Innovation to AMU and AMR in veterinary medicine

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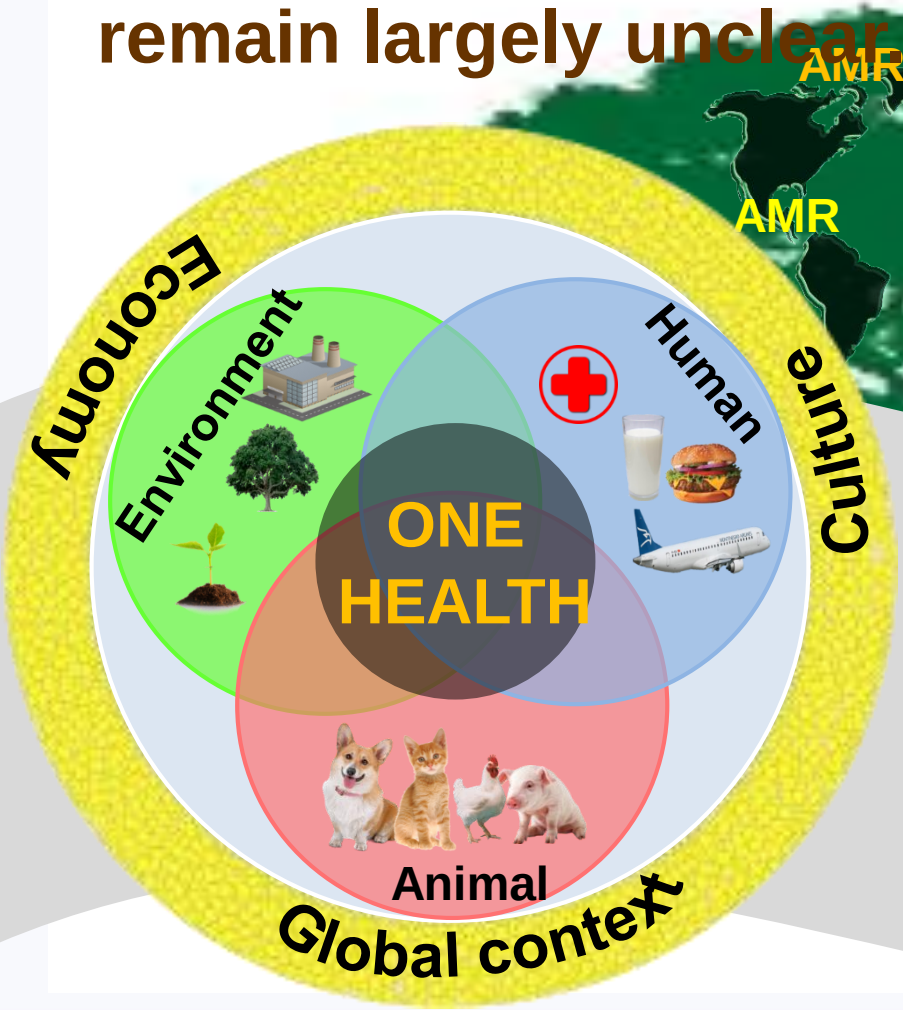
Facts on AMR

- AMR is a serious-global issue.
- Root causes of AMR remain largely unclear



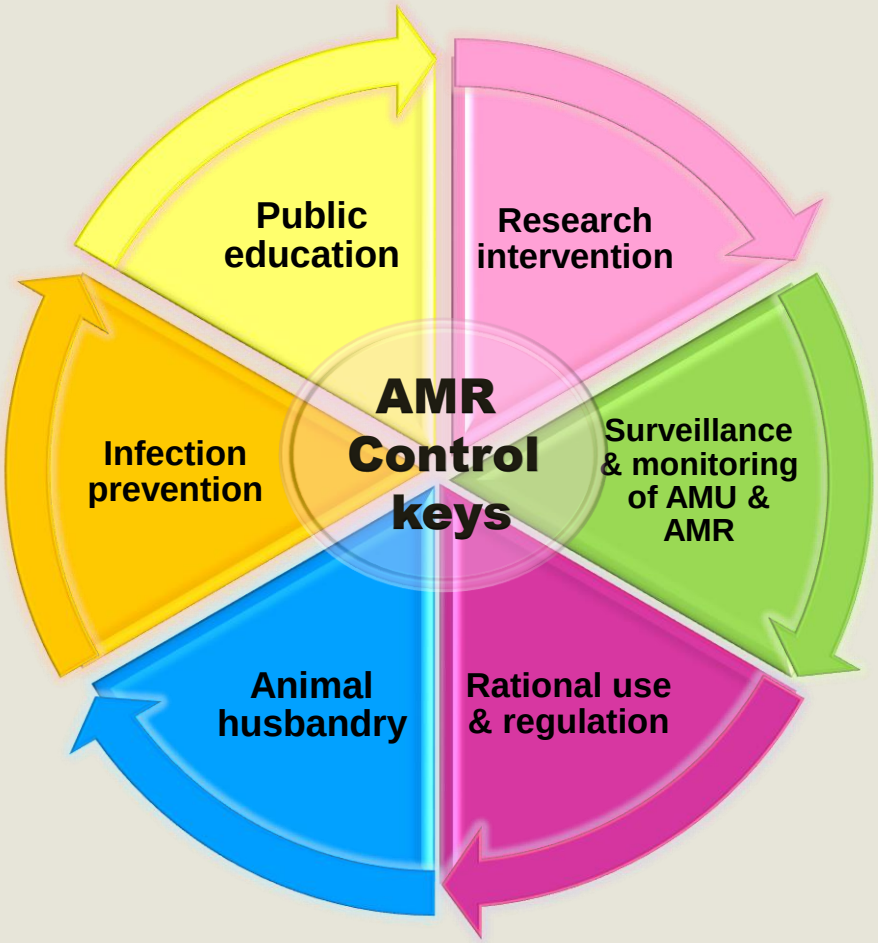
AMR is a one health

Facts on AMR

1. AMR has happened long time ago.
2. AMR can be mitigated but not be eradicated.
3. AMR management must be very well planned
4. It is a doubt if AMR prevention & control program will be successful.

Solutions of AMR

AMR control keys



Policy development

Human development

Scientific/ technical development

Product development

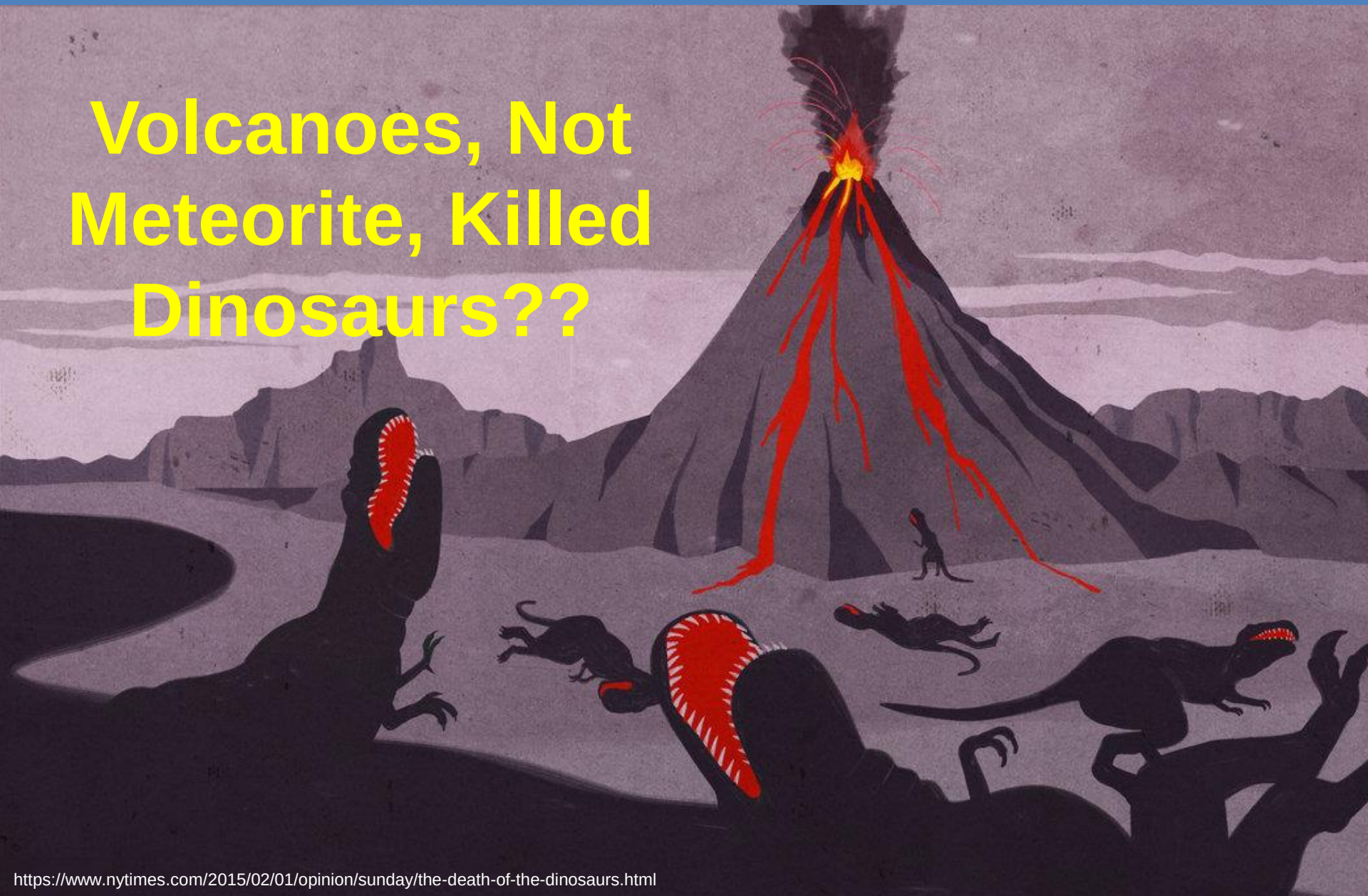
Innovation: an important element to fight AMR.

Multi-sectoral interventions, cross border strategies and innovations are required to fight antimicrobial resistance.

Gudrun Mernitz (2017)

Innovation: To track and implement new ways to prevent AMR infection and their spread

No innovation or Die !!!!!



https://www.nytimes.com/2015/02/01/opinion/sunday/the-death-of-the-dinosaurs.html

Innovation: an important element to fight AMR.

New innovative products & services need to grow.

