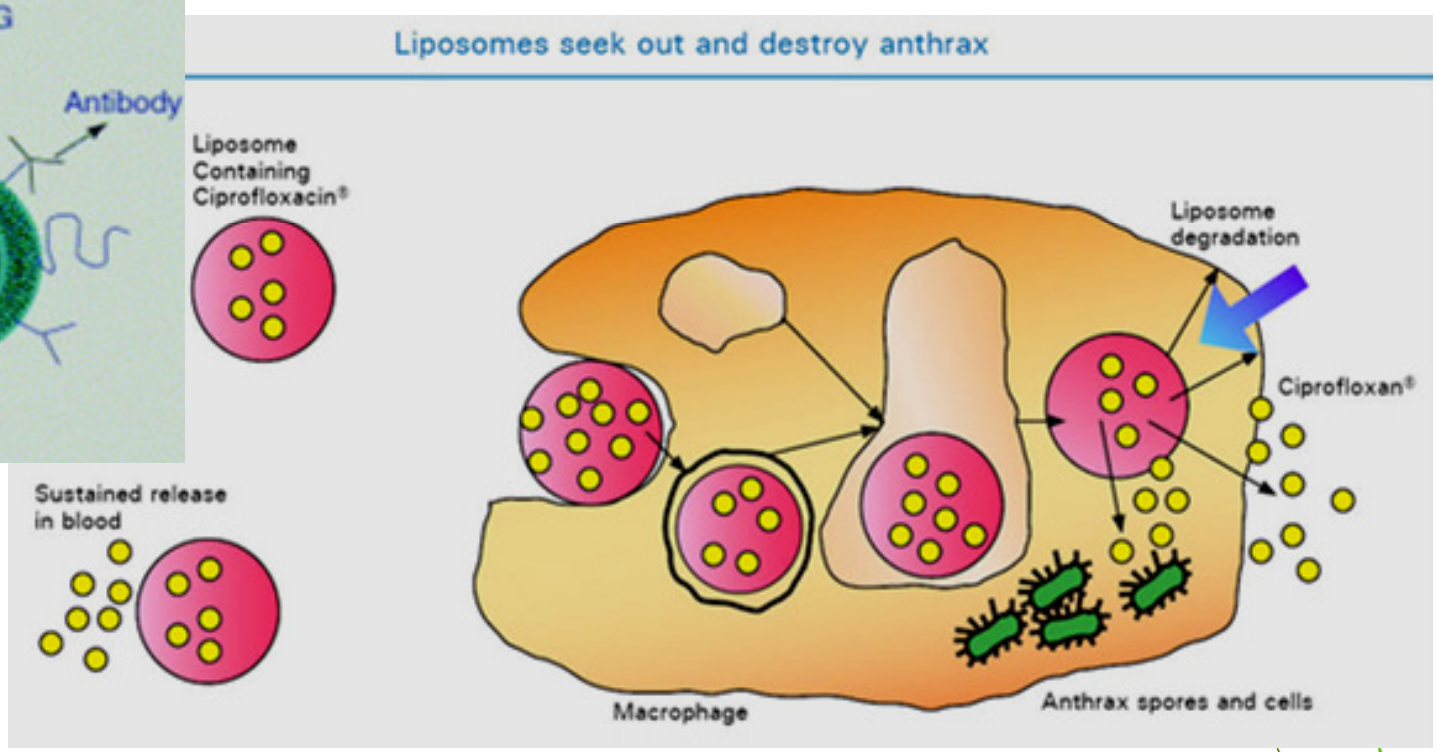
Liposomes





***Source**: http://s3.amazonaws.com/readers/healthmad/2007/07/22/43701_0.jpg*

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Genetics

*Researchers **genetically reprogrammed** an E. coli serotype. It can kill even other groups of bacteria responsible for infections difficult to treat present in: lungs, bladder or implanted medical devices.*

Genetically reprogrammed E. coli

*Sursa imagini: http://sa-mcp.s3.amazonaws.com/up-image/img_rend/500/188.jpg **(stânga)***
*http://www.biosciencetechnology.com/sites/biosciencetechnology.com/files/legacyimages/bt1310acs.jpg **(dreapta)***

