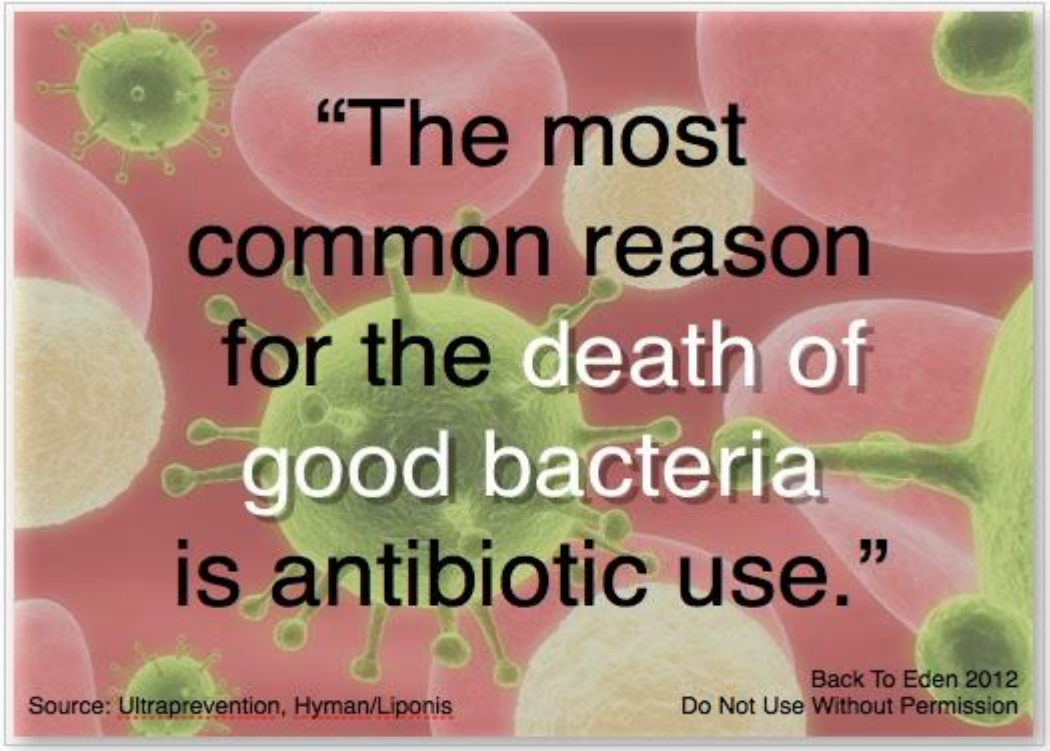
“Políticas de Controlo de Infeção e de Antibioterapia: Perspetivas Atuais”

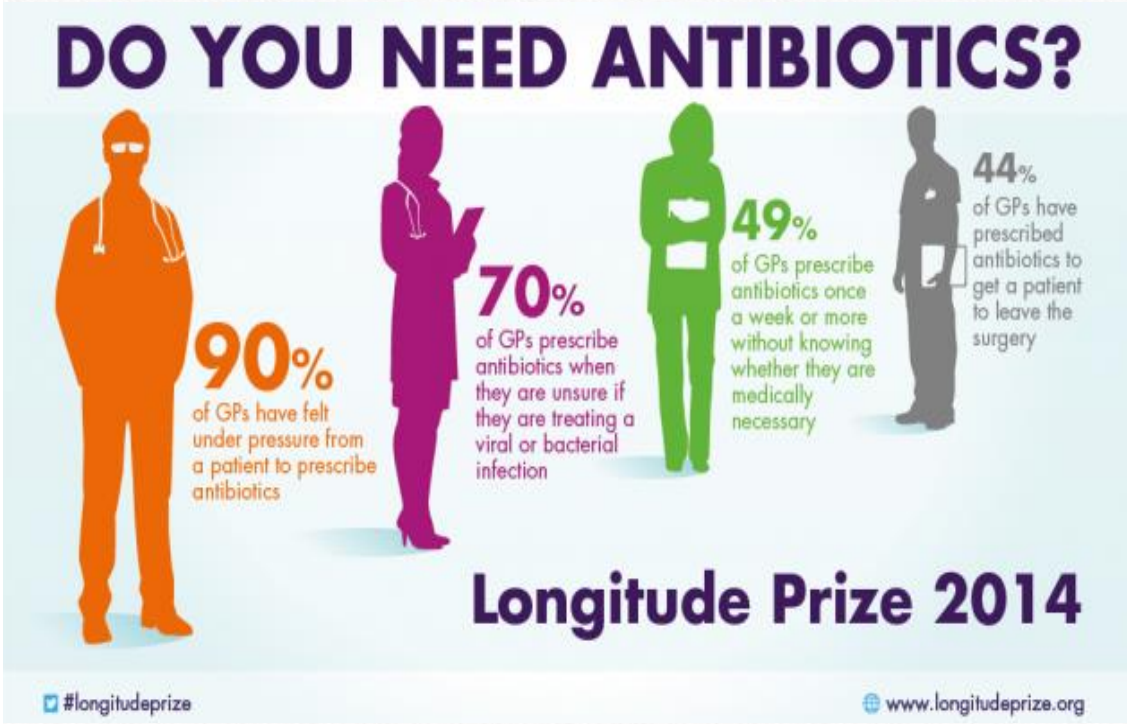
José M. D. Poças

Diretor do SDI CHS HSB Setúbal

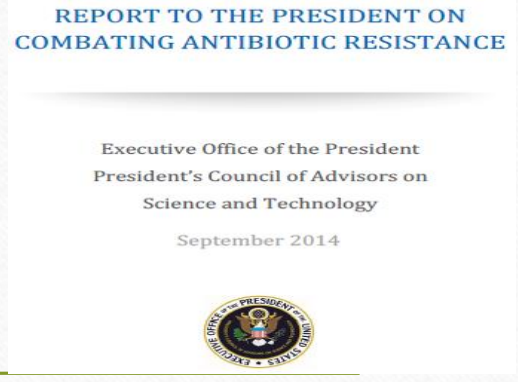
Presidente Interino da CCIPRA

INTRODUÇÃO


"The most common reason for the death of good bacteria is antibiotic use."
Source: Ultraprevention, Hyman/Liponis
Back To Eden 2012
Do Not Use Without Permission


DO YOU NEED ANTIBIOTICS?
90% of GPs have felt under pressure from a patient to prescribe antibiotics
70% of GPs prescribe antibiotics when they are unsure if they are treating a viral or bacterial infection
49% of GPs prescribe antibiotics once a week or more without knowing whether they are medically necessary
44% of GPs have prescribed antibiotics to get a patient to leave the surgery
Longitude Prize 2014
#longitudeprize
www.longitudeprize.org

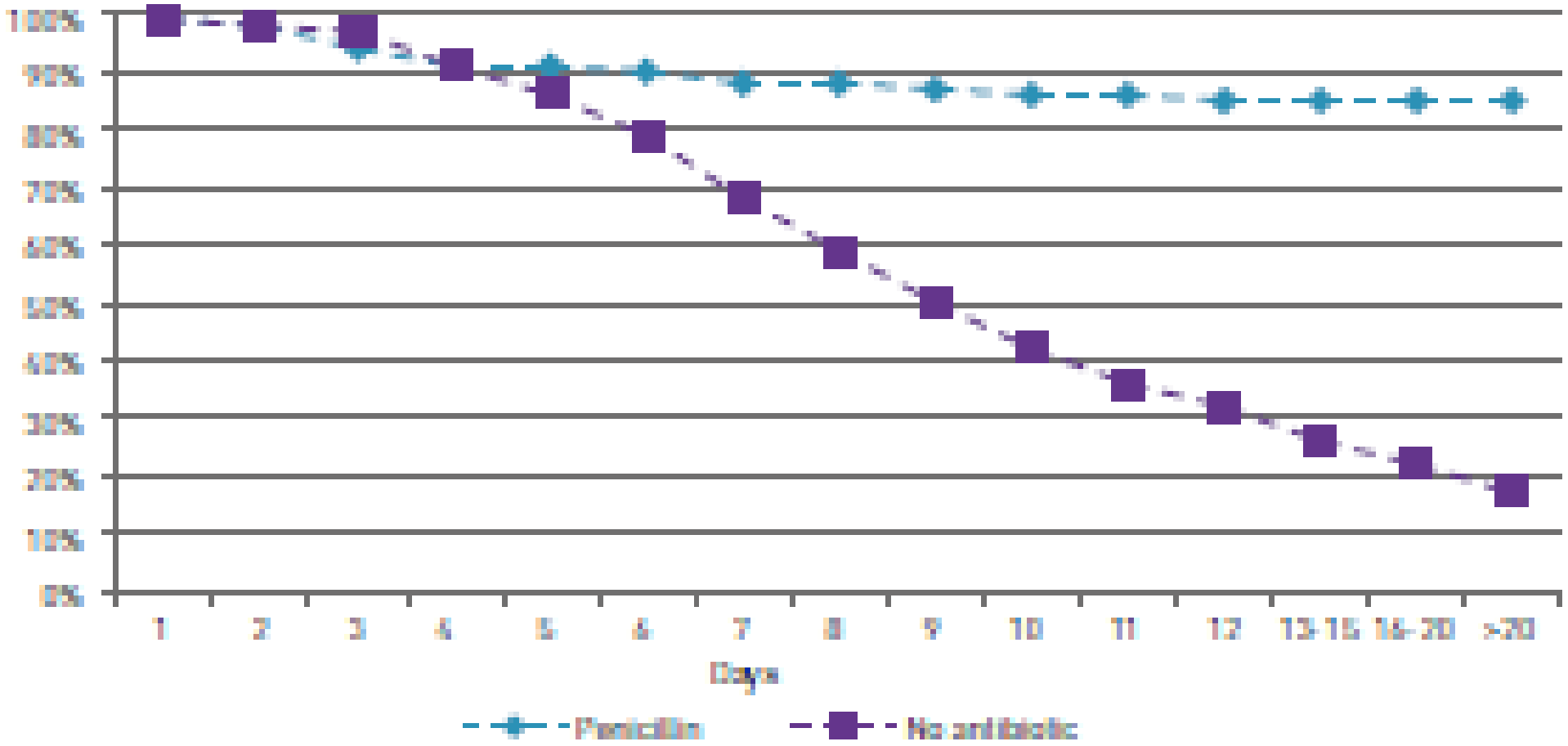
Um mero exercício de memória …



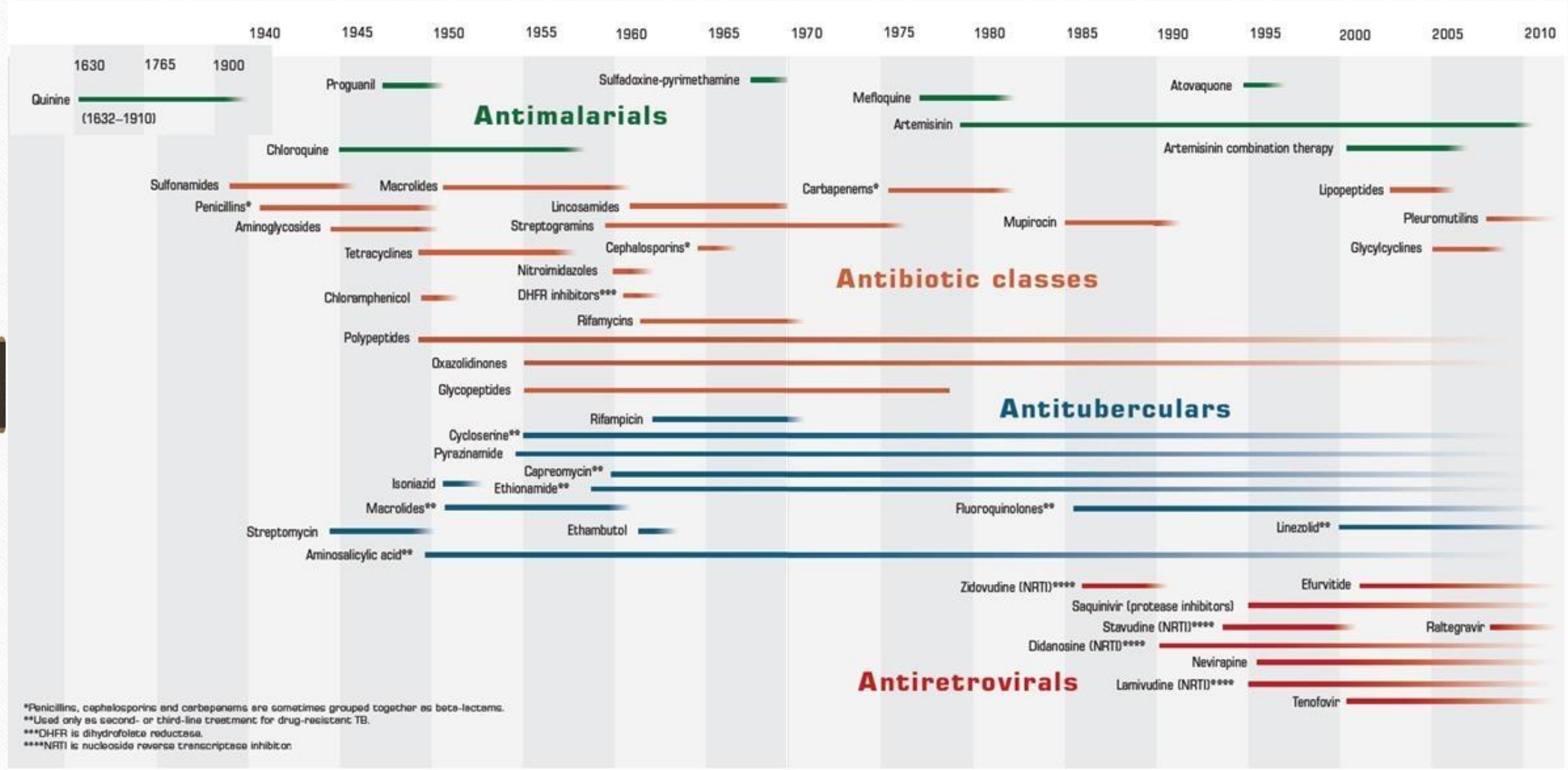
- ***"Para um cidadão americano do séc. XXI, é muito difícil imaginar o que era o mundo antes da existência dos antibióticos. No início do séc. XX, cerca de 9 em 1.000 mulheres parturientes morriam, 40% das quais por sépsis. Nalgumas cidades, 30% das crianças morriam no 1º ano de vida. 1 em cada 9 pessoas que tivessem uma infeção com alguma gravidade falecia, mesmo nos casos que atingiam exclusivamente a pele. A mortalidade da pneumonia era de 30% e a da meningite de 70%. As otites causavam frequente surdez, as amigdalites complicavam-se muitas vezes de febre remática e esta de insuficiência cardíaca. Os procedimentos cirúrgicos complicavam-se com muita frequência de processos infeciosos com elevada morbilidade e mortalidade associadas."***

- ***"O panorama mudou posteriormente de forma radical por três factos decisivos: Melhoria das condições sanitárias gerais, a vacinação em massa e a descoberta dos antibióticos. Ao longo do s. XX, as mortes por causa infeciosa diminuíram bastante, tendo contribuído para um aumento da esperança de vida em cerca de 29 anos. Os antimicrobianos, em particular, permitiram salvar anualmente muitos milhões de vidas. Primeiramente desenvolvidos na década de 30, a sua comercialização expandiu-se vertiginosamente na década seguinte. Conduziram a uma série de outros avanços nos cuidados médicos, designadamente no domínio cirúrgico (queimados, transplantados, intervencionados ao caração, etc.), através da prevenção e tratamento das complicações infeciosas associadas."***

Figure 9 Survival after pneumococcal pneumonia with bloodstream infection before and after penicillin treatment became available.



Adapted from Austrian et al. [3].

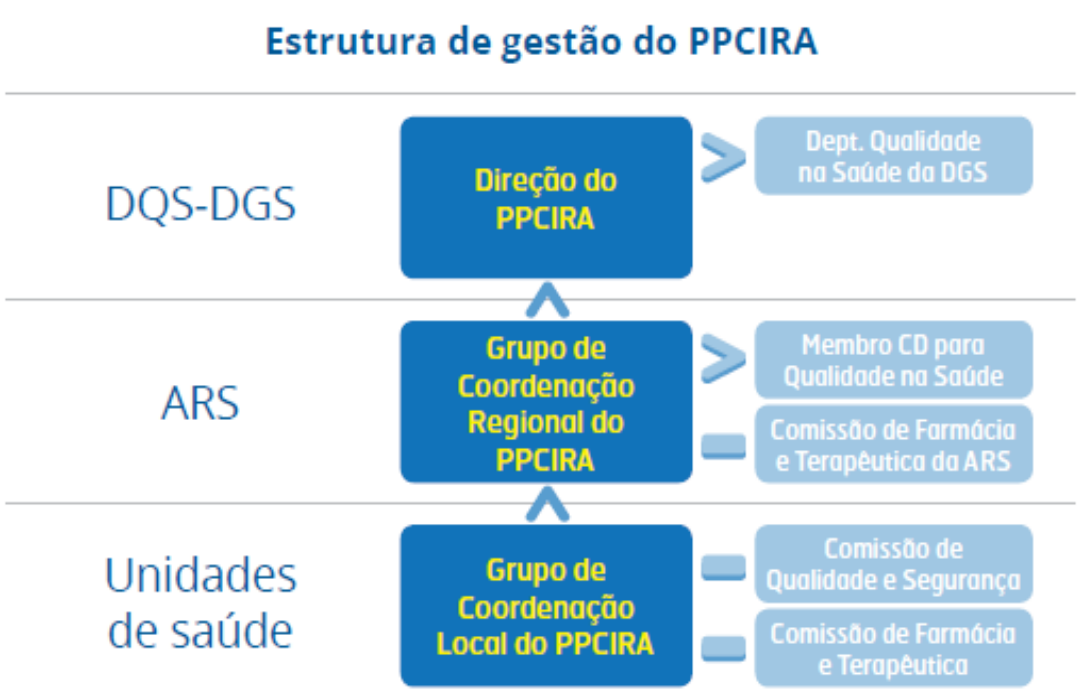

1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
1630
1765
1900
Quinine
(1632–1910)
Proguanil
Sulfadoxine-pyrimethamine
Mefloquine
Atovaquone
Artemisinin
Antimalarials
Chloroquine
Artemisinin combination therapy
Sulfonamides
Macrolides
Carbapenems*
Lipopeptides
Penicillins*
Lincosamides
Pleuromutilins
Aminoglycosides
Streptogramins
Mupirocin
Tetracyclines
Cephalosporins*
Glycylcyclines
Nitroimidazoles
Antibiotic classes
Chloramphenicol
DHFR inhibitors***
Rifamycins
Polypeptides
Oxazolidinones
Glycopeptides
Antituberculars
Rifampicin
Cycloserine**
Pyrazinamide
Capreomycin**
Isoniazid
Ethionamide**
Macrolides**
Fluoroquinolones**
Streptomycin
Ethambutol
Linezolid**
Aminosalicylic acid**
Zidovudine (NRTI)****
Efurvitide
Saquinivir (protease inhibitors)
Stavudine (NRTI)****
Raltegravir
Didanosine (NRTI)****
Nevirapine
Antiretrovirals
Lamivudine (NRTI)****
Tenofovir
*Penicillins, cephalosporins and carbepenems are sometimes grouped together as beta-lactams.
**Used only as second- or third-line treatment for drug-resistant TB.
***DHFR is dihydrofolate reductase.
****NRTI is nucleoside reverse transcriptase inhibitor.

PATIENT SAFETY AND HEALTHCARE-ASSOCIATED INFECTIONS: *REPORT FROM THE*

COMMISSION TO THE COUNCIL June 2014

2. ESTRUTURA DE GESTÃO E OPERACIONALIZAÇÃO DO PROGRAMA

Figura 1. Estrutura de gestão do Programa de Prevenção e Controlo de Infeções e de Resistência aos Antimicrobianos (PPCIRA)



Fonte: PPCIRA / DGS / 2013

Sistemas de vigilância epidemiológica

DE RESISTÊNCIAS AOS ANTIMICROBIANOS

- Microrganismos problema
- Microrganismos alerta
- EARS Net

DE CONSUMO DE ANTIBIÓTICOS

- Antimicrobianos em ambulatório
- Antimicrobianos em hospital
- ESAC Net
- Antimicrobianos em veterinária

DE INFECÇÃO

- **HELICS UCI**
- **HELICS ILC**
- **INF UCI Nenatal**
- **INCS**
- **UCC**
- **IPI**

Uma nova Norma de colaboração DGS - INSA

DGS desde 1899 Direção-Geral da Saúde

"Microrganismos problema"

Consideram-se microrganismos "problema", os microrganismos que causam frequentemente doença e com taxas de resistência epidemiologicamente significativa.

Origem invasiva (do Sangue e LCR):

- ***Pseudomonas aeruginosa***
- ***Acinetobacter spp.***
- ***Enterobacteriaceae***
- ***Staphylococcus aureus***
- ***Enterococcus faecalis e Enterococcus faecium***
- ***Streptococcus pneumoniae***

Outra origem: ***Clostridium difficile*.**

instituto_Nacional de Saúde
Doutor Ricardo Jorge

DGS desde 1899
Direção-Geral da Saúde

Norma de Vigilância Epidemiológica das Resistências aos Antimicrobianos

- ❑ Ao INSA compete verificar e registar a receção dos microrganismos. A DGS e o INSA tomam conhecimento da notificação do microrganismo "alerta" em simultâneo. O INSA acusará a receção da mesma aos notificadores;
- ❑ O INSA informa a DGS e o Laboratório de origem sobre a confirmação do resultado do microrganismo "alerta" isolado;
- ❑ O INSA envia à DGS os resultados acumulados sobre os microrganismos "problema" com uma periodicidade não superior a 6 meses;
- ❑ A DGS promove o contato com o Laboratório de Microbiologia e com os GCL-PPCIRA da Instituição de origem para que, localmente:
  - exista notificação interna da deteção do microrganismo para a Direção Clínica e Direção de Enfermagem;
  - sejam adotadas medidas adequadas para o controlo e prevenção de transmissão cruzada;
  - seja disponibilizada colaboração técnico-científica

O PROBLEMA no MUNDO

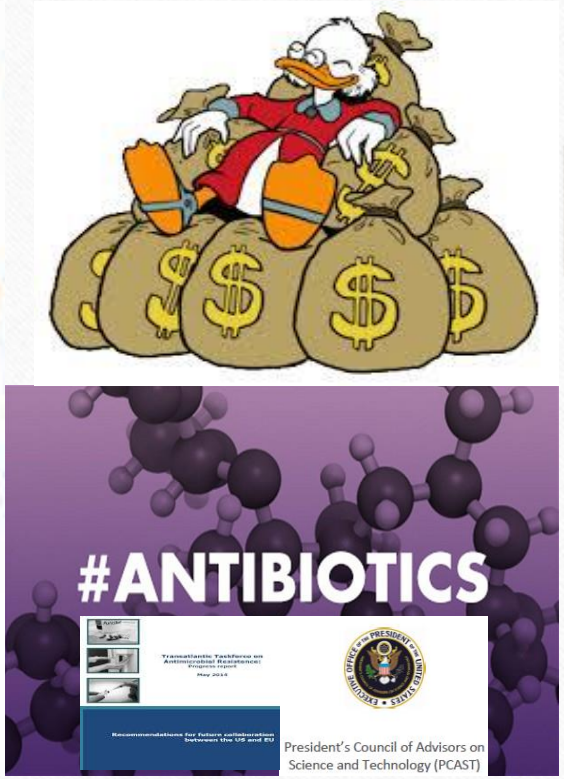
GET SMART

Know When Antibiotics Work

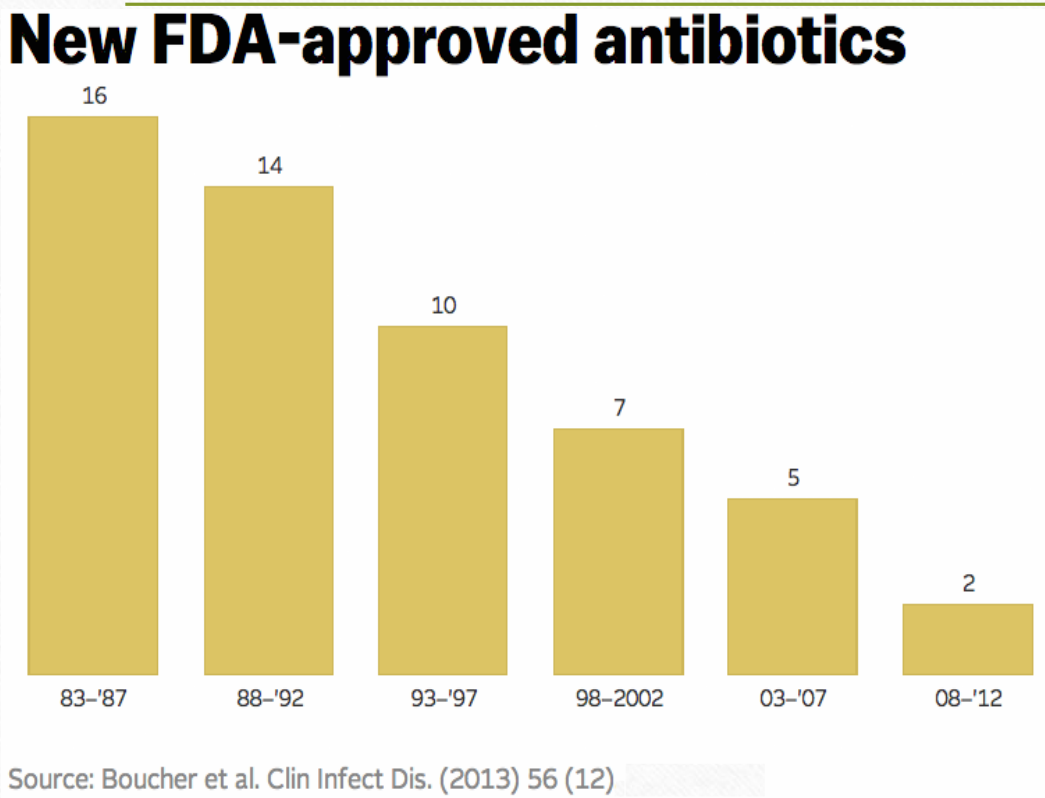
www.cdc.gov/getsmart

Os enormes custos associados!

- **Impacto da Multirresistência aos ABs (Relatórios CDC e TATFAR, 2014)**
  - **20–35 biliões USD/ano (perdas diretas)**
  - **35 biliões USD/ano (perdas de produtividade)**
  - **8 milhões de dias d internamento hospitalar**
  - **2 milhões de pessoas infetadas / ano**
  - **23 - 99.000 mortes / ano nos EUA**
  - **Financiamento público na investigação de novos antibióticos insuficiente: 450 milhões USD/ano**
  - **Na CEE: 25 - 175.000 pessoas morrem / ano**



A escassez de novos antibióticos



Source: Boucher et al. Clin Infect Dis. (2013) 56 (12)

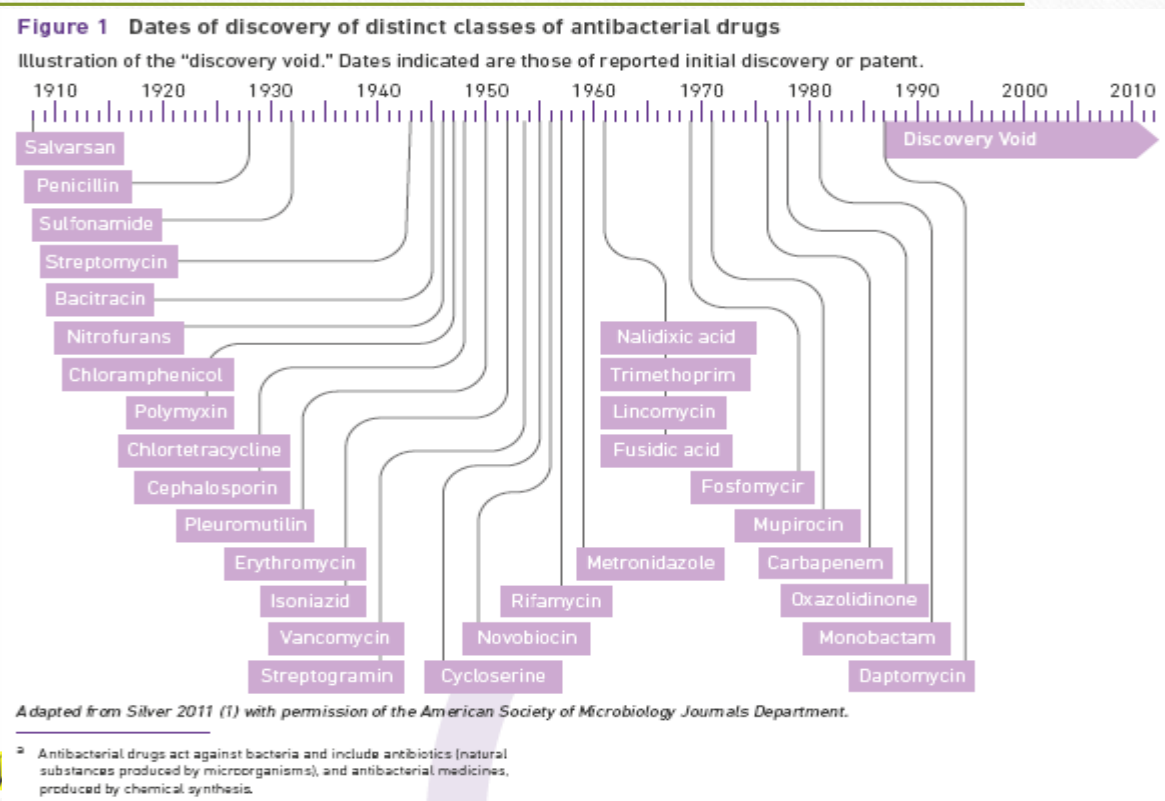
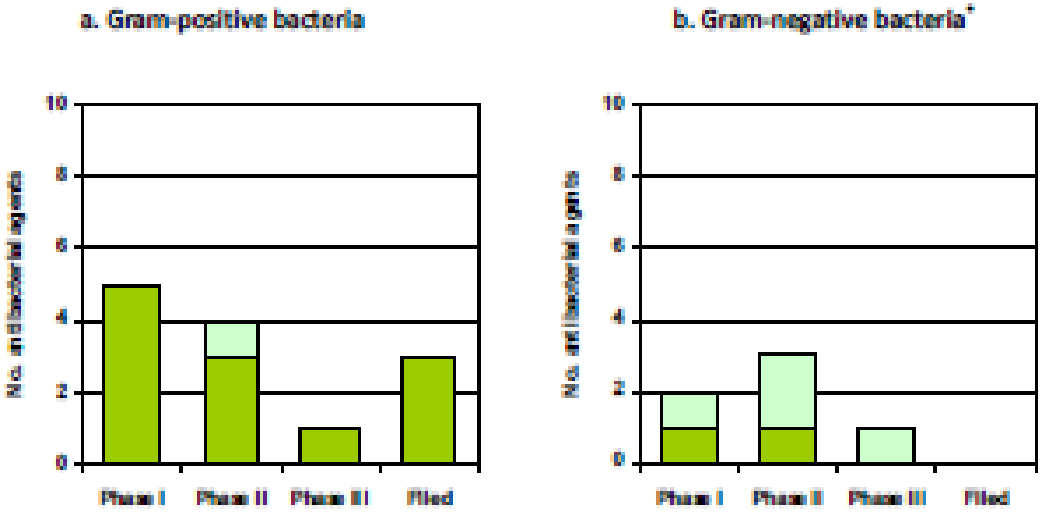
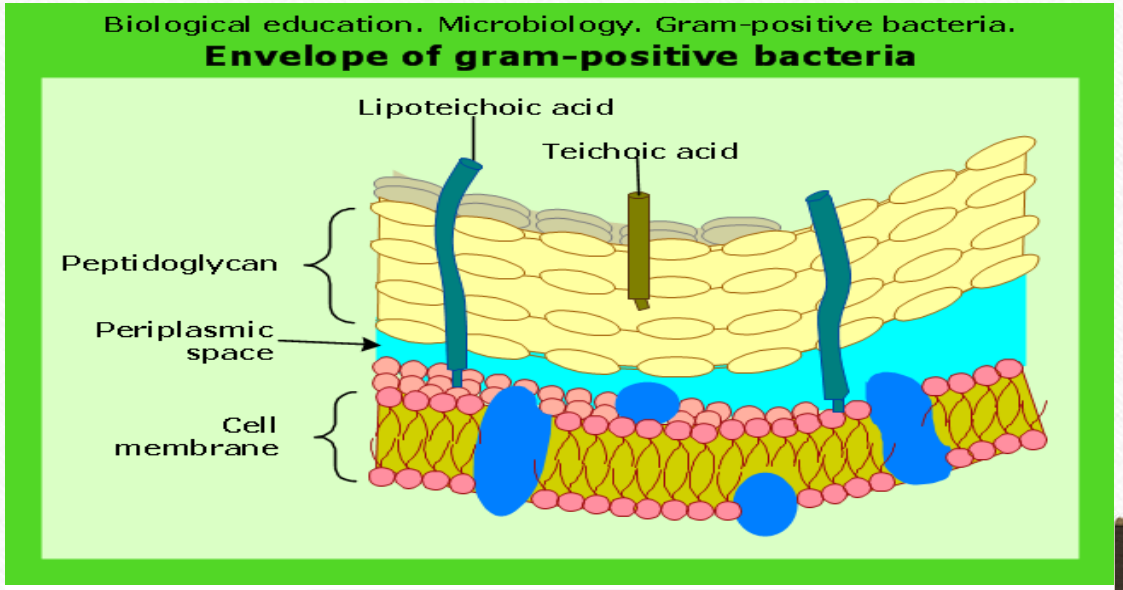


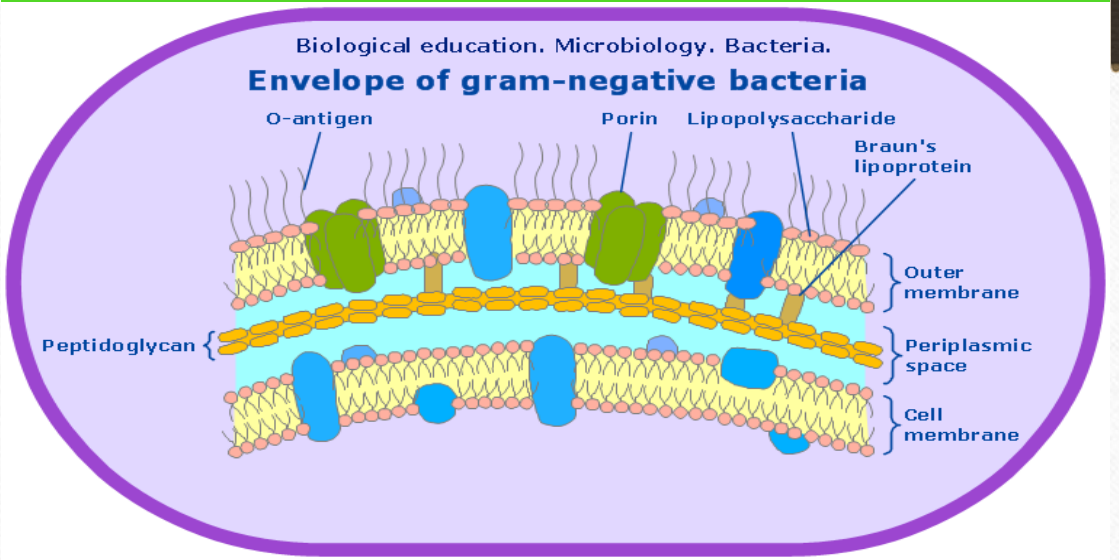
Figure 4.4.5 New systemic antibacterial agents with a new target or new mechanism of action and *in vitro* activity based on actual data (dark colour bars) or assumed *in vitro* activity based on class properties or mechanisms of action (light colour bars) against the selected bacteria (best-case scenario), by phase of development (n=15).[554 552] Data made available courtesy of the EMEA



Note: In vitro activity based on actual data is depicted at the bottom of each column in darker colour. Assumed in vitro activity based on class properties or mechanisms of action (where applicable) is depicted in a lighter colour at the top of each column.