- Alternatives to ABO
- Novel antibiotics
- New AMR diagnostic tool
- Surveillance instrument
- Effective vaccine
- New business models for sustainable ABO
- New R&D system for novel ABO

1. Novel ABO molecules?

Novel antibiotic molecules

The antibiotic era

1950-60s	1970-90s	2000s	2010s
• Narrow spectrum • Gram (+) • Natural products	• Broad spectrum • Gram (+)/(-) • Medical chemistry & semisynthetic products	• Narrow spectrum • Gram (+) • Target based	• Narrow spectrum • Gram (-) targeted • Natural products? • Alternative products

Modified from the antibiotic pipeline. What can we expect? (Theuretzbacher, www.drive-ab.eu)

https://www.nytimes.com/2015/02/08/opinion/sunday/the-death-of-the-dinosaurs.html

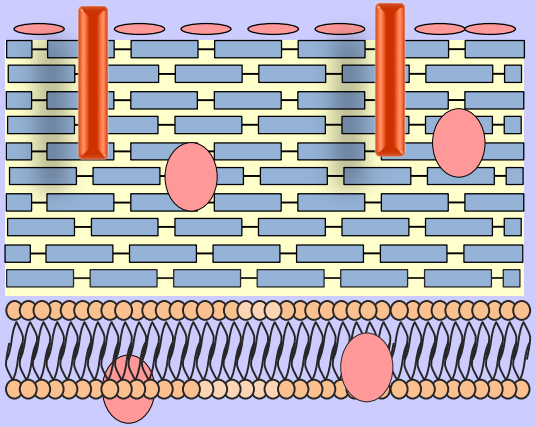
Different cell wall in different bacteria

GRAM-POSITIVE BACTERIA

GRAM-NEGAITIVE BACTERIA

Outside

Teichoic acid



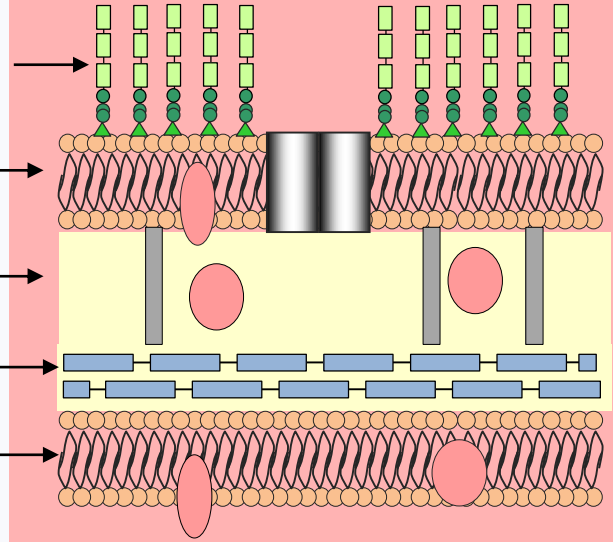
Lipopolysaccharide

Phospholipid

Lipoprotein

Peptidoglycan

Phospholipid



OM

PM

IM

Inside

Alternative approaches

- Probiotics
- Symbiotics
- Enzyme
- Bateriophage
- Immunomodulators
- Prebiotics
- Organic acids
- Herb extract
- Genetics

CATEGORY	COMPANY	PHASE
Antibodies		
Bezlotoxumab	Merck & Co.	III
MEDI3902	MedImmune	II
Aerumab	Aridis Pharmaceuticals	II
Salvecin	Aridis Pharmaceuticals	II
MEDI4893	MedImmune	II
Aurexis	Bristol-Myers Squibb	II
ASN100	Arsanis	II
514G3	XBiotech	I/II
Aerucin	Aridis Pharmaceuticals	I/II
Lysins		
N-Rephasin	Intron Biotechnology	I
CF-301	ContraFect	I

CATEGORY	COMPANY	PHASE
Peptides		
POL7080	Polyphor	II
Brilacidin	Cellceutix	II
Probiotics		
RBX2660	Rebiotix	II
VP20621	Shire	II
SER-109	Seres Therapeutics	II
Vaccines		
Cdiffense	Sanofi Pasteur	III
VLA43	Valneva	II/III
VLA84	Valneva	II
SA4Ag	Pfizer	II
PF-06425090	Pfizer	II
Group B streptococcus vaccine	GlaxoSmithKline	II

Sources: Pew Charitable Trusts as of May 2016, company information; http://cen.acs.org/articles/94/i35/Antibiotics-bugs-always-win.html

Do we still need new antibiotics?

Yes, absolutely.

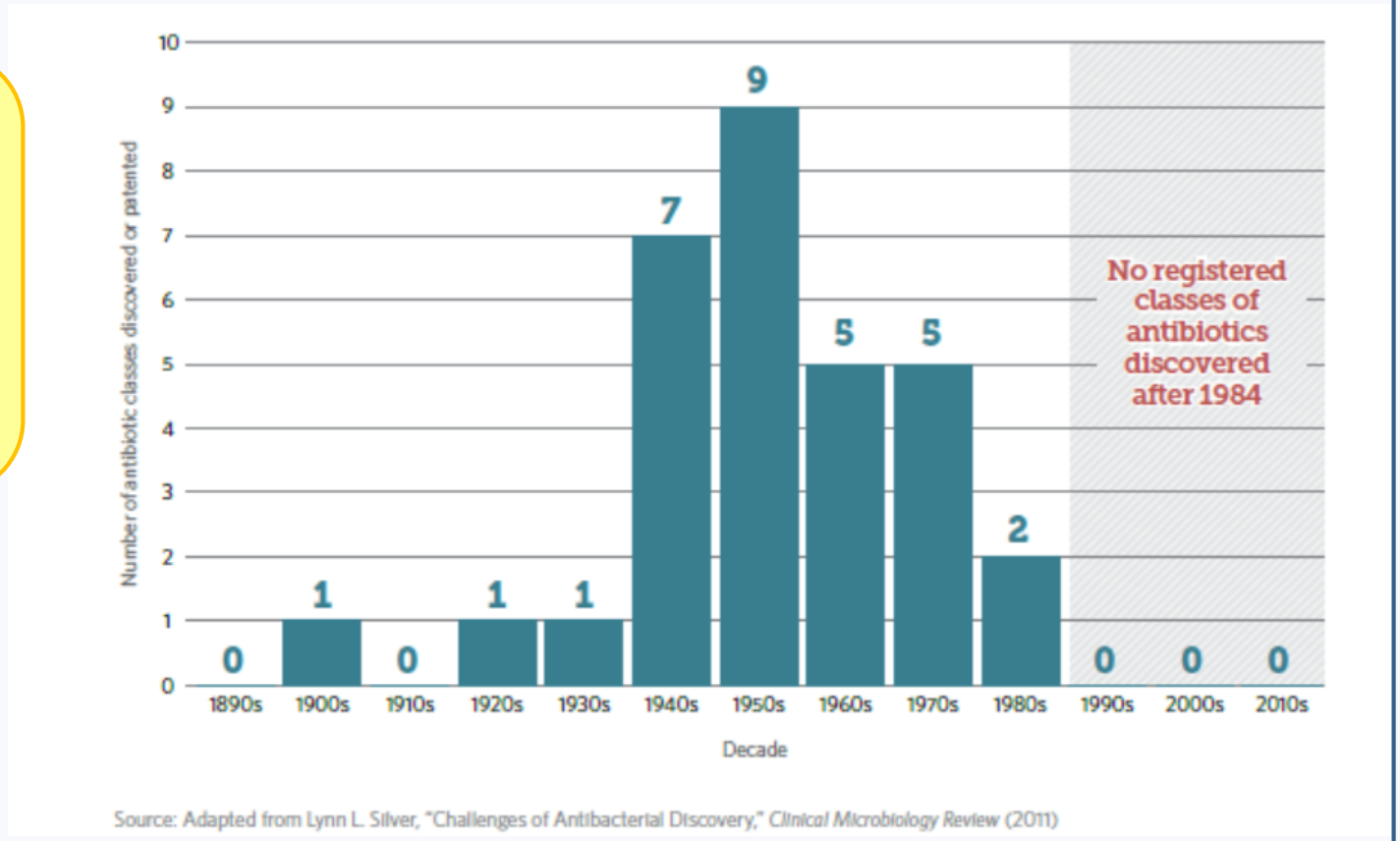
- Even ABO are used prudently, AMR can still occur.
- No perfect replacement of ABO exist.
- What we need are ABO in new classes.

https://www.nytimes.com/2015/02/01/opinion/sunday/the-death-of-the-dinosaurs.html

We need new classes of ABO but..

Fact:
Resistance to an ABO can lead to resistance to other ABO in the same class.

Discovery of new types of ABO in more than 3 decades



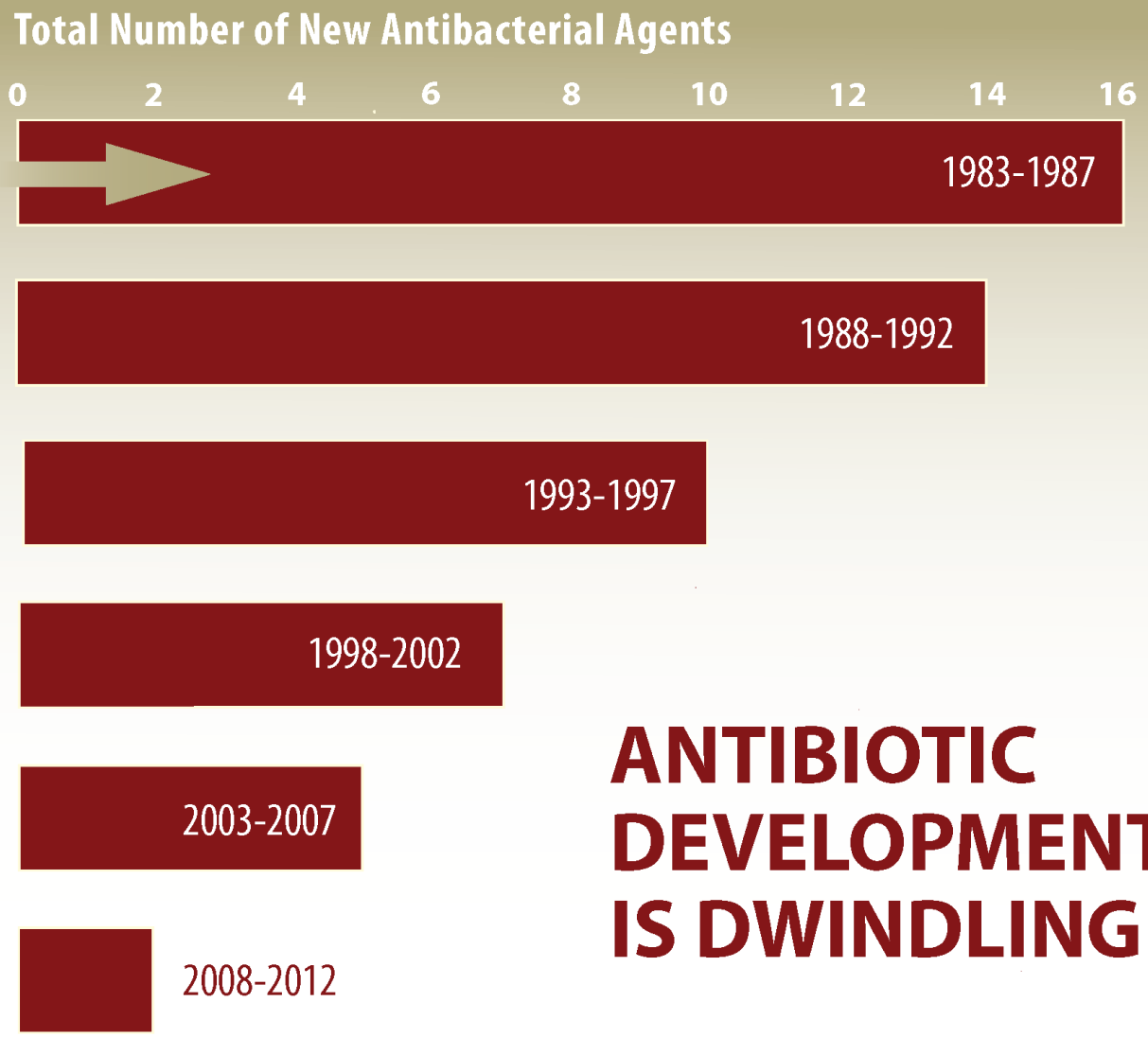
From A Scientific Roadmap for Antibiotic Discovery (The Pew Charitable Trusts, 2016)

https://www.nytimes.com/2015/02/01/opinion/sunday/the-death-of-the-dinosaurs.html

We need new classes of ABO but...

