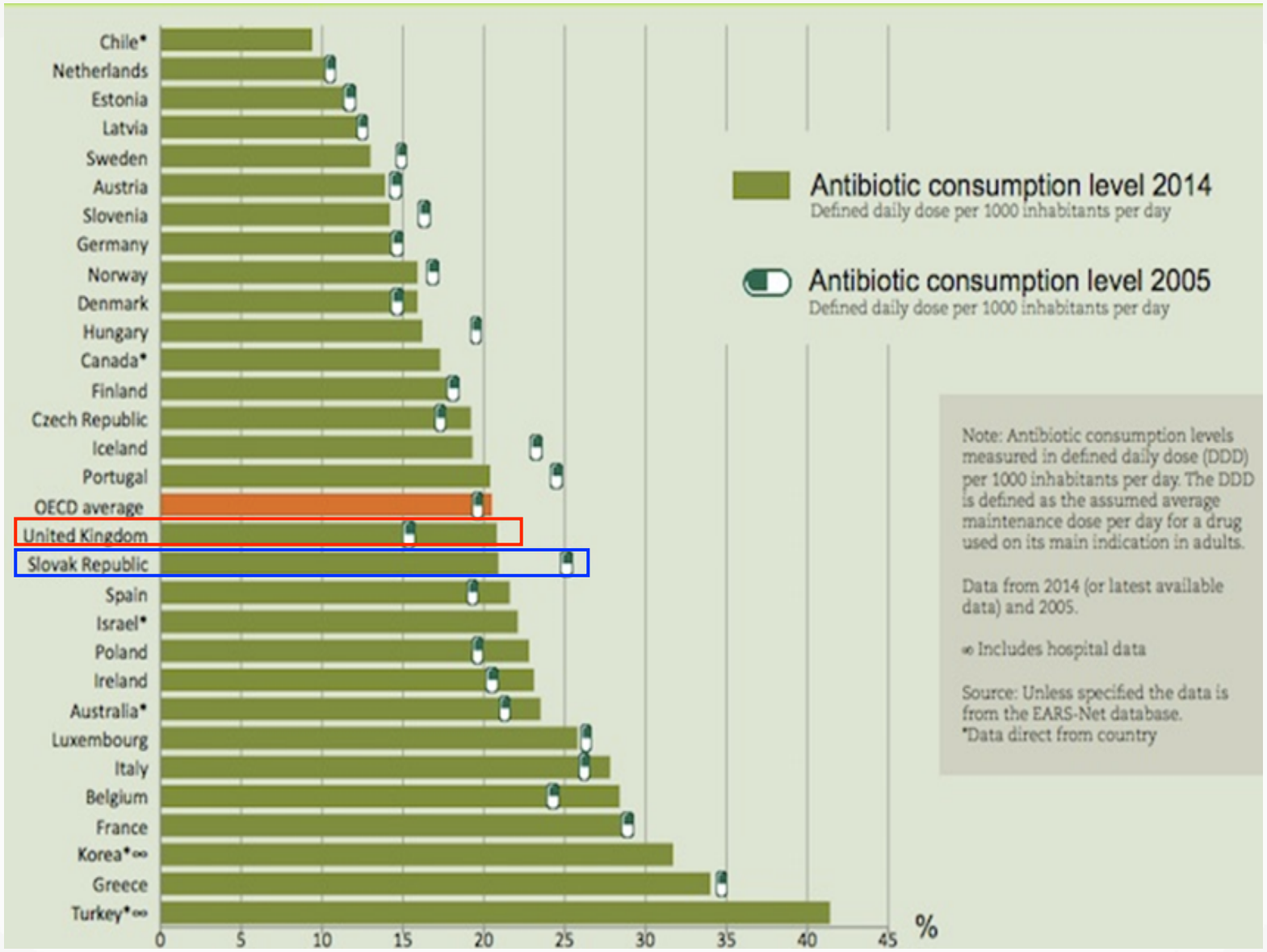
Milano, MiCo Centro Congressi
17 | 18 | 19 MARZO 2017