** Two carbapenems have been omitted from Figure 4.4.5b since they are no more active than earlier carbapenems against Gram-negative bacteria. The relative novelty of these agents was based on a better profile of activity against antibiotic-resistant Gram-positive bacteria and are therefore included in Figure 4.4.5a.*





CMR

Investigational Antimicrobial Agents of 2013

Michael J. Pucci,[a]* Karen Bush[b]

Achillion Pharmaceuticals, New Haven, Connecticut, USA[a]; Indiana University, Bloomington, Indiana, USA[b]

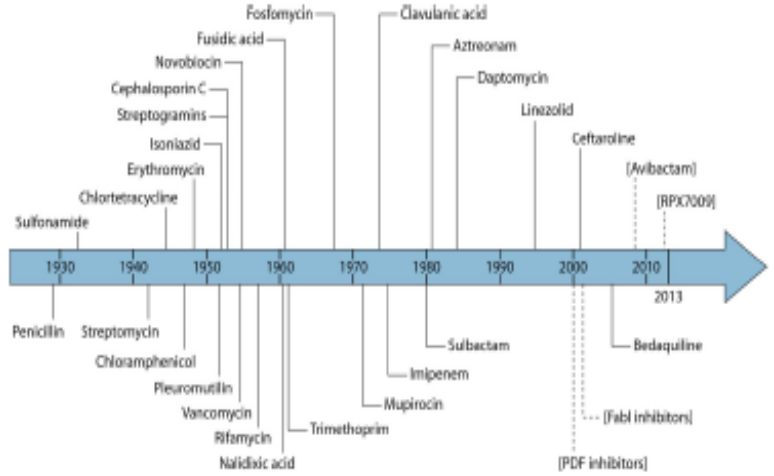


FIG 9 Timeline of the first reports of antibacterial agents or inhibitors with novel structures or activities. Brackets and dashed lines indicate unapproved investigational agents or classes.

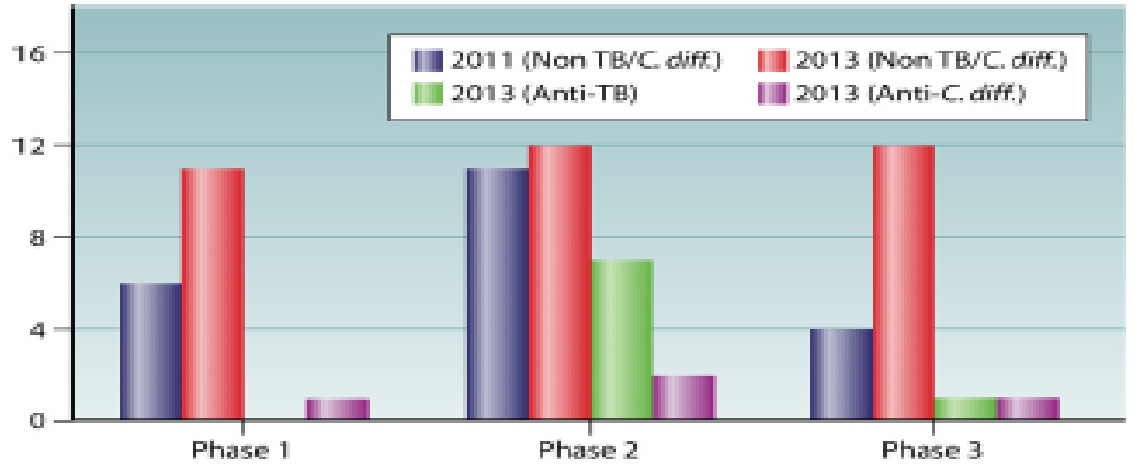


FIG 10 Clinical development status of investigational drugs in the 2011 pipeline (9) compared to 2013. Note that in 2011 agents active against *Clostridium difficile* or *Mycobacterium tuberculosis* were not included in the survey.

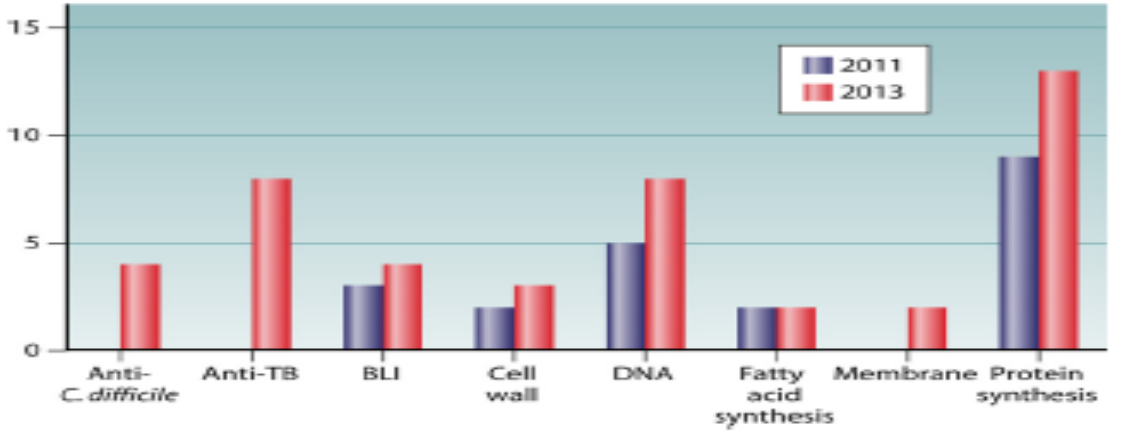
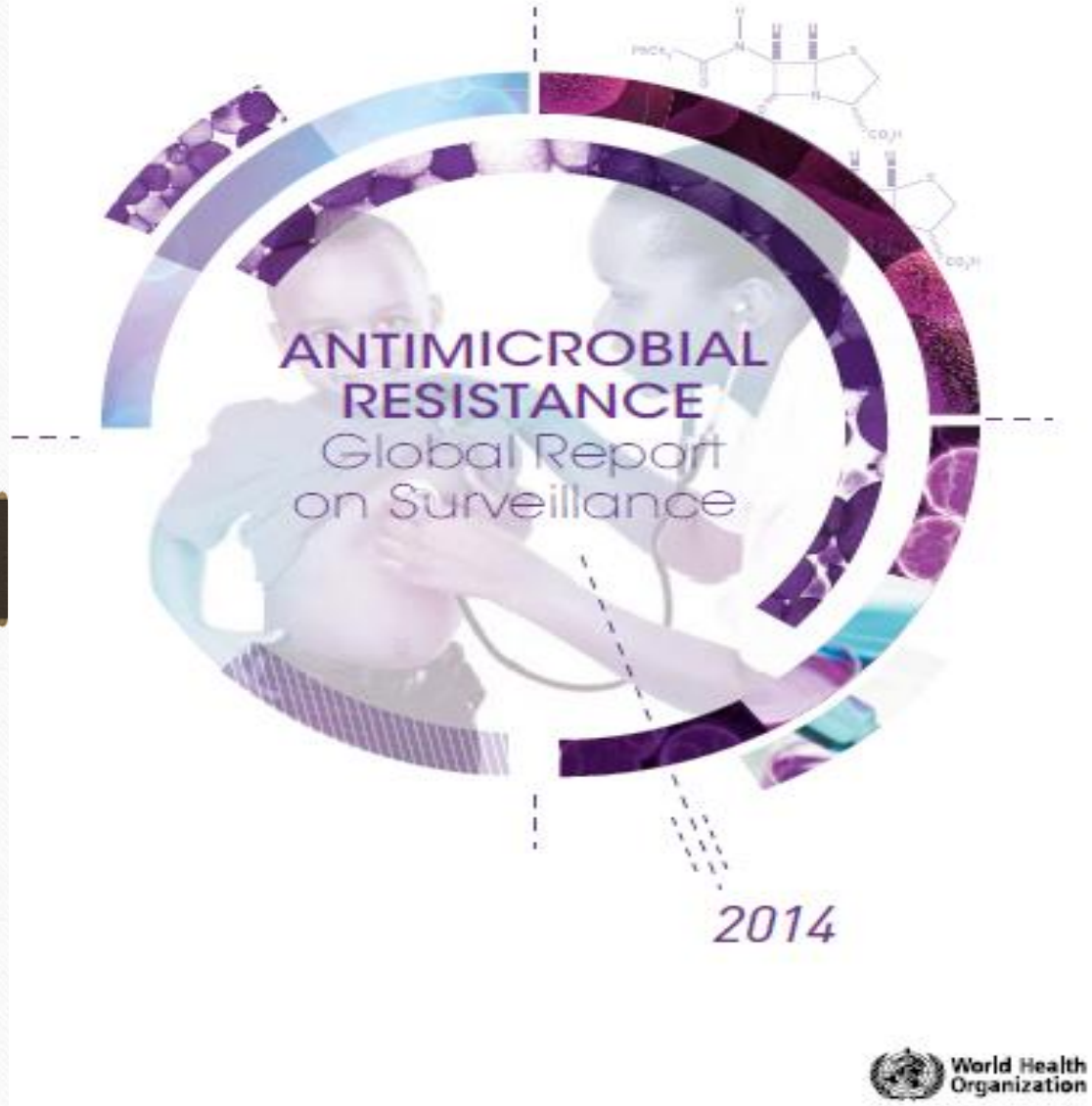


FIG 1 A comparison of investigational antimicrobial agents that have entered at least phase 1 clinical studies based on 2011 survey (9) and the current review, grouped according to bacterial target. Note that the 2011 survey did not include agents active against *Clostridium difficile* or *Mycobacterium tuberculosis*. BLI, β-lactamase inhibitors.



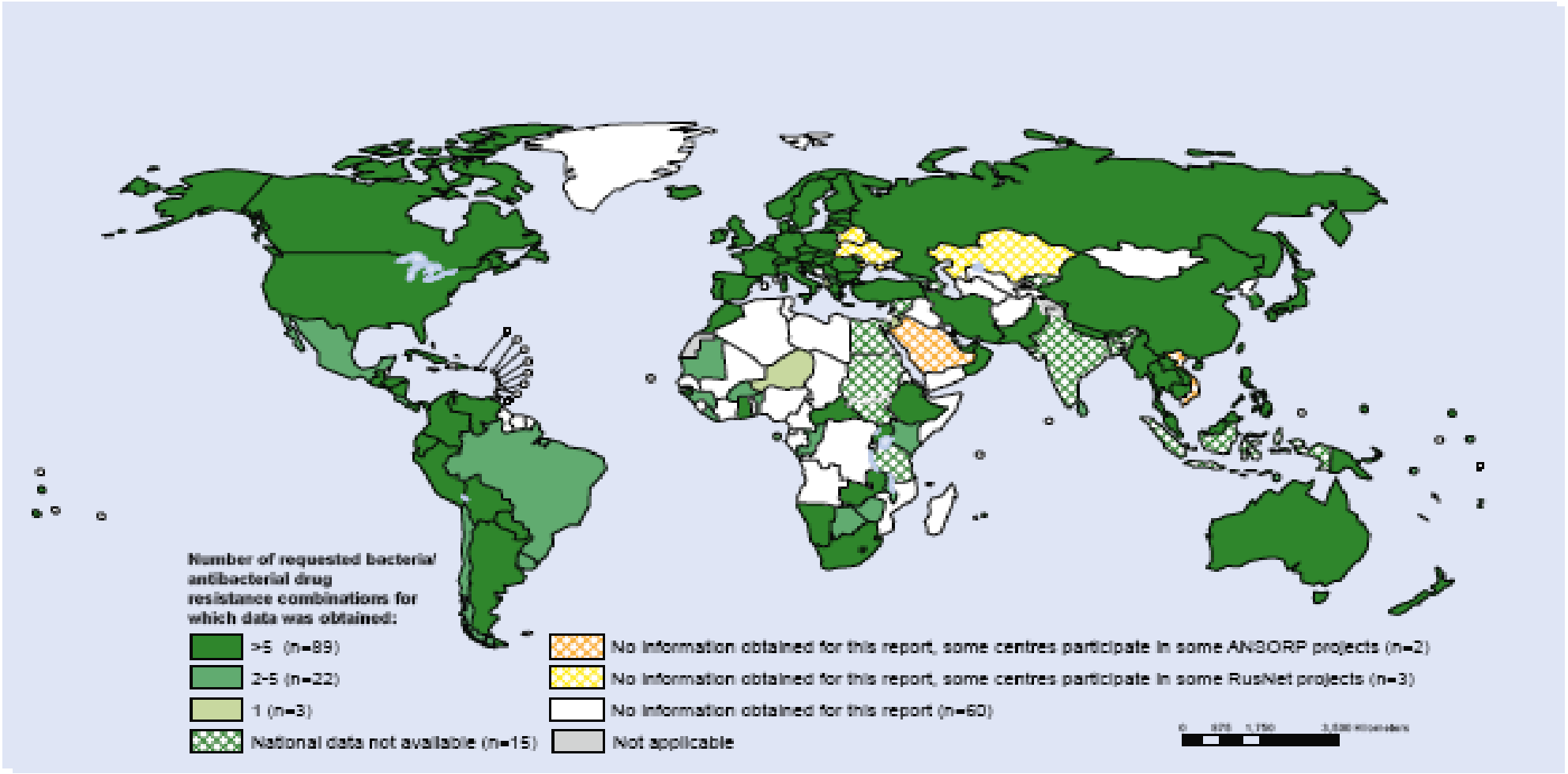
Bacteria commonly causing infections in hospitals and in the community

Name of bacterium/ resistance	Examples of typical diseases	No. out of 194 Member States providing data	No. of WHO regions with national reports of 50% resistance or more
Escherichia coli/	Urinary tract infections, blood stream infections		
- vs 3rd gen. cephalosporins		86	5/6
- vs fluoroquinolones		92	5/6
Klebsiella pneumoniae/	Pneumonia, blood stream infections, urinary tract infections		
- vs 3rd gen. cephalosporins		87	6/6
- vs 3rd carbapenems		71	2/6
Staphylococcus aureus/	Wound infections, blood stream infections		
- vs methicillin "MRSA"		85	5/6

Bacteria mainly causing infections in the community

Name of bacterium/ resistance	Examples of typical diseases	No. out of 194 Member States providing data	No of WHO regions with national reports of 25% resistance or more
Streptococcus pneumoniae/ - non-susceptible or resistant to penicillin	Pneumonia, meningitis, otitis	67	6/6
Nontyphoidal Salmonella/	Foodborne diarrhoea, blood stream infections		
- vs fluoroquinolones		68	3/6
Shigella species/	Diarrhoea ("bacillary dysenteria")		
- vs fluoroquinolones		35	2/6
Neisseria gonorrhoea/ - vs 3rd gen. cephalosporins	Gonorrhoea	42	3/6

Figure 2 Availability of data on resistance for selected bacteria–antibacterial drug combinations, 2013



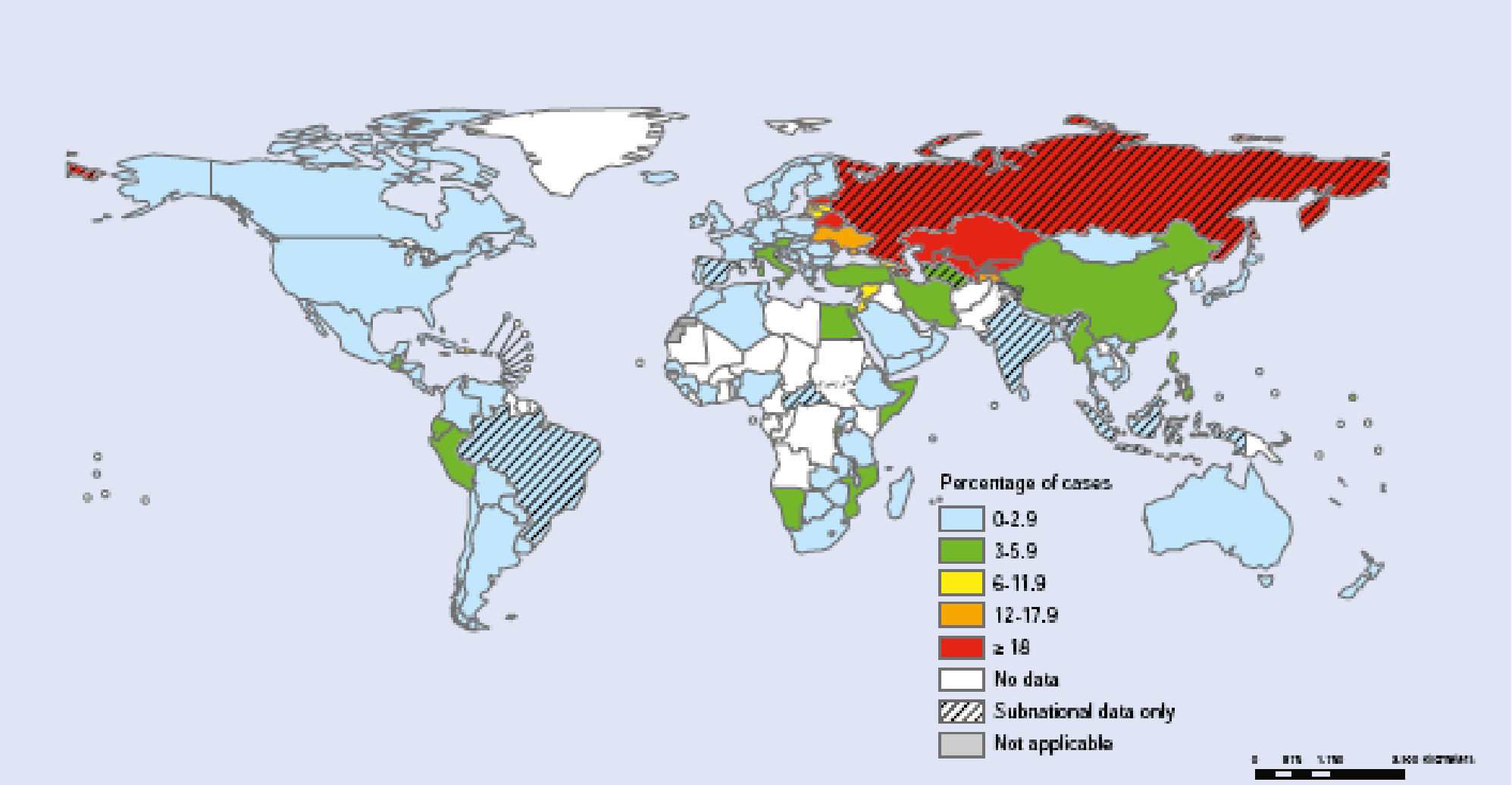
Number of reported bacteria is based on the information obtained based on request to national official sources on antibacterial susceptibility testing of at least one of the requested combinations, regardless of denominator data.
Data from United Arab Emirates originate from Abu Dhabi only.

Table 15 Estimated proportions of multidrug-resistant cases among new and previously treated TB cases, 2012, by WHO region

	New			Previously treated		
WHO region	% MDR	95% confidence intervals		% MDR	95% confidence intervals	
AFR	2.3	0.2	4.4	10.7	4.4	17
AMR	2.2	1.4	3.0	13.5	4.7	22.3
EMR	3.5	0.1	11.3	32.5	11.5	53.5
EUR	15.7	9.5	21.9	45.3	39.2	51.5
SEA	2.2	1.6	2.8	16.1	11.1	21
WPR	4.7	3.3	6.1	22.1	17.6	26.5
Global	3.6	2.1	5.1	20.2	13.3	27.2

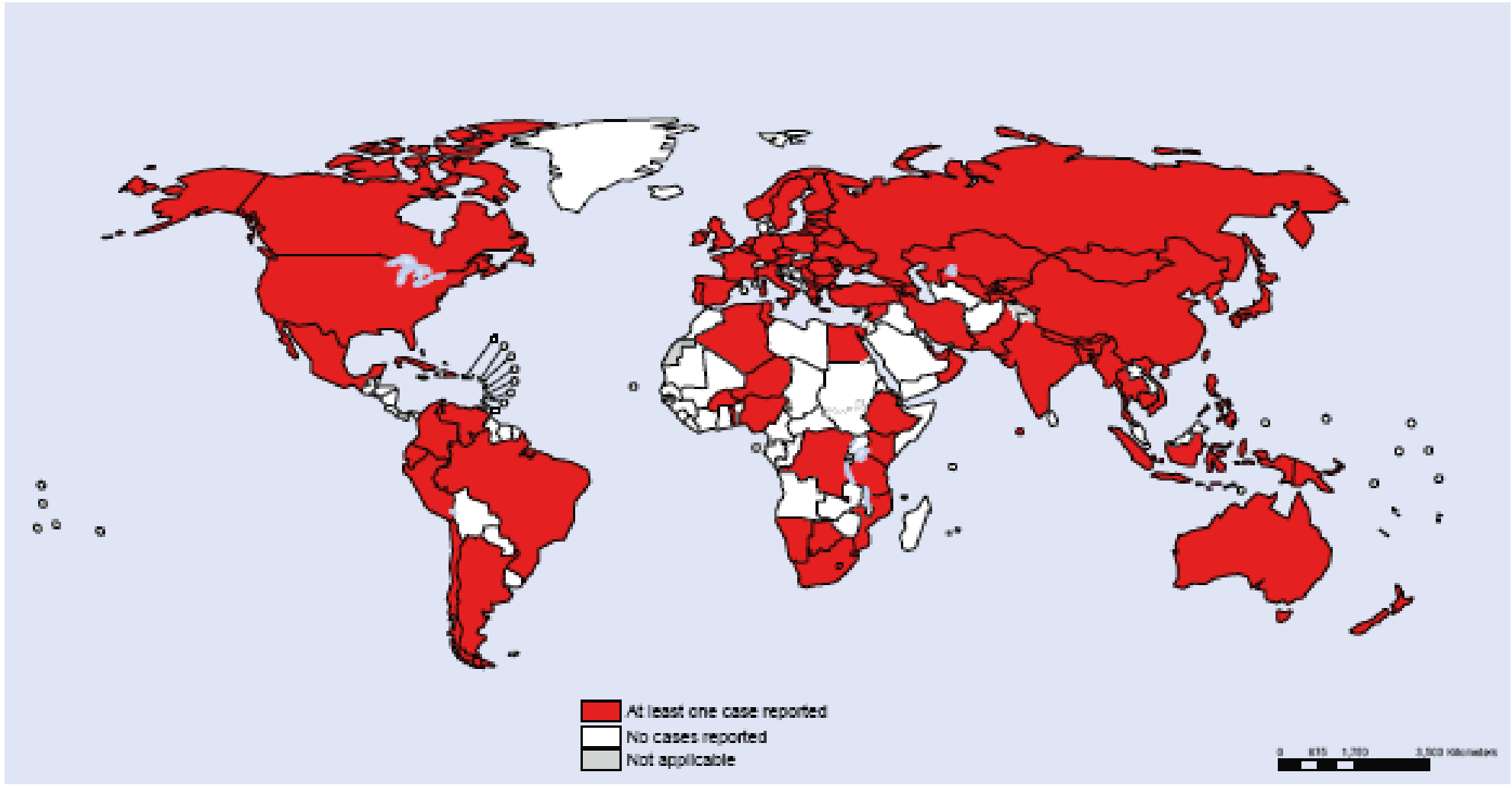
AFR, African Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; MDR, multidrug resistance; SEA, South-East Asia Region; WPR, Western Pacific Region.

Figure 15 Proportion of new TB cases with multidrug resistance (MDR-TB) worldwide[a]

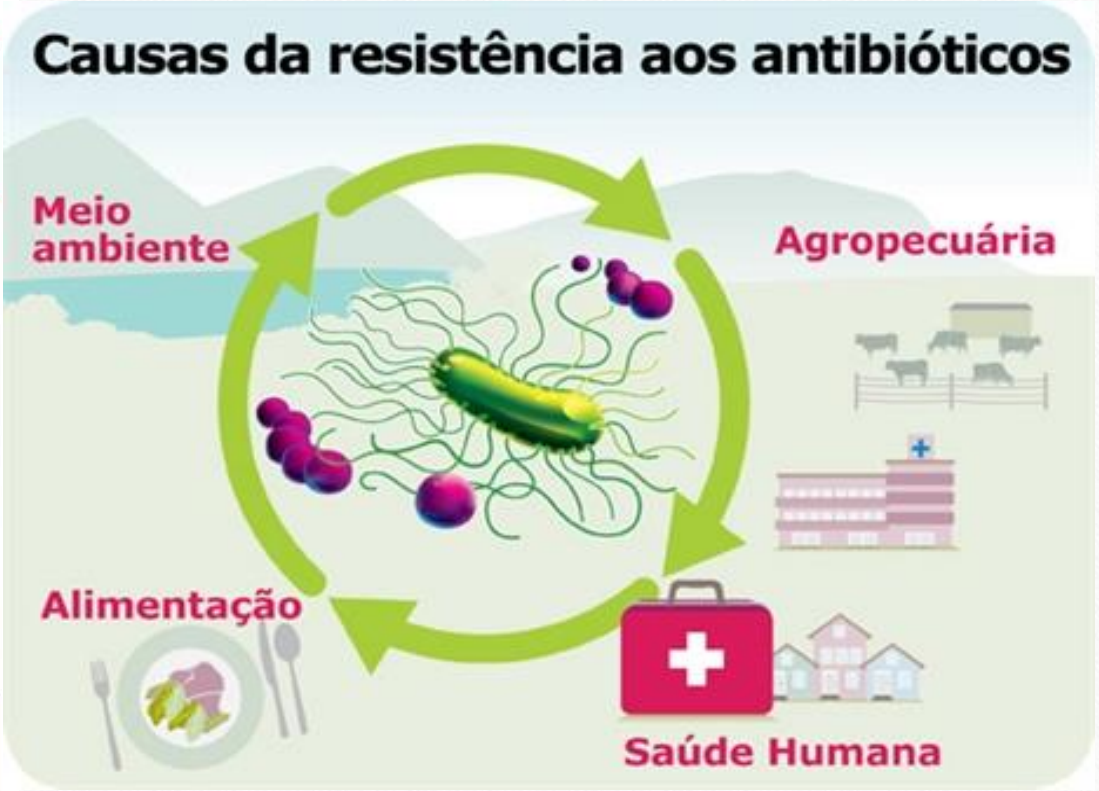


Numbers are based on the most recent year for which data have been reported, which varies among countries.