Fact:

The number of antibiotics being developed has steadily been decreasing since the 1980s.



ANTIBIOTIC DEVELOPMENT IS DWINDLING

Source: *The Epidemic of Antibiotic-Resistant Infections*, CID 2008:46 (15 January)
Clin Infect Dis. (2011) May 52 (suppl 5): S397-S428. doi: 10.1093/cid/cir153

What are novel ABO in the pipeline?

COMPOUND	DRUG CLASS	DEVELOPER	ACTIVE AGAINST ESKAPE PATHOGEN OR URGENT THREAT
Baxdela	Fluoroquinolone	Melinta Therapeutics	Possibly active
Cadazolid	Quinolonyl-oxazolidinone	Actelion Pharmaceuticals	Active
Carbavance	Carbapenem/β-lactamase inhibitor	Medicines Co.	Active
Eravacycline	Tetracycline	Tetraphase Pharmaceuticals	Active
Fosfomycin	Phosphonic acid derivative	Zavante Therapeutics	Active
Iclaprim	Dihydrofolate reductase inhibitor	Motif Bio	
Lefamulin	Pleuromutilin	Nabriva Therapeutics	
MK-7655	Carbapenem/β-lactamase inhibitor	Merck & Co.	Active
Omadacycline	Tetracycline	Paratek Pharmaceuticals	Active
Plazomicin	Aminoglycoside	Achaogen	Active
S-649266	Cephalosporin	Shionogi	Active
Solithromycin	Macrolide	Cempra	Active
Taksta	Fusidane	Cempra	
Zabofloxacin	Fluoroquinolone	Dong Wha Pharmaceutical	
Zavicefta	Cephalosporin/β-lactamase inhibitor	AstraZeneca/Allergan	Active

ESKAPE = *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species

Sources: Pew Charitable Trusts as of May 2016, company information

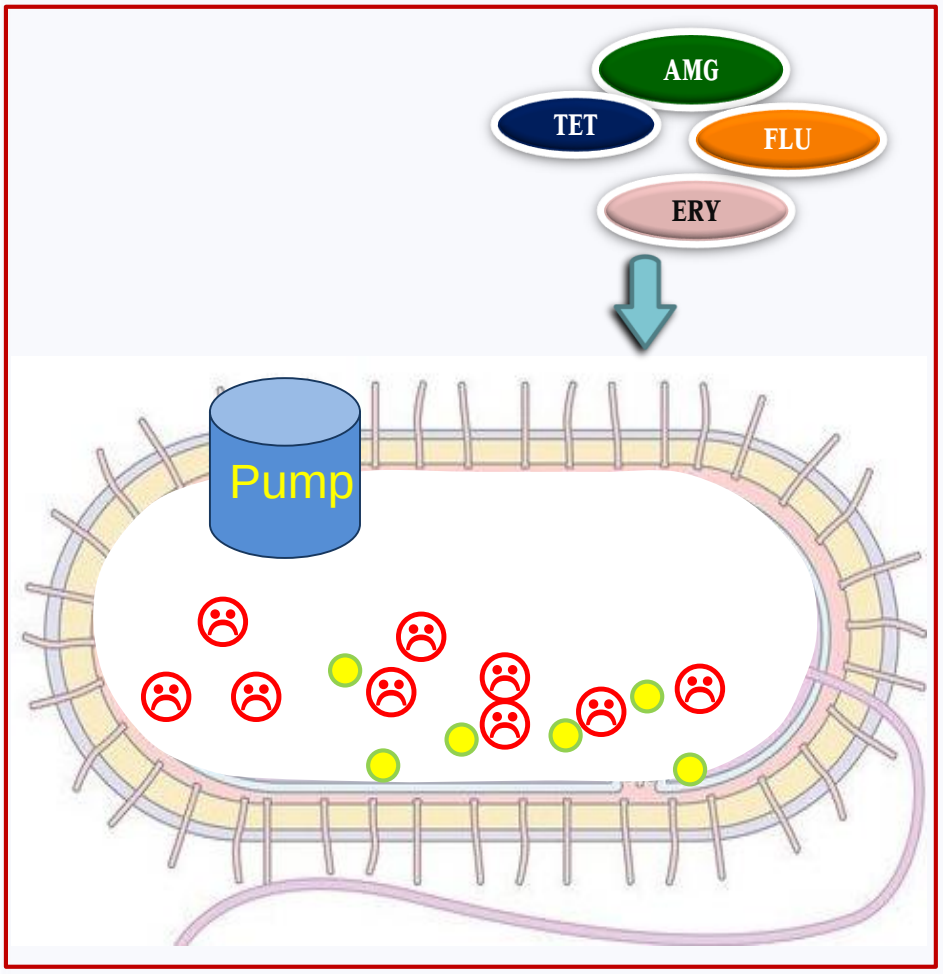
2. Help ABO to work better!!

How can we help ABO to work better?

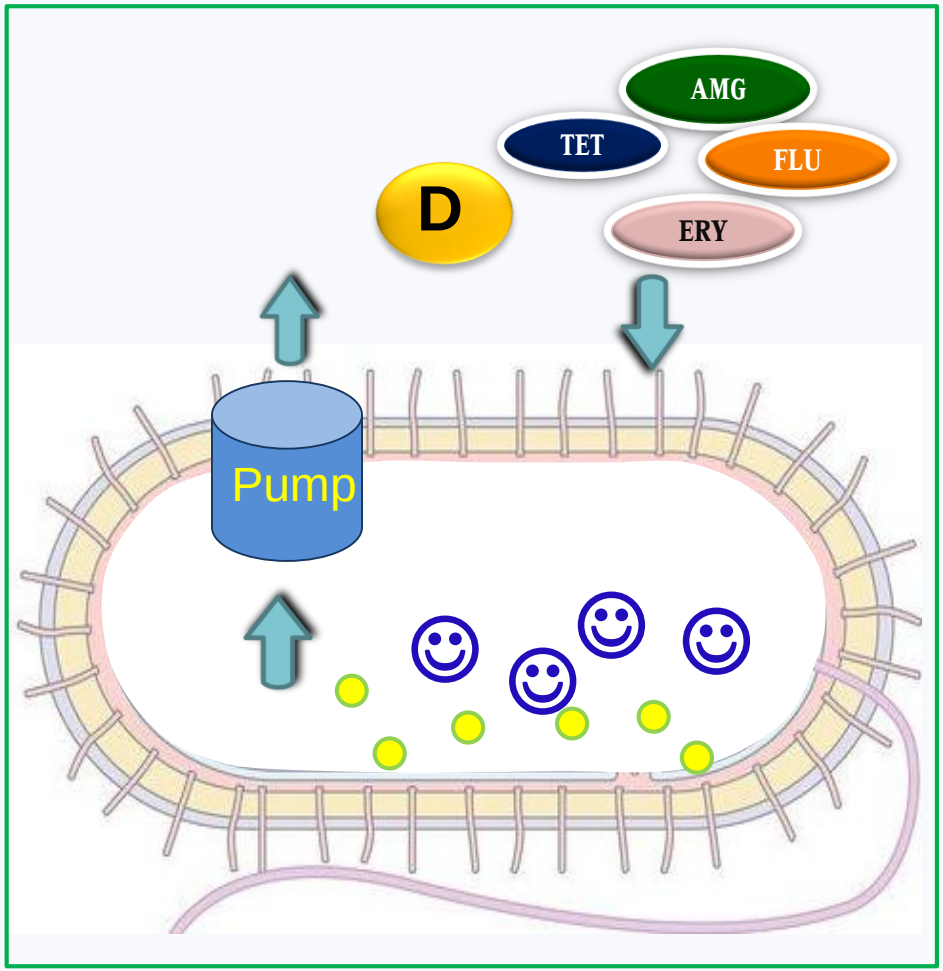
Efflux pump inhibitors (EPIs) as new antimicrobial agents against *Pseudomonas aeruginosa*

What are (multidrug) efflux pumps?

Efflux pump is OFF.

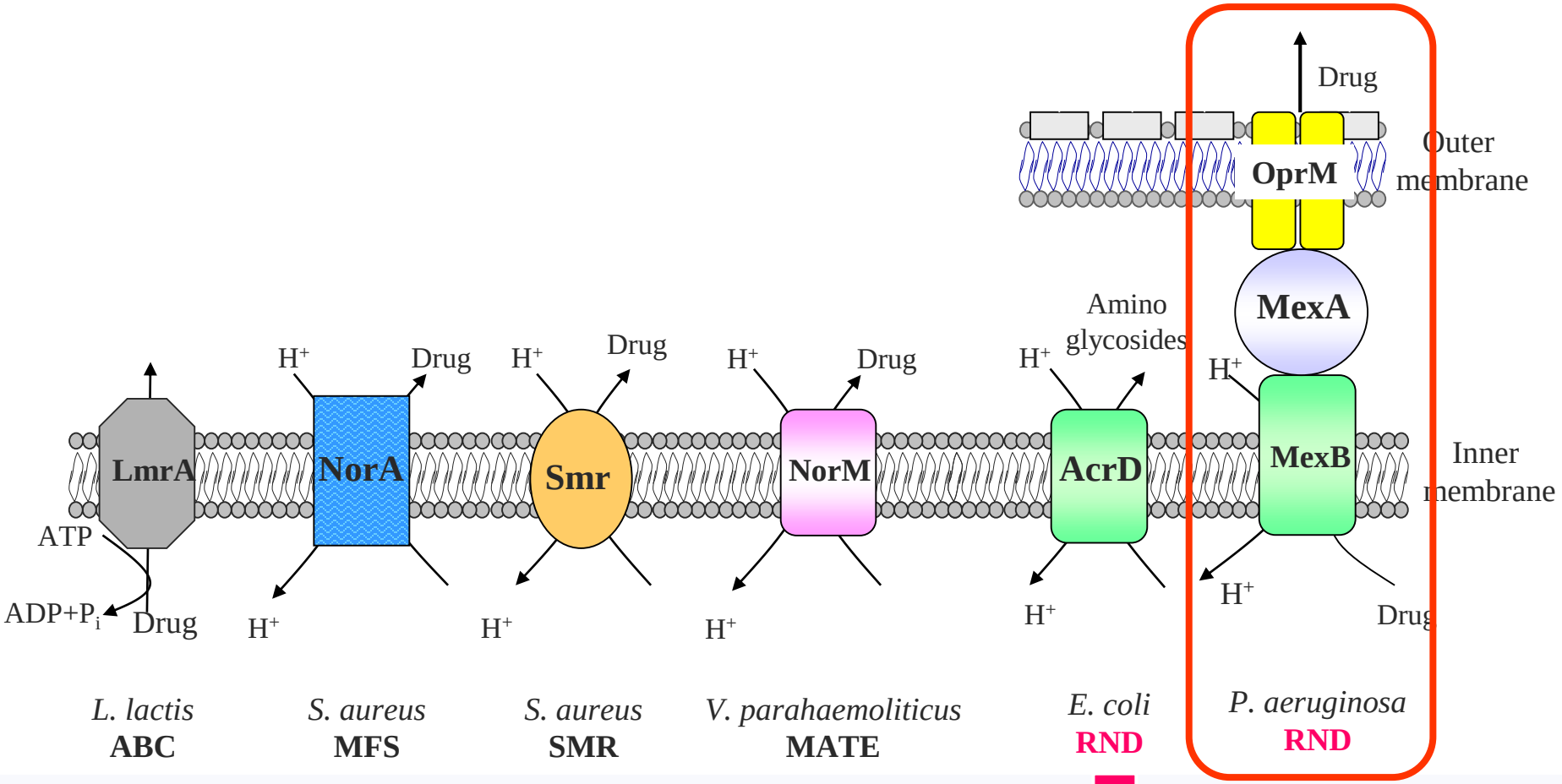


Efflux pump is ON.