FarmacistaPiù

Emergenza antibiotico resistenza: nuove strategie per sconfiggere il pericolo

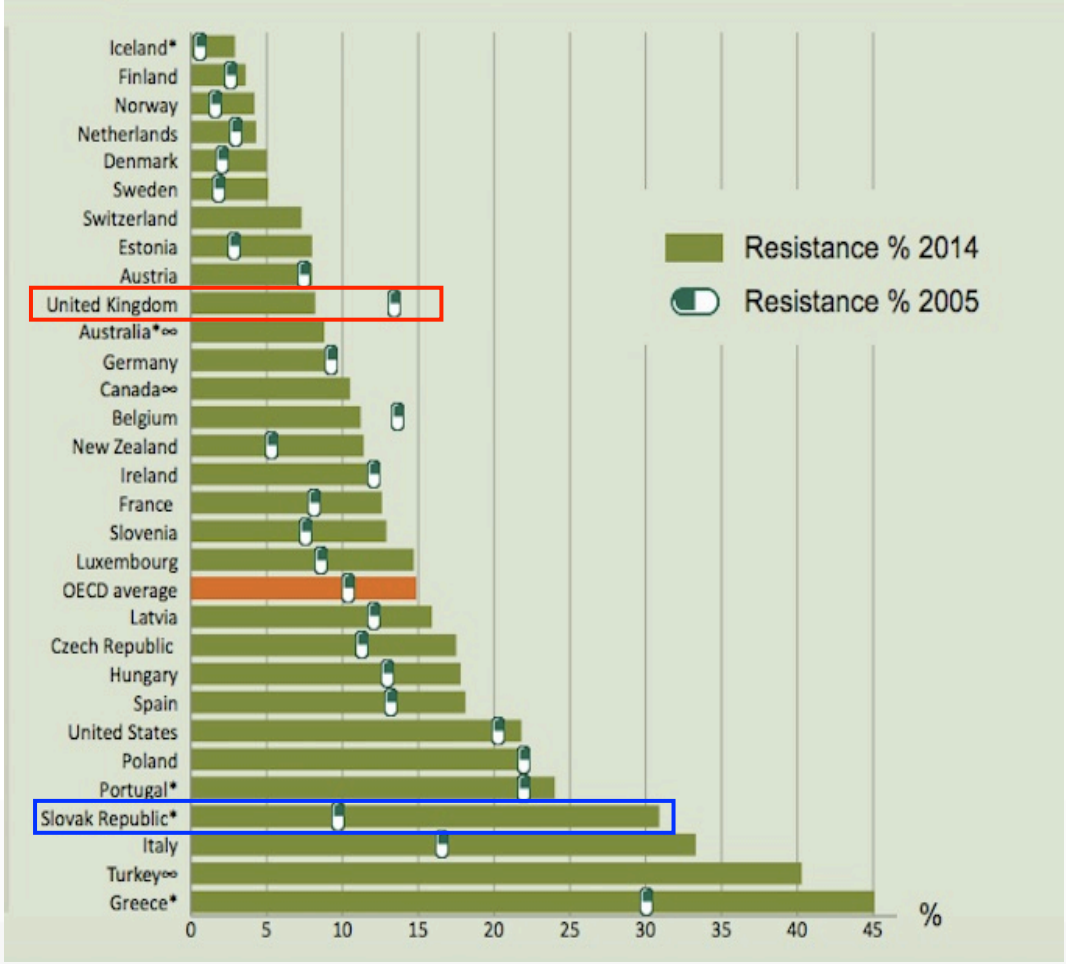
Gianni Sava

SIF
SOCIETÀ ITALIANA DI FARMACOLOGIA


Chile*
Netherlands
Estonia
Latvia
Sweden
Austria
Slovenia
Germany
Norway
Denmark
Hungary
Canada*
Finland
Czech Republic
Iceland
Portugal
OECD average
United Kingdom
Slovak Republic
Spain
Israel*
Poland
Ireland
Australia*
Luxembourg
Italy
Belgium
France
Korea*∞
Greece
Turkey*∞
0
5
10
15
20
25
30
35
40
45
%
Antibiotic consumption level 2014
Defined daily dose per 1000 inhabitants per day
Antibiotic consumption level 2005
Defined daily dose per 1000 inhabitants per day
Note: Antibiotic consumption levels measured in defined daily dose (DDD) per 1000 inhabitants per day. The DDD is defined as the assumed average maintenance dose per day for a drug used on its main indication in adults.
Data from 2014 (or latest available data) and 2005.
∞ Includes hospital data
Source: Unless specified the data is from the EARS-Net database.
*Data direct from country

Trends across OECD countries

Antibiotic resistance is growing

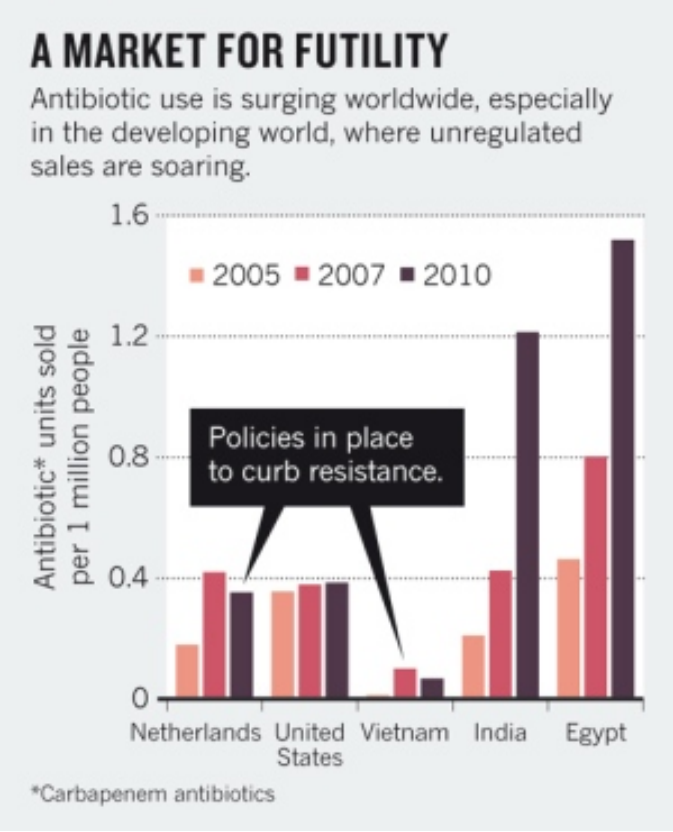


OECD 2016

But … in the low- middle-income Countries…

The convergence of factors such as **poor public health infrastructure, rising incomes, a high burden of disease, and cheap, unregulated sales** of antibiotics has created ideal conditions for a **rapid rise in resistant infections**.

Over-the-counter, non prescription sales of carbapenems in India are among the highest in the world and contribute to growing carbapenem resistance among Gram-negative organisms.