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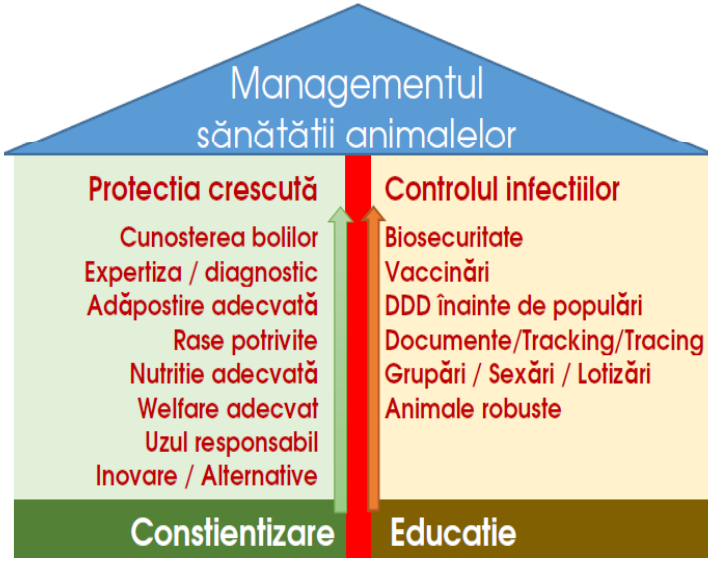
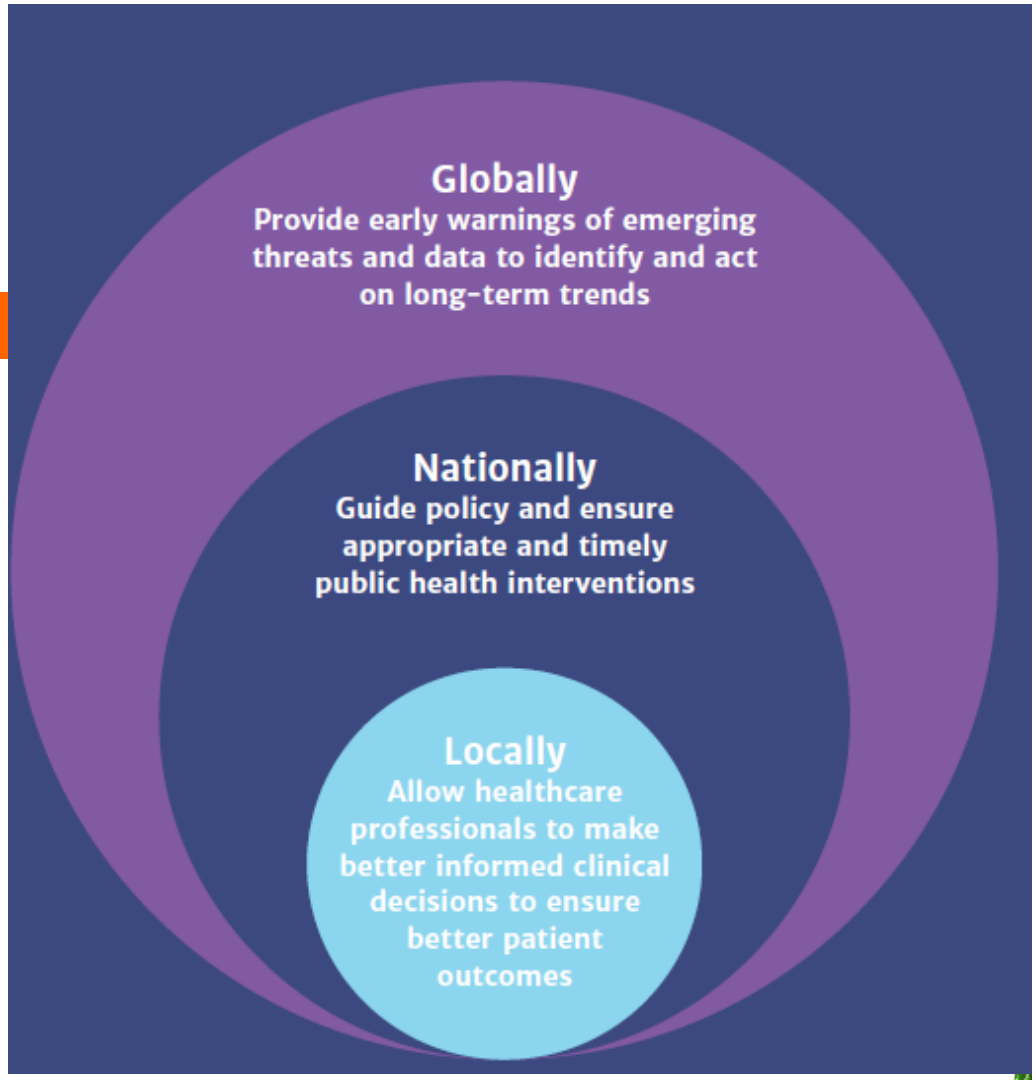
Conclusions