Drug Targets

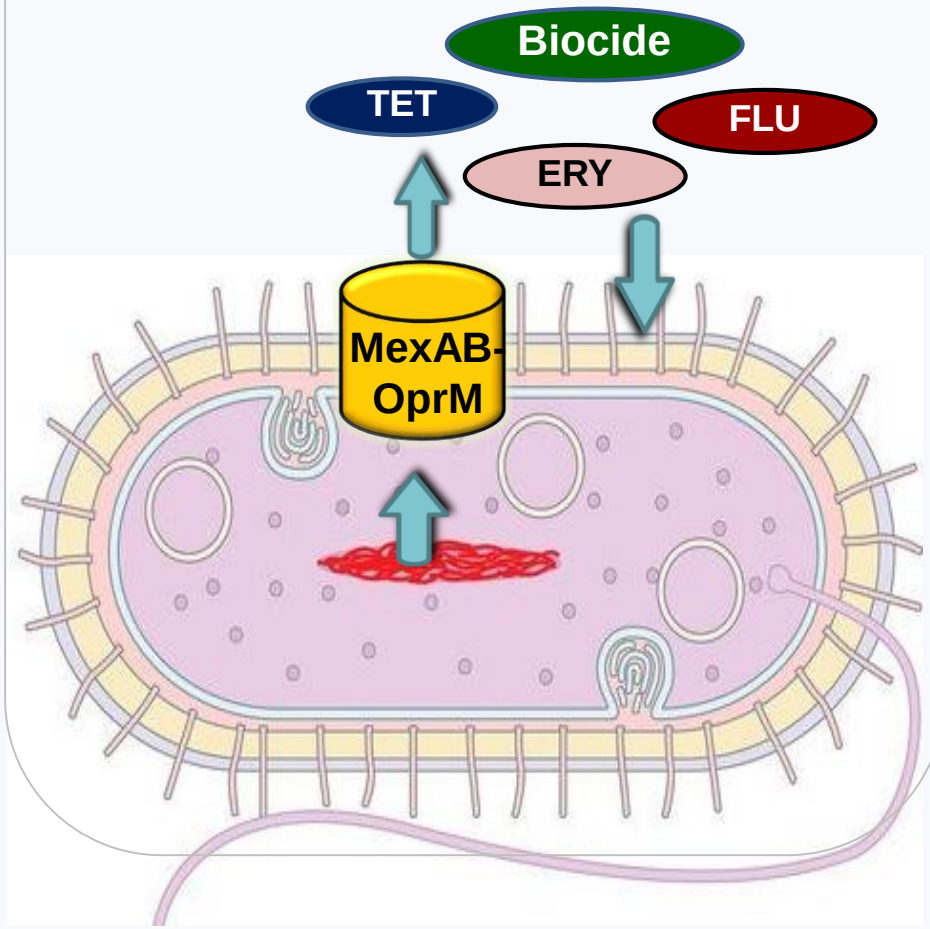
Six families of efflux pumps in bacteria



RND = Resistance Nodulation Cell Division Family

MEX systems in *P. aeruginosa*

MexAB-OprM



Substrates spectrum of MexAB –OprM

β-Lactams (carbenicillin, novobiocin), β-Lactamase inhibitors (clavulanic acid), carbapenems (meropenem), chloramphenicol, tetracycline, macrolides(erythromycin), fluoroquinolones, rifampin, trimethoprim, fusidic acid, triclosan

Chuanchuen et al,/2001. Antimicrob. Agents Chemother.

Substrate spectrum of MeX systems

MexAB –OprM

β-Lactams (carbenicillin, novobiocin), β-Lactamase inhibitors (clavulanic acid), carbapenems (meropenem), chloramphenicol, tetracycline, macrolides(erythromycin), fluoroquinolones, rifampin, trimethoprim, fusidic acid, triclosan

MexCD –OprJ

Cnovobiocin, 4th generation cephalosporins (cefepime, cefpirome), cephems, chloramphenicol, tetracycline, fluoroquinolones, macrolides (erythomycin), triclosan

MexEF –OprN

Chloramphenicol, fluoroquinolones, trimethoprim, carbapenems (imipenem, panipenem), triclosan

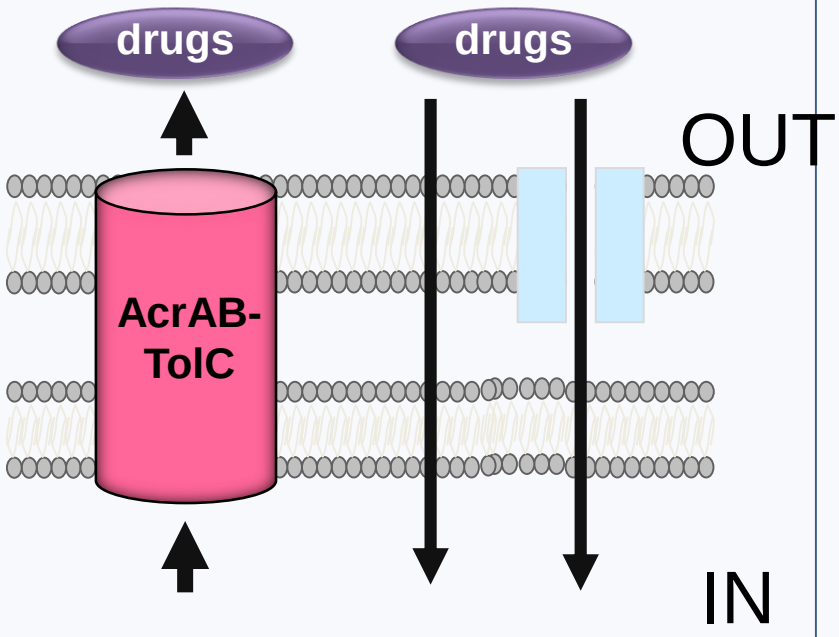
MexXY

Aminoglycosides, macrolides(erythomycin), tetracycline

Efflux pumps in foodborne pathogens

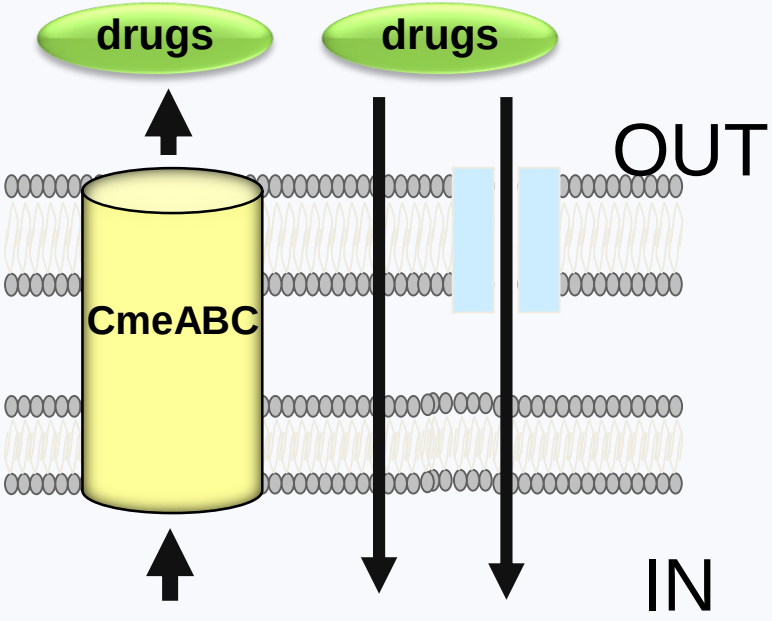
AcrAB-TolC
in *Salmonella* & *E. coli*

Ampicillin,chloramphenicol, erythromycin, triclosan, chloroxylenol, chlorhexidine

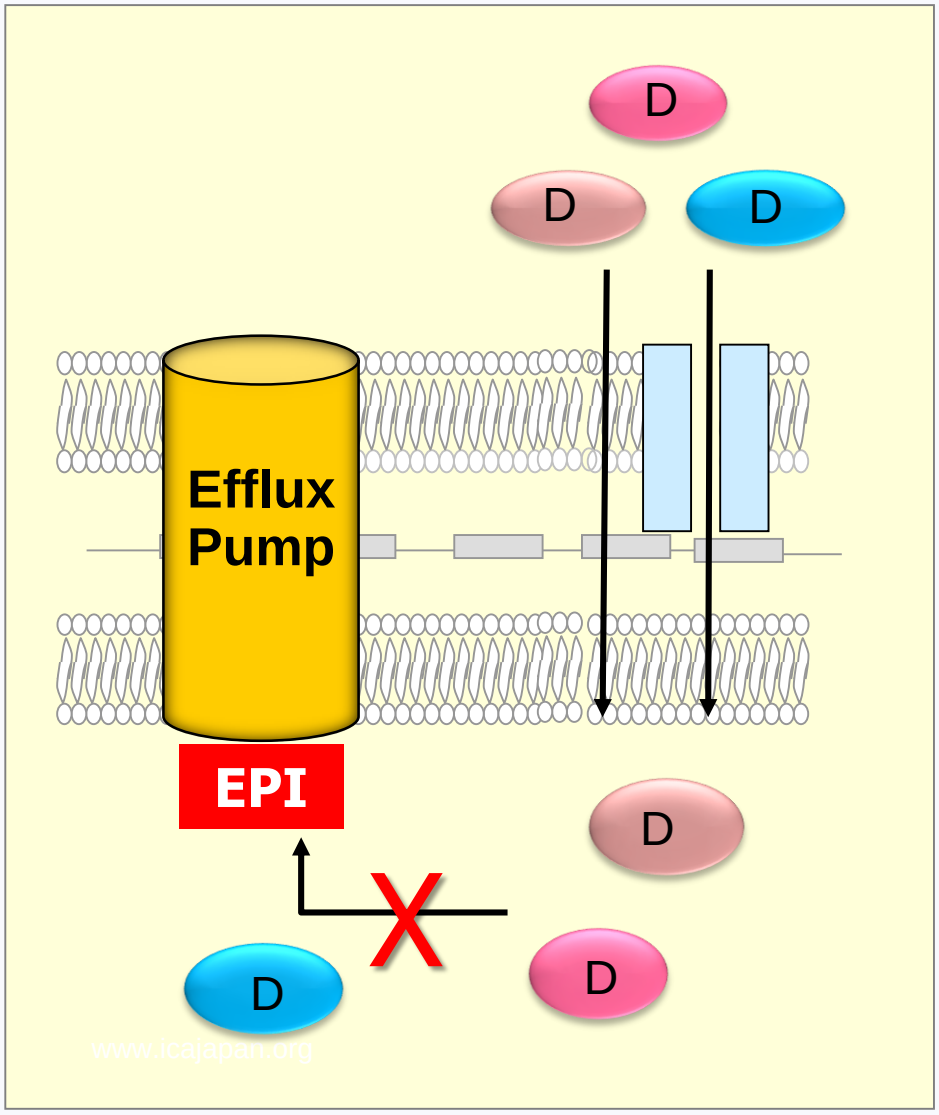


CmeABC
in *Campylobacter*

erythromycin ciprofloxacin



Reduce efflux, increase ABO efficacy



Potential Efflux Pump Inhibitors (EPIs)