Figure 16 Countries that notified at least one case of extensively drug-resistant TB (XDR-TB) by the end of 2012



O PROBLEMA em PORTUGAL



EUROPEAN ANTIBIOTIC AWARENESS DAY

A European Health Initiative

ecdc

Summary of the latest data on antibiotic resistance in the European Union

November 2013

Highlights on antibiotic resistance

- Antibiotic resistance is a serious threat to public health in Europe, leading to increasing healthcare costs, prolonged hospital stays, treatment failures, and sometimes death.
- Over the last four years (2009 to 2012), resistance to third-generation cephalosporins in *K. pneumoniae* and *E. coli* increased significantly at EU/EEA level. Combined resistance to third-generation cephalosporins and two other important antimicrobial groups (fluoroquinolones and aminoglycosides) also increased significantly at EU/EEA level for *K. pneumoniae*, but not for *E. coli*.
- The increasing trend of combined resistance in *K. pneumoniae* means that only a few therapeutic options (e.g., carbapenems) remain available for treatment of infected patients.
- Carbapenems form a major last-line class of antibiotics to treat infections with multidrug-resistant Gram-negative bacteria such as *K. pneumoniae* and *E. coli*, both common causes of pneumonia, urinary tract infections and bloodstream infections. However, the percentage of carbapenem-resistant *K. pneumoniae* is already high and increasing in some countries in the EU.
- Antimicrobial resistance data for *Acinetobacter* spp. are available in EARS-Net for the first time. Data for 2012 show large inter-country variations in Europe, and high levels of resistance (>25%) to carbapenems in nearly half of the reporting countries.
- In contrast, in the past few years, the percentage of meticillin-resistant *Staphylococcus aureus* (MRSA) has shown a significant decreasing trend at EU/EEA level, and either a continuous decrease or a stabilising trend was observed in most EU/EEA countries during the last four years. Nevertheless, MRSA remains above 25% in almost one fourth of the reporting countries, mainly in southern and eastern Europe.
- Prudent antibiotic use and comprehensive infection control strategies targeting all healthcare sectors (acute care hospitals, long-term care facilities and ambulatory care) are the cornerstones of effective interventions that aim to prevent selection and transmission of antibiotic-resistant bacteria.

ecdc

TECHNICAL DOCUMENT

HELICSwin.Net 1.3.8
User manual

Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals

ecdc

SURVEILLANCE REPORT

Surveillance of antimicrobial consumption in Europe

2011

www.ecdc.europa.eu

Figure 2. *Klebsiella pneumoniae*: percentage of invasive isolates with resistance to carbapenems, EU/EEA, 2009 (top) and 2012 (bottom)

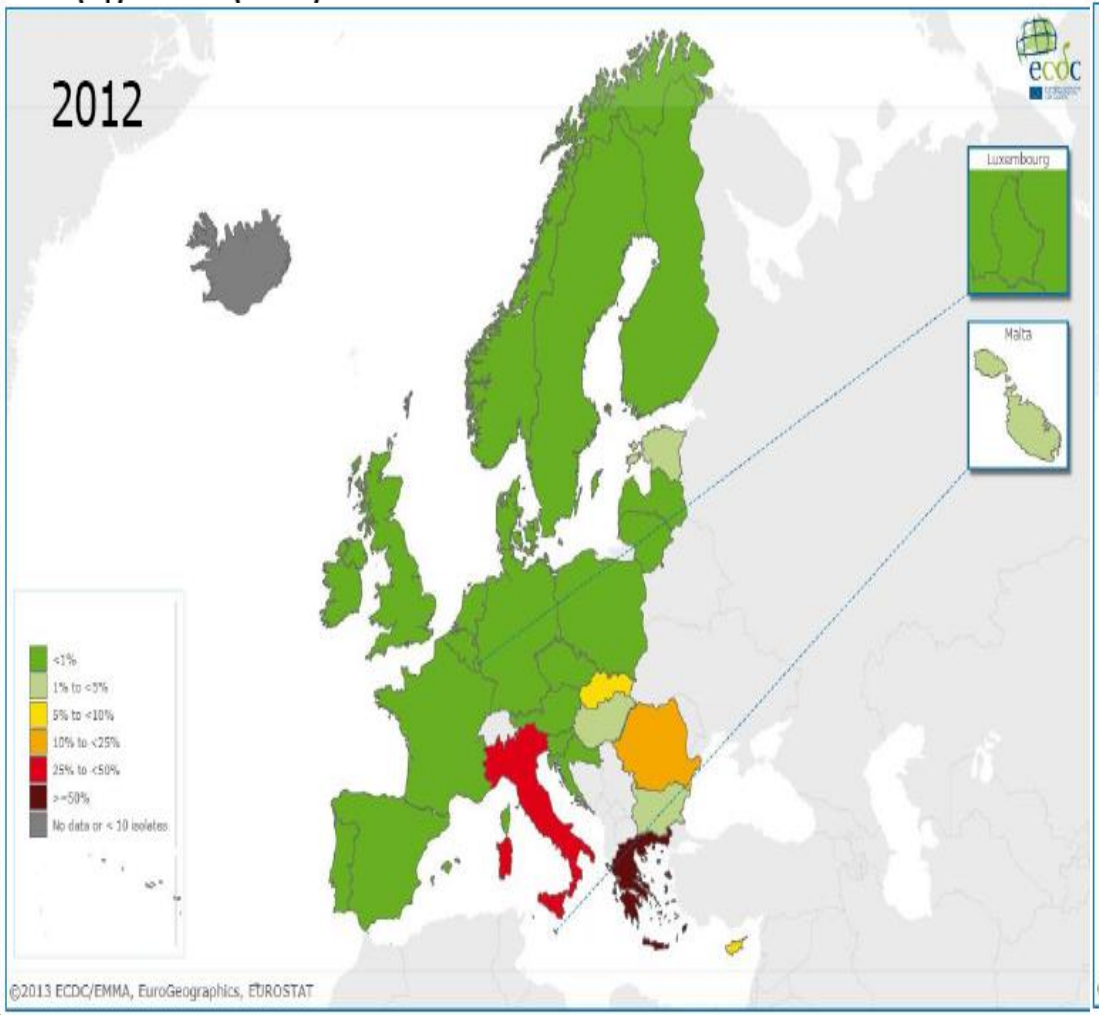


Figure 3. *Escherichia coli*: percentage of invasive isolates with resistance to third-generation cephalosporins, EU/EEA, 2009 (top) and 2012 (bottom)

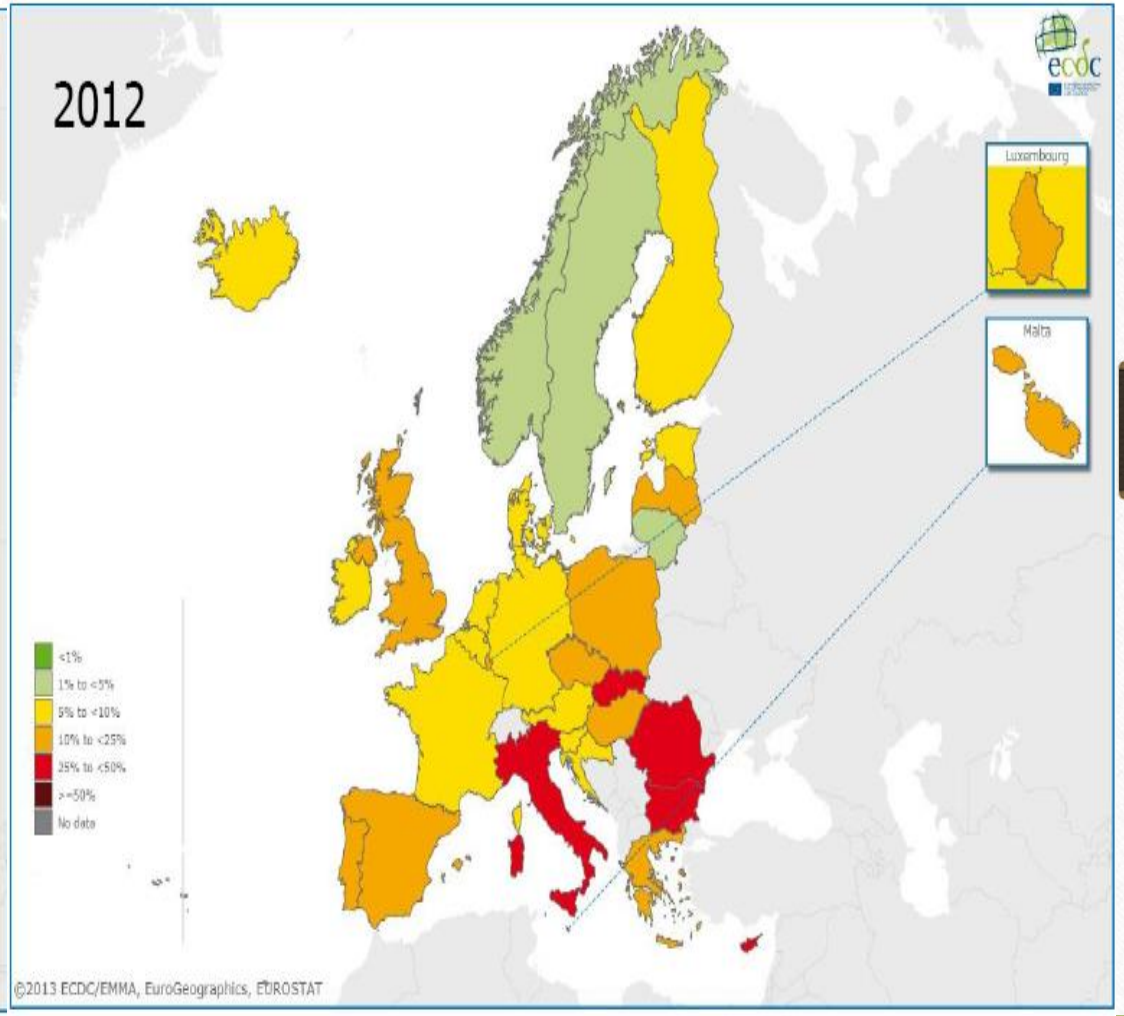


Figure 5. *Acinetobacter* species: percentage of invasive isolates with resistance to carbapenems, EU/EEA, 2012

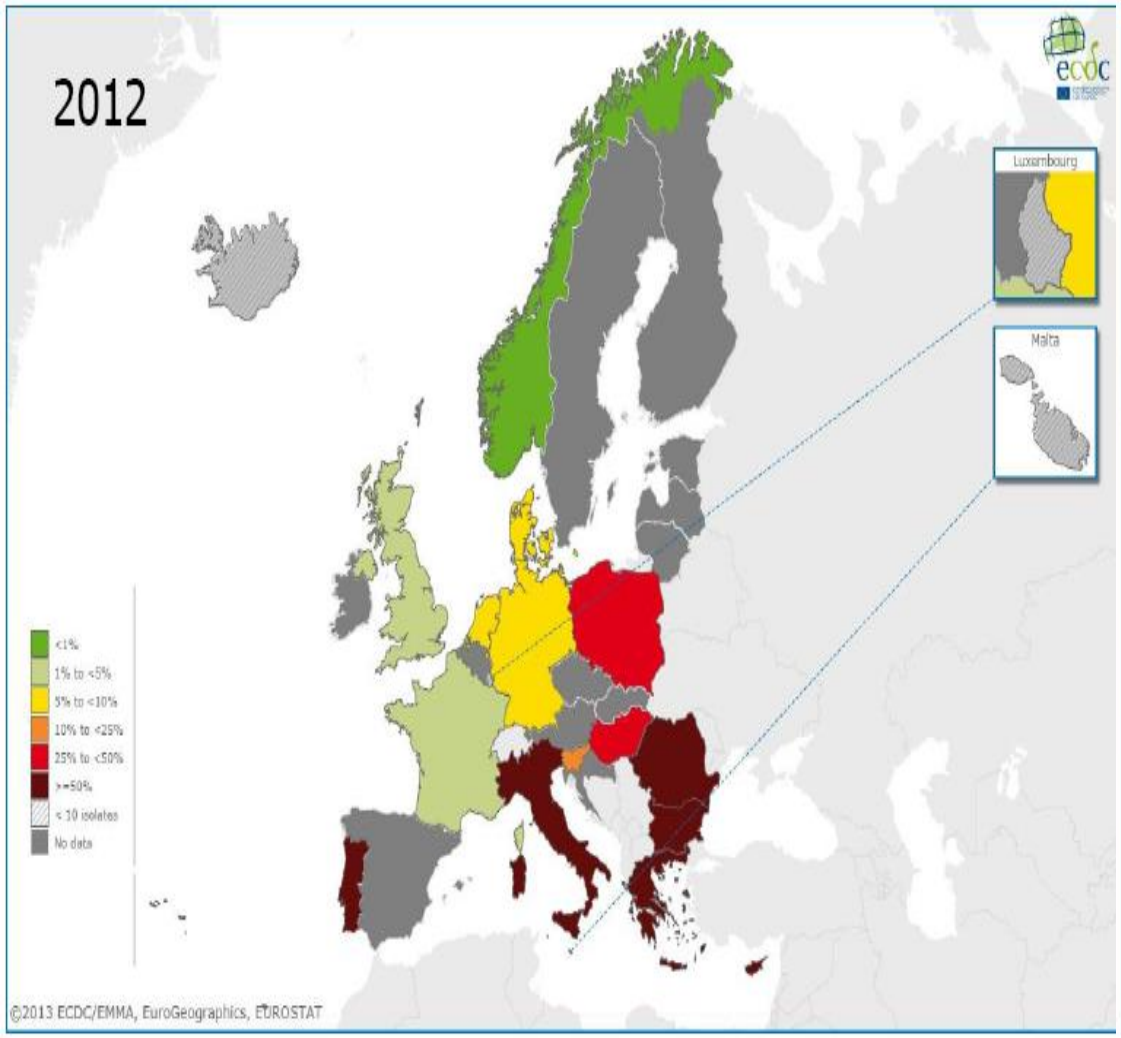
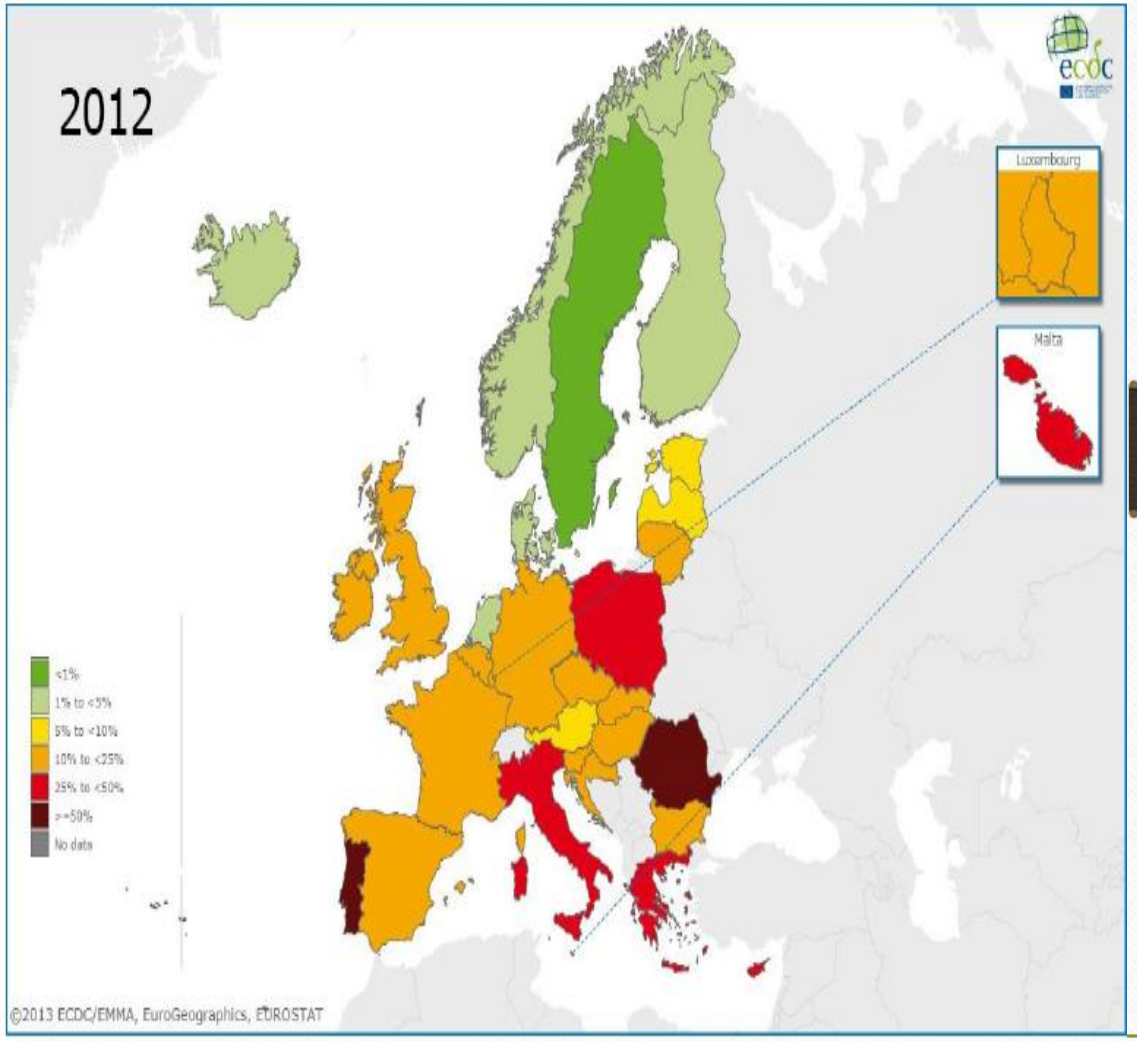
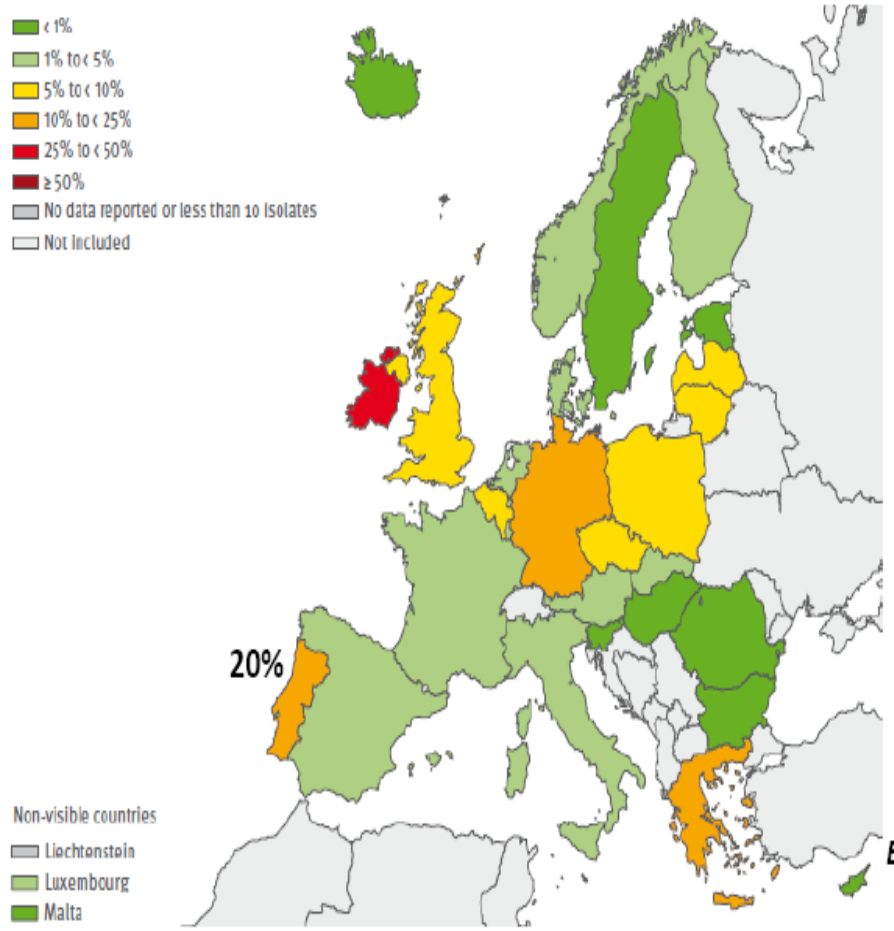


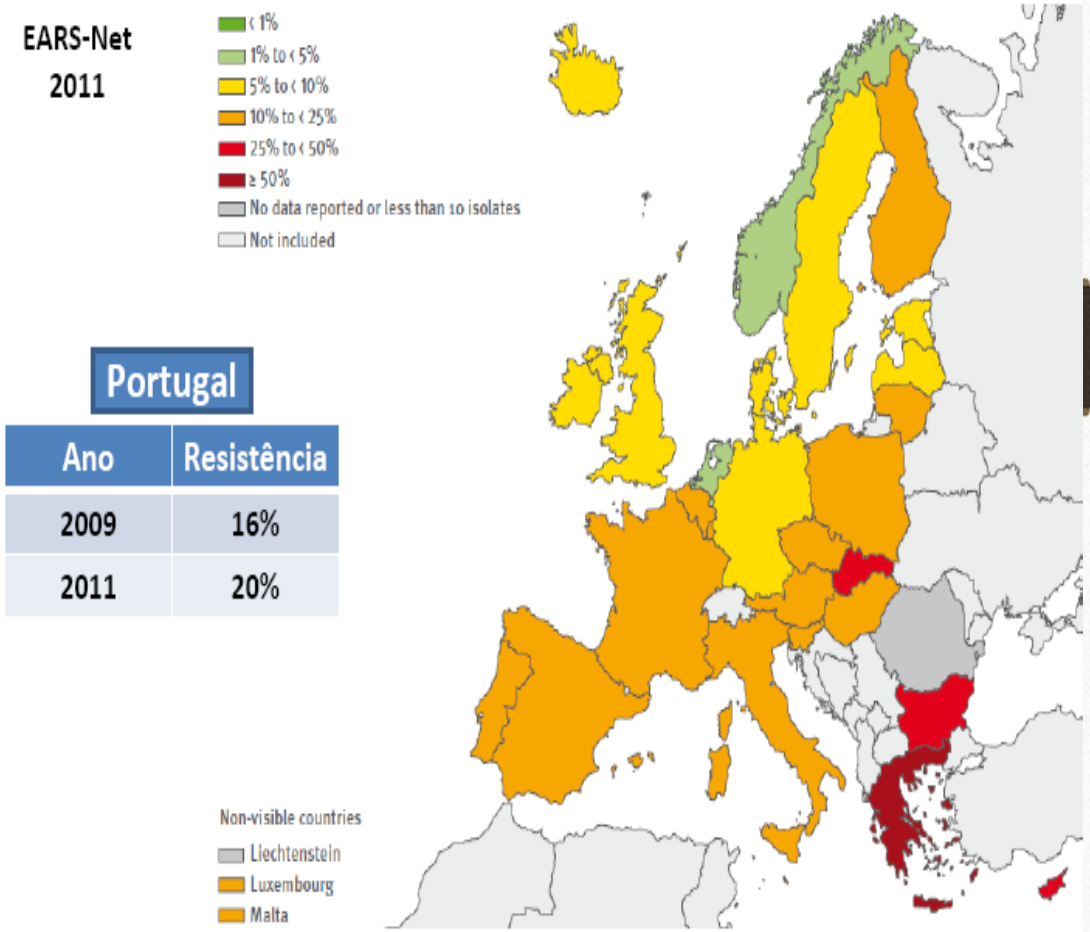
Figure 6. *Staphylococcus aureus*: percentage of invasive isolates with resistance to meticillin (MRSA), EU/EEA, 2009 (top) and 2012 (bottom)



Enterococcus faecium resistente à vancomicina



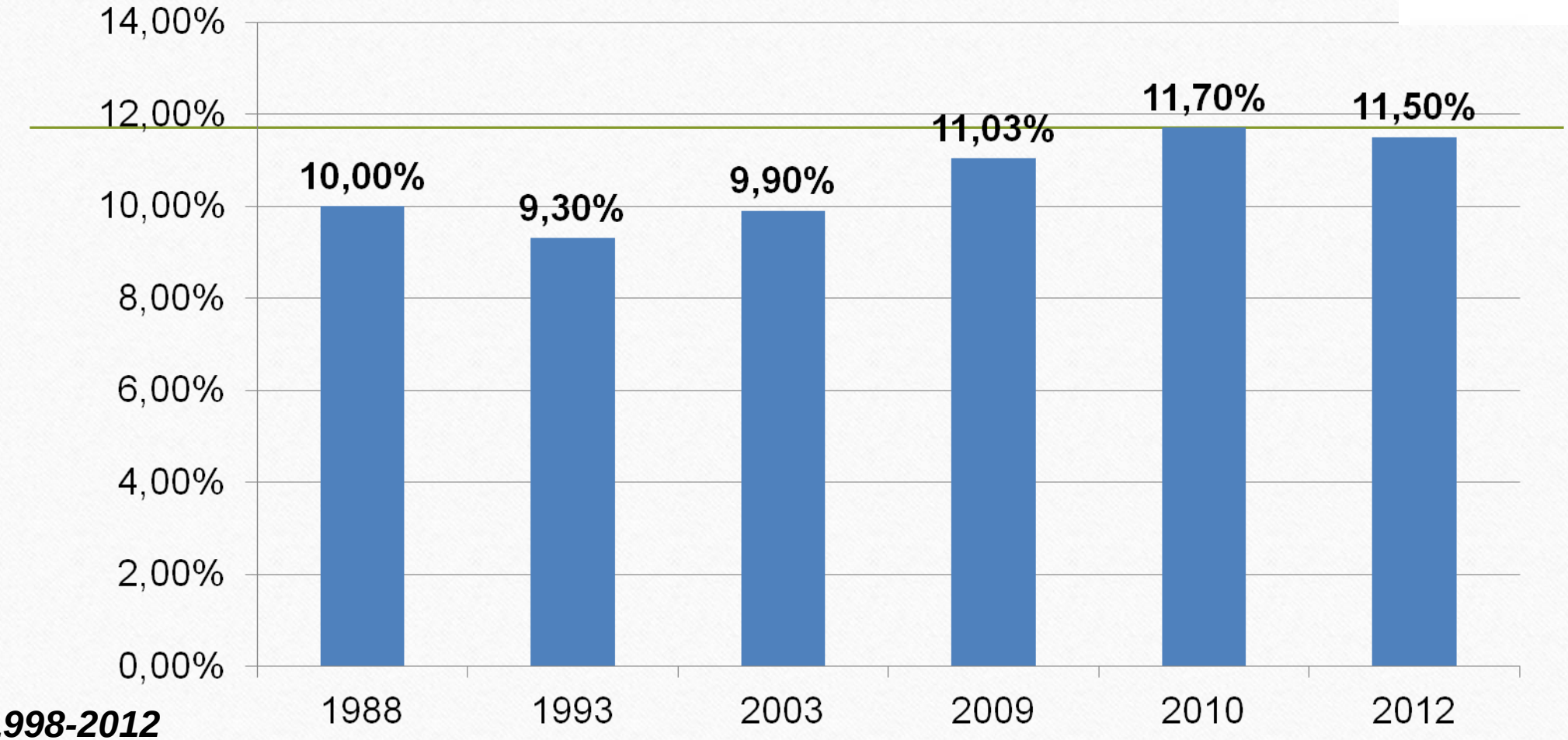
Pseudomonas aeruginosa resistentes a carbapenemes



Portugal

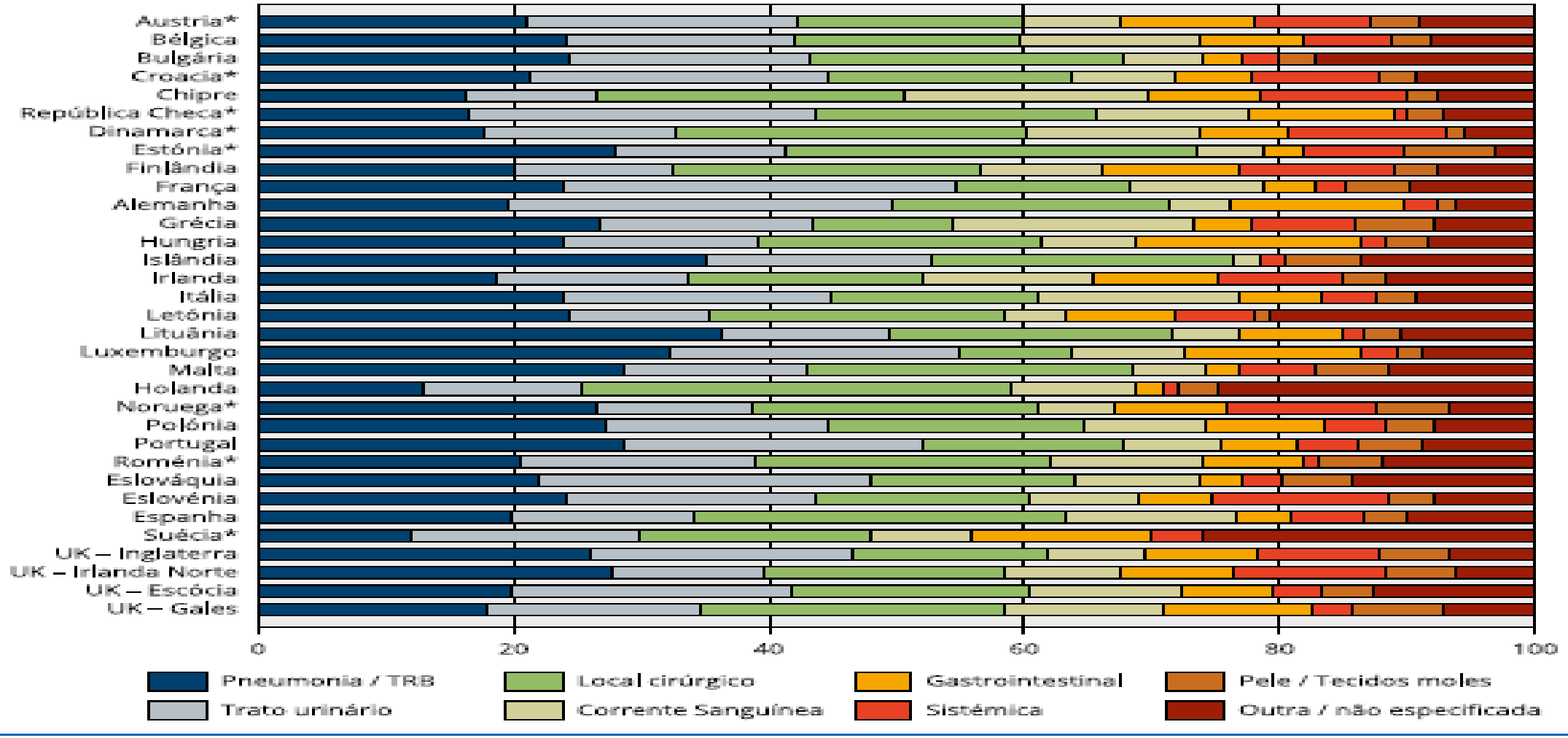
Ano	Resistência
2009	16%
2011	20%

Prevalência de infeção hospitalar



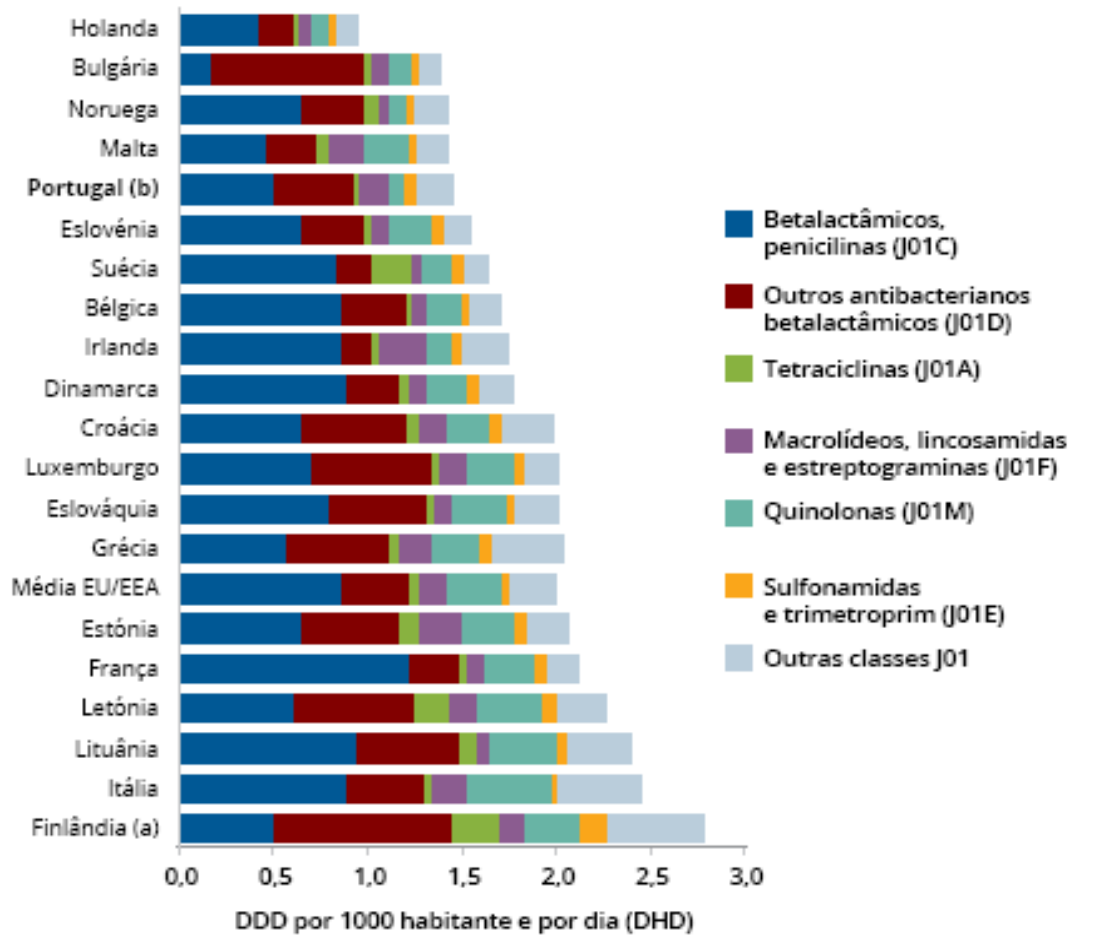
IPI 1998-2012

Distribuição da prevalência das infeções hospitalares por localização, por país, ECDC PPS 2011–2012



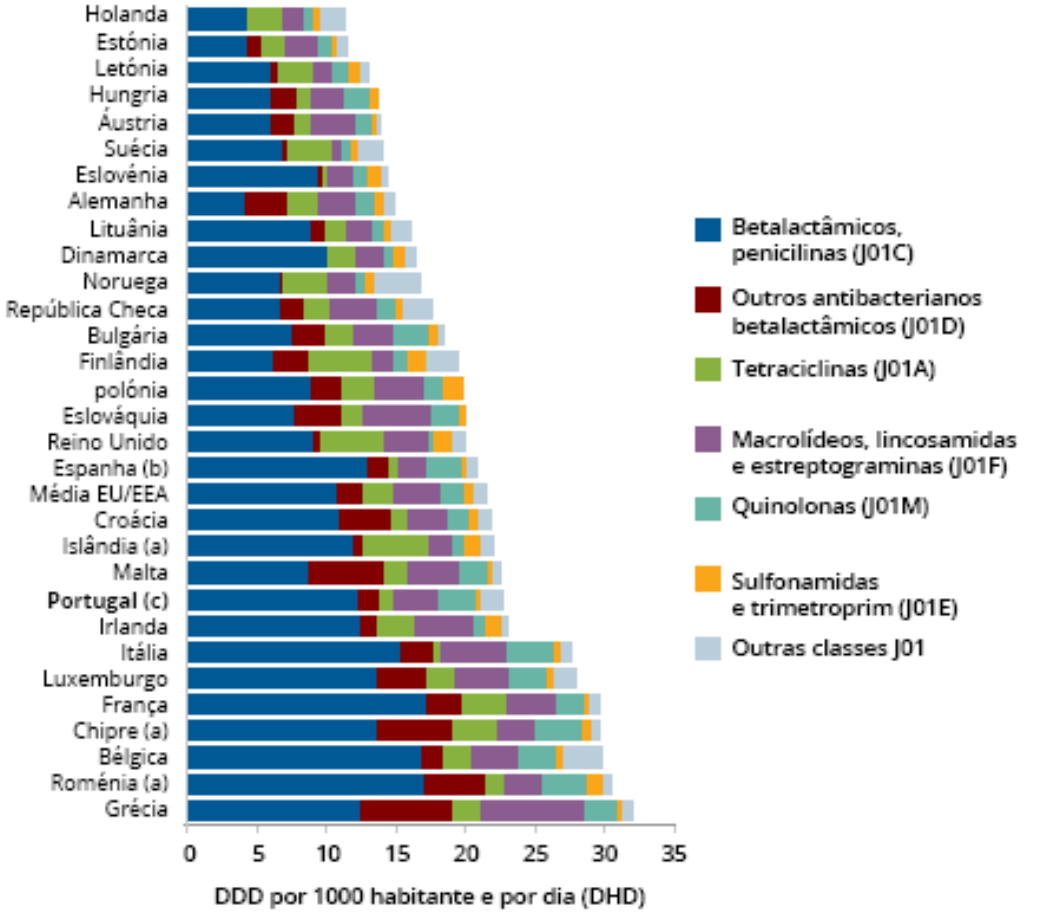
Fonte: ECDC SURVEILLANCE REPORT – Point prevalence survey of healthcare associated infections and antimicrobial use in European acute care hospitals 2011–2012

Figura 21. Consumo de antibacterianos de uso sistémico no sector hospitalar (em DHD), Europa, 2012



(a) Os dados incluem consumo em centros remotos de cuidados de saúde primários e lares de idosos.
(b) Os dados correspondem somente a hospitais públicos.
Fonte: European Centre for Disease Prevention and Control. Surveillance of antimicrobial consumption in Europe 2012. Stockholm: ECDC; 2014 (adaptado).