Source: EPRUMA, 2008





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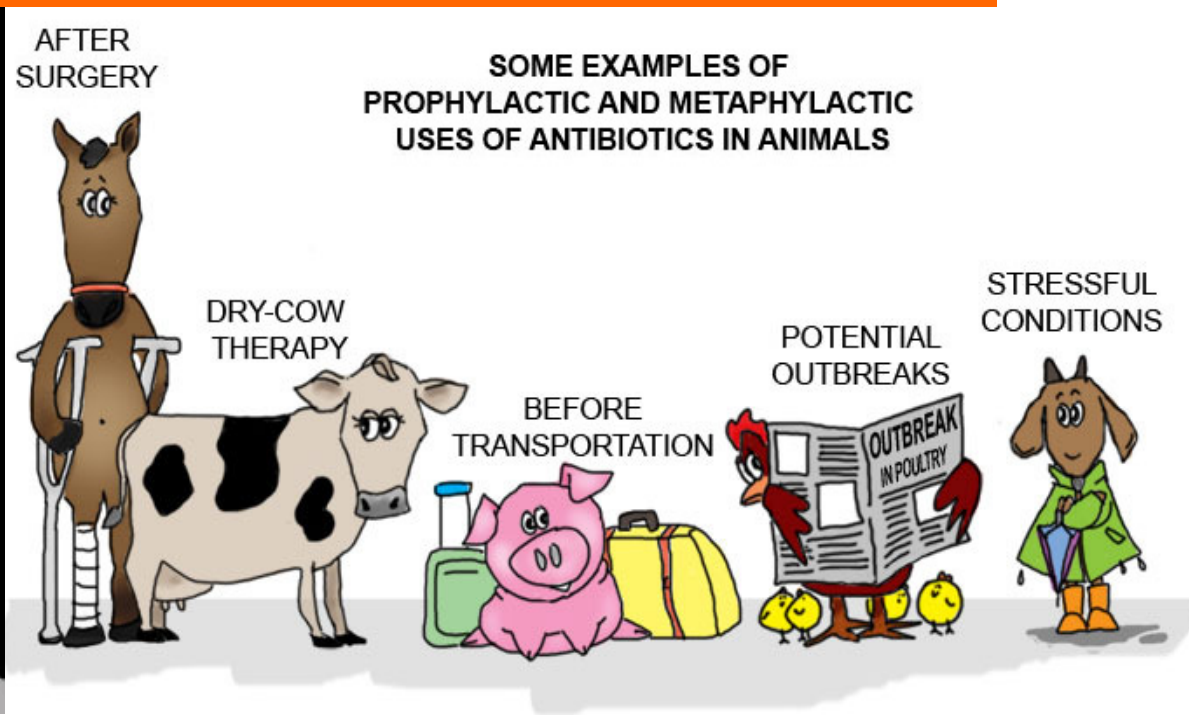
Key -actor	*Specific contribution*
Profile organizations (national and regional))	• *education about antibiotics and their use* • *stimulating the awareness of antibiotic resistance* • *regulating the circulation of antibiotics* • *restricting the use of growth promoters in animals* • *regulation and control of the use of antibiotics in animals* • *identification and quantification of regional resistance phenomena* • *knowing the established risk standards for resistance* • *simultaneous monitoring of the use of human and veterinary antibiotics* • *advertising in the field*
Veterinarians	• *promoting the prudent use of antibiotics in animals* • *improving hygiene conditions in cabinets, hospitals or interventions* • *use narrow spectrum agents whenever possible* • *not all infections need antibiotics* • *the use of vaccines as a means of preventing infections* • *limit antibiotic doses in case of surgery* • *the use of antibiotics only in bacterial infections and not for non-infectious ones* • *developing local guidelines for the use of antibiotics*
Manufacturers of animal origin food products	• *improving hygiene in breeding/growing units* • *reducing or eliminating the use of antibiotics as growth promoters* • *improving livestock technologies*
Researchers	• *the study and launch of new representatives or classes of antibiotic agents* • *the study and launch of new anti-infective vaccines* • *the study and launch of medical devices (eg impregnated catheters)* • *performing risk-benefit analyzes for the use of growth promoters* • *assessing the environmental impact following the use of antibiotics* • *assessment of the processing and distribution of food products*