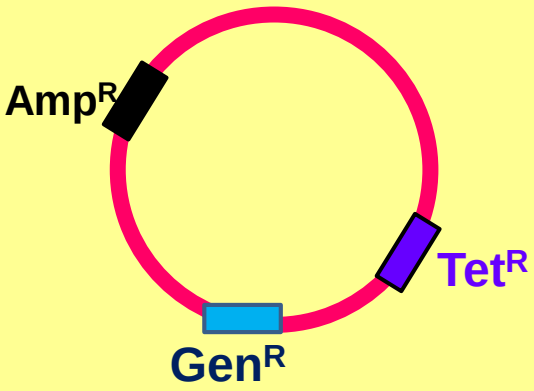
- PAβN (MC-207,110 or PAβN)
- 1-(1-Naphthylmethyl)-Piperazine (NMP) & the Arylpiperazine Analogs
- D13-9001 & the Pyridopyrimidinone Analogs
- Pyranopyridines (MBX2319)

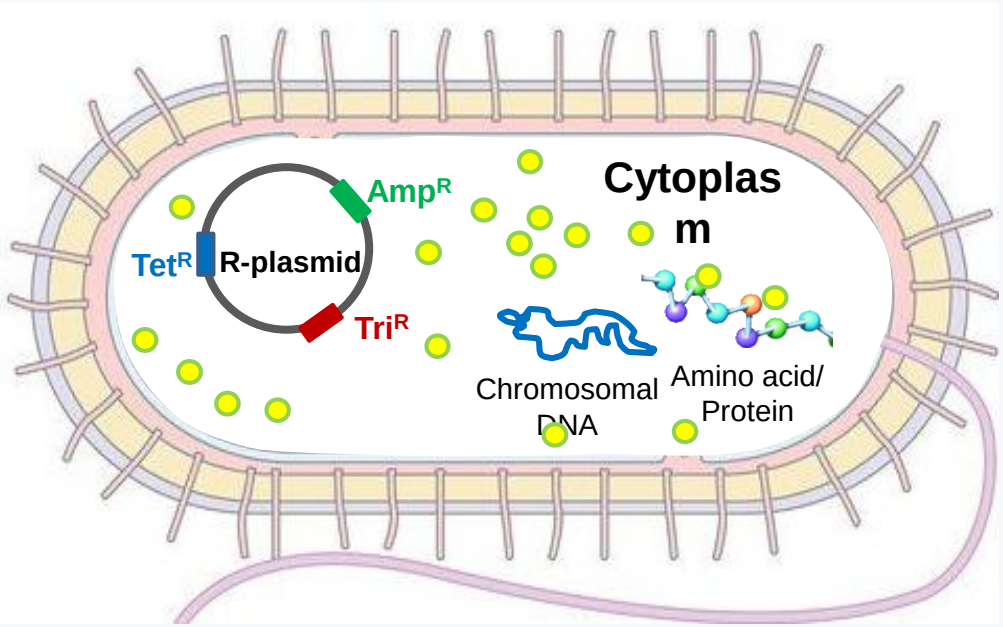
Herbs

3. Reduce R-plasmid spread!!

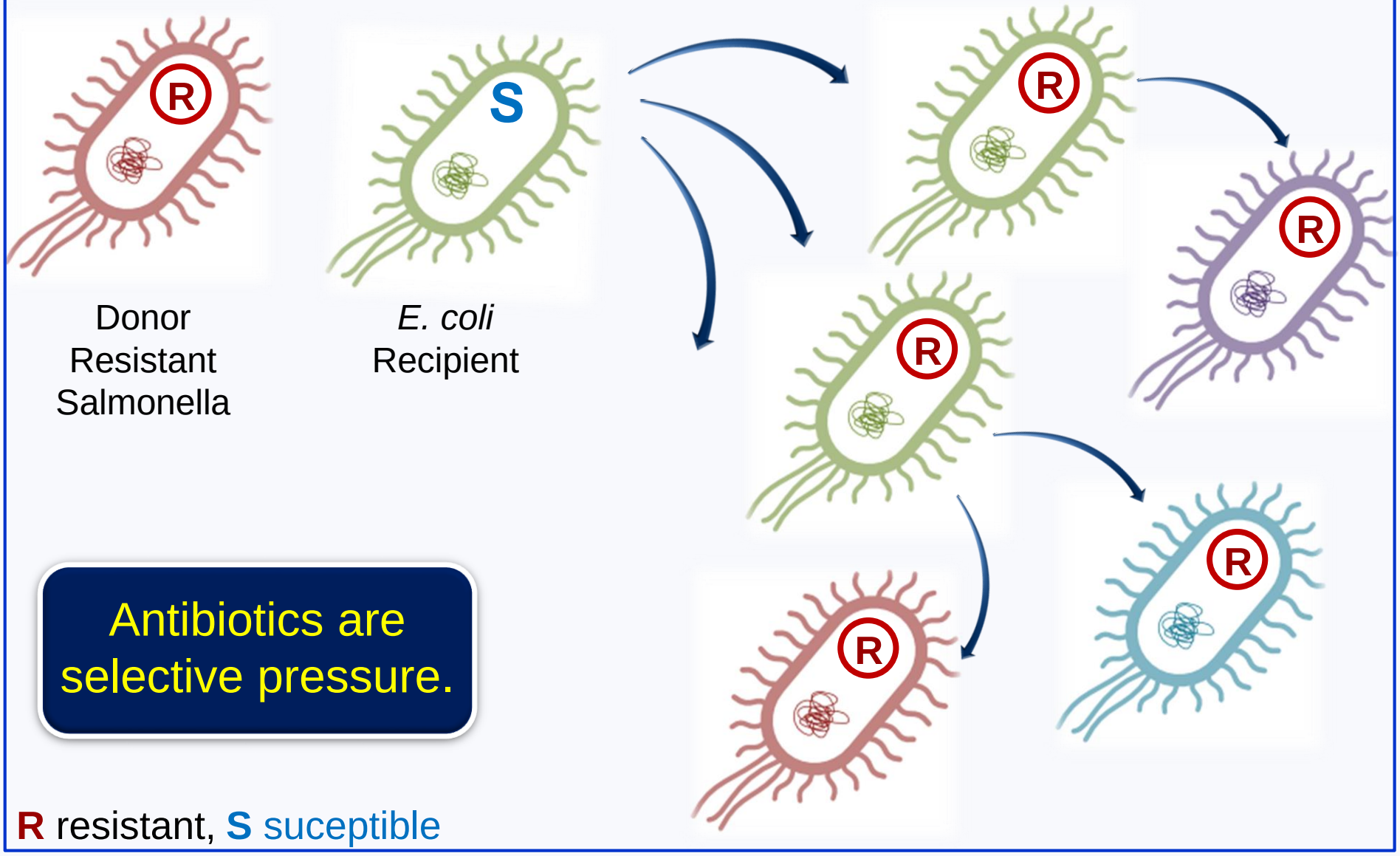
Horizontal spread of resistance determinants

R plasmid





Resistance gene transfer: Conjugation



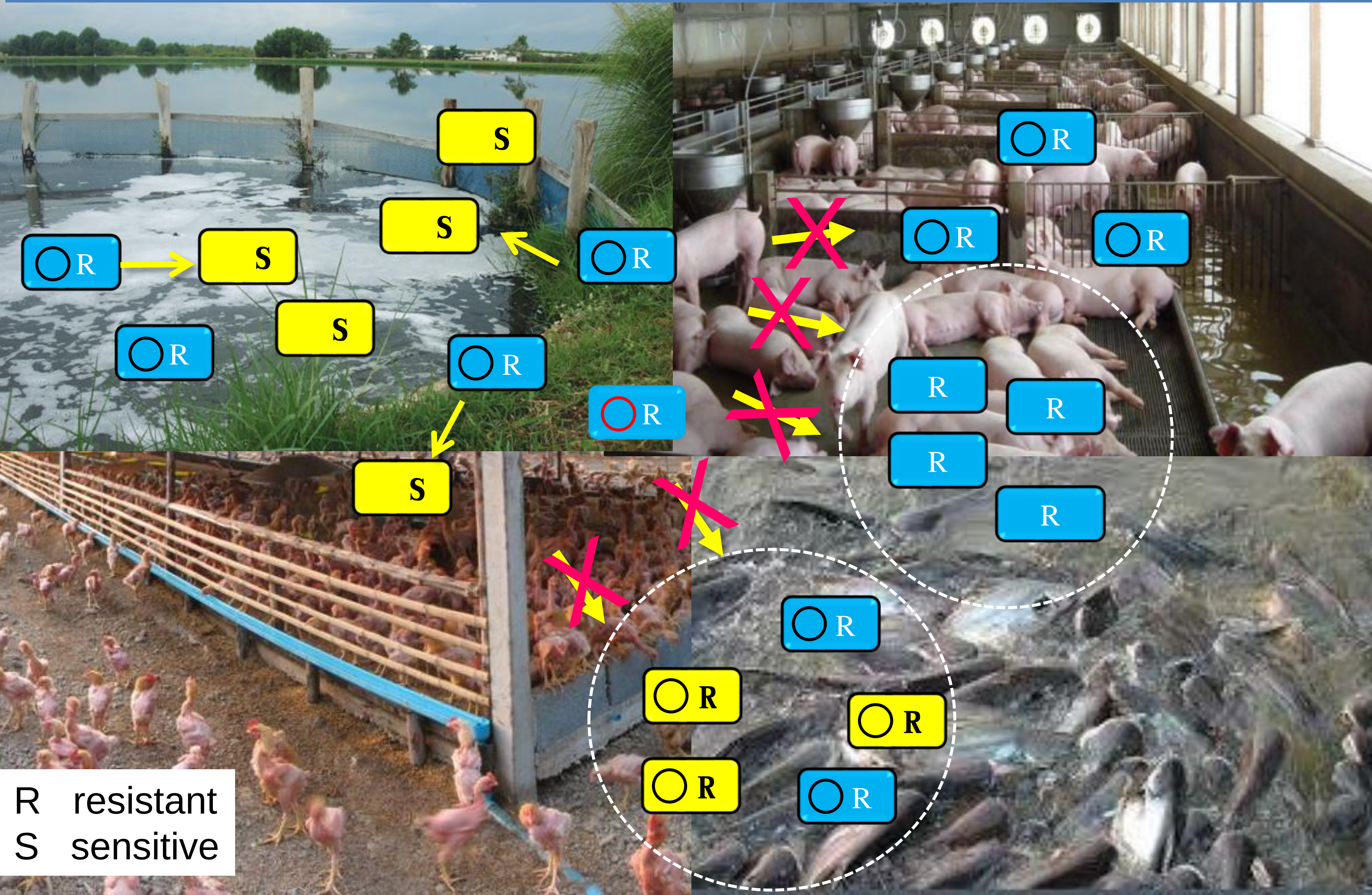
Donor
Resistant
Salmonella

E. coli
Recipient

Antibiotics are selective pressure.