Figura 15. Consumo de antibacterianos de uso sistémico na comunidade (em DHD), Europa, 2012



(a) Dados globais, incluindo o sector hospitalar.
(b) Dados referentes apenas a reembolsos, isto é, não incluem o consumo sem prescrição médica e outras formas não comparticipadas.
(c) Dados referem-se à colocação dos armazenistas nas farmácias
Fonte: European Centre for Disease Prevention and Control. Surveillance of antimicrobial consumption in Europe 2012. Stockholm: ECDC; 2014 (adaptado).

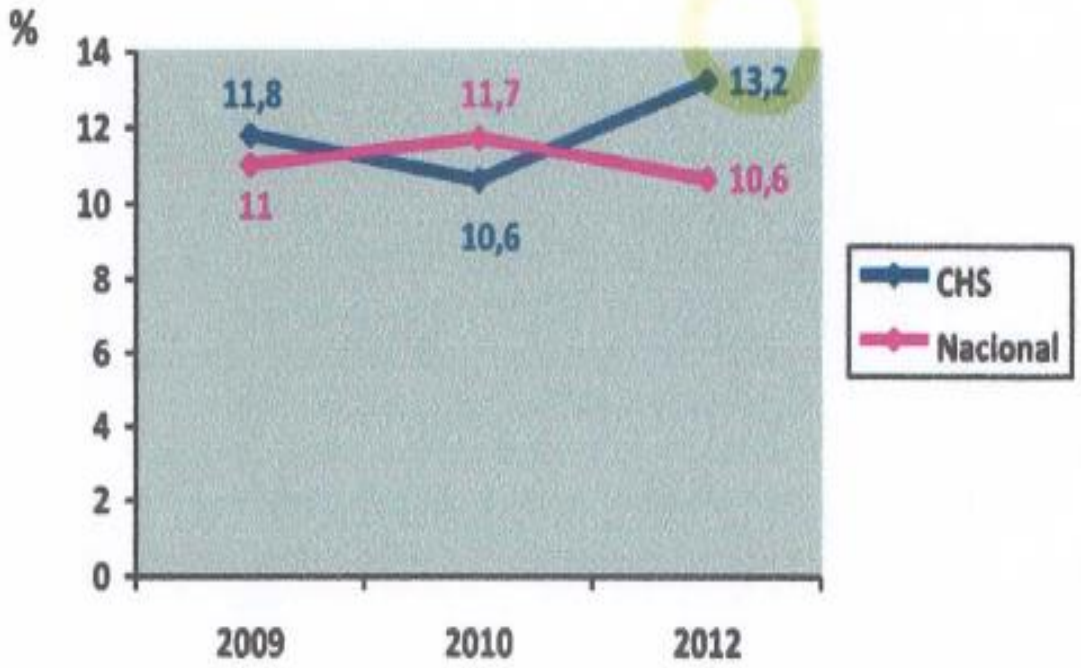
Indicadores e metas

DGS desde 1899 Direção-Geral da Saúde

- Número de hospitais aderentes à vigilância de microrganismos resistentes em 2014 / Número de hospitais do Sistema Nacional de Saúde em 2014 ≥ 50%.
- DDD de consumo hospitalar de carbapenemes em 2015 / DDD de consumo hospitalar de carbapenemes em 2011 ≤ 95%
- DDD de consumo ambulatório de quinolonas em 2015 / DDD de consumo ambulatório de quinolonas em 2011 ≤ 95%
- Número de bacterémias por MRSA por 1000 dias de internamento em 2015 / Número de bacterémias por MRSA por 1000 dias de internamento em 2012 ≤ 90%
- Taxa de bacterémias por MRSA no total de bacterémias por *Staphylococcus aureus* em 2015 / Taxa de bacterémias por MRSA no total de bacterémias por *Staphylococcus aureus* em 2012 ≤ 90%

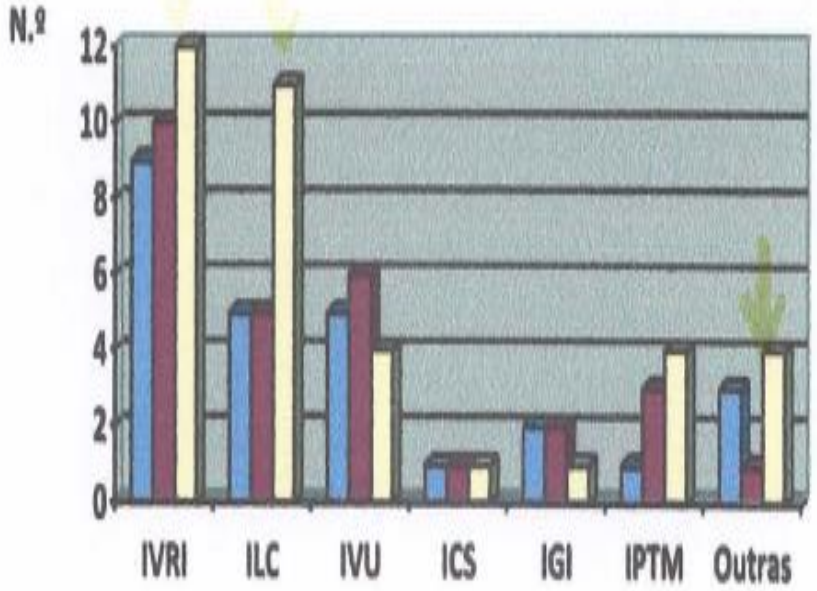
O PROBLEMA no CHS

Prevalência de Infeção Associada aos Cuidados de Saúde (IACS) no CHS



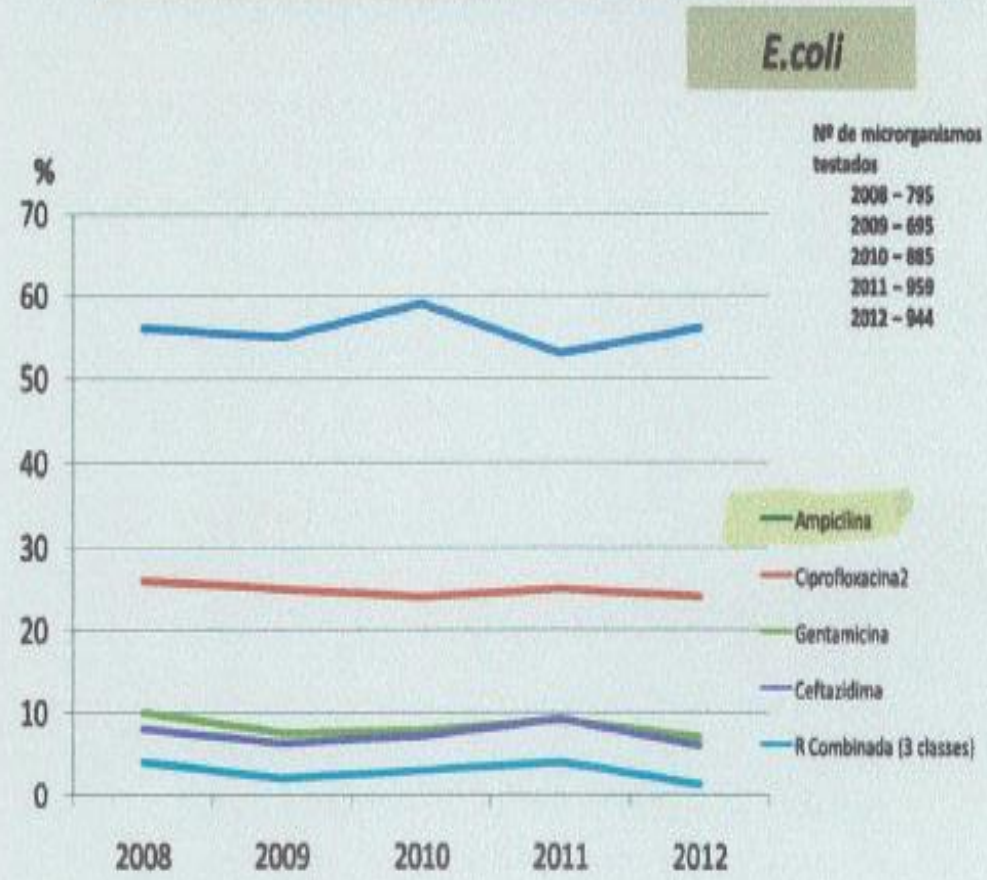
Taxa de Prevalência de Infeção Hospitalar (IACS): Nº Doentes com IACS/ Nº Total de Doentes

LOCALIZAÇÃO DAS IACS

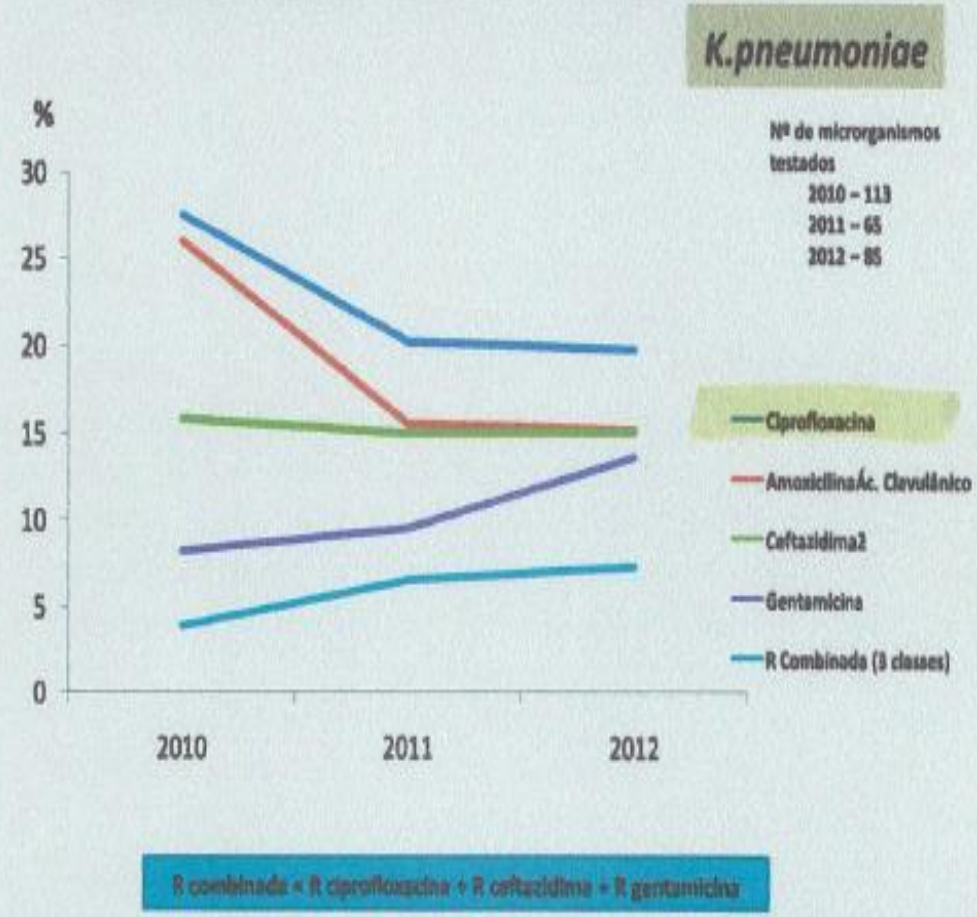


IVRI: Infeção das Vias Respiratórias Inferiores; ILC: Infeção Local Cirúrgico; IVU: Infeção das Vias Urinárias; ICS: Infeção Corrente Sanguínea; IGI: Infeção Gastrointestinal; IPTM: Infeção da Pele e Tecidos Moles.

Prevalência de resistências aos antibióticos
CHS 2008 - 2012



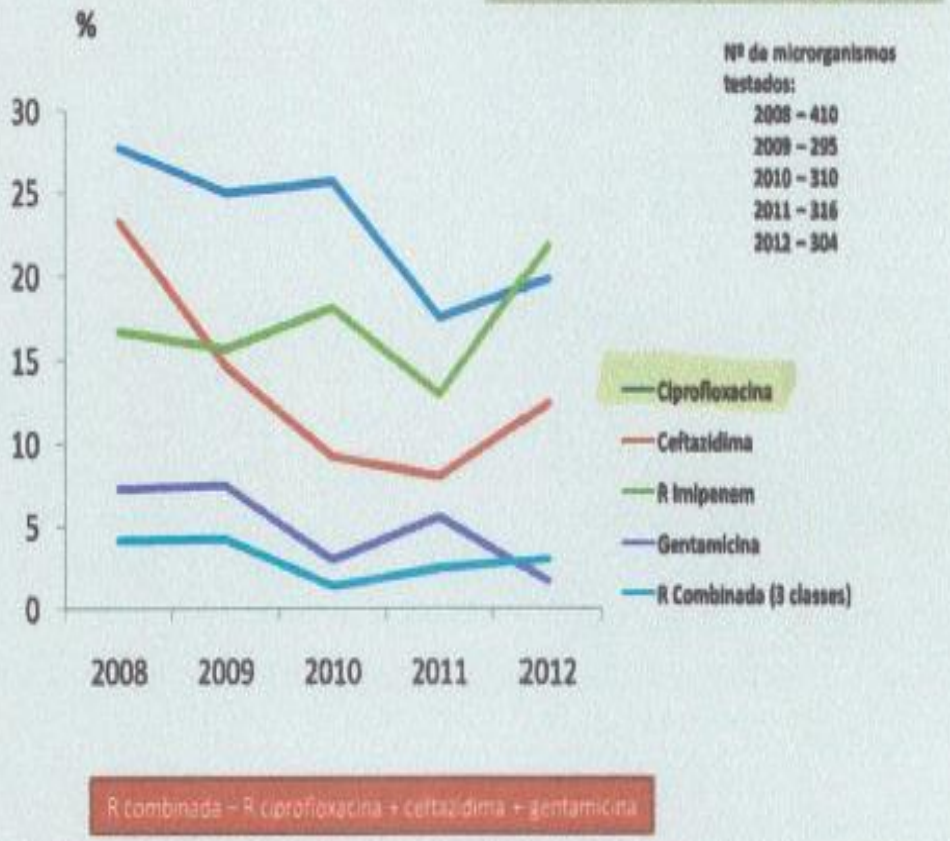
Prevalência de resistências aos antibióticos
CHS 2010 - 2012



R combinada = R ciprofloxacina + R ceftazidima + R gentamicina

Prevalência de resistências aos antibióticos
CHS 2008 - 2012

Pseudomonas aeruginosa

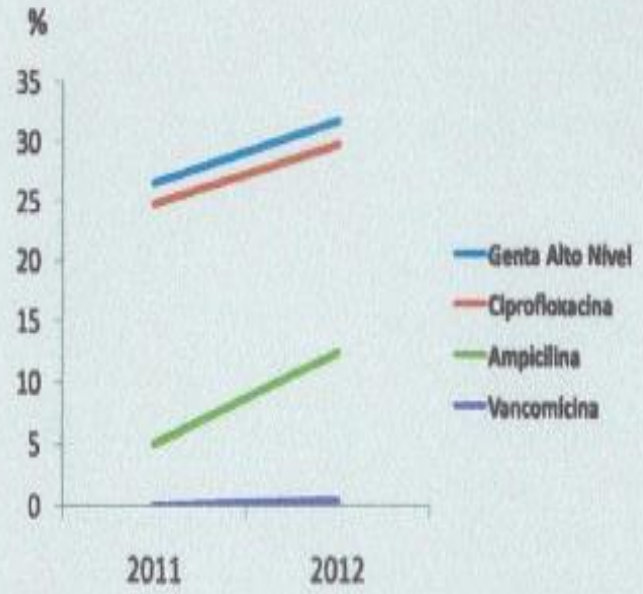


R combinada – R ciprofloxacina + ceftazidima + gentamicina

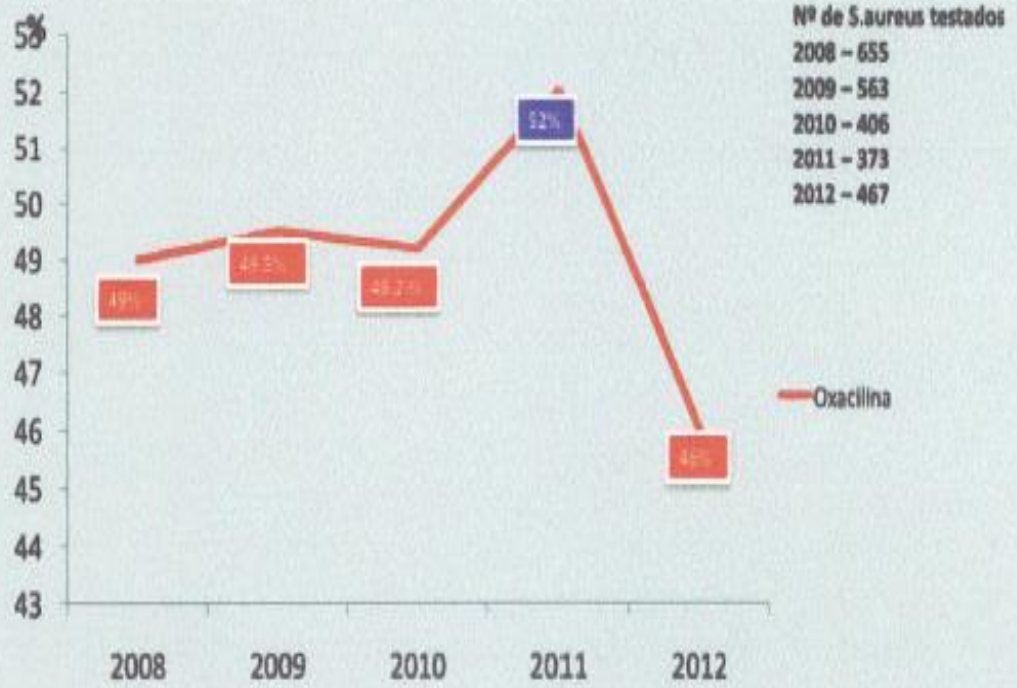
Prevalência de resistências aos antibióticos
CHS 2011 - 2012

Nº de microrganismos testados
2010 – 179
2011 – 180
2012 – 236

E. faecalis

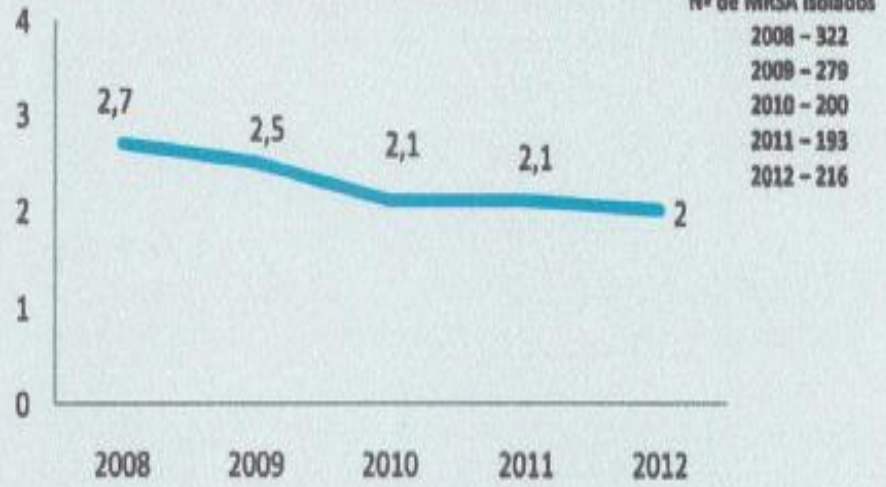


Prevalência de resistência à oxacilina
MRSA - CHS 2008 - 2012



Prevalência de resistências aos antibióticos
CHS 2008 - 2012

MRSA



Taxa de Incidência – N.º Isolamentos MRSA/ 1000 dias de internamento

Gráfico 9. Prescrição de antimicrobianos com intenção de tratamento

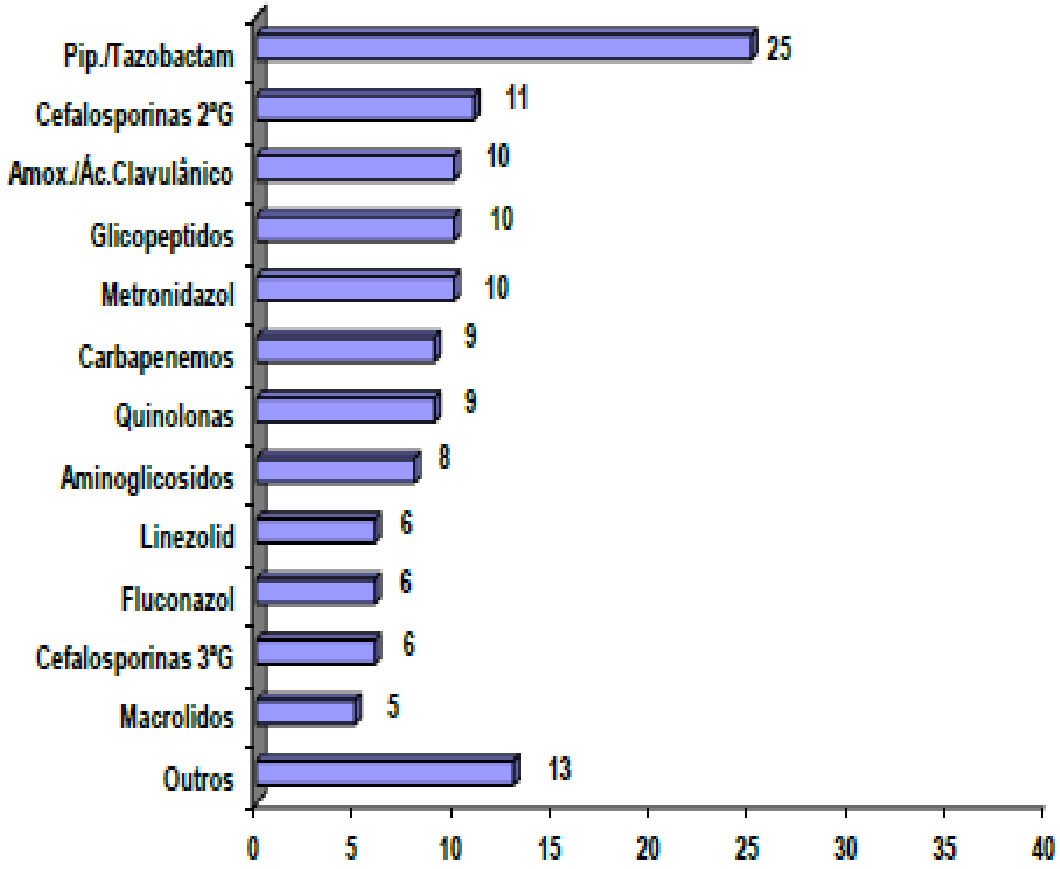
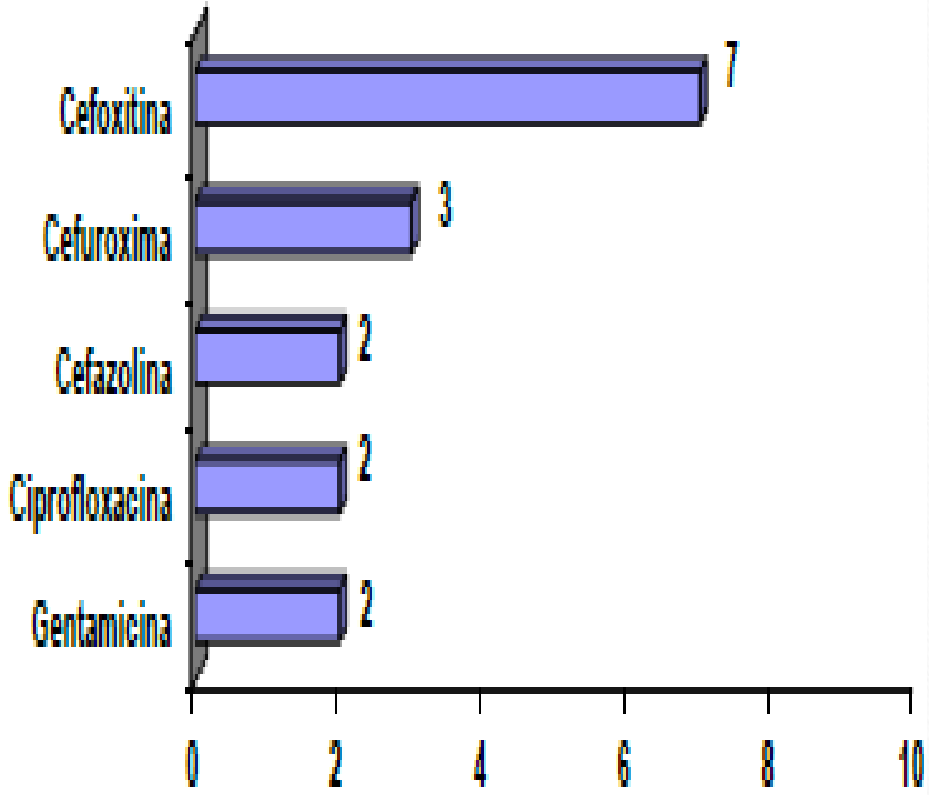
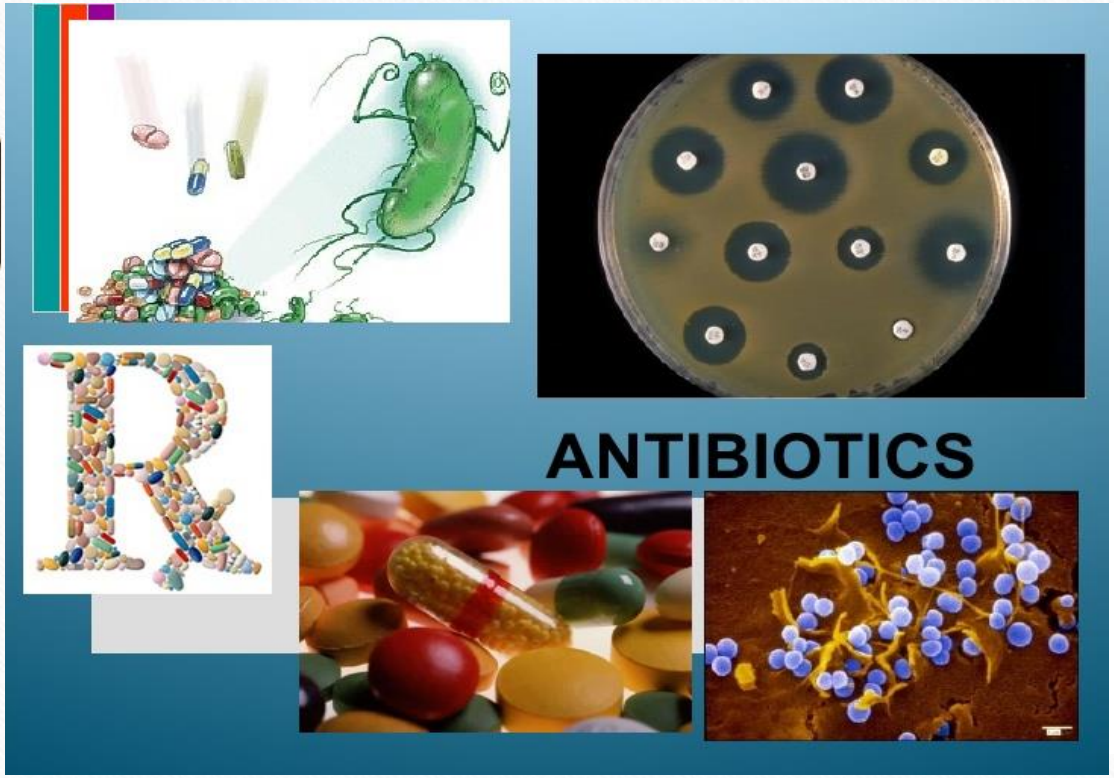


Gráfico 10. Prescrição de antimicrobianos para profilaxia cirúrgica



AS SOLUÇÕES MAIS CONSENSUAIS



Department of Health

Department for Environment Food & Rural Affairs

Northern Ireland Executive

Llywodraeth Cymru Welsh Government

The Scottish Government Riaghaltas na h-Alba

UK Five Year Antimicrobial Resistance Strategy 2013 to 2018

NICE National Institute for Health and Care Excellence

Infection

Prevention and control of healthcare-associated infections in primary and community care

Issued: March 2012

NICE clinical guideline 139
guidance.nice.org.uk/cg139

Interventions to improve antibiotic prescribing practices for hospital inpatients (Review)

Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, Ramsay CR, Wiffen PJ, Wilcox M

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2013, Issue 4

http://www.thecochranelibrary.com

WILEY

MAJOR ARTICLE

Quality and Strength of Evidence of the Infectious Diseases Society of America Clinical Practice Guidelines

Abdur Rahman Khan,[1] Sobia Khan, Valerie Zimmerman, Larry M. Baddour,[3] and Imad M. Tleyjeh[1,2,3,4]

[1]Division of Infectious Diseases, Department of Medicine, and [2]Research Centre, King Fahd Medical City, Riyadh, Saudi Arabia; and [3]Division of Infectious Diseases, Department of Medicine, and [4]Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota

(See the editorial commentary by Deresinski, on pages 1157–1159.)

Objective. To describe the distribution and temporal trends of the quality and strength of evidence supporting recommendations in the Infectious Diseases Society of America (IDSA) clinical practice guidelines.

Methods. Guidelines either issued or endorsed by IDSA from March 1994 to July 2009 were evaluated using the IDSA–US Public Health Service Grading System. In this system, the letters A–E signify the strength of the recommendation, and numerals I–III indicate the quality of evidence supporting these recommendations. The distribution of the guideline recommendations among strength of recommendation and quality of evidence classes was quantified. Temporal changes between the first and current guideline version were evaluated.

Results. Approximately one-half (median, 50.0%; interquartile range [IQR], 38.1%–58.6%) of the recommendations in the current guidelines are supported by level III evidence (derived from expert opinion). Evidence from observational studies (level II) supports 31% of recommendations (median, 30.9%; IQR, 23.3%–43.2%), whereas evidence based on ≥1 randomized clinical trial (level I) constitutes 16% of the recommendations (median, 15.8%; IQR, 5.8%–28.3%). The strength of recommendation was mainly distributed among classes A (median, 41.5%; IQR, 28.7%–55.6%) and B (median, 40.3%; IQR, 27.1%–47.9%). Among guidelines with ≥1 revised version, the recommendations moved proportionately toward more level I evidence (+12.4%). Consequently, there was a proportional increase in class A recommendations (+11.1%) with a decrease in class C recommendations (–23.5%).

Conclusions. The IDSA guideline recommendations are primarily based on low-quality evidence derived from nonrandomized studies or expert opinion. These findings highlight the limitations of current clinical infectious diseases research that can provide high-quality evidence. There is an urgent need to support high-quality research to strengthen the evidence available for the formulation of guidelines.