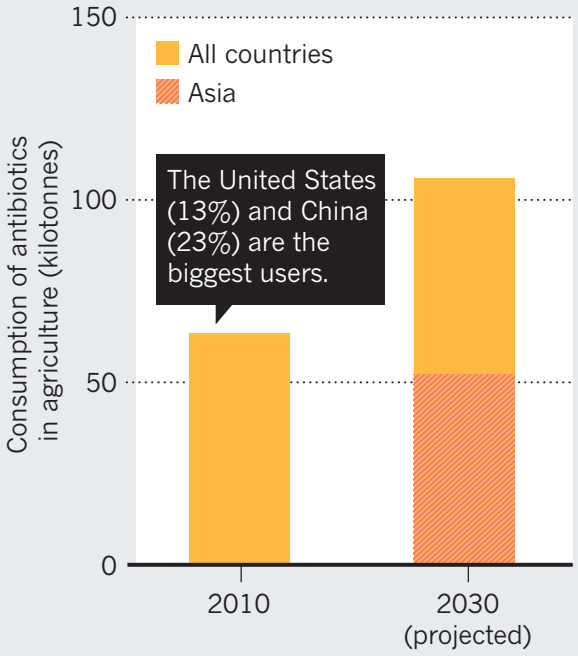
ISSOUF SANOGO/AFP/Getty

Unregulated sales of medicines in developing countries contribute to the rise in antimicrobial resistance.

The use of antibiotics in livestock is growing worldwide.

FARM FORECAST

By 2030, the use of antimicrobials in agriculture in Asia alone could equal 82% of global agricultural consumption in 2010. The drugs are largely given to promote growth or prevent infections, rather than to treat disease.



STR/AFP/GETTY

Antibiotic use in livestock has contributed to drug resistance around the world.

Antibiotic pollution of waterways creates superbugs

-up to **80% of an antibiotic dose passes straight through the body**;
-most of the antibiotics used in medical treatment or during animal production may end up in waste water;
-waste treatment plants generally don't remove antibiotics very well.

-most researchers agree that total **agricultural and medical use exceeds 250,000 tonnes** per year.

-if 50% of an antibiotic dose is subsequently excreted, then **125,000 tonnes of antibiotics are released into the environment** each year (excluding the release from pharmaceutical plants). Antibiotics are then likely to find their way into rivers, lakes and dams.

-this makes 12.5×10^{16} micrograms of antibiotic released into 9×10^{16} litres of freshwater each year. This results in a **final concentration of about 1.4 micrograms per litre**.

Michael Gillings, Macquarie University March 11, 2015

The consequences of this pollution are potentially very serious. Where the concentration of antibiotics is enough to inhibit bacterial growth, it's almost certain to result in the **appearance of antibiotic-resistant strains**.

This happens because **microorganisms** in the environment collectively **carry and share enormous numbers of genes for resistance**, virulence and other general nastiness.

These genes can hop from one bacterial species to another, and **the presence of antibiotics favours cells that have acquired these genes for resistance**.

The most worrying trend is the spread of **resistance to** carbapenems, the '**antibiotics of last resort**'

Melissa Dankel/CDC

Methicillin-resistant *Staphylococcus aureus* (MRSA) is now invulnerable to many antibiotics.

"A post-antibiotic era — in which **common infections** and minor injuries **can kill** — far from being an apocalyptic fantasy, is instead a very real possibility for the twenty-first century,"

WHO PRIORITY PATHOGENS LIST FOR R&D OF NEW ANTIBIOTICS

Priority 1: CRITICAL[#]

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter, fluoroquinolone-resistant

Salmonella *spp.*, fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

Streptococcus pneumoniae, penicillin-non-susceptible

Haemophilus influenzae, ampicillin-resistant

Shigella *spp.*, fluoroquinolone-resistant

open concerns

Too few novel antibiotics coming to market to replace those lost due to resistance development

Antibiotic innovation in **academia is not filling the void** due to misaligned incentive structures and lack of vital knowledge of drug discovery

'**Targeting an organism inside another organism**' have not been given enough attention

NATURE | NEWS

Antibiotics funding splurge gets mixed reception

Multimillion dollar initiative **prioritizes drug development over discovery** of new molecules.

28 July 2016

Bioorganic & Medicinal Chemistry 24 (2016) 6409–6419

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Discovery, pharmacology, and clinical profile of omadacycline, a novel aminomethylcycline antibiotic

S. Ken Tanaka, Judith Steenbergen *, Stephen Villano

Paratek Pharmaceuticals, Inc., 75 Park Plaza, 4th Floor, Boston, MA 02116, United States

PLOS ONE

RESEARCH ARTICLE

Rational Design of Antibiotic Treatment Plans: A Treatment Strategy for Managing Evolution and Reversing Resistance

Portia M. Mira[1], Kristina Crona[2], Devin Greene[2], Juan C. Meza[1], Bernd Sturmfels[3], Miriam Barlow[1]*

Ginovyan *et al. BMC Complementary and Alternative Medicine* (2017) 17:50
DOI 10.1186/s12906-017-1573-y

BMC Complementary and Alternative Medicine

RESEARCH ARTICLE Open Access

Antimicrobial activity of some plant materials used in Armenian traditional medicine

Editorial

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Future Medicinal Chemistry

Disarming pathogens: benefits and challenges of antimicrobials that target bacterial virulence instead of growth and viability

THE PEW CHARITABLE TRUSTS

The Pew Charitable Trusts / Research & Analysis / A Scientific Roadmap for Antibiotic Discovery

REPORT

A Scientific Roadmap for Antibiotic Discovery

A sustained and robust pipeline of new antibacterial drugs and therapies is critical to preserve public health

May 11, 2016

Antibiotic Resistance Project

Drug name*	Development phase†	Company	Type of therapeutic	Potential indication(s)‡
Aerucin	Phase 1	Aridis Pharmaceuticals Inc.	antibody	Bacterial infections
CF-301	Phase 1	ContraFect Corp.	lysin	Bacteremia (*Staphylococcus aureus*)
NDV-3	Phase 1	NovaDigm Therapeutics Inc.	vaccine	Prevention of bacterial infections (*S. aureus*)
514G3	Phases 1/2	XBiotech Inc.	antibody	Bacteremia (*S. aureus*)
N-Rephasin	Phase 1§	Intron Biotechnology Inc.	lysin	Bacterial infections (*S. aureus*)