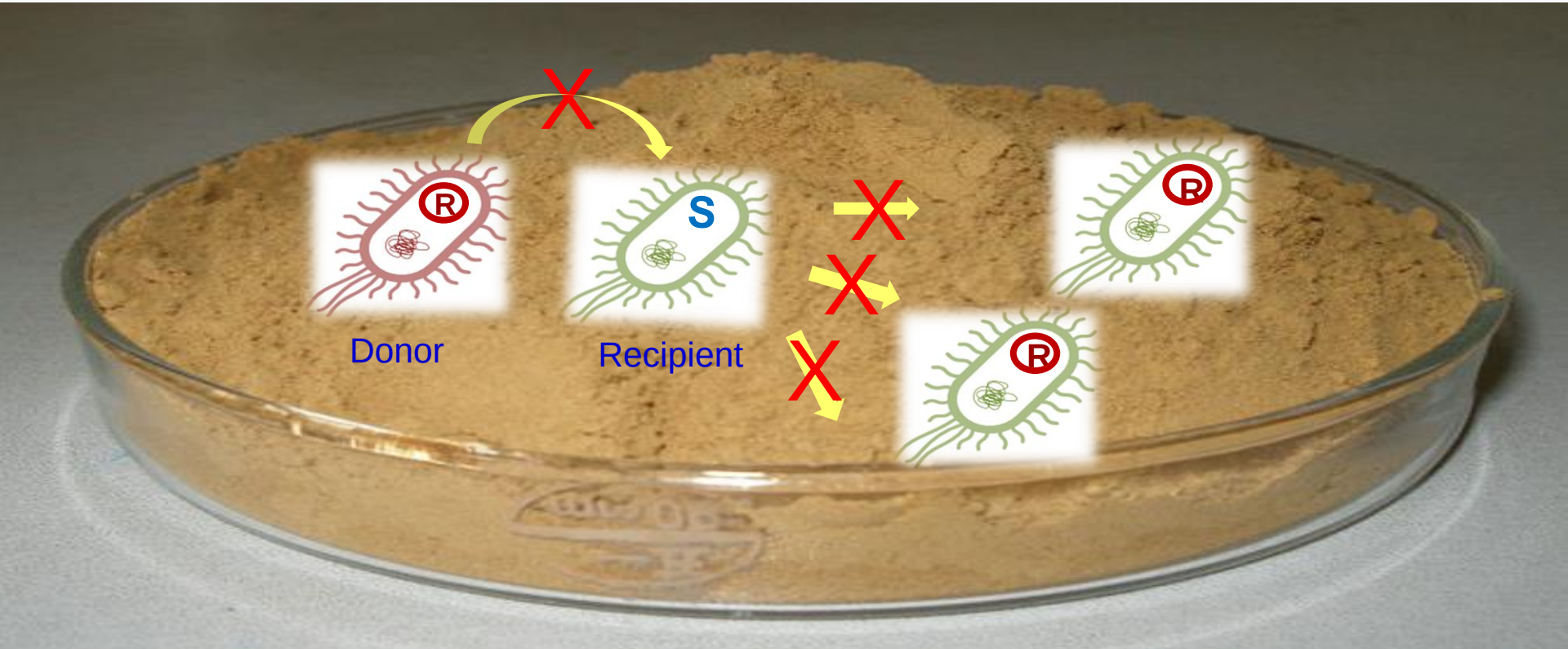
R resistant, **S** suceptible

A pool of AMR bacteria and determinants



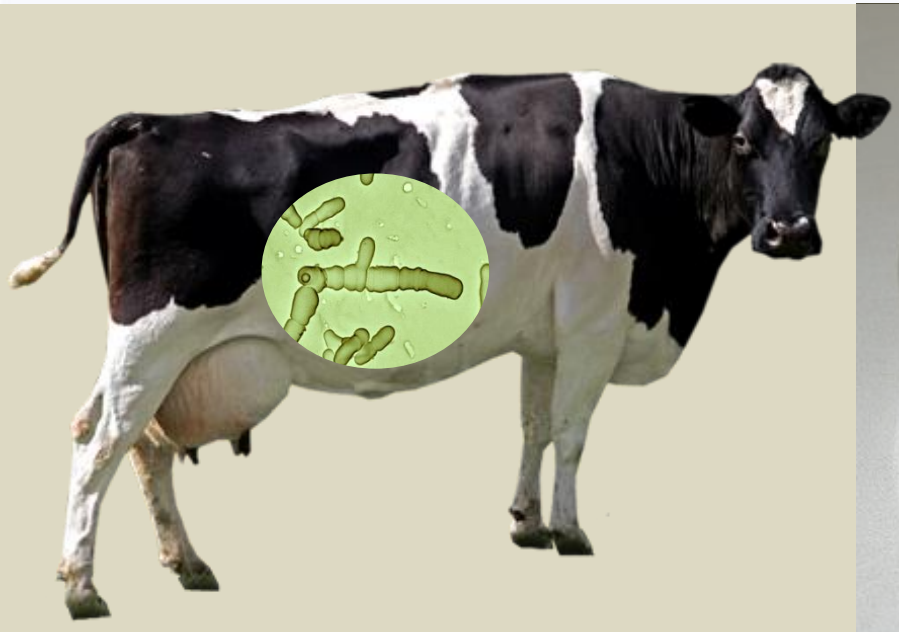
Reduce plasmid transfer, Reduce AMR spread

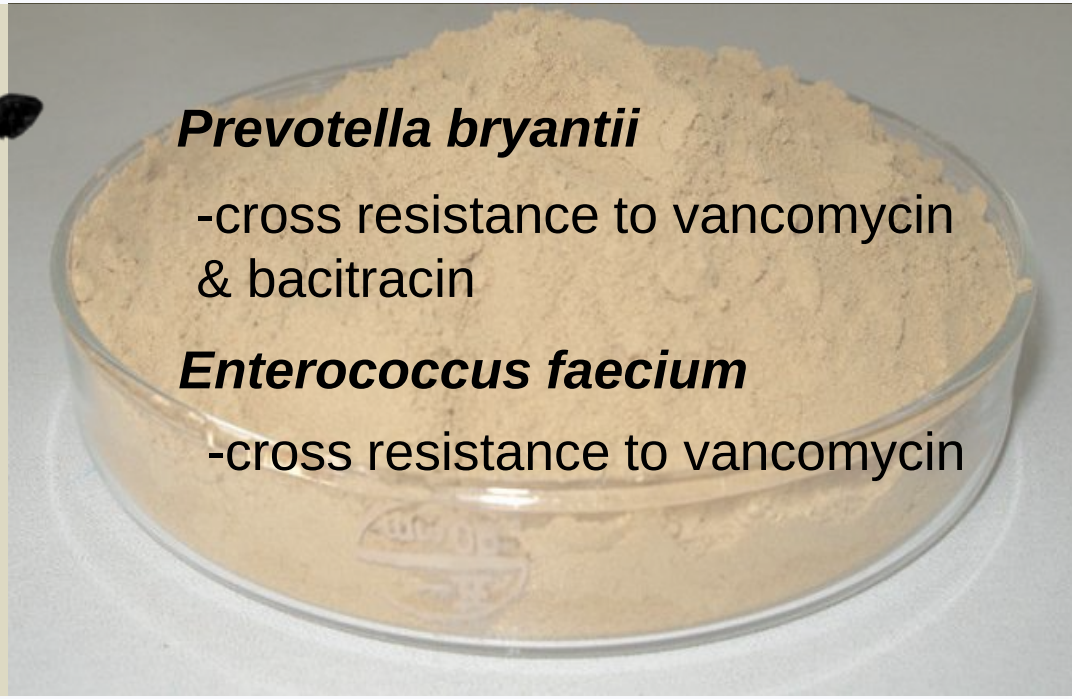
- ***In vitro* Plasmid curing:**
  e.g. SDS, acridine orange, ethidium bromide
- **Inhibition of plasmid transfer:**
  e.g. Phosphoglycolipids (bambermycin or moenomycin)



What should be concerned?

Cross resistance between phosphoglycolipids and antibiotics in commensal bacteria