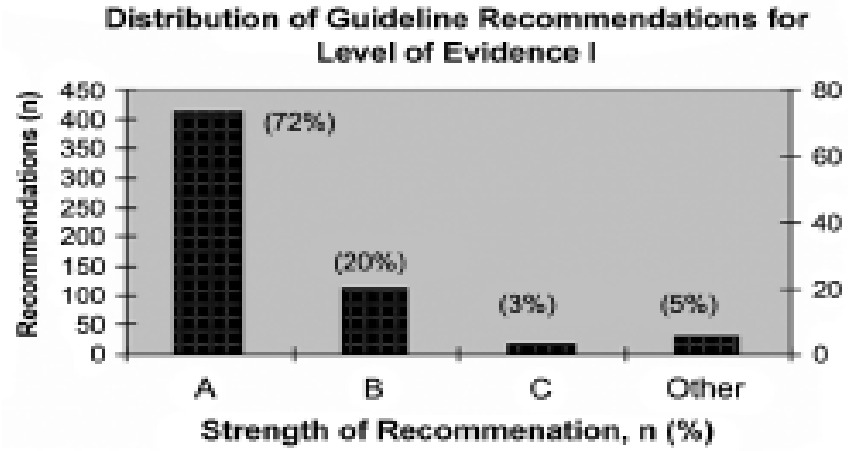


Figure 1. Distribution of the strength (classes) of recommendations across the level of evidence I.

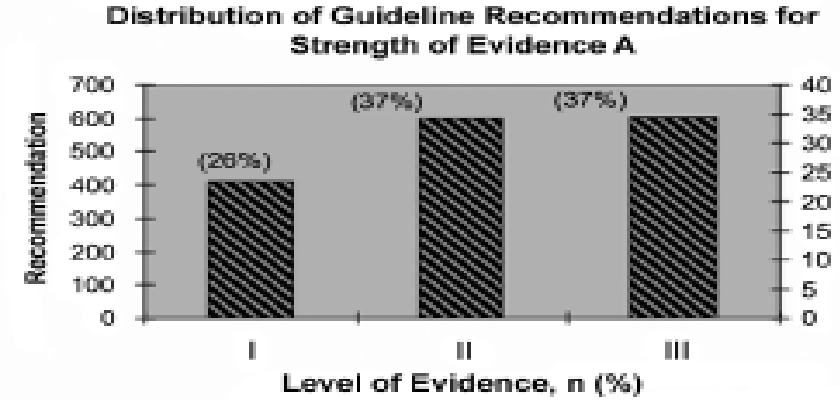


Figure 2. Distribution of the levels of evidence across the strength (classes) of recommendation A.

Shifting the Paradigm for Promoting Appropriate Antibiotic Use

Ralph Gonzales, MD, MSPH[1] and Joshua P. Metlay, MD, PhD[2]

[1]Department of Medicine, Division of General Internal Medicine, University of California, San Francisco, CA, USA; [2]Department of Medicine, Division of General Internal Medicine, University of Pennsylvania, Philadelphia, PA, USA.

Int. J. Environ. Res. Public Health **2013**, *10*, 4274-4305; doi:10.3390/ijerph10094274

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International Journal of
Environmental Research and
Public Health
ISSN 1660-4601
www.mdpi.com/journal/ijerph

Review

Strategies to Minimize Antibiotic Resistance

Chang-Ro Lee [1,†], Ill Hwan Cho [2,3], Byeong Chul Jeong [1] and Sang Hee Lee [2,†,*]

[1] Department of Biological Sciences, Myongji University, 116 Myongjiro, Yongin, Gyeonggido 449-728, Korea; E-Mails: crlee@mju.ac.kr (C.-R.L.); bcjeong@mju.ac.kr (B.C.J.)
[2] National Leading Research Laboratory, Department of Biological Sciences, Myongji University, 116 Myongjiro, Yongin, Gyeonggido 449-728, Korea; E-Mail: guunsung_guy12@hotmail.com
[3] Department of Chemistry, University of British Columbia, Vancouver, BC V6T 1Z4, Canada

† These authors contributed equally to this work.

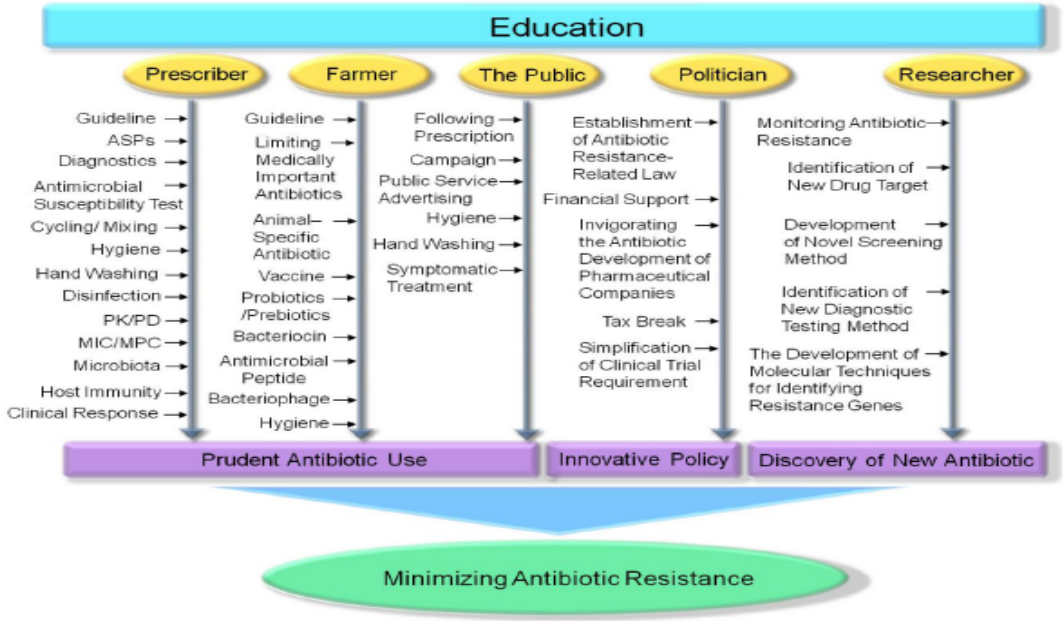
* Author to whom correspondence should be addressed; E-Mail: sangheelee@mju.ac.kr; Tel.: +82-31-330-6195; Fax: +82-31-335-8249.

Received: 5 August 2013; in revised form: 2 September 2013 / Accepted: 3 September 2013 / Published: 12 September 2013

Abstract: Antibiotic resistance can be reduced by using antibiotics prudently based on guidelines of antimicrobial stewardship programs (ASPs) and various data such as pharmacokinetic (PK) and pharmacodynamic (PD) properties of antibiotics, diagnostic testing, antimicrobial susceptibility testing (AST), clinical response, and effects on the microbiota, as well as by new antibiotic developments. The controlled use of antibiotics in food animals is another cornerstone among efforts to reduce antibiotic resistance. All major resistance-control strategies recommend education for patients, children (e.g., through schools and day care), the public, and relevant healthcare professionals (e.g., primary-care physicians, pharmacists, and medical students) regarding unique features of bacterial infections and antibiotics, prudent antibiotic prescribing as a positive construct, and personal hygiene (e.g., handwashing). The problem of antibiotic resistance can be minimized only by concerted efforts of all members of society for ensuring the continued efficiency of antibiotics.

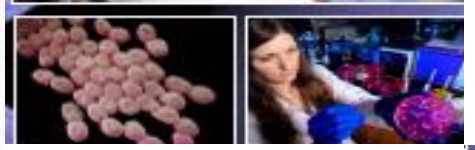
Keywords: antibiotic resistance; strategy; antibiotic prescribing; antimicrobial stewardship programs; education; hygiene; food animal; new antibiotics

Figure 5. Strategies to minimize antibiotic resistance. Education is the very important strategy. The multidisciplinary core group, including physicians, pharmacists, microbiologists, epidemiologists and infectious disease specialists, can be the teachers educating various members of society. ASPs, PK/PD, and MIC/MPC mean antimicrobial stewardship programs, pharmacokinetic/pharmacodynamics properties of drug, and the minimum inhibitory concentration/the mutant prevention concentration, respectively.



Transformation of Antimicrobial Stewardship Programs Through Technology and Informatics

Ravina Kullar, PharmD, MPH[a,*], Debra A. Goff, PharmD, FCCP[b]



ORIGINAL ARTICLES

Impact of a Computerized Integrated Antibiotic Authorization System

Israel Potasman MD FIDSA[1], Gabriela Naftali Mgr Pharm[2] and Moti Grupper MD[3]

BMJ Quality Improvement Reports

Electronic prescribing: Reducing delay to first dose of antibiotics for patients in intensive care

Philippa C Matthews, Tri Wangrangsimakul, Mark Borthwick, Clare Williams, Ivor Byren, Douglas Wilkinson

Oxford University Hospitals NHS Trust

Core Elements of Hospital Antibiotic Stewardship Programs

Journal of Antimicrobial Chemotherapy (2008) 62, 608–616

doi:10.1093/jac/dkn218

Advance Access publication 11 June 2008

JAC

Electronic antibiotic stewardship—reduced consumption of broad-spectrum antibiotics using a computerized antimicrobial approval system in a hospital setting

K. L. Buising[1,2*†], K. A. Thursky[1,2†], M. B. Robertson[3], J. F. Black[1,4], A. C. Street[1,2], M. J. Richards[1,2] and G. V. Brown[1,2,4]

Infectious Diseases

INVITED ARTICLE CLINICAL PRACTICE

The "Epic" Challenge of Optimizing Antimicrobial Stewardship: The Role of Electronic Medical Records and Technology

Ravina Kullar,[1,*] Debra A. Goff,[2] Lucas T Schulz,[3] Barry C Fox,[4] and Warren E. Rose[5]

Journal of Pharmacology & Pharmacotherapeutics

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J Pharmacol Pharmacother. 2014 Apr-Jun; 5(2): 83–87.

doi: 10.4103/0976-500X.130042

PMCID: PMC4008927

Switch over from intravenous to oral therapy: A concise overview

Jissa Maria Cyriac and Emmanuel James

- Antibióticos
  - 20-50% das prescrições são desnecessárias ou desapropriadas
- Bases essências p/ Programa *Stewardship*
  - Colheita prévia de produtos p/ ex. mibrobiológico
  - Instituição de AB na 1ª hora
  - Reavaliação às 48 horas
  - *Descalação* de acordo c/ os resultados
  - Passagem de EV p/ PO
- c/ Programas informáticos
  - Redução da mortalidade até 40% na sépsis (Epic)
  - Redução dos consumos em 35%
  - Redução da despesa em 900.000 USD / instituição / ano (USA)

J Antimicrob Chemother 2012; 67 Suppl 1: i51–i63
doi:10.1093/jac/dks202

Journal of Antimicrobial Chemotherapy

Improving the quality of antibiotic prescribing in the NHS by developing a new Antimicrobial Stewardship Programme: *Start Smart—Then Focus*

Diane Ashiru-Oredope[1], Mike Sharland[2], Esmita Charani[3], Cliodna McNulty[4] and Jonathan Cooke[3,5]* on behalf of ARHAI Antimicrobial Stewardship Group†

(a)

Department of Health
Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI)

DH Department of Health

Antimicrobial stewardship

Right Drug, Right Dose, Right Time, Right Duration.. .....Every time.

SINGLE DOSE SURGICAL PROPHYLAXIS*1

Surgical prophylaxis
ONE DOSE

Within 60 minutes of knife to skin[2]

- Clean surgery involving placement of a prosthesis or implant
- Clean contaminated surgery
- Contaminated surgery

→ DOCUMENT

*A **repeat** dose of prophylaxis is required when the operation longer than the **half life** given. **Antibiotic treatment** should be given (in addition to prophylaxis) to patients having surgery on a **dirty** or **infected wound**

References:
1. NICE Clinical Guideline 74. Surgical Site Infection – Prevention and treatment of surgical site infection Available at http://www.nice.org.uk/nicemedia/pdf/CG74NICEGuideline.pdf [Accessed 11 August 2011]
2. World Alliance for Patient Safety WHO surgical safety checklist June 2008. Available at http://www.who.int/patientsafety/safesurgery/tools resources/SSSL Checklist finalJun.08 pdf Accessed 08 August 2011

(b)

Department of Health
Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI)

DH Department of Health

Antimicrobial stewardship (ASP)

Right Drug, Right Dose, Right Time, Right Duration.. .....Every time.

START SMART → THEN FOCUS → CLINICAL REVIEW & ASP DECISION AT 48 HOURS

- Take history of relevant allergies
- Comply with local prescribing guidance
- Document clinical indication and dose on dug chart and in clinical notes
- Include review/stop date or duration
- Ensure relevant microbiological specimens taken

Clinical review, check microbiology, make and document ASP decision

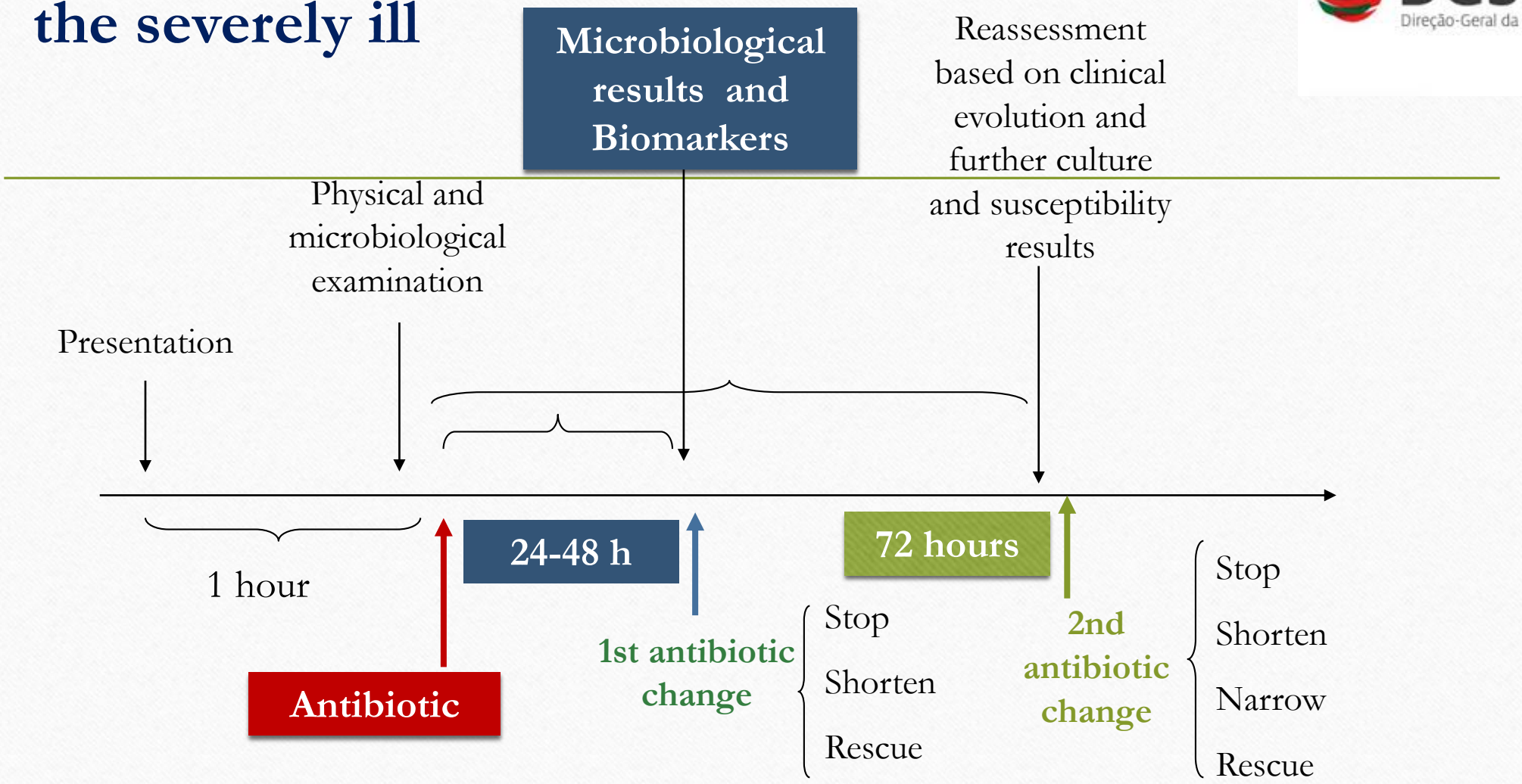
- 1. STOP
- 2. IV/oral switch
- 3. Change: to narrow spectrum agent
- 4. Continue and review again at 72 hours
- 5. OPAT*

→ DOCUMENT DECISION

*Outpatient Parenteral Therapy

Figure 10. (a) Antimicrobial Stewardship in Secondary Care—Surgical Prophylaxis Algorithm. (b) Antimicrobial Stewardship in Secondary Care—Antibiotic Treatment Algorithm.

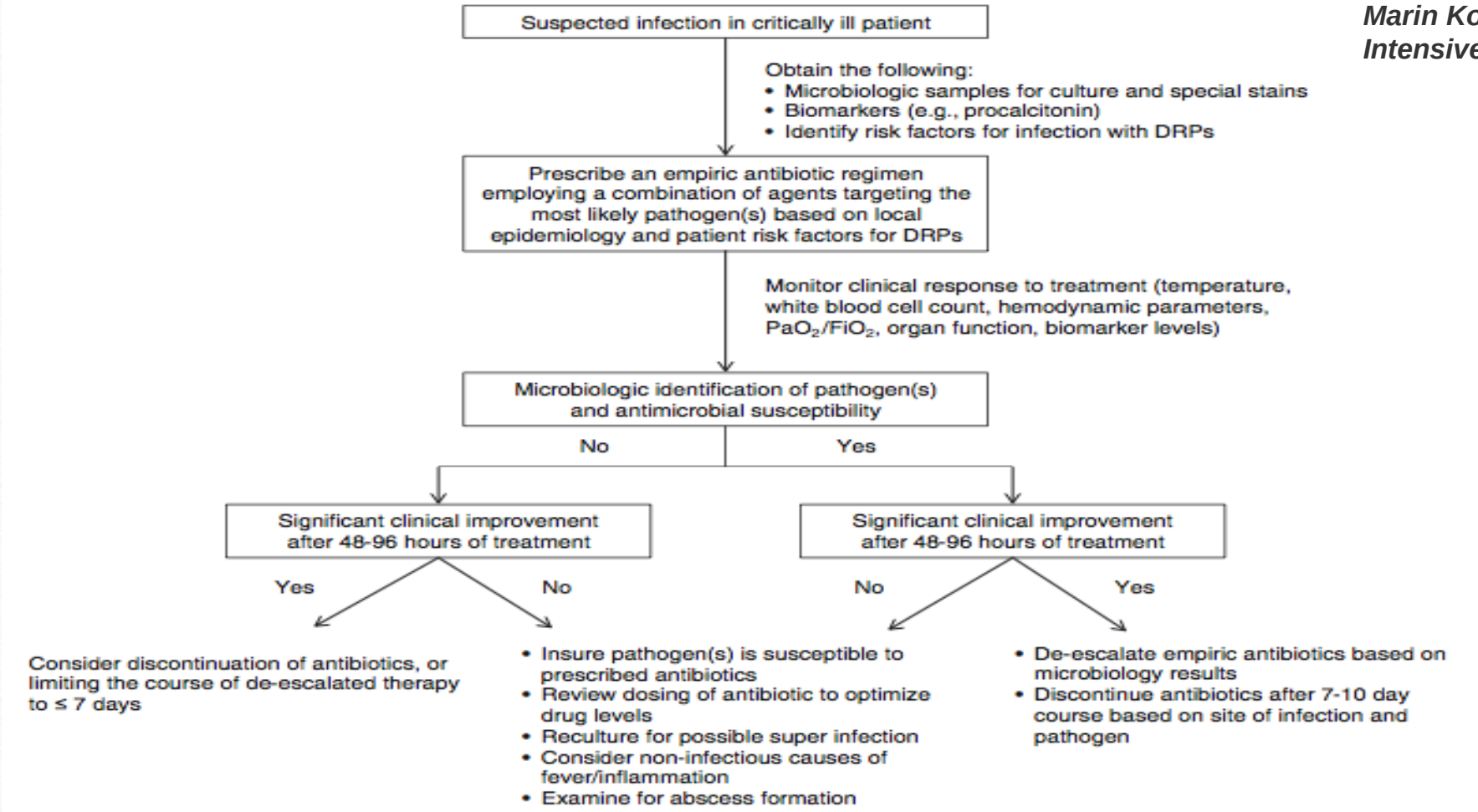
Antibiotic strategy for the severely ill



Descalação - guia prático

What can be expected from antimicrobial de-escalation in the critically ill?

Marin Kollef
Intensive Care Med 2014;40:92-95



DGS desde 1899 Direção-Geral da Saúde

DOI: 10.7860/JCDR/2014/8778.4469

Review Article

Internal Medicine Section

Burden of Antibiotic Resistance in Common Infectious Diseases: Role of Antibiotic Combination Therapy

KISHOR C MEHTA[1], RAMESH R DARGAD[2], DHAMMRAJ M BORADE[3], ONKAR C SWAMI[4]

ABSTRACT

Globally, antimicrobial resistance is alarming concern especially in commonly reported disease entities like respiratory tract infection, enteric fever and infections associated with gram-negative bacilli (GNB). Rational use of antimicrobial drugs reported significant decrease in bacterial burden and may also reduce the risk of disease progression. However, at times in particular indication, certain patient and pathogen factor limits the selection and use of specific antibiotic therapy while in some case, due to presence of additional risk factor, aggressive therapy is required to achieve clinical reemission and prevent complications. Delay in start of suitable antibiotic therapy is another imperative factor for treatment failure and rise of drug resistance.

With rapidly increasing antibiotic resistance and decline in new antibiotic drug development, the toughest challenge remains to maintain and preserve the efficacy of currently available antibiotics. Therefore, the best rational approach to fight these infections is to 'hit early and hit hard' and kills drug-susceptible bacteria before they become resistant. The preferred approach is to deploy two antibiotics that produce a stronger effect in combination than if either drug were used alone. Various society guidelines in particular indications also justify and recommend the use of combination of antimicrobial therapy. Combination therapies have distinct advantage over monotherapy in terms of broad coverage, synergistic effect and prevention of emergence of drug resistance.

Author	Cohort	Study design	n	Drug Combination	Outcome
Weiss et al., [8]	Pneumococcal bacteremia	Monocenter, retrospective	95	β-lactam plus macrolide	Lower mortality with combination
Dudas et al., [15]	CAP	Multicenter, prospective	2963	β-lactam plus macrolide	Lower mortality and reduced length of stay
Waterer et al., [16]	Pneumococcal bacteremia	Multicenter, retrospective	225	β-lactam plus macrolide	Lower mortality
Lodies TP et al., [17]	CAP	Multicenter, retrospective	845	β-lactam plus macrolide	Lower mortality
Rodrigo C et al., [18]	CAP	Multicenter, retropective	5240	β-lactam plus macrolide	Lower mortality

[Table/Fig-4]: Published clinical studies on combination of antibiotic therapy in-hospitalized patients with CAP

American Thoracic Society (ATS)	British Thoracic Society (BTS)	Infectious Disease Society of America (IDSA)	Canadian Infectious Disease Society (CIDS)
Outpatients with Comorbidities and Previous Antibiotic Therapy			
Cephalosporin or β-lactam/β-lactamases inhibitor plus macrolide or Doxycycline or respiratory quinolone	Preferred: Amoxicillin plus macrolide or amoxicillin-clavulanic acid or cephalosporin (I,II or III generation) plus macrolide Alternative: respiratory quinolone or respiratory quinolone plus benzylpenicillin	Cephalosporin or β-lactam/β-lactamases inhibitor plus macrolide or a respiratory quinolone	Cephalosporin (I,II or III generation) plus macrolide
Cap That Requires Hospitalization			
No risk for *P. aeruginosa* infection: Cephalosporin or β-lactam/β-lactamase inhibitor plus macrolide or a respiratory quinolone Risk for *P. aeruginosa* infection: Antipseudomonal β-lactam plus antipseudomonal quinolone or Antipseudomonal β-lactam plus aminoglycoside and macrolide or respiratory quinolone		Cephalosporin or β-lactam/β-lactamase inhibitor plus macrolide or a respiratory quinolone	No risk for *P. aeruginosa* infection: First choice: respiratory quinolone plus III generation cephalosporin or β-lactam/ β-lactamase inhibitor Second choice: Macrolide plus III generation cephalosporin or β-lactam/ β-lactamase inhibitor Risk for *P. aeruginosa* infection: Antipseudomonal quinolone plus Antipseudomonal β-lactam/ Antipseudomonal β-lactam plus aminoglycoside and macrolide Antipseudomonal: β-lactam plus a

[Table/Fig-5]: Recommendation by various societies' guidelines on combination of therapy [19,20,21]

SUPPLEMENT ARTICLE

Use of Electronic Health Records and Clinical Decision Support Systems for Antimicrobial Stewardship

Graeme N. Forrest,[1] Trevor C. Van Schooneveld,[2] Ravina Kullar,[3] Lucas T. Schulz,[4] Phu Duong,[3] and Michael Postelnick[5]

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Electronic health records (EHRs) and clinical decision support systems (CDSSs) have the potential to enhance antimicrobial stewardship. Numerous EHRs and CDSSs are available and have the potential to enable all clinicians and antimicrobial stewardship programs (ASPs) to more efficiently review pharmacy, microbiology, and clinical data. Literature evaluating the impact of EHRs and CDSSs on patient outcomes is lacking, although EHRs with integrated CDSSs have demonstrated improvements in clinical and economic outcomes. Both technologies can be used to enhance existing ASPs and their implementation of core ASP strategies. Resolution of administrative, legal, and technical issues will enhance the acceptance and impact of these systems. EHR systems will increase in value when manufacturers include integrated ASP tools and CDSSs that do not require extensive commitment of information technology resources. Further research is needed to determine the true impact of current systems on ASP and the ultimate goal of improved patient outcomes through optimized antimicrobial use.

Keywords. antimicrobial stewardship; clinical decision support system; electronic health record.

Table 2. Clinical Decision Support Systems and Patient Outcomes

Reference Number	Study Design	Software	Setting	Results	Notes
[9]	Pre–Post	TheraDoc	ICU	Significant declines in antibiotic susceptibility mismatches, duration of excess drug doses, and orders for antibiotics to which the patient was allergic ($P < .01$). Also had a 70% reduction in ADE ($P = .018$).	No differences in mortality between groups
[10]	Prospective	TheraDoc	Inpatient	22.8% decline in antibiotic use, a $70 per-patient decrease in antibiotic costs, a decline in antibiotic adverse events, and a decline in hospital mortality over a 7-year period (3.65% to 2.65%, $P < .001$).	Time period evaluated was from 1988 to 1994
[56]	Cluster randomized	TheraDoc	Community clinics	Antibiotic prescribing rate declined from 84.1 to 75.3 prescriptions per 100 person-years ($P = .03$). Also reduced inappropriate antibiotic prescribing, from 32% to 5% ($P = .03$).	Macrolides reduced 28%, cephalosporins 7%, and penicillins 6%
[57]	Pre–post	Unknown	PPRnet—outpatients	Inappropriate antibiotic use declined 0.6% for ARI and 16.6% for broad antibiotics in adults.	Modest effect
[58]	Prospective interventional	Unknown	PPRnet	Antibiotic use did not change (+1.57%), decrease in broad antibiotic use for ARI (−16%).	Decreased broad antibiotic use
[59]	Retrospective observational	Unknown	Veterans Affairs—outpatients	Increase in antibiotic usage (0.63 to 0.72, $P = .001$).	No effect seen targeting ARI antibiotics
[60]	Prospective	Local program	Outpatients	Overall antibiotic prescribing 39% vs non-CDSS of 43%. ARI was 54% vs 59%.	CDSS form only used in 6% of ARI visits
[61]	Prospective	TheraDoc	Pediatrics	59% reduction in erroneous antimicrobial use, 28% decline in excess dose-days. No change in ADE or susceptibility mismatches.	
[62]	Cluster-randomized study	TREAT	Inpatient	Better empiric antibiotic therapy (70% vs 57%, $P < .001$). Length of stay and costs (−12%) also reduced.	No impact on mortality
[63]	Survival analysis	TREAT	Inpatient, single center	The ITT group 180-day survival in the control group was 68% vs 71% in the intervention group ($P = .1$). In the PP analysis, the survival percentages were 68% vs 74% ($P = .04$).	Analysis of only 1 center of whole study that analyzed 30-day mortality
[64]	Prospective	Antibiograms	ICU	Increased susceptibility to imipenem (18.3%/year) and gentamicin (11.6%/year).	No clinical outcomes data.

Abbreviations: ADE, adverse drug event; ARI, acute respiratory infection; CDSS, clinical decision support system; ICU, intensive care unit; ITT, intent to treat; PP, per protocol; PPRnet, Practice Partners Research Network.

Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions

Jason A Roberts, Mohd H Abdul-Aziz, Jeffrey Lipman, Johan W Mouton, Alexander A Vinks, Timothy W Felton, William W Hope, Andras Farkas, Michael N Neely, Jerome J Schentag, George Drusano, Otto R Frey, Ursula Theuretzbacher, Joseph L Kuti, on behalf of The International Society of Anti-Infective Pharmacology and the Pharmacokinetics and Pharmacodynamics Study Group of the European Society of Clinical Microbiology and Infectious Diseases

Infections in critically ill patients are associated with persistently poor clinical outcomes. These patients have severely altered and variable antibiotic pharmacokinetics and are infected by less susceptible pathogens. Antibiotic dosing that does not account for these features is likely to result in suboptimum outcomes. In this Review, we explore the challenges related to patients and pathogens that contribute to inadequate antibiotic dosing and discuss how to implement a process for individualised antibiotic therapy that increases the accuracy of dosing and optimises care for critically ill patients. To improve antibiotic dosing, any physiological changes in patients that could alter antibiotic concentrations should first be established; such changes include altered fluid status, changes in serum albumin concentrations and renal and hepatic function, and microvascular failure. Second, antibiotic susceptibility of pathogens should be confirmed with microbiological techniques. Data for bacterial susceptibility could then be combined with measured data for antibiotic concentrations (when available) in clinical dosing software, which uses pharmacokinetic/pharmacodynamic derived models from critically ill patients to predict accurately the dosing needs for individual patients. Individualisation of dosing could optimise antibiotic exposure and maximise effectiveness.

	BestDose v1·0	ID-ODS	MWPharm	DoseMe	TCIWorks	First-dose	WinAUIC	CADDy Program v4.e
Method of pharmacokinetic assessment	Bayesian non-parametric approach	Bayesian parametric approach	Bayesian parametric approach	Bayesian parametric approach	Bayesian parametric approach	Population parametric approach	Non-linear regression	Non-linear regression
Adaptive feedback?	Yes	Yes	Yes	Yes	Yes	No	No	No
Web, server, or terminal based?	Terminal	Terminal and server	Terminal and server	Terminal and server	Terminal and server	Web	Terminal	Web or server
Compatibility	Windows	Mac, Windows, Linux, Android, iOS	Windows	Mac, Windows, Linux, Android, IOS	Mac, Windows	Mac, Windows, Linux, Android, iOS	Windows	Mac, Windows, Linux, Android, IOS
Smart phone application?	No	Yes	No	Yes	No	Yes	No	No
Patient covariates in dose predictions?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Output from program?	Doses and pharmacokinetic parameter estimates	Dosing regimens, pharmacokinetic parameter estimates, and PTAs	Doses and pharmacokinetic parameter estimates	Doses and pharmacokinetic parameter estimates	Doses and pharmacokinetic parameter estimates	Doses	Pharmacokinetic parameter estimates	Doses
IT support available within 24 h?*	Yes	Yes	No	Yes	Yes	No	No	Yes
Capacity for ICU and non-ICU dosing?	Yes	Yes	Yes	Yes	Yes	No	No	No
Further information	http://www.lapk.org	http://www.optimum-dosing-strategies.org	http://www.mediware.cz/index_en.html	www.doseme.com.au	www.tciworks.info	http://www.firstdose.org/	Contact the developers (Dr Jerome Schentag: schentag@buffalo.edu)	www.jjpreisenberger.de
Cost	Current version is free.	Free	€1250 per license	Dependent on requirements	Free	Free	Free	Free

ICU=intensive care unit. IT=information technology. PTA=probability of target attainment. ID-ODS=Individually Designed Optimum Dosing Strategies. WinAUIC=Windows Antibiotic Utilisation Information and Consultation. *Response time often depends on the severity of the problem for the user (for non-urgent issues, responses might exceed 24 h).

Table 2: Characteristics of various antibiotic dosing programs

Review

Effects of computer-aided clinical decision support systems in improving antibiotic prescribing by primary care providers: a systematic review

Jakob Holstiege,[1] Tim Mathes,[2] Dawid Pieper[2]

Audit and feedback of antibiotic use

Utilising electronic prescription data

M. T. Bayuo[1,2]; K. Oliver[3]; B. Egan[3]; L. Li[3]; K. Richardson[4]; I. Senaratna[5]; J. I. Westbrook[1]; R. O. Day[2,6]

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[3]Centre for Health Systems & Safety Research, Australian Institute of Health Innovation, UNSW Medicine, University of New South Wales, Sydney, Australia;
[4]Department of Pharmacy, St Vincent's Hospital, Sydney, Australia;
[5]Department of Microbiology, St Vincent's Hospital, Sydney, Australia;
[6]UNSW Medicine, University of New South Wales, Sydney, Australia

BJCP British Journal of Clinical Pharmacology

Therapeutic drug monitoring of antimicrobials

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BMC Infectious Diseases

REVIEW Open Access

How do we use therapeutic drug monitoring to improve outcomes from severe infections in critically ill patients?