Drug name*	Development phase†	Company	Type of therapeutic	Potential indication(s)‡
Aurexis (tefibazumab)	Phase 2	Bristol-Myers Squibb Co.	antibody	Bacteremia (*S. aureus*), chronic *S. aureus* infection in cystic fibrosis patients
Brilacidin	Phase 2	Cellceutix Corp.	antimicrobial peptide	Acute bacterial skin and skin structure infections
MEDI4893	Phase 2	MedImmune Inc.	antibody	Pneumonia (*S. aureus*)
Group B Streptococcus vaccine	Phase 2	Novartis International AG#	vaccine	Prevention of Group B *Streptococcal* infection
PF-06425090	Phase 2	Pfizer Inc.	vaccine	Recurrent *Clostridium difficile* infection
SA4Ag	Phase 2	Pfizer Inc.	vaccine	Prevention of *S. aureus* infection
POL7080	Phase 2	Polyphor Ltd.	antimicrobial peptide	Ventilator-associated bacterial pneumonia (*Pseudomonas aeruginosa*), lower respiratory tract infection, bronchiectasis
RBX2660	Phase 2	Rebiotix Inc.	probiotic	Recurrent *C. difficile* infection
SER-109	Phase 2	Seres Therapeutics Inc.	probiotic	Recurrent *C. difficile* infection
VP20621	Phase 2	Shire PLC	probiotic	Recurrent *C. difficile* infection

Drug name*	Development phase†	Company	Type of therapeutic	Potential indication(s)‡
Pagibaximab	Phases 2/3	Biosynexus Inc.	antibody	Prevention of bacteremia in very low birth weight neonates (*S. aureus*)
IC43	Phases 2/3	Valneva SE	vaccine	Prevention of ventilator-associated bacterial pneumonia (*P. aeruginosa*)
Salvecin (AR-301)	Phase 2§	Aridis Pharmaceuticals Inc.	antibody	Pneumonia (*S. aureus*)
Aerumab (AR-101)	Phase 2§	Aridis Pharmaceuticals Inc.	antibody	Pneumonia (*P. aeruginosa*), ventilator-associated bacterial pneumonia (*P. aeruginosa*)
MEDI3902	Phase 2§	MedImmune Inc.	antibody	Prevention of ventilator-associated bacterial pneumonia (*P. aeruginosa*)
IC84	Phase 2§	Valneva SE	vaccine	Recurrent *C. difficile* infection
Bezlotoxumab and Actoxumab	Phase 3	Merck & Co. Inc.	antibody	Recurrent *C. difficile* infection
Cdiffense	Phase 3	Sanofi Pasteur SA	vaccine	Prevention of *C. difficile* infection

molecules
MDPI

Review

Nanoparticles: Alternatives Against Drug-Resistant Pathogenic Microbes

Gudepalya Renukaiah Rudramurthy [1], Mallappa Kumara Swamy [2,*], Uma Rani Sinniah [2,*] and Ali Ghasemzadeh [2]

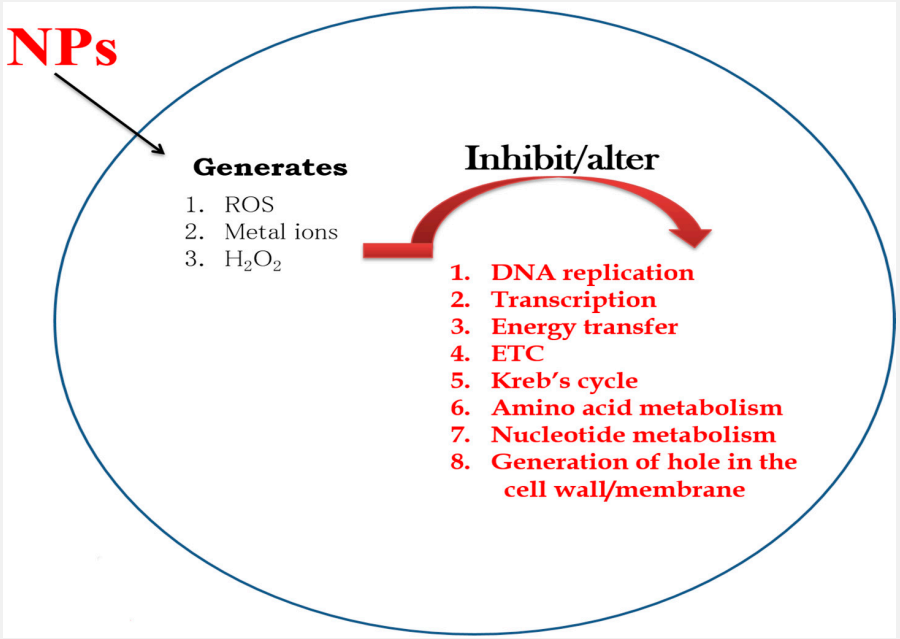


Figure 1. Mechanism of action of various nanoparticles (NPs) on microbial cells.

Molecules 2016, 21, 836

Table 1. Mode of action of various nanoparticles/nanocomposites against pathogenic microbes.