Prevotella bryantii

-cross resistance to vancomycin & bacitracin

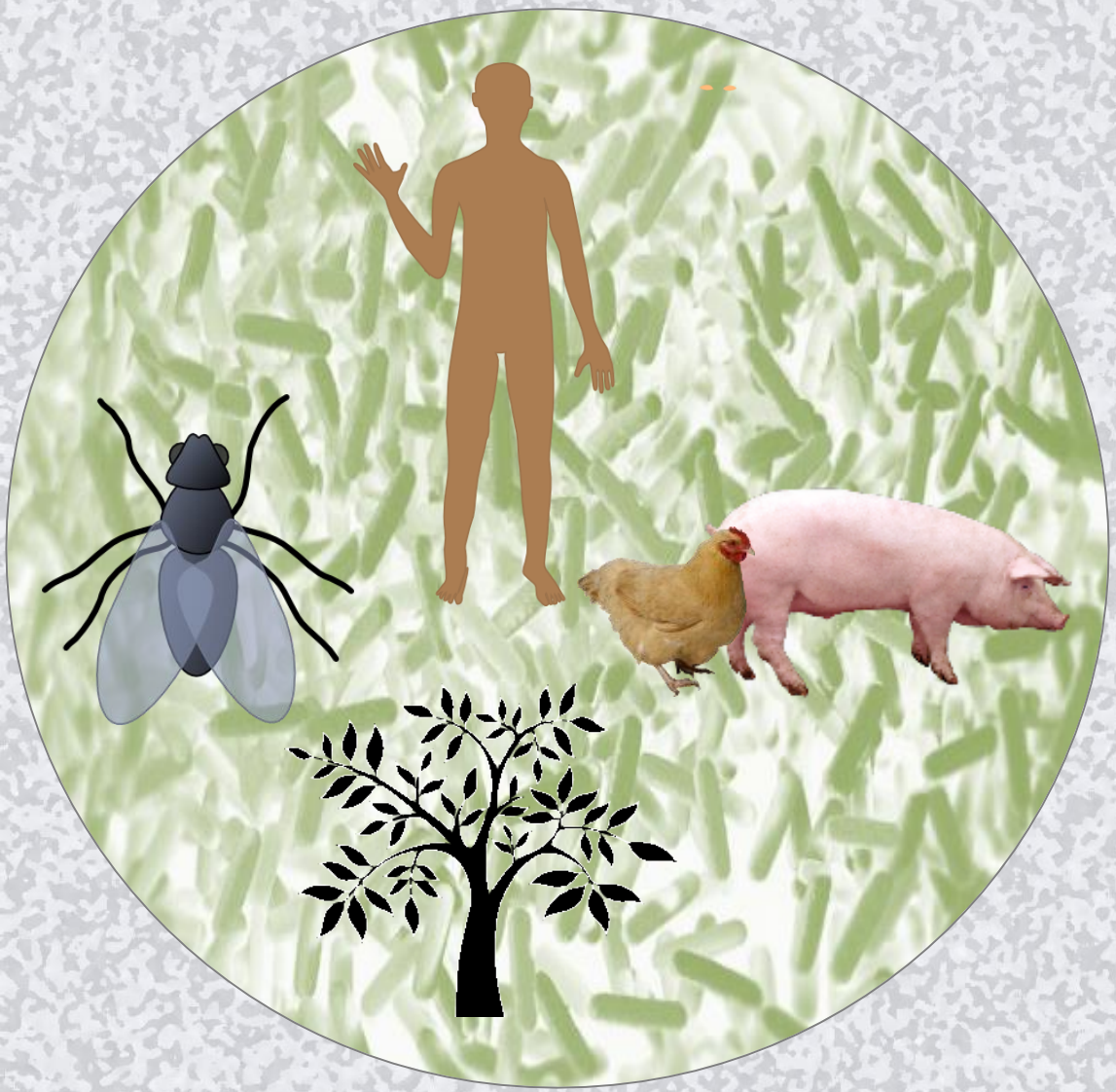
Enterococcus faecium

-cross resistance to vancomycin

Edwards et al (2007); Handwerger and Kolokathis (1990)

4. Unlock the mystery of microbiome!!

What is microbiome?

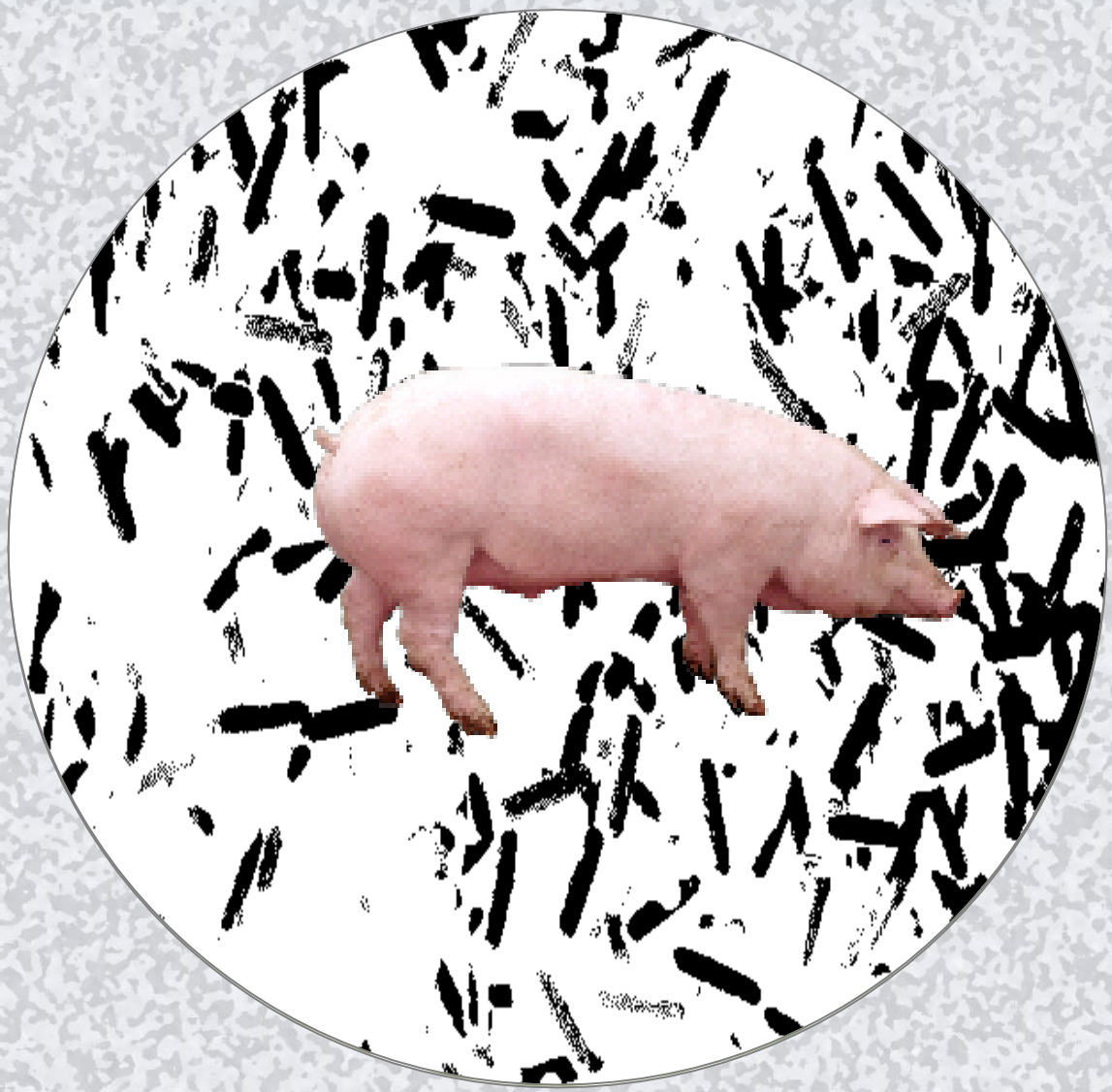


The full complement of microorganisms, their genes and their metabolites in commensal, symbiotic and pathogenic microorganisms including bacteria, archaea, fungi, and viruses.

Naturally-occurring germs in and on bodies skin, gut, mouths, respiratory tracts, and urinary tracts.

Help in digestion and detoxification, immunity, protecting against invading pathogens, and maintaining overall health.

Antibiotics disrupt microbiome.



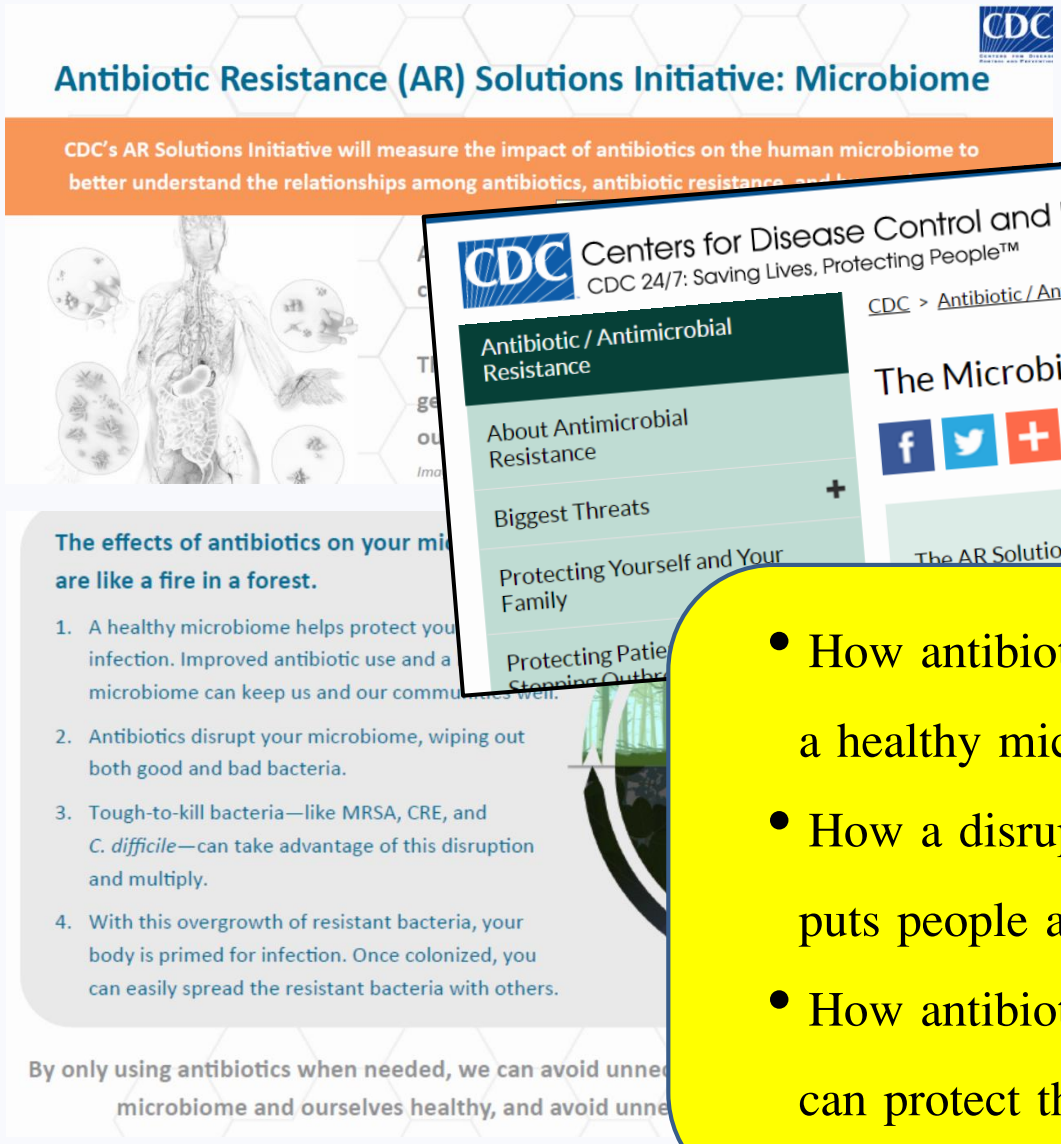
Microbiomes disrupted by antibiotics are vulnerable to infections by resistant bacteria.