Gloria Wong[1†], Fekade Bruck Sime[2,3†], Jeffrey Lipman[1,4] and Jason A Roberts[1,2,4*]

Abstract

High mortality and morbidity rates associated with severe infections in the critically ill continue to be a significant issue for the healthcare system. In view of the diverse and unique pharmacokinetic profile of drugs in this patient population, there is increasing use of therapeutic drug monitoring (TDM) in attempt to optimize the exposure of antibiotics, improve clinical outcome and minimize the emergence of antibiotic resistance. Despite this, a beneficial clinical outcome for TDM of antibiotics has only been demonstrated for aminoglycosides in a general hospital patient population. Clinical outcome studies for other antibiotics remain elusive. Further, there is significant variability among institutions with respect to the practice of TDM including the selection of patients, sampling time for concentration monitoring, methodologies of antibiotic assay, selection of PK/PD targets as well as dose optimisation strategies. The aim of this paper is to review the available evidence relating to practices of antibiotic TDM, and describe how TDM can be applied to potentially improve outcomes from severe infections in the critically ill.

Keywords: TDM, Antibiotic, Pharmacokinetics, Pharmacodynamics

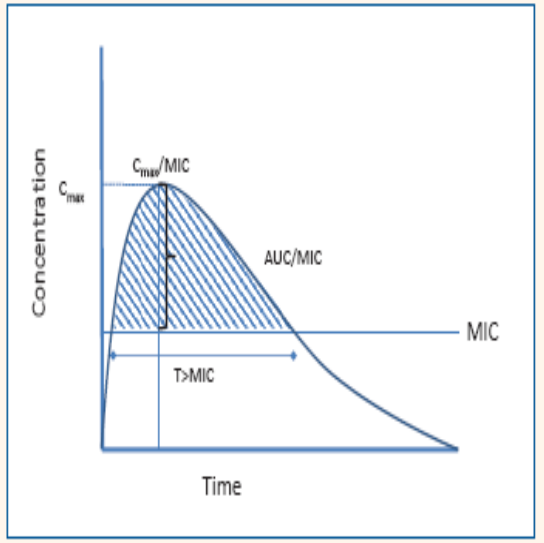
Comparative Effectiveness Review Number 136

Effective Health Care Program

Pharmacokinetic/Pharmacodynamic Measures for Guiding Antibiotic Treatment for Hospital-Acquired Pneumonia

Executive Summary

Figure A. Ratios related to the minimum inhibitory concentration of the organisms



AUC = antibiotic area under the curve; AUC/MIC = the ratio of the antibiotic area under the curve to the time above the minimum inhibitory concentration needed to inhibit microorganisms; Cmax = the maximum serum concentration needed to inhibit microorganisms; Cmax/MIC = ratio of maximum serum concentration (or peak) to the time above the minimum inhibitory concentration needed to inhibit microorganisms; MIC = minimum inhibitory concentration; T = time.

From Medscape Education Infectious Diseases

Optimizing Dosing Strategies: The Key to Antimicrobial Stewardship

Edward J. Septimus, MD

Posted: 07/25/2012

Table B. Strength of evidence for using PK/PD measures to influence dosing or monitoring

Outcome	No. of Studies (Subjects)	Risk of Bias	Consistency	Directnes	Precision	Overall Strength of Evidence
Clinical response	1 prospective cohort (n=638)	High	NA	Indirect	Imprecise	Insufficient
Treatment failure	1 prospective cohort (n=638)	High	NA	Indirect	Precise	Insufficient
Mechanical ventilation	1 prospective cohort (n=638)	High	NA	Direct	Imprecise	Insufficient
Mortality (composite of death and leaving AMA)	1 prospective cohort (n=638)	High	NA	Direct	Precise	Insufficient

AMA = against medical advice; NA = not applicable; PK/PD = pharmacokinetic/pharmacodynamic.

1521-0081/65/3/1053–1090$25.00
Pharmacological Reviews
http://dx.doi.org/10.1124/pr.111.005769
Pharmacol Rev 65:1053–1090, July 2013

ASSOCIATE EDITOR: DAN ANDERSSON

Pharmacokinetic-Pharmacodynamic Modeling of Antibacterial Drugs

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PK/PD models in antibacterial development

Tony Velkov[1], Phillip Bergen[2], Jaime Lora-Tamayo[1,3], Cornelia B. Landersdorfer[2], and Jian Li[1,*]

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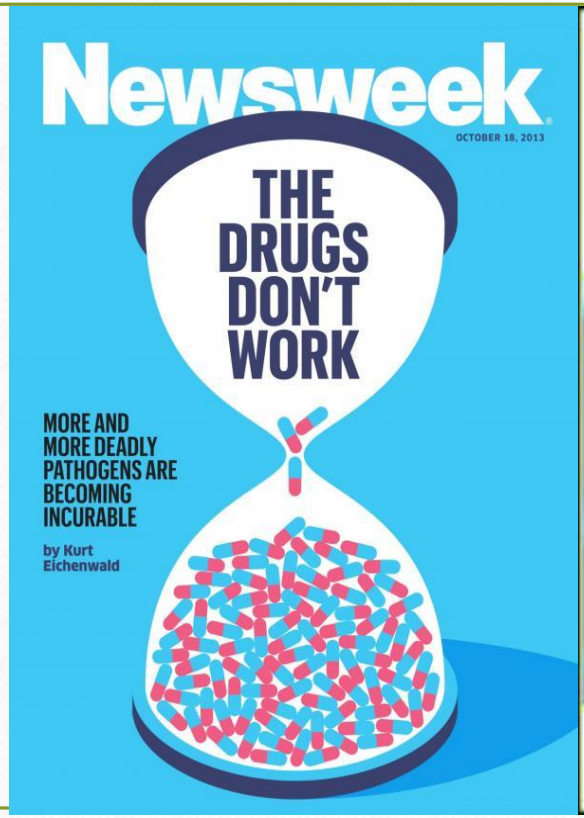
Abstract

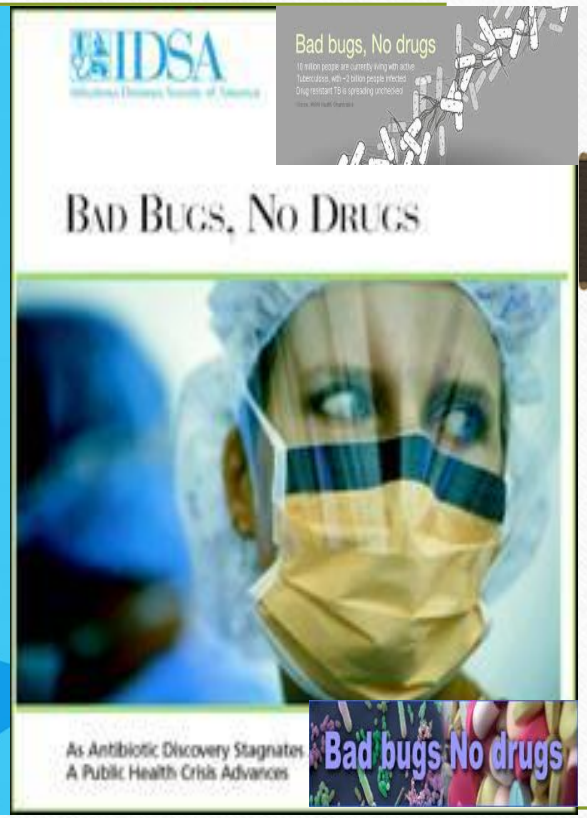
There is an urgent need for novel antibiotics to treat life-threatening infections caused by bacterial 'superbugs'. Validated *in vitro* pharmacokinetic/pharmacodynamic (PK/PD) and animal infection models have been employed to identify the most predictive PK/PD indices and serve as key tools in the antibiotic development process. The results obtained can be utilized for optimizing study designs in order to minimize the cost and duration of clinical trials. This review outlines the key *in vitro* PK/PD and animal infection models which have been extensively used in antibiotic discovery and development. These models have shown great potential in accelerating drug development programs and will continue to make significant contributions to antibiotic development.

AS SOLUÇÕES EM DISCUSSÃO

Necessidade de maior investimento na inovação

- Mercado Farmacêutico
  - Volume de Vendas de Antibióticos
    - 48% gastos c/ Antimicrobianos
    - < 5% Total de Medicamentos
    - Em 2004 1,6% das novas moléculas em investigação eram antibióticos
    - Cada novo antibiótico: 400 – 800 milhões de USD





The right prevention and treatment for the right patient at the right time

Strategic Research Agenda for Innovative Medicines Initiative 2

efpia
European Federation of Pharmaceutical Industries and Associations

Vaccines Europe
An industry for healthy lives

ebe
european biopharmaceutical enterprises

imi
Innovative Medicines Initiative

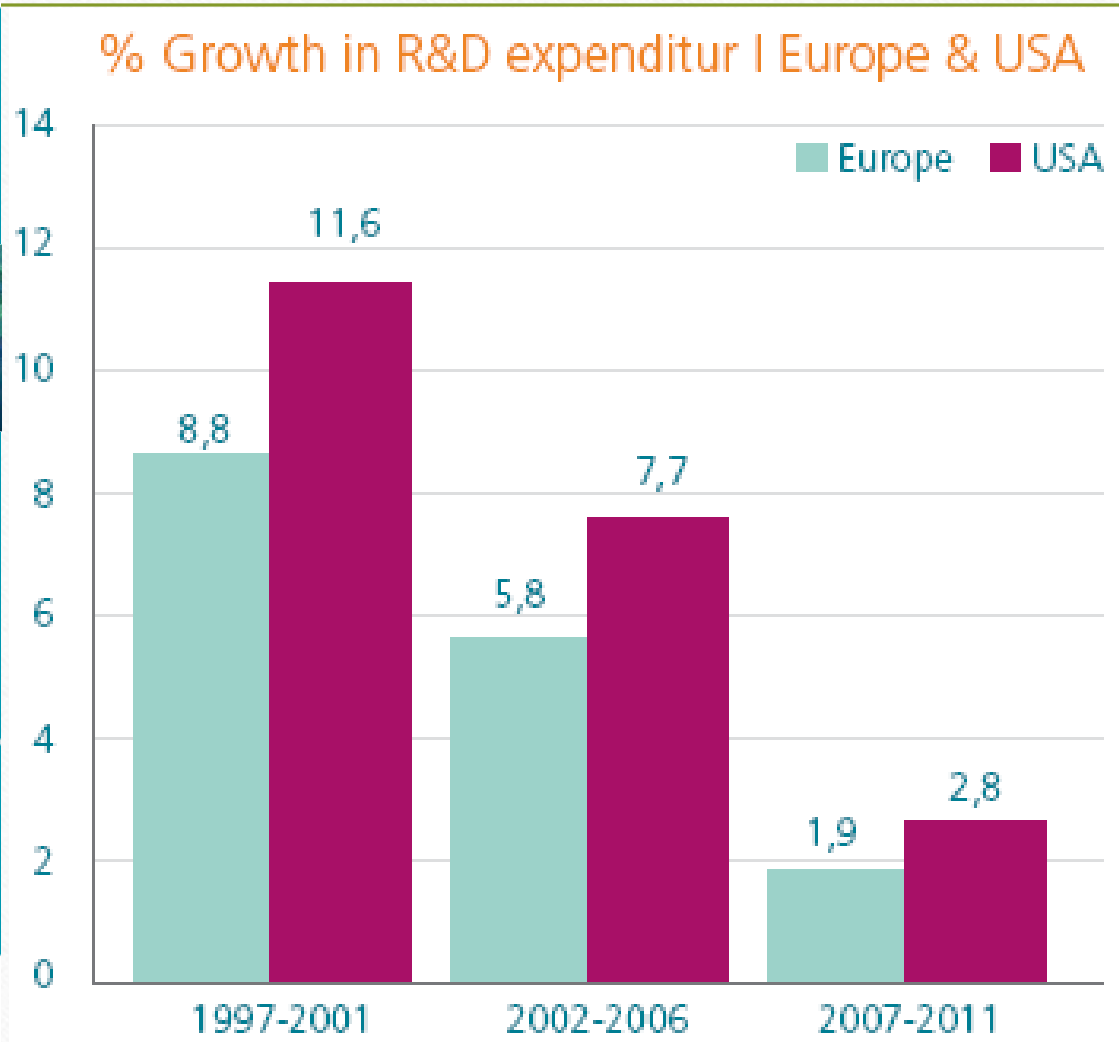


Figure 4: Growth in R&D has slowned in both Europe and the US.
Source: EFPIA/PhRMA

WASHINGTON JOURNAL OF LAW, TECHNOLOGY & ARTS
VOLUME 9, ISSUE 1 SUMMER 2013

REPAIRING THE ANTIBIOTIC PIPELINE: CAN THE GAIN ACT DO IT?

Caitlin Forsyth[1]

Cite as: 9 WASH. J.L. TECH. & ARTS 1 (2013)
https://digital.lib.washington.edu/dspace-law/handle/1773.1/1267

HALI
Healthcare Associated Infections in European Long Term Care Facilities

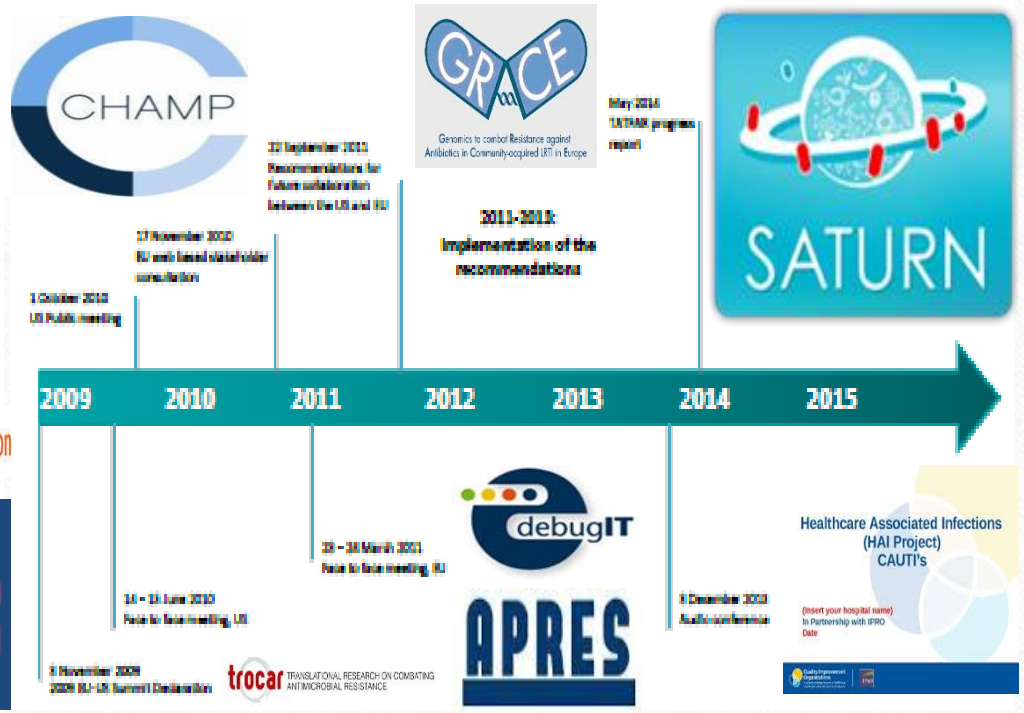
Transatlantic Taskforce on Antimicrobial Resistance: Progress report

COLD? FLU? GET WELL WITHOUT ANTIBIOTICS
A European Health Initiative

May 2014 e-Bug Project Information

Recommendations for future collaboration between the US and EU

Annex E: Timeline of the Transatlantic Task Force on Antimicrobial Resistance (TATFAR), 2009-2013



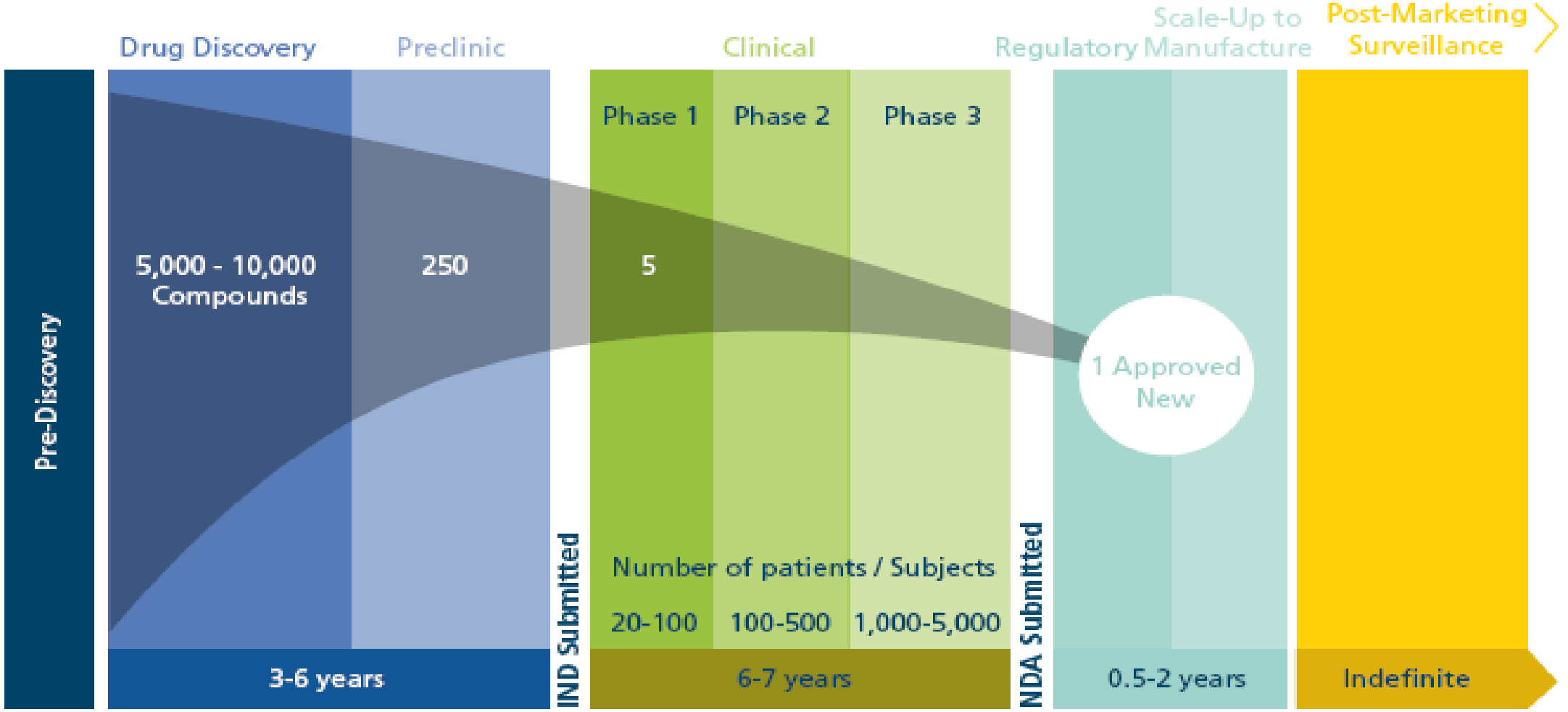


Figure 6: With the cost of developing a medicine estimated at $1.2 billion, attrition rates in pharmaceutical R&D are unsustainable. Source CBO, Research and Development in the Pharmaceutical Industry, 2006.

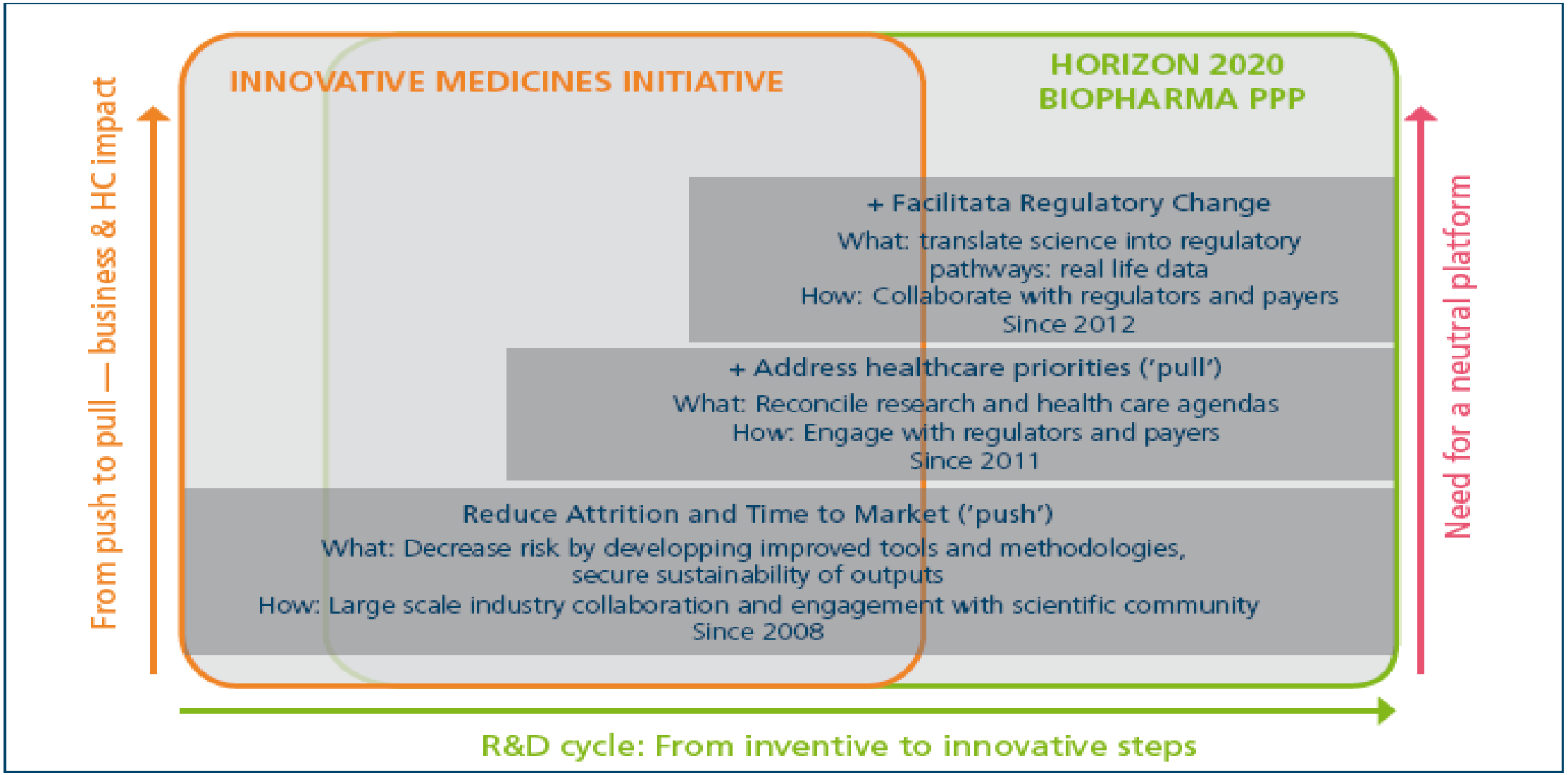


Figure 5: Transition from IMI1 to IMI2.

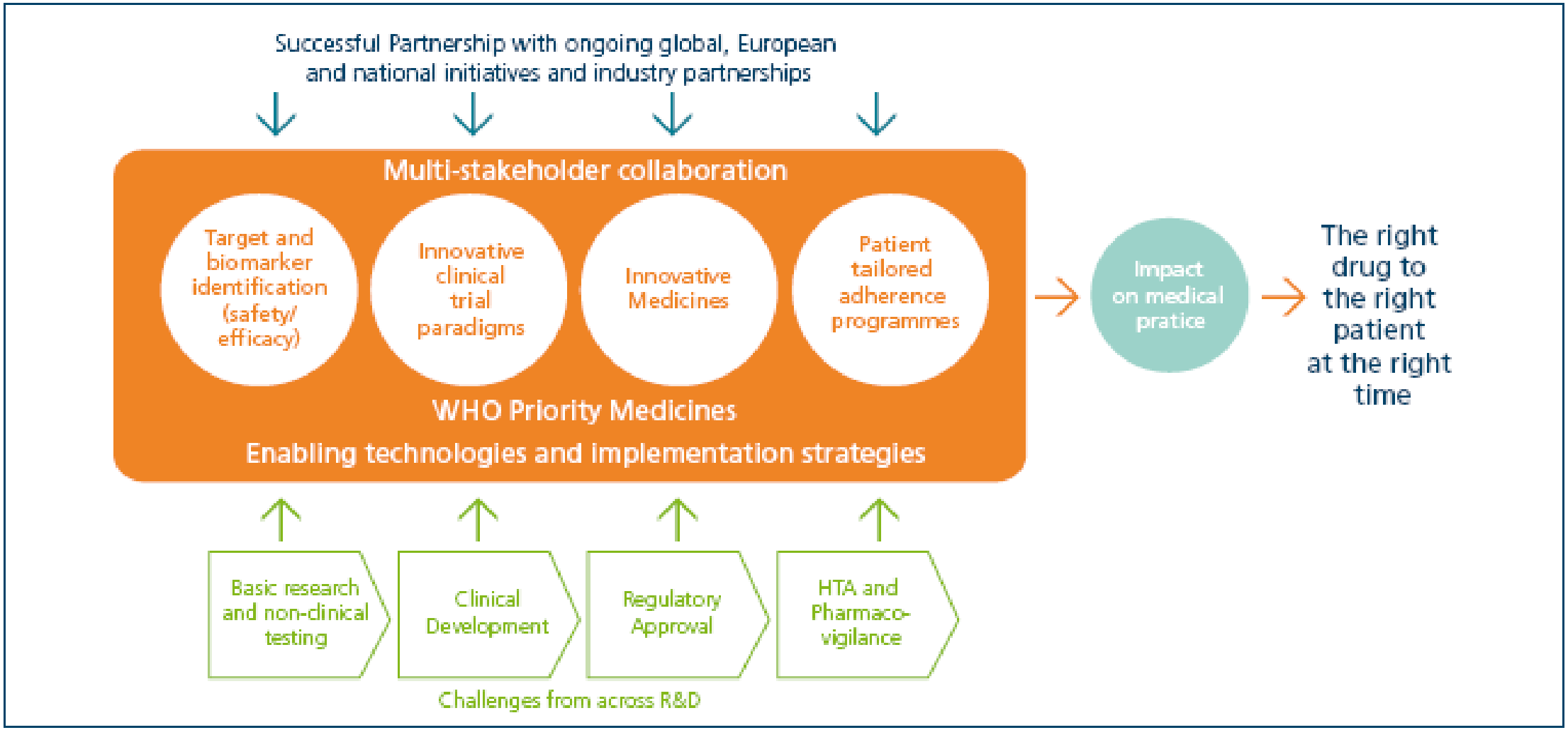
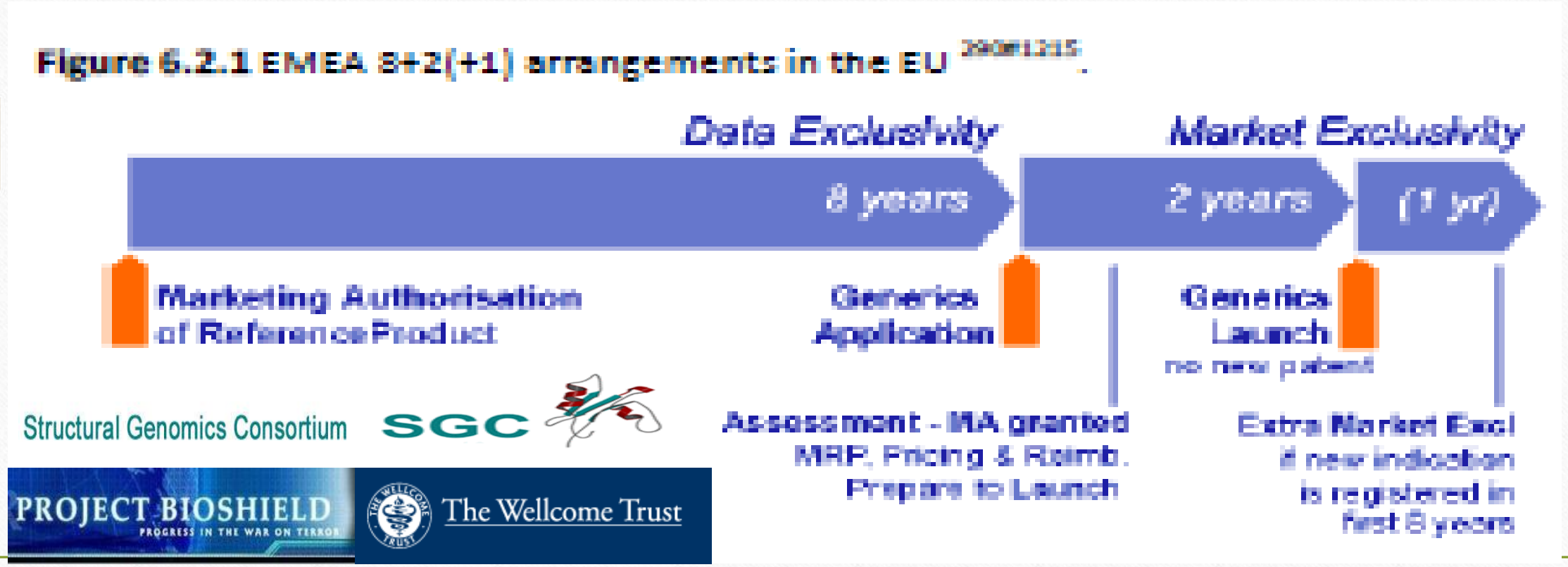


Figure 8: IMI2 will partner with ongoing initiatives to create cross-disciplinary, international research teams to deliver effective and integrated healthcare solutions for priority medicines.

Acordo com a Indústria Farmacêutica



OCCASIONAL ESSAY

Novel Approaches Are Needed to Develop Tomorrow's Antibacterial Therapies

Brad Spellberg[1,2], John Bartlett[3], Rich Wunderink[4], and David N. Gilbert[5]

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Abstract

Society faces a crisis of rising antibiotic resistance even as the pipeline of new antibiotics has been drying up. Antibiotics are a public trust; every individual's use of antibiotics affects their efficacy for everyone else. As such, responses to the antibiotic crisis must take a societal perspective. The market failure of antibiotics is due to a combination of scientific challenges to discovering and developing new antibiotics, unfavorable economics, and a hostile regulatory environment. Scientific solutions include changing the way we screen for new antibiotics. More transformationally, developing new treatments that seek to disarm pathogens without killing them, or that modulate the host inflammatory response to infection, will reduce selective pressure and hence minimize resistance emergence. Economic transformation will require new business models to support antibiotic development. Finally, regulatory reform is needed so that clinical development programs are feasible, rigorous, and clinically relevant. Pulmonary and critical care specialists can have tremendous impact on the continued availability of effective antibiotics. Encouraging use of molecular diagnostic tests to allow pathogen-targeted, narrow-spectrum antibiotic therapy, using short rather than unnecessarily long course therapy, reducing inappropriate antibiotic use for probable viral infections, and reducing infection rates will help preserve the antibiotics we have for future generations.

Keywords: antibiotics; antibiotic resistance; market failure; drug; regulations

Chem Biol Drug Des 2015; **85:** 14–21

Special Issue Antibacterials

Machine-Learning Techniques Applied to Antibacterial Drug Discovery

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The emergence of drug-resistant bacteria threatens to revert humanity back to the preantibiotic era. Even now, multidrug-resistant bacterial infections annually result in millions of hospital days, billions in healthcare costs, and, most importantly, tens of thousands of lives lost. As many pharmaceutical companies have abandoned antibiotic development in search of more lucrative therapeutics, academic researchers are uniquely positioned to fill the pipeline. Traditional high-throughput screens and lead-optimization efforts are expensive and labor intensive. Computer-aided drug-discovery techniques, which are cheaper and faster, can accelerate the identification of novel antibiotics, leading to improved hit rates and faster transitions to preclinical and clinical testing. The current review describes two machine-learning techniques, neural networks and decision trees, that have been used to identify experimentally validated antibiotics. We conclude by describing the future directions of this exciting field.

Virulence-targeted antibacterials: concept, promise, and susceptibility to resistance mechanisms

Ségolène Ruer[1,2], Nikos Pinotsis[3], David Steadman[4], Gabriel Waksman[3*] and Han Remaut[1,2*]

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Review

Quorum Quenching Agents: Resources for Antivirulence Therapy

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Abstract: The continuing emergence of antibiotic-resistant pathogens is a concern to human health and highlights the urgent need for the development of alternative therapeutic strategies. Quorum sensing (QS) regulates virulence in many bacterial pathogens, and thus, is a promising target for antivirulence therapy which may inhibit virulence instead of cell growth and division. This means that there is little selective pressure for the evolution of resistance. Many natural quorum quenching (QQ) agents have been identified. Moreover, it has been shown that many microorganisms are capable of producing small molecular QS inhibitors and/or macromolecular QQ enzymes, which could be regarded as a strategy for bacteria to gain benefits in competitive environments. More than 30 species of marine QQ bacteria have been identified thus far, but only a few of them have been intensively studied. Recent studies indicate that an enormous number of QQ microorganisms are undiscovered in the highly diverse marine environments, and these marine microorganism-derived QQ agents may be valuable resources for antivirulence therapy.