Thank you for your attention!

[redacted]

Source:
http://blog.nouadreapta.org/wp-content/uploads/2011/01/caricatura_zilei-23411-250x300.jpg



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Consulted bibliography

***Sales** of veterinary antimicrobial agents in 30 European countries in 2015. Trends from 2010 to 2015. **Seventh ESVAC** report 30 October 2017. EMA/184855/2017 - Veterinary Medicines Division*

*Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) Report European **Centre for Disease Prevention and Control (ECDC),** European Food Safety Authority (EFSA) and European Medicines Agency (EMA) Approved: 28 June 2017 EFSA Journal 2017;15(7):4872*

doi: 10.2903/j.efsa.2017.4872

***Commission Guidelines** for the prudent use of antimicrobials in veterinary medicine / Orientări pentru utilizarea prudentă a substanţelor antimicrobiene în medicina veterinară (2015/C 299/04)*

***Lista O.I.E** a agentilor antimicrobieni importanti în medicina veterinară*

http://cmvro.ro/files/download/noutati/Lista_OIE_a_agentilor_antimicrobieni.pdf

***Ghidul EPRUMA**, 2015, 2018 - http://epruma.com*

***Selzer PM.** (2009). Antiparasitic and Antibacterial Drug Discovery - From Molecular Targets to Drug Candidates. Wiley-Blackwell-VCH, DE. ISBN: 978-3-527-32327-2*

http://file.zums.ac.ir/ebook/072-Antiparasitic%20and%20Antibacterial%20Drug%20Discovery%20rom%20Molecular%20Targets%20to%20Drug%20Candidates%20(D.pdf

***Cristina RT.** Farmacovigilenţă & Legislaţia produselor medical veterinare. Cursurile SNEC 2013. Disponibil la: http://www.veterinarypharmacon.com/docs/1222-2013-SNEC.pdf*

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Further bibliography

Aarestrup FM, Seyfarth AM, Emborg HD, Pedersen K, Hendriksen RS, Bager F. *2001. Effect of Abolishment of the Use of Antimicrobial Agents for Growth Promotion on Occurrence of Antimicrobial Resistance in Fecal Enterococci from Food Animals in Denmark. Antimicrobial gents and Chemotherapy. 45(7):2054-2059.*

American Veterinary Medical Association. *2005. Judicious Therapeutic Use of Antimicrobials.*

Boerlin P, White DG. *2006. Antimicrobial Resistance and its Epidemiology. Antimicrobial therapy in Veterinary Medicine 4th eds, S Giguère, JF Prescott, JD Baggot, RD Walker and PM Dowling, eds. Blackwell Publishing, Ames Iowa, USA. Bowman HHM. 1947. Antibiosis. The Ohio Journal of Science. 47(5):177-191.*

Chopra I, Roberts M. *2001. Tetracycline Antibiotics: Mode of Action, Applications, Molecular Biology and Epidemiology of Bacterial Resistance. Microbiology and Molecular Biology Reviews. 65(2):232-260*