Type of Nanoparticles	Mode of Action	Susceptible Microbes
Silver (Ag) nanoparticles	Interfere with the electron transport chain and transfer of energy through the membrane. Inhibit DNA replication and respiratory chain in bacteria and fungi.	Methicillin-resistant *Staphylococcus aureus*, *Staphylococcus epidermidis*. Vancomycin-resistant *Enterococcus faecium* and *Klebsiella pneumoniae*
Magnesium oxide (MgO) nanoparticles	Formation of reactive oxygen species (ROS), lipid peroxidation, electrostatic interaction, alkaline effect.	*S. aureus*, *E. coli*, *Bacillus megaterium*, *Bacillus subtilis*
Titanium dioxide (TiO_2) nanoparticles	Formation of superoxide radicals, ROS, and site-specific DNA damage.	*E. coli*, *S. aureus*, and also against fungi
Zinc oxide (ZnO) nanoparticles	Hydrogen peroxide generated on the surface of ZnO penetrates the bacterial cells and effectively inhibits growth. Zn^{2+} ions released from the nanoparticles damage the cell membrane and interact with intracellular components.	*E. coli*, *Listeria monocytogenes*, *Salmonella*, and *S. aureus*
Gold (Au) nanoparticles	Generate holes in the cell wall. Bind to the DNA and inhibit the transcription process.	Methicillin-resistant *S. aureus*
Copper oxide (CuO) nanoparticles	Reduce bacteria at the cell wall. Disrupt the biochemical processes inside bacterial cells.	*B. subtilis*, *S. aureus*, and *E. coli*
Iron-containing nanoparticles	Through ROS-generated oxidative stress. ROS, superoxide radicals (O^{2-}), singlet oxygen ($^1O_2$), hydroxyl radicals (OH^-), and hydrogen peroxide (H_2O_2).	*S. aureus*, *S. epidermidis*, and *E. coli.*
Aluminum (Al) nanoparticles	Disrupt cell walls through ROS.	*E. coli*
Bismuth (Bi) nanoparticles	Alter the Krebs cycle, and amino acid and nucleotide metabolism.	Multiple-antibiotic resistant *Helicobacter pylori*
Carbon-based nanoparticles	Severe damage to the bacterial membrane, physical interaction, inhibition of energy metabolism, and impairment of the respiratory chain.	*E. coli*, *Salmonella enteric*, *E. faecium*, *Streptococcus* spp., *Shewanella oneidensis*, *Acinetobacter baumannii*, *Burkholderia cepacia*, *Yersinia pestis*, and *K. pneumonia*

Molecules 2016, 21, 836

Infect Dis Clin North Am. 2014 Jun;28(2):177-93. doi: 10.1016/j.idc.2014.02.001.

Health care provider education as a tool to enhance antibiotic stewardship practices.

Ohl CA[1], Luther VP[2].

Antibiotic stewardship education for health care providers gives a foundation of knowledge and an environment that facilitates and supports optimal antibiotic prescribing.

There is a need to extend this education to medical students and health care trainees. Education using passive techniques is modestly effective for increasing prescriber knowledge, whereas education using active techniques is more effective for changing prescribing behavior. Such education has been shown to enhance other antibiotic stewardship interventions.

Virulence 4:2, 192–202; February 15, 2013; © 2013 Landes Bioscience

How to educate prescribers in antimicrobial stewardship practices

Céline Pulcini[1,2] and Inge C. Gyssens[3,4,*]

Widespread antimicrobial use has compromised its value, leading to a crisis of antimicrobial resistance. **A major cause of misuse is insufficient knowledge of prescribing of antimicrobials in many categories of professionals**.

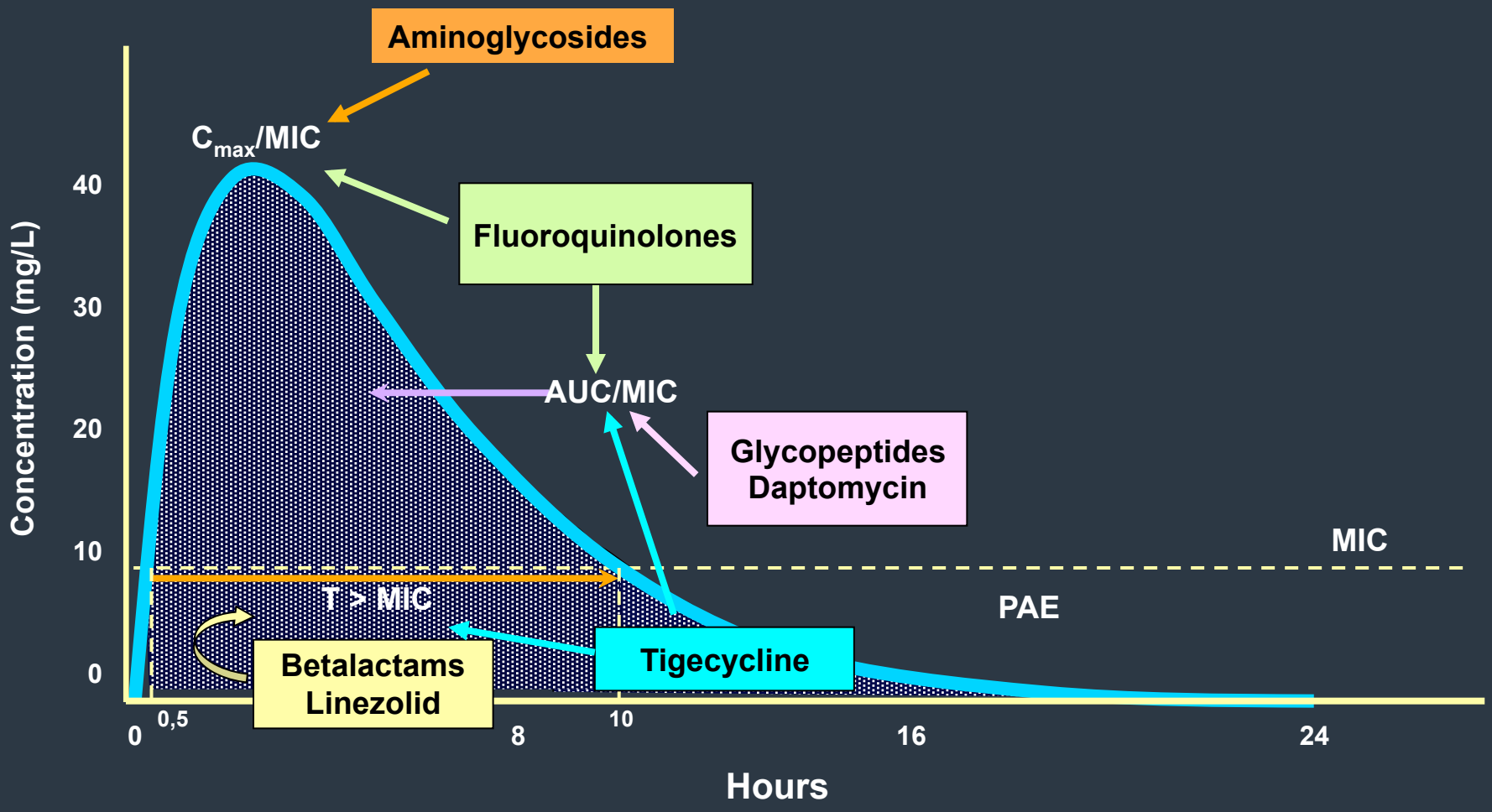
It is now crucial that academia and ministries of Health and Education jointly focus on an **adapted undergraduate medical/professional curriculum that teaches all necessary principles of** microbiology, infectious diseases and **clinical pharmacology**, with emphasis on the principles of prudent prescribing.