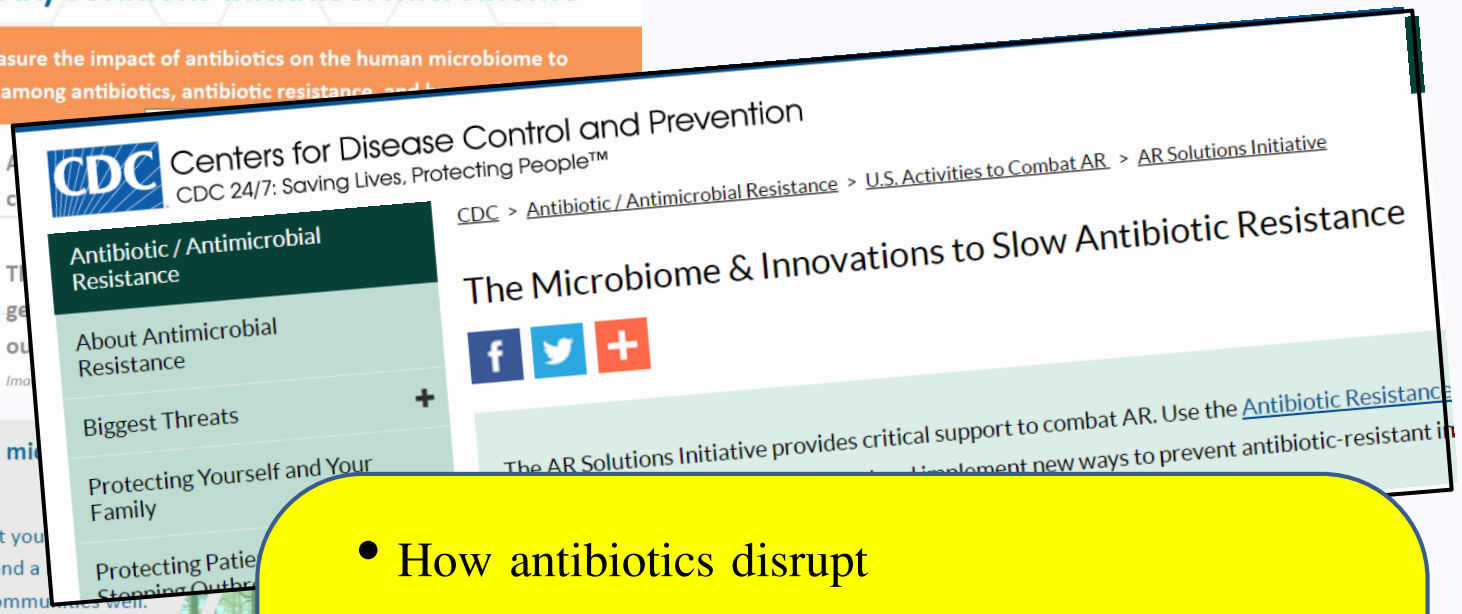
Resistant bacteria can colonize and cause infection. This puts people at risk for potentially untreatable illnesses.

The patients can carry resistant bacteria and easily spread these bacteria to other people, especially those who also have a disrupted microbiome.

https://www.nytimes.com/2015/02/01/opinion/sunday/the-death-of-the-dinosaurs.html

Research on microbiome





- How antibiotics disrupt a healthy microbiome
- How a disrupted microbiome puts people at risk
- How antibiotic stewardship can protect the microbiome

https://www.nytimes.com/2015/02/01/opinion/sunday/the-death-of-the

Example of research on microbiome

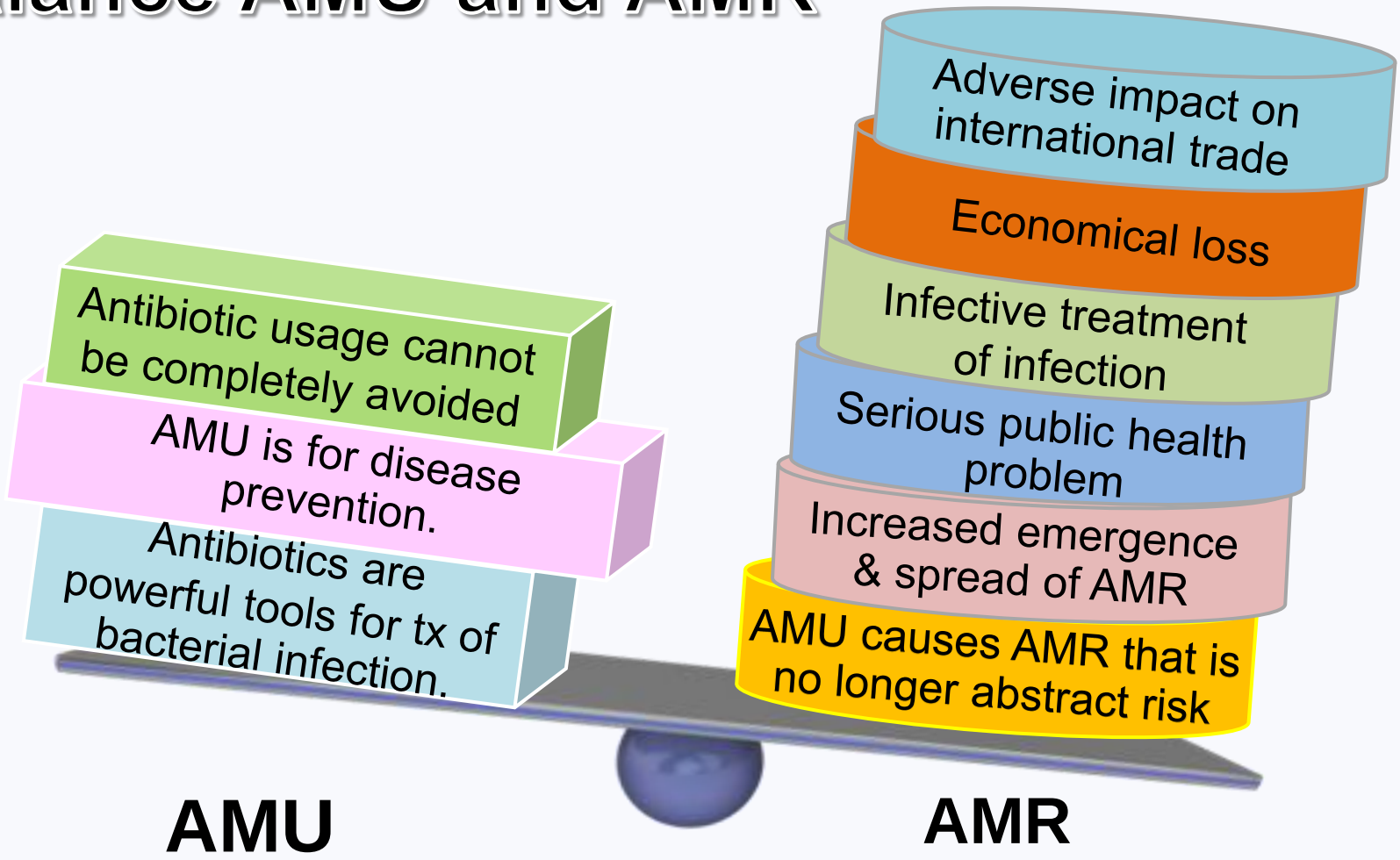
Characterization of the gut microbiome in an animal species:

- How antibiotic treatments disrupt normal gut bacteria
- How animal growth might be promoted
- How bacterial diseases might be treated without using antibiotics

https://www.nytimes.com/2011/09/01/opinion/sunday/the-death-of-the-dinosaurs.html

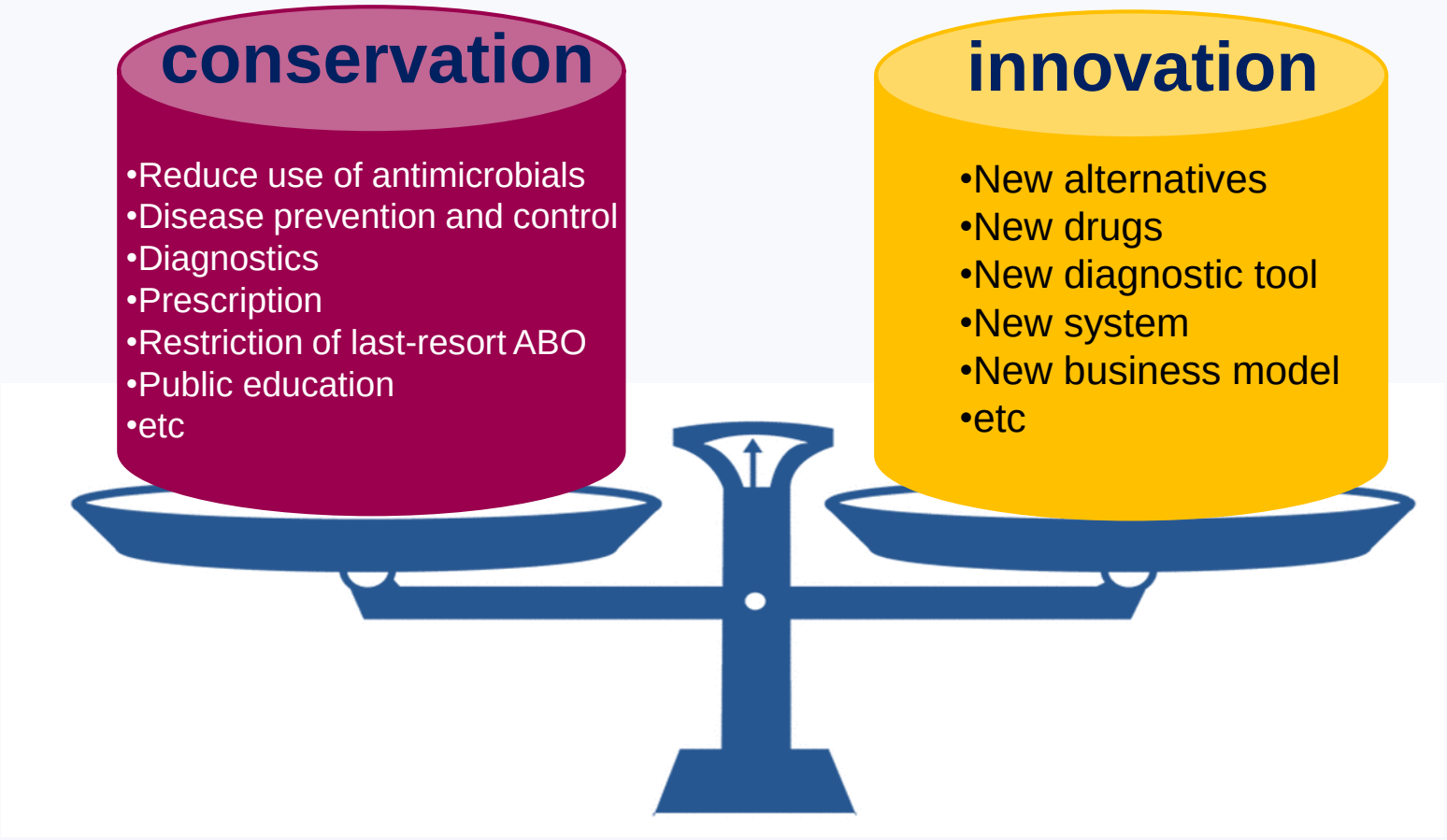
Take home message!!

Balance AMU and AMR



Take home message!!

Balance conservation and innovation.



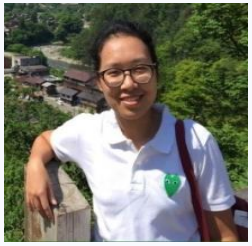















Thank You

Research Unit in Microbial Food Safety & Antimicrobial Resistance

Center for Antimicrobial Resistance Monitoring in Foodborne Pathogens (*in cooperation with WHO*)

GFN: SE Asia & Western Pacific

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