Dixon B. *2006. Sulfa's true Significance. Microbe 1(11): 500-501.*

Forbes BA, Sahm DF, Weissfeld AS. *1998. Bailey And Scott's Diagnostic Microbiology, 10th ed. Mosby, US*

Giguère S. *2006. Antimicrobial Drug Action and Interaction: An Introduction. Antimicrobial therapy in Veterinary Medicine 4th edn , S Giguère, JF Prescott, JD Baggot, RD Walker and PM Dowling, eds. Blackwell Publishing, Ames Iowa, USA.*

Gootz TD. *1990. Discovery and Development of New Antimicrobial Agents. Clin Microbiol Rev 3(1)13-31.*

Cristina RT. *CMVRO Vetexpo Bucureşti 21-23/06/2012. Consideraţii asupra Reglementarilor legate de: Comercializarea şi utilizarea produselor medicinale produselor medicinale veterinare. Disponibil la: http://www.veterinarypharmacon.com/docs/1089-2012-R.T.%20Cristina-Bucuresti-CMVRO.pdf*

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Further bibliography

Cristina RT. *2014. Medicamente de uz veterinar: Perioada perioada de aşteptare / Consecinţele pentru sănătatea publică. Legislaţia european europeană. Prezentările SNEC, disponibil la: http://www.veterinarypharmacon.com/docs/1296-2014-SNEC.pdf.*

Cristina RT. *2016. Orientari privind utilizarea prudentă si ratională a antibioticelor la animale. Prezentările SNEC, disponibil la: http://www.veterinarypharmacon.com/docs/1634-2016_SNEC_CRISTINA_T_Romeo.pdf*

Cristina RT Doma OA, Dumitrescu E, Muselin F, Chirilă BA. *2018. Despre evoluţia şi implicaţiile fenomenului rezistenţei la medicamentele antiinfecţioase şi antiparazitare de uz veterinar şi evoluţia acestui fenomen în România. Medicamentul Veterinar / Veterinary Drug, 12(1):4-49.*

Guardabassi L, Courvalin P. *2006. Modes of Antimicrobial Action and Mechanisms of Bacterial Resistance. Antimicrobial Resistance in Bacteria of Animal Origin. FM Aarestrup, eds. ASM Press, Washington DC, USA.*

Keyes K, Lee MD, Maurer JJ. *2003. Antibiotics: Mode of Action, Mechanisms of Resistance and Transfer. Microbial Food Safetry in Animal Agriculture Current Topics. ME Torrence and RE Isaacson, eds. Iowa State Press, Ames, Iowa, USA.*

Levy SB. *2002. The Antibiotic Paradox, 2nd edn. Perseus Publishing, USA*

Weese JS. *2006. Prudent Use of Antimicrobials. Antimicrobial therapy in Veterinary Medicine 4th eds, S Giguère, JF Prescott, JD Baggot, RD Walker and PM Dowling, eds. Blackwell Publishing, Ames Iowa, USA.*

Copyright © 2010. Autoritatea Naţională Sanitară Veterinară şi pentru Siguranţa Alimentelor

Web sites:

https://www.frontiersin.org/articles/10.3389/fmicb.2016.01196/full
http://www.who.int/drugresistance/documents/baselinesurveynov2015/en/
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/vet_mrl_search.jsp&mid=WC0b01ac058008d7ad
COMMISSION REGULATION (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin
http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/11/WC500008770.pdf
https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/antimicrobial-resistance-europe-2015.pdf
http://amrls.cvm.msu.edu/images/vph/HUMAN-HEALTH-IMPACT
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/580710/1101060-v1-Understanding_the_PCU_-_gov_uk_guidance.pdf
http://www.veterinarypharmacon.com/docs/899-Curs-4-5.S.II.pdf
https://www.youtube.com/watch?v=NGwP471sehI
https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf
https://ec.europa.eu/transparency/regdoc/rep/1/2017/RO/COM-2017-339-F1-RO-MAIN-PART-1.PDF
http://ec.europa.eu/transparency/regdoc/rep/1/2011/RO/1-2011-748-RO-F1-1.Pdf

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