Keywords: quorum sensing; quorum quenching; marine; AHL-degrading activity; antivirulence therapy; antibiotic resistance

	Target	Anti-virulence target	Compounds	Reference
Attachment/ Biofilm	Type 1 pili	- chaperone-subunit complex - chaperone-usher complex - binding pocket - Fimbrial expression	AL1 Pilicides Mannose derivatives Galabiose derivatives Indole	(140) (141, 152, 154) (18, 155-157, 159) (2-8, 158) (196)
	Curli	- curli biogenesis - DnaK chaperone - AcrB/TolC pumps	Curlicides Inhibitors Inhibitors	(180-182) (183) (184, 185)
Secretion/ membrane	Efflux pump	- AcrB/TolC (curli-deficient)	Inhibitors	(184, 185)
	T2SS	- Secretin	2-imino-5-arylidene thiazolidinone	(136, 180, 181)
	T3SS	- Secretin - ATPase YscN - Secretion (unknown targets)	2-imino-5-arylidene thiazolidinone Inhibitors Small molecules Salicylidene acylhydrazide compounds	(136, 180, 181) (182) (183) (185)
	T4SS	- VirB8 dimerization	Salicylidene acylhydrazide B81-2	(180, 184)
	Exopolysaccharides	- enzymatic degradation of EPS	Glycosidase, Protease, DNAse	(187-191)
	Lipopolysaccharides	- Lipid A modification	Inhibitors, Indole	(203-204)
	Membrane	- disruption of permeability	Indole	(197)
Communication/ signalling	Quorum Sensing	- enzyme responsible for AHL synthesis (MTAN) - LuxR / transcription - QS regulator folding	SAM analogues AHL receptor antagonists (natural and synthetic) Indole	(116, 118, 122) (123-132) (205-206)
	c-di GMP	- diguanylate cyclase - expression of c-di-GMP	Inhibitors	(218, 219)
	Two-component system	- TCS expression/activity	Inhibitors/Indole	(203-204)
Secreted molecules	Toxins	- ADP-ribosyltransferase toxins - Shiga toxin	Heterobifunctional inhibitors	(188)

Upsala Journal of Medical Sciences. 2014; 119: 199–204

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REVIEW ARTICLE

Antimicrobial peptides

MARTIN MALMSTEN

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Abstract

With increasing antibiotics resistance, there is an urgent need for novel infection therapeutics. Since antimicrobial peptides provide opportunities for this, identification and optimization of such peptides have attracted much interest during recent years. Here, a brief overview of antimicrobial peptides is provided, with focus placed on how selected hydrophobic modifications of antimicrobial peptides can be employed to combat also more demanding pathogens, including multi-resistant strains, without conferring unacceptable toxicity.

Key words: *AMP, antimicrobial peptide, bacteria, liposome, membrane*

OPEN

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www.nature.com/ijos

REVIEW

Strategies for combating bacterial biofilm infections

Hong Wu[1,2], Claus Moser[1], Heng-Zhuang Wang[1], Niels Høiby[1,2] and Zhi-Jun Song[1,3]

Formation of biofilm is a survival strategy for bacteria and fungi to adapt to their living environment, especially in the hostile environment. Under the protection of biofilm, microbial cells in biofilm become tolerant and resistant to antibiotics and the immune responses, which increases the difficulties for the clinical treatment of biofilm infections. Clinical and laboratory investigations demonstrated a perspicuous correlation between biofilm infection and medical foreign bodies or indwelling devices. Clinical observations and experimental studies indicated clearly that antibiotic treatment alone is in most cases insufficient to eradicate biofilm infections. Therefore, to effectively treat biofilm infections with currently available antibiotics and evaluate the outcomes become important and urgent for clinicians. The review summarizes the latest progress in treatment of clinical biofilm infections and scientific investigations, discusses the diagnosis and treatment of different biofilm infections and introduces the promising laboratory progress, which may contribute to prevention or cure of biofilm infections. We conclude that, an efficient treatment of biofilm infections needs a well-established multidisciplinary collaboration, which includes removal of the infected foreign bodies, selection of biofilm-active, sensitive and well-penetrating antibiotics, systemic or topical antibiotic administration in high dosage and combinations, and administration of anti-quorum sensing or biofilm dispersal agents.

International Journal of Oral Science advance online publication, 12 December 2014; doi:10.1038/ijos.2014.65

Keywords: antibiotic resistance; antimicrobial treatments; bacterial biofilm; chronic infection

frontiers in
MICROBIOLOGY

ORIGINAL RESEARCH ARTICLE
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Combining flagellin and human β-defensin-3 to combat bacterial infections

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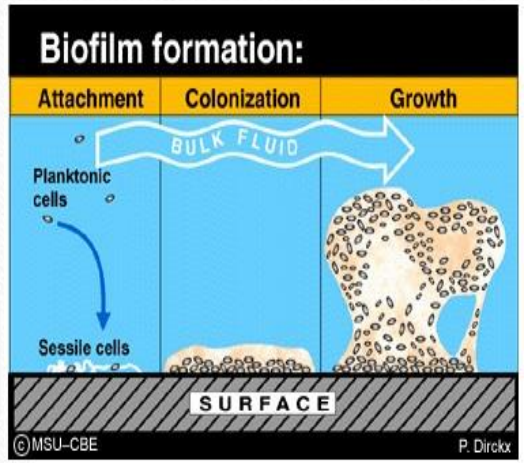
The discovery and therapeutic use of antibiotics made a major contribution to the reduction of human morbidity and mortality. However, the growing resistance to antibiotics has become a matter of huge concern. In this study we aimed to develop an innovative approach to treat bacterial infections utilizing two components: the human antibacterial peptide β-defensin-3 (BD3) and the bacterial protein flagellin (F). This combination was designed to provide an efficient weapon against bacterial infections with the peptide killing the bacteria directly, while the flagellin protein triggers the immune system and acts against bacteria escaping from the peptide's action. We designed, expressed and purified the fusion protein flagellin BD3 (FBD3) and its two components, the F protein and the native BD3 peptide. FBD3 fusion protein and native BD3 peptide had antibacterial activity *in vitro* against various bacterial strains. FBD3 and F proteins could also recognize their receptor expressed on target cells and stimulated secretion of IL-8. In addition, F and FBD3 proteins had a partial protective effect in mice infected by pathogenic *Escherichia coli* bacteria that cause a lethal disease. Moreover, we were able to show partial protection of mice infected with *E. coli* using a flagellin sequence from *Salmonella*. We also explored flagellin's basic mechanisms of action, focusing on its effects on CD4+ T cells from healthy donors. We found that F stimulation caused an increase in the mRNA levels of the Th1 response cytokines IL12A and IFNγ. In addition, F stimulation affected its own receptor.

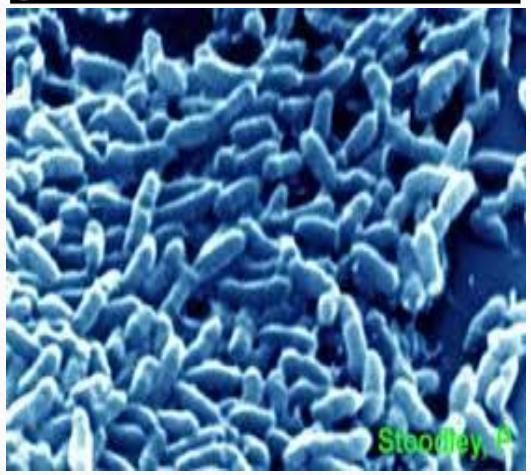
Keywords: antibacterial peptide β-defensin-3 (BD3), flagellin (F), fusion protein (FBD3), bacterial infection, antibacterial activity, TLR5 receptor, human CD4+ T cells

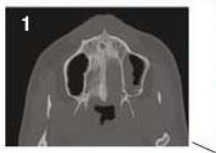
BIOFILMES HUMANOS

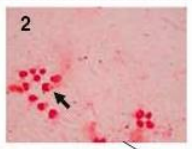
del Pozo e Patel *Clin Pharm Ther* Vol 82, 2007

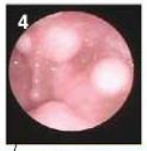
80% das infecções crónicas (NIH 1997)

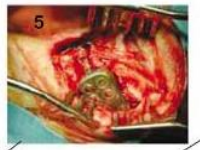


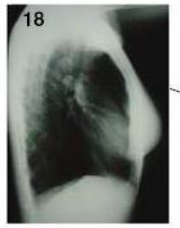


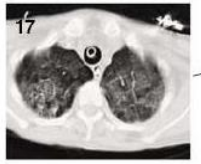


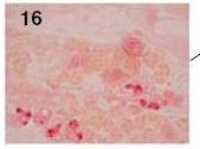


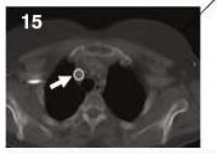


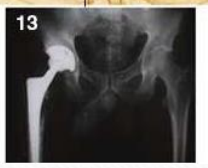


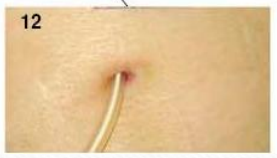


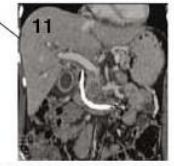


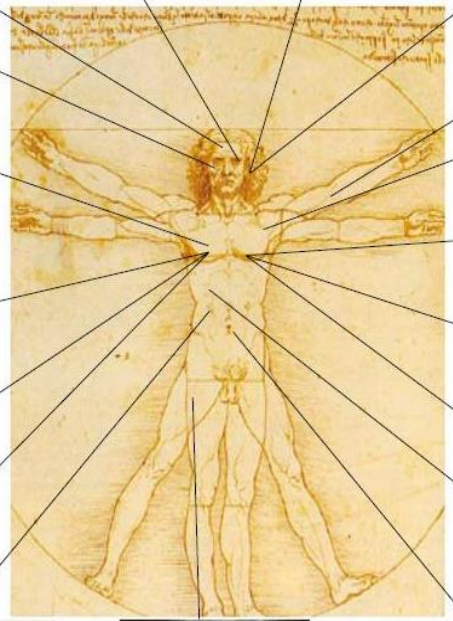


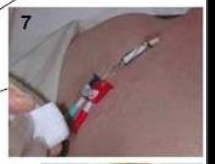


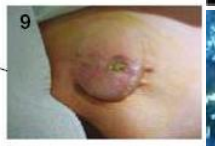


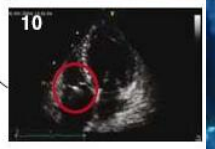


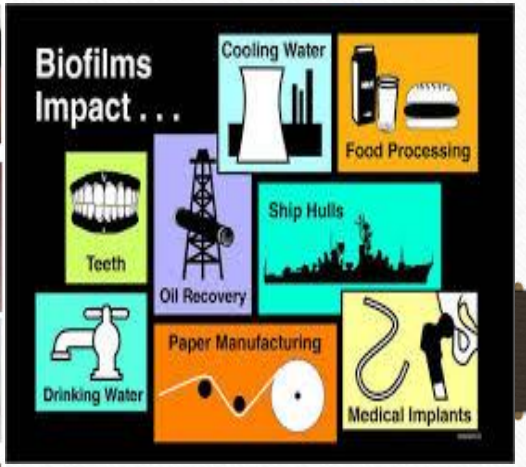


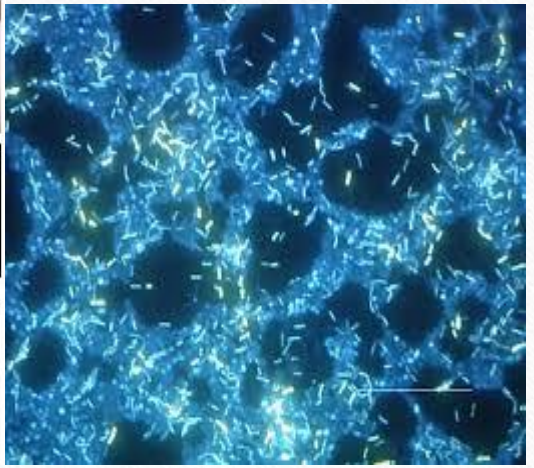












frontiers in
PHARMACOLOGY

REVIEW ARTICLE
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Challenges and future prospects of antibiotic therapy: from peptides to phages utilization

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Bacterial infections are raising serious concern across the globe. The effectiveness of conventional antibiotics is decreasing due to global emergence of multi-drug-resistant (MDR) bacterial pathogens. This process seems to be primarily caused by an indiscriminate and inappropriate use of antibiotics in non-infected patients and in the food industry. New classes of antibiotics with different actions against MDR pathogens need to be developed urgently. In this context, this review focuses on several ways and future directions to search for the next generation of safe and effective antibiotics compounds including antimicrobial peptides, phage therapy, phytochemicals, metalloantibiotics, lipopolysaccharide, and efflux pump inhibitors to control the infections caused by MDR pathogens.

Table 1 | Major types of antimicrobial compounds with their mechanisms of action.

Future therapy	Mechanism	Contemporary strategies to improve activity
Antimicrobial peptides	Attach and insert into membrane bilayers to form pores by "barrel-stave," "carpet," or "toroidal-pore" mechanisms. DNA and macromolecule synthesis inhibitors.	Optimization of peptide length and content of their sequences. Conversion into peptidomimetics. Generation of targeted antimicrobial peptides (Peptide antibiotic conjugation). Generation of antimicrobial peptides as prodrug candidates. Antimicrobial peptides loaded into nanoparticle or micelles for sustained release.
Phage therapy	Bacteriophages are viruses that act as pathogens against bacteria and completely lyse the bacteria.	Genetically engineered phages. Genetically engineered phase as antibiotic delivery. Engineered bacteriophage for phage targeted drug delivery. Scale up of endolysin production.
Phytochemicals	Multiple actions.	Search for novel compounds and cost-effective methods of extraction and purification of phytochemical. Transgenic production in plant and microbial system to enhance number of novel compounds. Search for endophytic fungal metabolomics for the production of novel compound of host. Synthesis and modification of natural structure and analogs.
Metalloantibiotic	Increased spectrum of conventional antibiotic action.	Synthetic or semi-synthetic antimicrobial compound development attaching metal to its structure. *In situ* reducing and capping of metal nanoparticle with enhanced antimicrobial activity.
Efflux pump inhibitor	Molecules to inhibit the active protein pump in the bacterial cell.	Chemical synthesis of effective efflux pumps inhibitor. Screening of efflux pump inhibitors from natural origin and modifying this compound synthetically. Rationally designed transmembrane peptide mimics.

Review Article

Bacteriophage therapy: a potential solution for the antibiotic resistance crisis

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Abstract

The emergence of multiple drug-resistant bacteria has prompted interest in alternatives to conventional antimicrobials. One of the possible replacement options for antibiotics is the use of bacteriophages as antimicrobial agents. Phage therapy is an important alternative to antibiotics in the current era of drug-resistant pathogens. Bacteriophages have played an important role in the expansion of molecular biology and have been used as antibacterial agents since 1966. In this review, we describe a brief history of bacteriophages and clinical studies on their use in bacterial disease prophylaxis and therapy. We discuss the advantages and disadvantages of bacteriophages as therapeutic agents in this regard.

Key words:. antibiotic resistance; bacteriophage; infectious disease

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MINIREVIEW

Bacteriophages as an Alternative Strategy for Fighting Biofilm Development

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Submitted 2 February 2013, revised 14 July 2013, accepted 6 February 2014

Abstract

The ability of microbes to form biofilms is an important element of their pathogenicity, and biofilm formation is a serious challenge for today's medicine. Fighting the clinical complications associated with biofilm formation is very difficult and linked to a high risk of failure, especially in a time of increasing bacterial resistance to antibiotics. Bacterial species most commonly isolated from biofilms include coagulase-negative staphylococci, *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter* spp. The frequent failure of antibiotic therapy led researchers to look for alternative methods and experiment with the use of antibacterial factors with a mechanism of action different from that of antibiotics. Experimental studies with bacteriophages and mixtures thereof, expressing lytic properties against numerous biofilm-forming bacterial species showed that bacteriophages may both prevent biofilm formation and contribute to eradication of biofilm bacteria. A specific role is played here by phage depolymerases, which facilitate the degradation of extracellular polymeric substances (EPS) and thus the permeation of bacteriophages into deeper biofilm layers and lysis of the susceptible bacterial cells. Much hope is placed in genetic modifications of bacteriophages that would allow the equipping bacteriophages with the function of depolymerase synthesis. The use of phage cocktails prevents the development of phage-resistant bacteria.

Key words: biofilm, bacteriophage, anti-biofilm activity

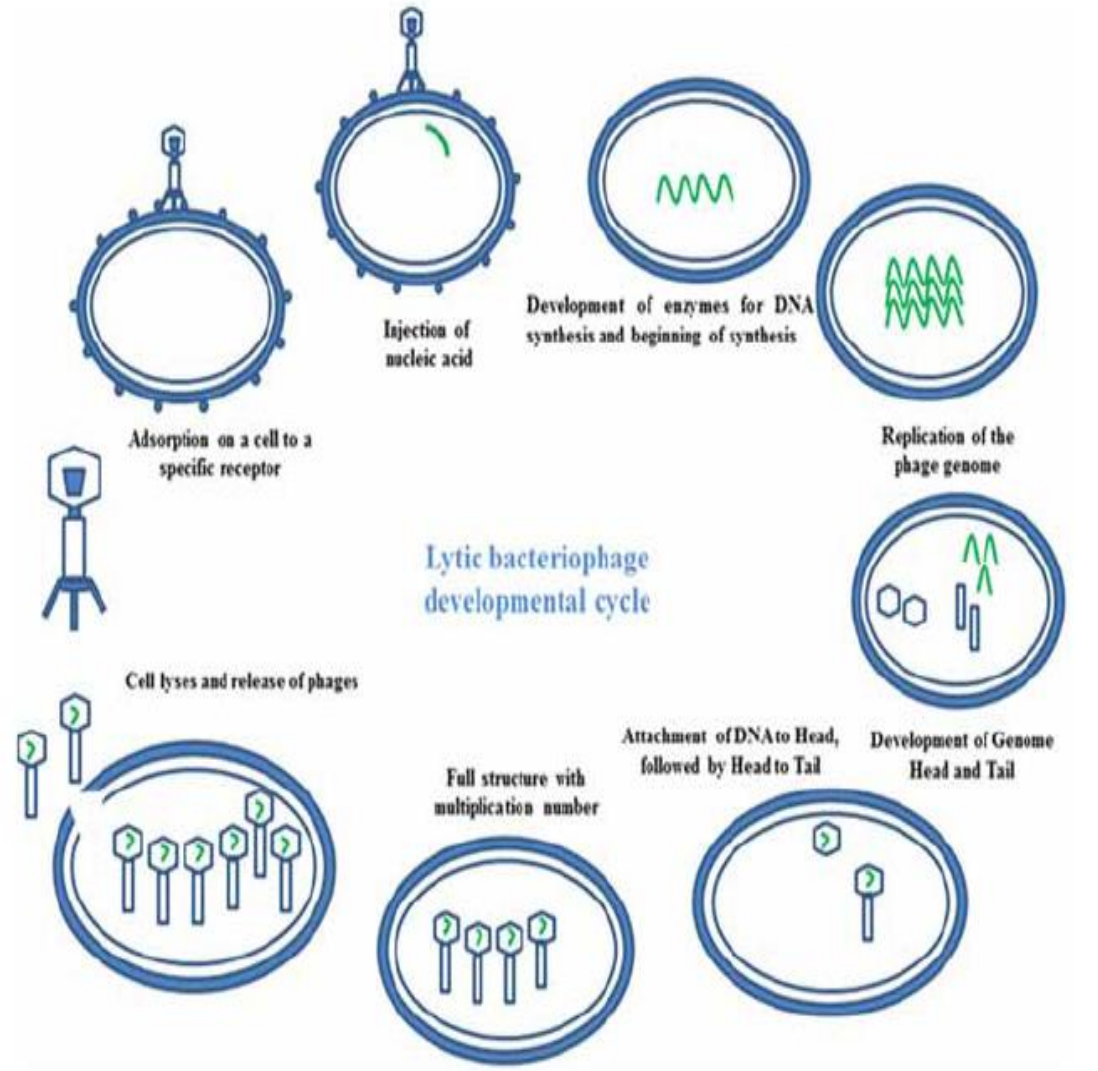

FIGURE 3 | Mechanism of phage therapy. Image represents the schematic diagram of developmental cycle of lytic bacteriophage.

Chem Biol Drug Des 2015; **85:** 4–13

Special Issue Antibacterials

Cost-effectiveness and Pricing of Antibacterial Drugs

Talitha I. Verhoef* and Stephen Morris

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Growing resistance to antibacterial agents has increased the need for the development of new drugs to treat bacterial infections. Given increasing pressure on limited health budgets, it is important to study the cost-effectiveness of these drugs, as well as their safety and efficacy, to find out whether or not they provide value for money and should be reimbursed. In this article, we systematically reviewed 38 cost-effectiveness analyses of new antibacterial agents. Most studies showed the new antibacterial drugs were cost-effective compared to older generation drugs. Drug pricing is a complicated process, involving different stakeholders, and has a large influence on cost-effectiveness. Value-based pricing is a method to determine the price of a drug at which it can be cost-effective. It is currently unclear what the influence of value-based pricing will be on the prices of new antibacterial agents, but an important factor will be the definition of 'value', which as well as the impact of the drug on patient health might also include other factors such as wider social impact and the health impact of disease.

Ann. N.Y. Acad. Sci. ISSN 0077-8923

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Issue: *Antimicrobial Therapeutics Reviews*

The evolution of the regulatory framework for antibacterial agents

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The rising tide of antibacterial resistance and the lack of a diverse, vibrant pipeline of novel antibacterial agents is a global crisis that impairs our ability to treat life-threatening infections. The recent introduction of a tiered approach to the regulatory framework in this area offers one path to resolving some of the challenges. By drawing heavily on the predictive power of the related sciences of pharmacokinetics and pharmacodynamics, smaller, focused clinical trial programs have become possible for agents that might not otherwise have been possible to progress. There are limitations to these pathways, and they are not easy to implement, but making reliable noninferiority-based approaches available is critical to reinvigorating the global antibiotic pipeline. With the recognition of these ideas by key regulatory authorities in recent guidance, the next challenges in this area will focus on interpretive breakpoints, the extent of data in the prescribing information, ensuring that multiple agents can be progressed, and the challenge of the antibiotic business model.

Keywords: regulatory framework; antibacterial drug development; antibacterial resistance


UNFORTUNATELY, NO AMOUNT OF ANTIBIOTICS WILL GET RID OF YOUR COLD.
NHS


TAKE CARE, NOT ANTIBIOTICS
Stop Ignoring Ecosystem Effects of Antimicrobial Agents

Schuetz et al. BMC Medicine 2011, 9:107
http://www.biomedcentral.com/1741-7015/9/107

BMC Medicine

REVIEW Open Access

Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future

Philipp Schuetz[1*], Werner Albrich[2] and Beat Mueller[2]

Abstract

There are a number of limitations to using conventional diagnostic markers for patients with clinical suspicion of infection. As a consequence, unnecessary and prolonged exposure to antimicrobial agents adversely affect patient outcomes, while inappropriate antibiotic therapy increases antibiotic resistance. A growing body of evidence supports the use of procalcitonin (PCT) to improve diagnosis of bacterial infections and to guide antibiotic therapy. For patients with upper and lower respiratory tract infection, post-operative infections and for severe sepsis patients in the intensive care unit, randomized-controlled trials have shown a benefit of using PCT algorithms to guide decisions about initiation and/or discontinuation of antibiotic therapy. For some other types of infections, observational studies have shown promising first results, but further intervention studies are needed before use of PCT in clinical routine can be recommended. The aim of this review is to summarize the current evidence for PCT in different infections and clinical settings, and discuss the reliability of this marker when used with validated diagnostic algorithms.

Cost-Effectiveness of Procalcitonin-Guided Antibiotic Therapy for Outpatient Management of Acute Respiratory Tract Infections in Adults

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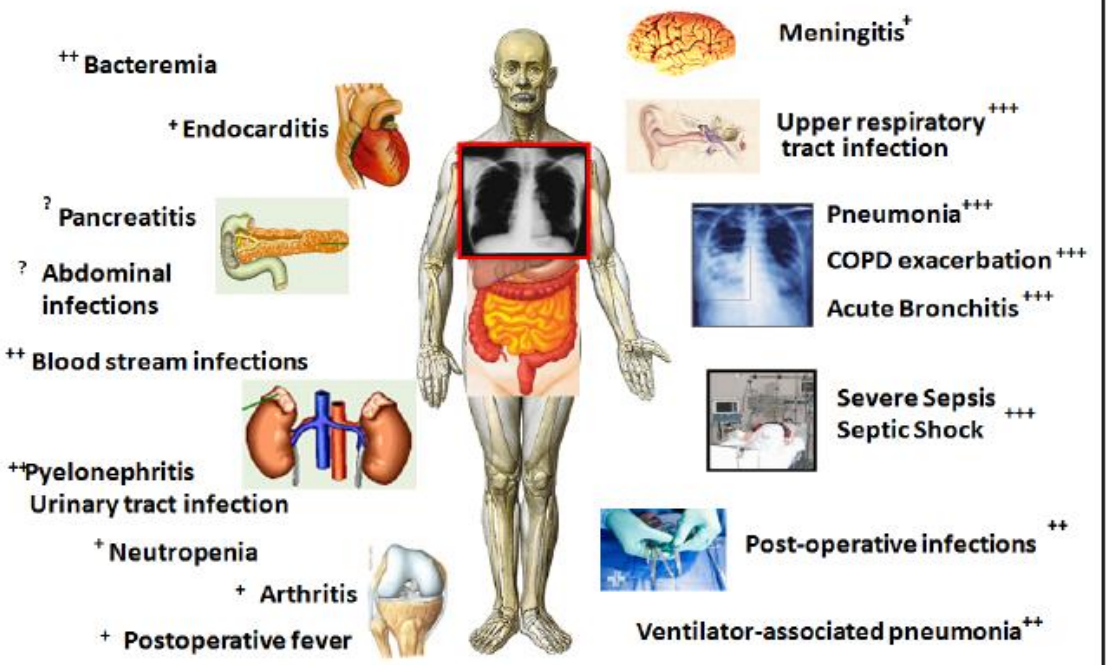
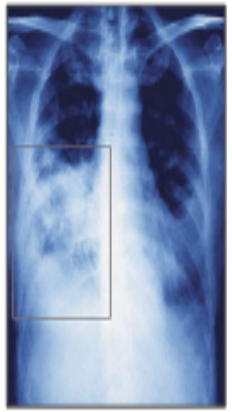


Figure 1 Available evidence concerning PCT in different infections derived from observational and randomized-controlled intervention studies. While for some infections, intervention studies have investigated benefit and harm of using PCT for antibiotic decisions (right side), for other infections only results from diagnostic (observation) studies are available with mixed results (left side). Abbreviations: PCT, procalcitonin. + moderate evidence in favor of PCT; ++ good evidence in favor of PCT; +++ strong evidence in favor of PCT; ? evidence in favor or against the use of PCT still undefined

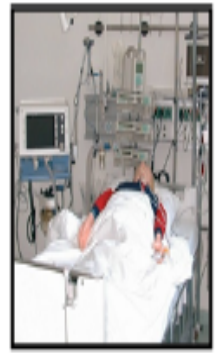
PCT algorithm for patients with respiratory tract infection



PCT (ug/L)	Bacterial Infection?	Recommendation for antibiotics	Important considerations and overruling criteria
10	Very likely	AB YES!	- **Consider the course of PCT** - **If antibiotics are initiated:** - Repeat PCT on days 3, 5, 7; stop antibiotics using the same cut offs - If peak PCT levels are very high, then stop when 80-90% decrease of peak - If PCT remains high, consider treatment failure
2			
1	likely	AB Yes	
0.5			
0.25	unlikely	AB No	- **If Antibiotics are withheld, control PCT after 6-24 hours** - **Initial antibiotics can be considered in case of:** - Respiratory or hemodynamic instability, severest comorbidities, ICU admission - **PCT < 0.1** ug/L: CAP with PSI V or CURB >3, COPD with GOLD IV - **PCT < 0.25** ug/L: CAP with PSI IV & V or CURB >2, COPD with GOLD III & IV
0.1			
	very unlikely	AB NO!	
0.01			

Figure 2 PCT algorithm in patients with respiratory tract infections in the Emergency Department. The clinical algorithm for antibiotic stewardship in patients with respiratory tract infections in the Emergency Department encourages (>0.5 µg/l or >0.25 µg/l) or discourages (<0.1 µg/l or <0.25 µg/l) initiation or continuation of antibiotic therapy more or less based on PCT specific cut-off ranges. Abbreviations: AB, antibiotic; LRTI, lower respiratory tract infection; PCT, procalcitonin; PSI, Pneumonia Severity Score.

PCT algorithm for stopping antibiotics in patients with sepsis in the ICU



PCT (ug/L)	Ongoing infection?	Recommendation for stopping antibiotics	Important considerations
10	Very likely	AB CONTINUE!	- **Consider the course of PCT** - **If antibiotics are continued:** - Daily measurement of PCT; discontinue antibiotics when PCT decreases >80% of the peak level or an absolute PCT value <0.5 µg/l is reached. - If PCT remains high, consider treatment failure
2			
1	likely	AB continue	
0.5			
0.25	unlikely	AB stop	- **Always consider clinical course of patients in addition to PCT levels** - **If Antibiotics are discontinued, close clinical evaluation is recommended**
0.1			
	very unlikely	AB STOP!	
0.01			

Figure 3 PCT algorithm in patients with sepsis in the ICU. In critically ill patients in the ICU, cut-offs are higher and initial empiric antibiotic therapy should be encouraged in all patients with suspicion of sepsis. PCT cut-offs are helpful in the subsequent days after admission to shorten the courses of antibiotic therapy in patients with clinical improvement. Abbreviations: AB, antibiotic; PCT, procalcitonin.

REVIEW ARTICLE

Promising New Assays and Technologies for the Diagnosis and Management of Infectious Diseases

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In the first decade of the 21st century, we have seen the completion of the human genome project and marked progress in the human microbiome project. The vast amount of data generated from these efforts combined with advances in molecular and biomedical technologies have led to the development of a multitude of assays and technologies that may be useful in the diagnosis and management of infectious diseases. Here, we identify several new assays and technologies that have recently come into clinical use or have potential for clinical use in the near future. The scope of this review is broad and includes topics such as the serum marker procalcitonin, gene expression profiling, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS), and nucleic acid aptamers. Principles that underlie each assay or technology, their clinical applications, and potential strengths and limitations are addressed.

Keywords. procalcitonin; gene expression profiling; mass spectrometry; MALDI-TOF MS; sepsis.

JOURNAL OF PROTEOMICS 97 (2014) 69–87

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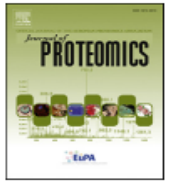

Review

Proteomics boosts translational and clinical microbiology☆,☆☆

F. Del Chierico[a,b], A. Petrucca[a,b,c], P. Vernocchi[a,b,d], G. Bracaglia[a,b], E. Fiscarelli[e], P. Bernaschi[f], M. Muraca[g], A. Urbani[g,h], L. Putignani[a,b,*]

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[c]Department of Diagnostic Science, Sant'Andrea Hospital, Via di Grottarossa 1035, 00185 Rome, Italy
[d]Interdipartimental Centre for Industrial Research-CIRI-AGRIFOOD, Alma Mater Studiorum, University of Bologna, Bologna, Italy
[e]Laboratory Medicine, Bambino Gesù Children's Hospital, IRCCS, Piazza Sant'Onofrio 4, 00165 Rome, Italy
[f]Unit of Microbiology, Bambino Gesù Children's Hospital, IRCCS, Piazza Sant'Onofrio 4, 00165 Rome, Italy
[g]Department of Experimental Medicine and Surgery, University "Tor Vergata", Rome, Italy
[h]IRCCS-Santa Lucia Foundation, Rome, Italy

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ABSTRACT

The application of proteomics to translational and clinical microbiology is one of the most advanced frontiers in the management and control of infectious diseases and in the understanding of complex microbial systems within human fluids and districts. This new approach aims at providing, by dedicated bioinformatic pipelines, a thorough description of pathogen proteomes and their interactions within the context of human host ecosystems, revolutionizing the vision of infectious diseases in biomedicine and approaching new viewpoints in both diagnostic and clinical management of the patient.