What can be done in the clinical setting

- Adjust use of antimicrobials according to local epidemiology
- Know the target pharmacokinetic/pharmacodynamic parameter for the specific drug in use
- Select the most appropriate administration modality according to pharmacokinetic/pharmacodynamic parameters
- Remember that standard susceptibility breakpoints may be inaccurate for the clinical scenario
- Maximize dosing, especially in severely ill patients, according to renal function, but limit the duration of therapy when possible
- Assess serum antimicrobial concentrations whenever possible
- Adopt combination therapy for 48–72 hours and then reevaluate empirical therapy
- Perform active surveillance

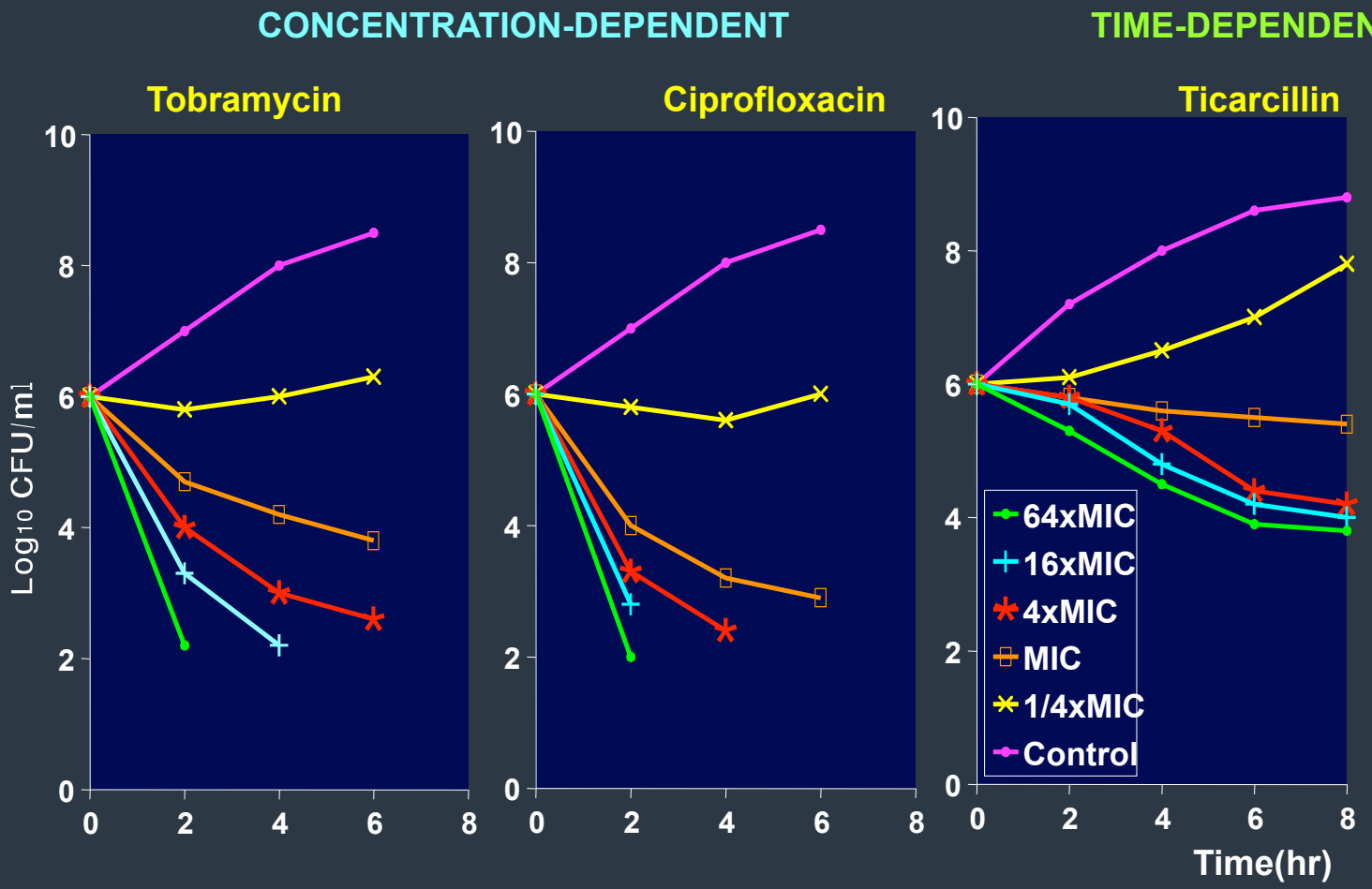
Adembri C and Novelli A, PK-PD and potential for providing dosing regimens that are less vulnerable to resistance Clin Pharmacokinet, 2009

PK-PD correlations

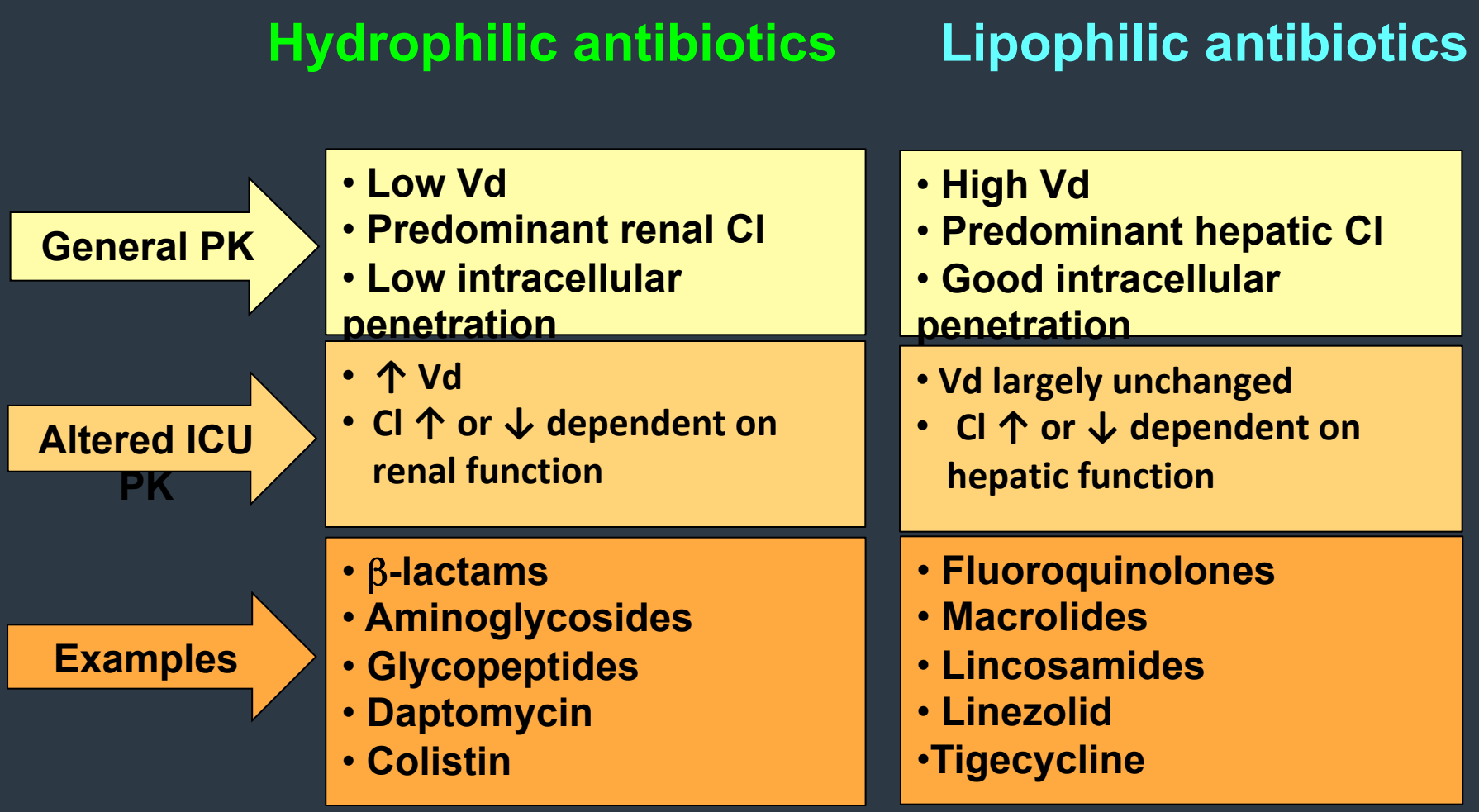


Antibacterial activity

Time-kill curves against P. aeruginosa ATCC 27853



W.A. Craig et al., 1991, modified



Roberts JA et al., Crit Care Med, 2009, mod

Daptomycin

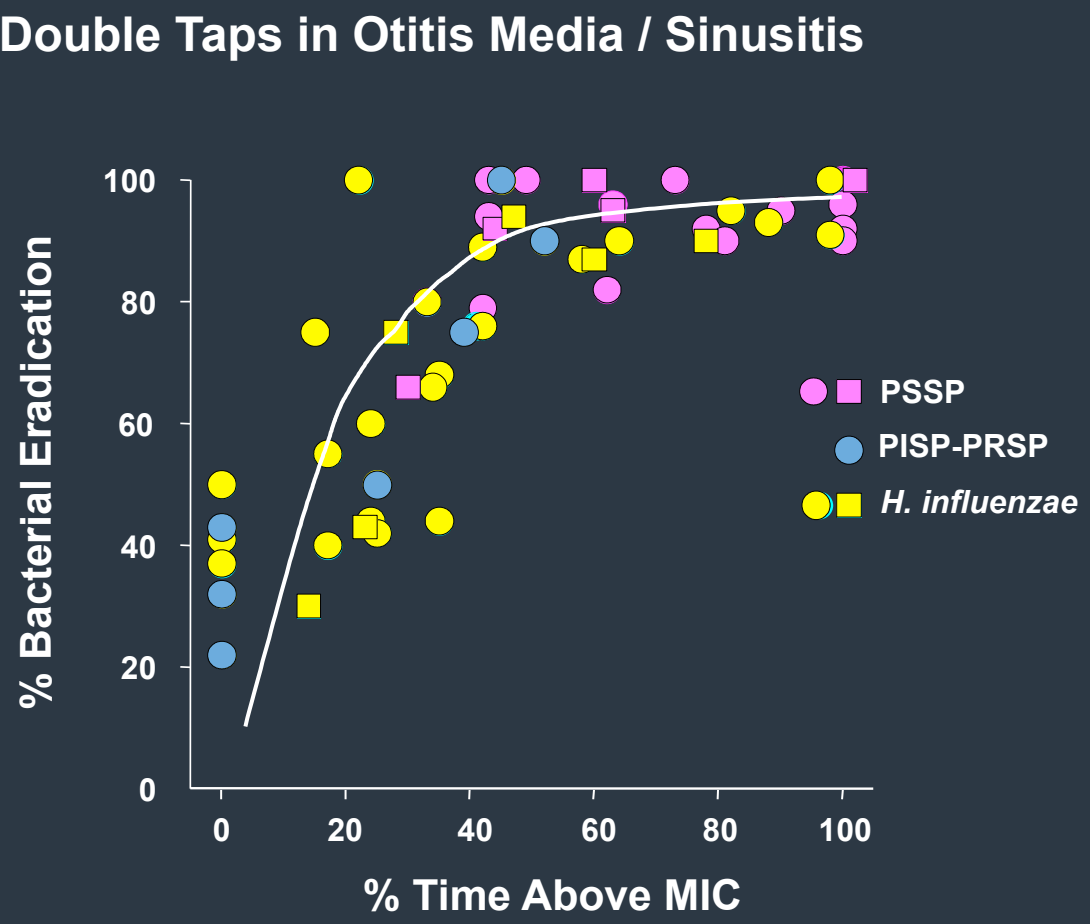
Mean pharmacokinetic parameters in healthy volunteers and severely ill patients

Parameter	6 mg/kg			8 mg/kg		
	Volunt.[a] (6)	Pts.[c] (13)	*P**	Volunt.[b] (6)	Pts.[c] (7)	*P**
C_{max} (mg/l)	86.4	55.7	< 0.01	106.2	85.1	= 0.05
t½ (h)	7.8	8.8	NS	7.3	8.6	NS
AUC (mg·h/l)	705	406.1	< 0.01	773.3	584.3	< 0.05
Cl (ml/h/kg)	8.6	18.0	< 0.05	10.1	20.4	< 0.05
Vd (l/kg)	0.096	0.22	< 0.01	0.102	0.25	< 0.01

( ) no. Cases * ANOVA test

[a] Dvorchik BH et al., Antimicrob Agents Chemother, 2009
[b] Benvenuto M et al., Antimicrob Agents Chemother, 2006
[c] Falcone M, Venditti M, Novelli A, 21st ECCMID-27th ISC Milan, Italy, 2011

Relationship between T>MIC for β-Lactams with bacterial eradication in children with otitis media and sinusitis



PSSP = penicillin-susceptible *S. pneumoniae;* PISP = penicillin-intermediate *S. pneumoniae;* PRSP = penicillin-resistant *S. pneumoniae; H. influenzae*

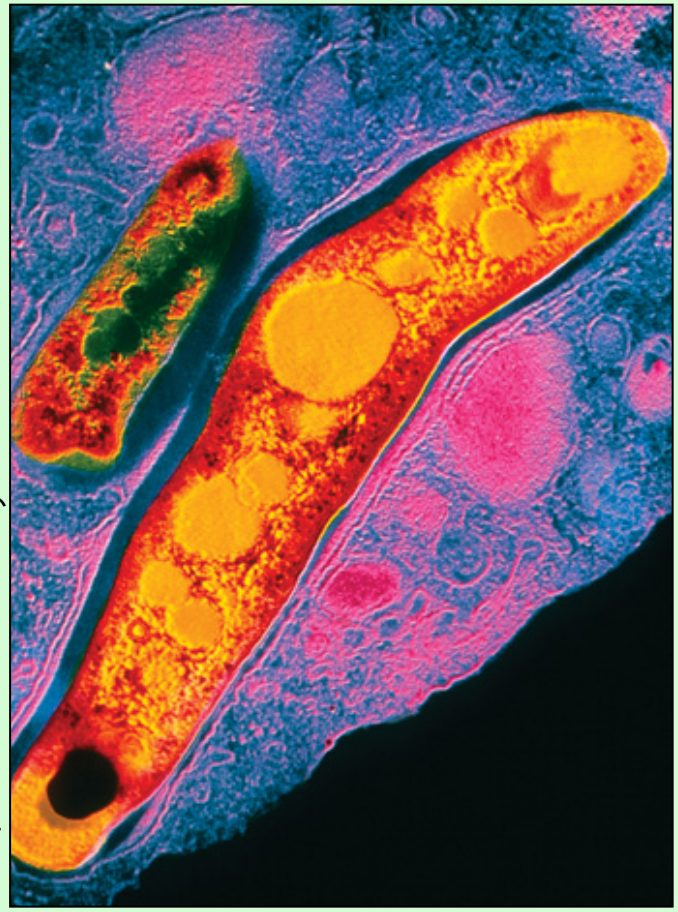
Craig WA. *Infect Dis Clin North Am.* 2003;17:479-501

Comment

by Rovina Ruslami, *Dick Menzies

oa **Finding the right dose of rifampicin, and the right dose of optimism**

After the widespread introduction of rifampicin in the early 1970s, it took another two decades, and more than **50 randomised trials with more than 20,000 participants to finalise the drugs, doses, and schedule** for the currently recommended regimen for newly diagnosed patients with active tuberculosis. **Yet this regimen has important drawbacks**, most notably the 6 months duration, and frequent toxicity.



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www.thelancet.com/infection Vol 17 January 2017