Indeed, in the last few years, many laboratories have matured a series of advanced proteomic applications, aiming at providing individual proteome charts of pathogens, with respect to their morph and/or cell life stages, antimicrobial or antimycotic resistance profiling, epidemiological dispersion. Herein, we aim at reviewing the current state-of-the-art on proteomic protocols designed and set-up for translational and diagnostic microbiological purposes, from axenic pathogens' characterization to microbiota ecosystems' full description. The final goal is to describe applications of the most common MALDI-TOF MS platforms to advanced diagnostic issues related to emerging infections, increasing of fastidious bacteria, and generation of patient-tailored phylotypes.

This article is part of a Special Issue entitled: Trends in Microbial Proteomics.

CMR
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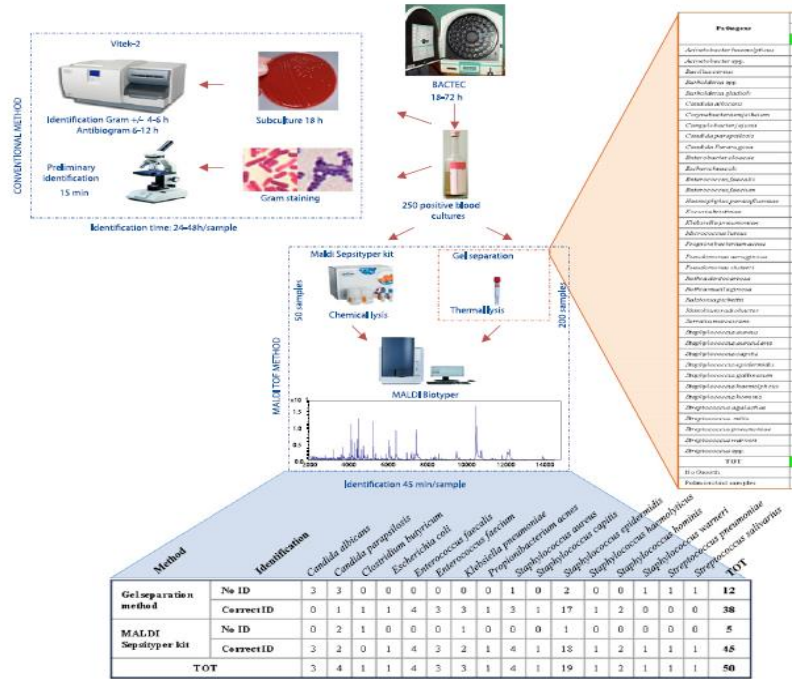
Matrix-Assisted Laser Desorption Ionization–Time of Flight Mass Spectrometry: a Fundamental Shift in the Routine Practice of Clinical Microbiology

Andrew E. Clark,[a] Erin J. Kaleta,[b] Amit Arora,[c] Donna M. Wolk[d,e,f]

Department of Veterinary Science and Microbiology, University of Arizona, Tucson, Arizona, USA[a]; Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA[b]; Department of Surgery, University of Arizona, Tucson, Arizona, USA[c]; Department of Pathology, University of Arizona Medical Center, Tucson, Arizona, USA[d]; The BIDS Institute, University of Arizona, Tucson, Arizona, USA[e]; Geisinger Health Systems, Danville, Pennsylvania, USA[f]



Method	Identification	Candida albicans	Candida parapsilosis	Clostridium butyricum	Escherichia coli	Enterococcus faecalis	Enterococcus faecium	Klebsiella pneumoniae	Propionibacterium acnes	Staphylococcus aureus	Staphylococcus capitis	Staphylococcus epidermidis	Staphylococcus haemolyticus	Staphylococcus hominis	Staphylococcus warneri	Streptococcus pneumoniae	Streptococcus salivarius	TOT
Gel separation method	No ID	3	3	0	0	0	0	0	0	1	0	2	0	0	1	1	1	12
	Correct ID	0	1	1	1	4	3	3	1	3	1	17	1	2	0	0	0	38
MALDI Sepsityper kit	No ID	0	2	1	0	0	0	1	0	0	0	1	0	0	0	0	0	5
	Correct ID	3	2	0	1	4	3	2	1	4	1	18	1	2	1	1	1	45
TOT		3	4	1	1	4	3	3	1	4	1	19	1	2	1	1	1	50

Fig. 6 – MALDI-TOF MS-based workflow for positive blood cultures designed by including both Sepsityper™ and homebrew protocols (*e.g.*, gel Vacutainer). The conventional methods based on Gram staining and biochemical identification are compared with the two fast MALDI-TOF MS-based workflows. In the inset, the tables with ID results for each identified species are reported.

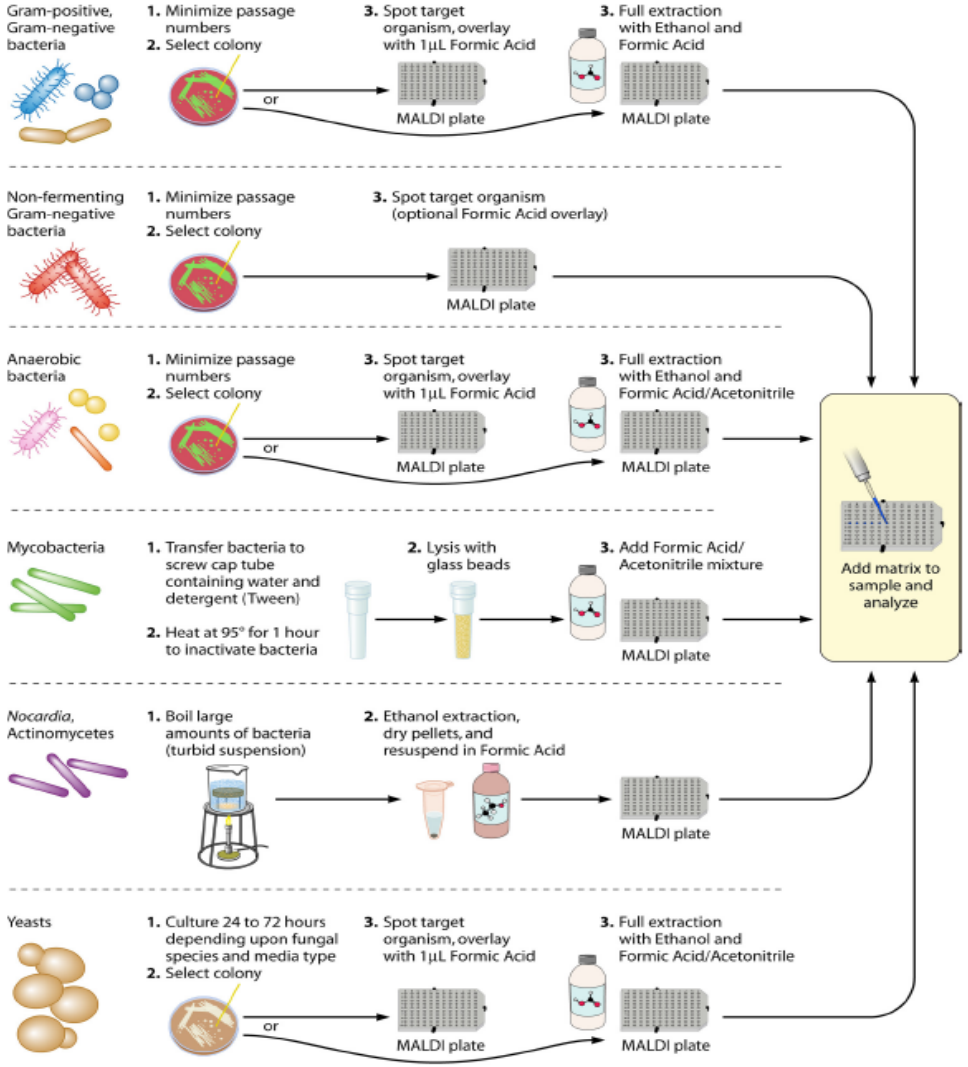


FIG 3 Additional suggestions for MALDI-TOF MS sample preparations for use with different classes of microbes. Different groups of microorganisms vary fundamentally in their cellular composition and architecture. These differences have been demonstrated to affect the quality of spectra generated during MS experiments and, thus, the accuracy of MALDI-TOF MS-derived identifications. As such, investigators from a number of independent studies have evaluated different methods for sample preparation of different groups of microorganisms, ranging directly from intact-cell to full-protein-extraction-based methodologies. Results from these studies are summarized here. Proper biological safety precautions should be followed with respect to dangerous members of these groups of organisms.

Journal of Antimicrobial Chemotherapy (2005) **55**, 6–9
doi:10.1093/jac/dkh482
Advance Access publication 5 November 2004

JAC

Antibiotic cycling or rotation: a systematic review of the evidence of efficacy

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Of the interventions designed to reduce antibiotic resistance rates in hospitals, one that is currently attracting considerable interest, particularly in the intensive care unit setting, is antibiotic cycling or rotation. Cycling is the scheduled rotation of one class of antibiotics with one or more different classes exhibiting comparable spectra of activity; in order to fulfil the definition, the cycle must be repeated. Following a search of the literature we identified 11 articles in which the authors claimed to have evaluated the efficacy of this intervention. Only four were suitable for review, but, owing to multiple methodological flaws and a lack of standardization, the results of these studies do not permit reliable conclusions regarding the efficacy of cycling. Further studies are therefore required in order to resolve this question. However, before such studies can be undertaken, there are a great many issues relating to cycling which must be addressed. For the time being, we advise against the routine implementation of this measure as a means of reducing antibiotic resistance rates.

Keywords: antibiotic resistance, interventions to optimize antibiotic prescribing, intensive care units

OPEN ACCESS Freely available online

PLOS | PATHOGENS

Cycling Empirical Antibiotic Therapy in Hospitals: Meta-Analysis and Models

Pia Abel zur Wiesch[1,2]*, Roger Kouyos[1,3]*, Sören Abel[4], Wolfgang Viechtbauer[5], Sebastian Bonhoeffer[1]

1 Institute of Integrative Biology, ETH Zurich, Zurich, Switzerland, **2** Division of Global Health Equity, Brigham and Women's Hospital/Harvard Medical School, Boston, Massachusetts, United States of America, **3** Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zurich, Switzerland, **4** Division of Infectious Diseases, Brigham and Women's Hospital/Harvard Medical School, Boston, Massachusetts, United States of America, **5** Department of Psychiatry and Psychology, School for Mental Health and Neuroscience, Faculty of Health, Medicine, and Life Sciences, Maastricht University, Maastricht, The Netherlands

Abstract

The rise of resistance together with the shortage of new broad-spectrum antibiotics underlines the urgency of optimizing the use of available drugs to minimize disease burden. Theoretical studies suggest that coordinating empirical usage of antibiotics in a hospital ward can contain the spread of resistance. However, theoretical and clinical studies came to different conclusions regarding the usefulness of rotating first-line therapy (cycling). Here, we performed a quantitative pathogen-specific meta-analysis of clinical studies comparing cycling to standard practice. We searched PubMed and Google Scholar and identified 46 clinical studies addressing the effect of cycling on nosocomial infections, of which 11 met our selection criteria. We employed a method for multivariate meta-analysis using incidence rates as endpoints and find that cycling reduced the incidence rate/1000 patient days of both total infections by 4.95 [9.43–0.48] and resistant infections by 7.2 [14.00–0.44]. This positive effect was observed in most pathogens despite a large variance between individual species. Our findings remain robust in uni- and multivariate metaregressions. We used theoretical models that reflect various infections and hospital settings to compare cycling to random assignment to different drugs (mixing). We make the realistic assumption that therapy is changed when first line treatment is ineffective, which we call "adjustable cycling/mixing". In concordance with earlier theoretical studies, we find that in strict regimens, cycling is detrimental. However, in adjustable regimens single resistance is suppressed and cycling is successful in most settings. Both a meta-regression and our theoretical model indicate that "adjustable cycling" is especially useful to suppress emergence of multiple resistance. While our model predicts that cycling periods of one month perform well, we expect that too long cycling periods are detrimental. Our results suggest that "adjustable cycling" suppresses multiple resistance and warrants further investigations that allow comparing various diseases and hospital settings.

UMA PROPOSTA de PLANO p/ o CHS

HOSPITAL DE SÃO BERNARDO S.A.

COMISSÃO CONTROLO INFECÇÃO

MANUAL DE RECOMENDAÇÕES DE BOAS PRÁTICAS NO CONTROLO DA INFECÇÃO NOSOCOMIAL

Setúbal
2000 - 2001

Centro Hospitalar de Setúbal, E.P.E. Hospital de São Bernardo Hospital Ortopédico Sant'Iago do Outão	*Controlo da Tuberculose incluindo Tuberculose Multi-Resistente*	Data de entrada em vigor:	04/04/2015
		Versão 04	08/01/2014
		Próxima revisão:	08/01/2017
		Cód. Documento:	CIF.04

Centro Hospitalar de Setúbal, E.P.E. Hospital de São Bernardo Hospital Ortopédico Sant'Iago do Outão	*Norma de Orientação Clínica (NOC)* **Terapêutica das Infecções Fúngicas por Candida Species na UCI**	Data da publicação:	08/06/2011
		Revisão A	15/06/2010
		Próxima revisão:	15/06/2013
		Cód. Documento:	NOC.UCIN.01

Centro Hospitalar de Setúbal, E.P.E. Hospital de São Bernardo Hospital Ortopédico Sant'Iago do Outão	*Procedimento para Prevenção da Infeção do Local Cirúrgico*	Data de entrada em vigor:	28/11/2012
		Versão 02	27/02/2013
		Próxima revisão:	27/02/2016
		Cód. Documento:	CIF.21

Centro Hospitalar de Setúbal, E.P.E. Hospital de São Bernardo Hospital Ortopédico Sant'Iago do Outão	*Norma de Orientação Clínica (NOC)* **Antibioterapia em Perfusão Endovenosa Contínua**	Data da publicação:	04/03/2009
		Revisão A	23/01/2008
		Próxima revisão:	23/01/2011
		Cód. Documento:	NOC.CHS.04

Centro Hospitalar de Setúbal, E.P.E. Hospital de São Bernardo Hospital Ortopédico Sant'Iago do Outão	*Norma de Orientação Clínica (NOC)* **Abordagem da Neutropénia Febril**	Data da publicação:	30/03/2011
		Revisão A	15/03/2011
		Próxima revisão:	15/03/2014
		Cód. Documento:	NOC.CHS.20

Centro Hospitalar de Setúbal, E.P.E. Hospital de São Bernardo Hospital Ortopédico Sant'Iago do Outão	*Norma de Orientação Clínica (NOC)* **Abordagem terapêutica de infecção MRSA**	Data da publicação:	16/11/2011
		Revisão A	27/10 /2011
		Próxima revisão:	27/10 /2014
		Cód. Documento:	NOC.CHS.30

Centro Hospitalar de Setúbal, E.P.E. Hospital de São Bernardo Hospital Ortopédico Sant'Iago do Outão	*Norma de Orientação Clínica (NOC)* **Norma de Orientação Clínica para Diagnóstico, Terapêutica e Quimioprofilaxia da Gripe Sazonal**	Data da publicação:	19/11/2014
		Versão 01	24/01/2014
		Próxima revisão:	24/01/2017
		Cód. Documento:	NOC.CHS.50

Centro Hospitalar de Setúbal, E.P.E. Hospital de São Bernardo Hospital Ortopédico Sant'Iago do Outão	*Norma de Orientação Clínica (NOC)* **Profilaxia Antibiótica em Cirurgia Geral**	Data da publicação:	15/02/2012
		Revisão A	30/12/2011
		Próxima revisão:	30/12/2014
		Cód. Documento:	NOC.CIGE.02

Centro Hospitalar de Setúbal, E.P.E. Hospital de São Bernardo Hospital Ortopédico Sant'Iago do Outão	*Norma de Orientação Clínica (NOC)* **Pneumonia Nosocomial** ***Serviço de Medicina Interna***	Data da publicação:	27/10/2009
		Revisão A	04/03/2009
		Próxima revisão:	04/03/2012
		Cód. Documento:	NOC.MEDI.02

Centro Hospitalar de Setúbal, E.P.E. Hospital de São Bernardo Hospital Ortopédico Santiago do Outão	REGULAMENTO DA COMISSÃO DE CONTROLO DE INFECÇÃO	Data de entrada em vigor:	09/08/2006
		Revisão C	02/06/2011
		Próxima revisão:	02/06/2014
		Cód. Documento:	REG.CCIF

Centro Hospitalar de Setúbal, E.P.E. Hospital de São Bernardo Hospital Ortopédico Santiago do Outão	Política de Controlo da Infecção	Data de entrada em vigor	10/10/06
		Revisão C	02/06/2011
		Próxima revisão:	02/06/2014
		Cód. Documento	CIF

Centro Hospitalar de Setúbal, E.P.E.

Comissão de Controlo de Infeção

Relatório

Inquérito de Prevalência de Infeção HSB - 2012

Janeiro 2013

Centro Hospitalar de Setúbal, E.P.E.
Hospital de São Bernardo
Hospital Ortopédico Santiago do Outão

Plano de Auditorias CCIPRA 2014/2015

Denominação	Objectivos	Calendarização por Serviços			
		2014		2015	
		1º Semestre	2º semestre	1º Semestre	2º semestre
Auditoria às Estruturas de Higienização das Mãos - CIF.14 Auditoria às Práticas de Higienização do Ambiente - CIF.01; CIF.09 Controlo Infeciosa na Rouparia - CIF.16	1. Identificar o modo como estão implementados os procedimentos existentes no Manual, relativos a estas áreas. 2. Avaliar o cumprimento das práticas profissionais para as áreas Práticas. 3. Detectar problemas e propor soluções.	Cardiologia Pediatria UCIN Puerpério Especialidades médicas Urgência Geral Urgência Pediátrica BO Central Ortopedia I Ortopedia II UCM	----	Gastro UCI Urgência Obstétrica e Ginecológica BO Partos Unidade de Esterilização Consultas Externas UDA Hospitais de Dia Infeciologia/ Pneumologia Medicina Cirurgia Geral Especialidades Cirúrgicas	----
PSCI Conhecimento		CHS	----	CHS	----
PSCI Cumprimento					
Acondicionamento Dispositivos Médicos Contaminados e Esterilizados		----	CHS	----	CHS
Auditoria à Triagem de Resíduos Hospitalares - GHE.02		CHS	----	CHS	----

O que foi feito desde o início de funções

- Reuniões
  - c/ a Comissão cessante
  - c/ a Enf.ª que vai permanecer (Enf.ª Felisbela Barroso)
  - c/ as Diretoras da Patologia Clínica (Microbiologia) e Farmácia
  - c/ os Diretores dos Serviços de Medicina Interna, Ortopedia e Cirurgia Geral
  - c/ a Diretora do BO
- Pasta de Documentos
  - Legislação
  - Normas Institucionais
  - Normas da DGS
  - Curso da DGS
  - Documentos e *"Guidelines"* de outras Organizações Nacionais e Internacionais
    - INSA, ECDC, CDC, NHS, NICE, COCHRANE, etc

Próximas iniciativas I

- Constituição de uma Comissão I
  - Elementos Executivos (c/ a concordância dos Diretores de S.)
    - Coordenador
      - (Proporei a Dr.ª Catarina Gonçalves)
    - Outros Elementos
      - Microbiologia e Farmácia
      - 1 Enfermeira
      - 1 Médico de: UCI, Medicina Interna, Cirurgia Geral e Ortopedia
- Constituição de uma Comissão II
  - Elementos consultivos (a serem indicados p/ Serviços e p/ CA)
    - Comissão de Farmácia
    - Bloco Operatório
    - Imunohematerapia
    - Medicina Ocupacional
    - Esterilização
    - Dietista
    - Administrador Hospitalar (SIEs, Rouparia, Higiene e Limpeza, Obras, Compras)

Próximas iniciativas II

- Delegados da Comissão (a serem indicados p/ Serviços c/ a concordância do Coordenador) de todos os Serviços c/ Internamento
  - 1 Médico
  - 1 Enfermeiro
- Elaboração / Atualização de
  - Organograma funcional
  - Regulamento interno
  - Plano de Ação
  - Plano de Auditorias
  - Políticas
  - Procedimentos
  - NOCs

Delimitação de Funções

- Membro da Comissão
  - Executivo
  - Consultivo
- Delegado
  - Médico
  - Enfermeiro
- Profissional
  - Médico
  - Enfermeiro

- Assegurar
  - Vigilância epidemiológica
    - Relatórios anual
  - Monitorizar Consumos de ABs
    - Relatório anual
  - Representação Externa
    - DGS, INSA, etc.
  - Formação Interna
    - Prescrição AB

O que é ainda fundamental (CA)

- Recursos Humanos
  - 1 Enfermeiro
  - 1 Farmacêutico
  - 1 Microbiologista
- Recursos Materiais
  - Laboratório de Microbiologia
    - Instalações
    - Equipamento
  - Programa informático
    - Vigilância epidemiológica
    - Consumo de ABs
    - Alertas clínicos (Alarmística)

Earlier microbiological diagnosis recent technological advances

- **MALDI-TOF** (matrix assisted laser desorption ionization time-of-flight mass spectometry) reduce identification time to 4 hours once blood cultures have become positive

- Change lab routine to maximize benefit from MADI-TOF, namely timetables

Leggieri N et al. Curr Opin Infect Dis 2010; 23: 311-9
Mancini N et al. Clin Microbiol Ver 2010; 23: 235-51

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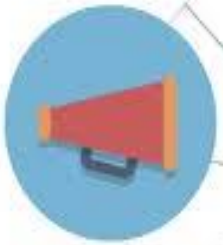
monitorização e ALARMÍSTICA



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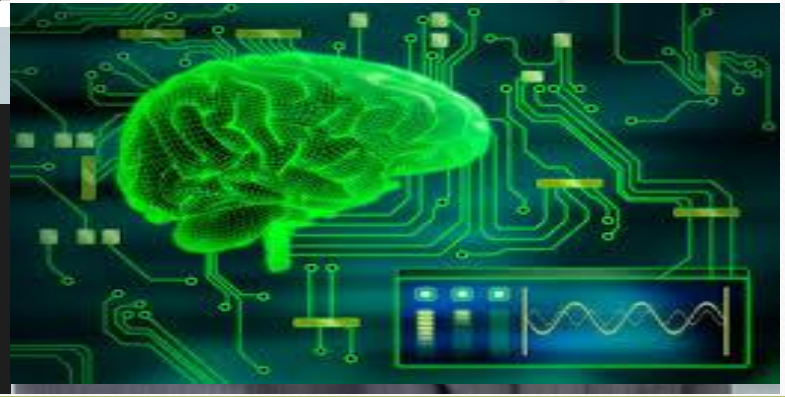
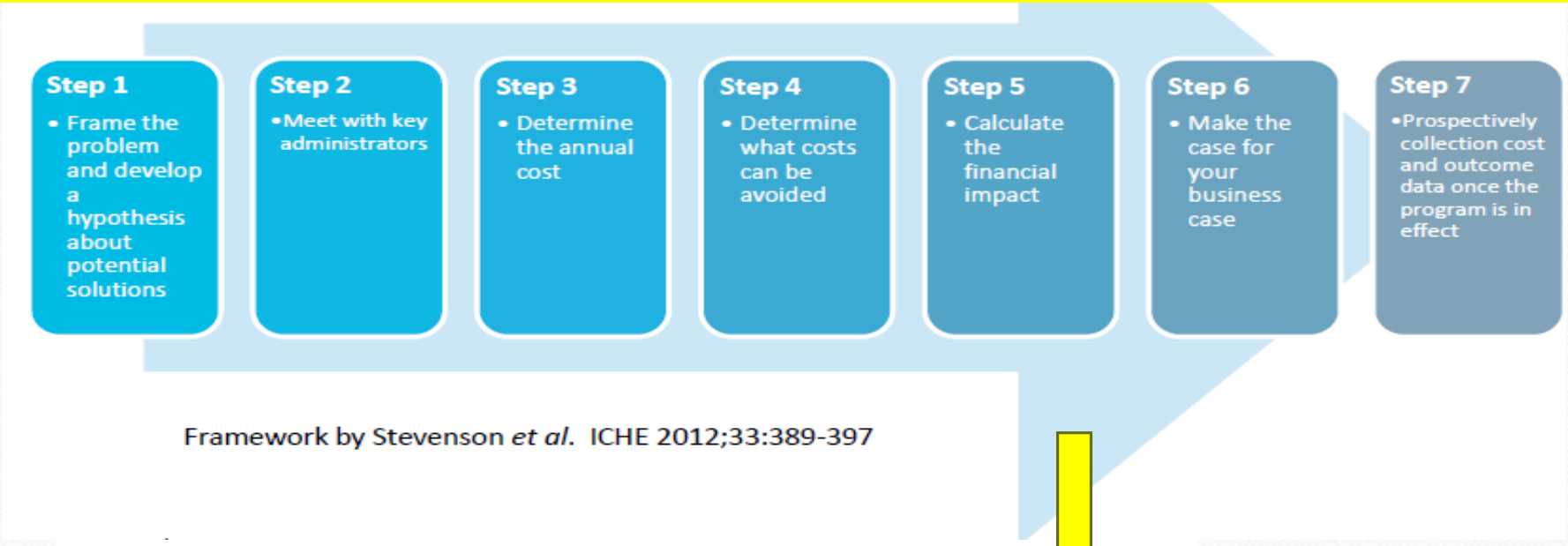
H. S. João, best Big Data Business Intelligence and Analytics Solution of the Year



How to Make a Hospital Business Case for an ASP

Cost efficciency associated with ASP is not the primary goal but it is an useful argument



Framework by Stevenson *et al.* ICHE 2012;33:389-397

DGS desde 1899 Direção-Geral da Saúde

CONCLUSÕES


HEALTH
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1924
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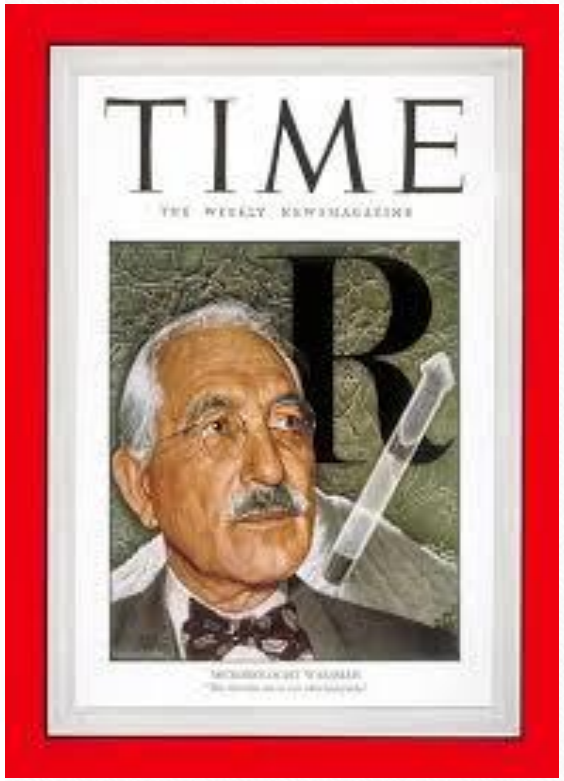
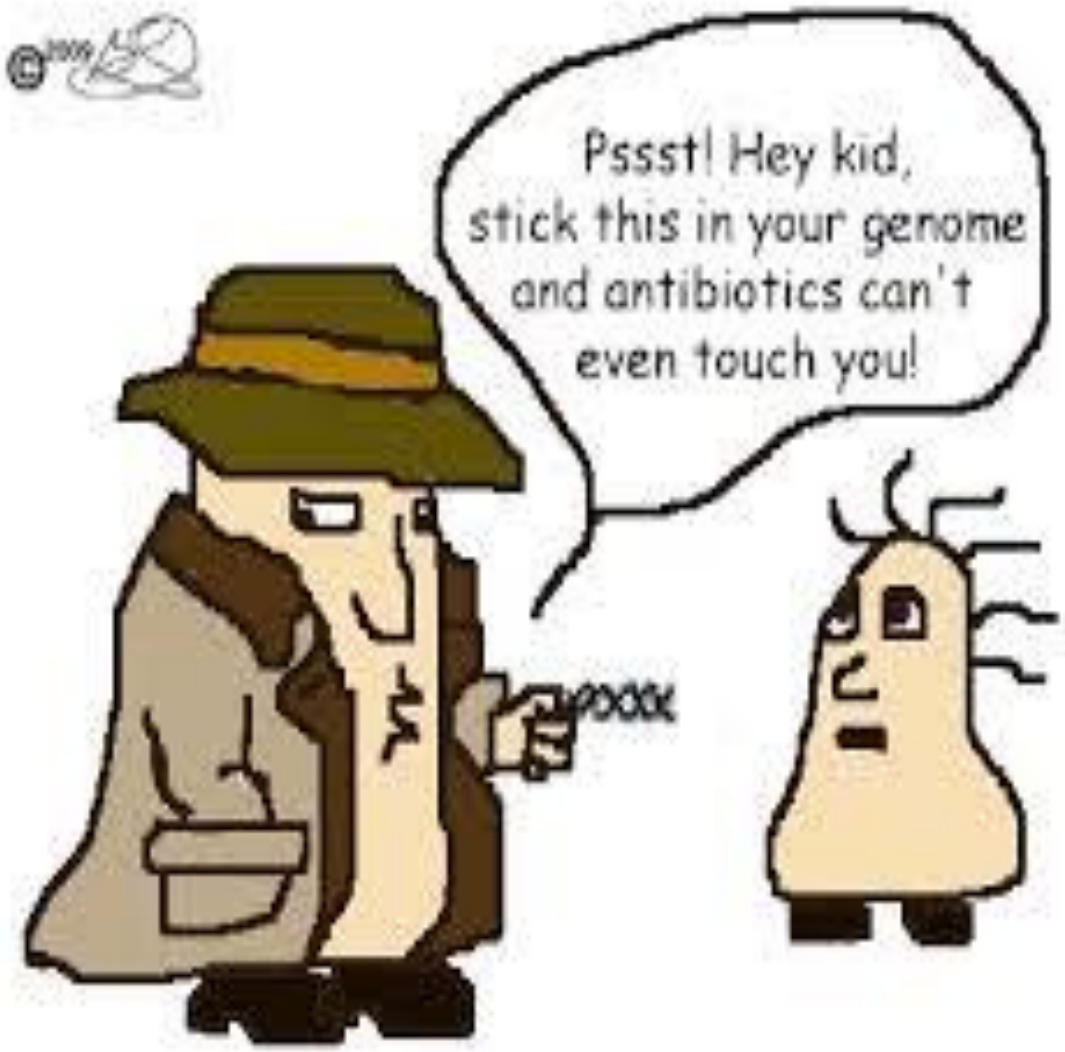
Christmas Seals
Fight Tuberculosis


NDC 39822-0706-1
LATEX FREE STOPPER
Streptomycin for Injection USP
1 gram*/ vial
FOR INTRAMUSCULAR USE
℞ only
X-GEN PHARMACEUTICALS INC
*This vial contains Sterile Streptomycin Sulfate USP equivalent to 1 gram Streptomycin.
See package insert for reconstitution instructions.
USUAL DOSAGE CONSULT PACKAGE INSERT
STORE DRY POWDER AT CONTROLLED ROOM TEMPERATURE 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].
Approx. Conc. mg/mL
Volume (mL) to be added
200 4.2
250 3.2
400 1.8
Sterile reconstituted solutions should be protected from light and may be stored at controlled room temperature up to 7 days.
Protect from light. Retain in carton until time of use.
Manufactured for:
X-GEN Pharmaceuticals Inc
Big Flats, NY 14814
Made In USA
STRP-VL-00
Non Varnish Area


TIME
THE WEEKLY NEWSMAGAZINE
℞


Pssst! Hey kid, stick this in your genome and antibiotics can't even touch you!


OVERUSE OF LIVESTOCK ANTIBIOTICS
DRUG-RESISTANT BACTERIA

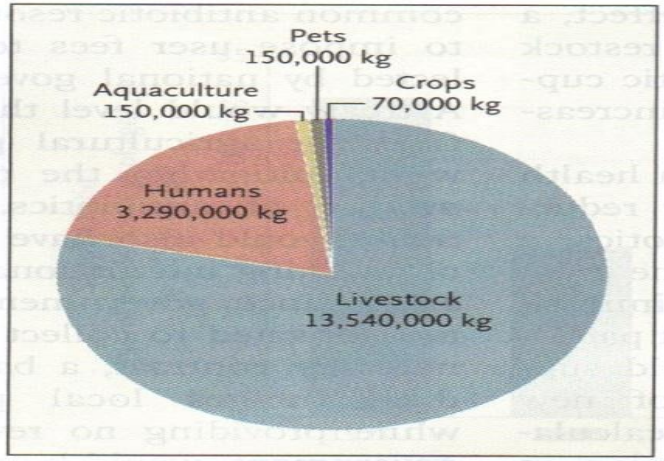
The NEW ENGLAND JOURNAL of MEDICINE

VOL. 369 NO. 26

ESTABLISHED IN 1812 DECEMBER 26, 2013 NEJM.ORG

Preserving Antibiotics, Rationally

Aidan Hollis, Ph.D., and Ziana Ahmed, B.A.Sc.



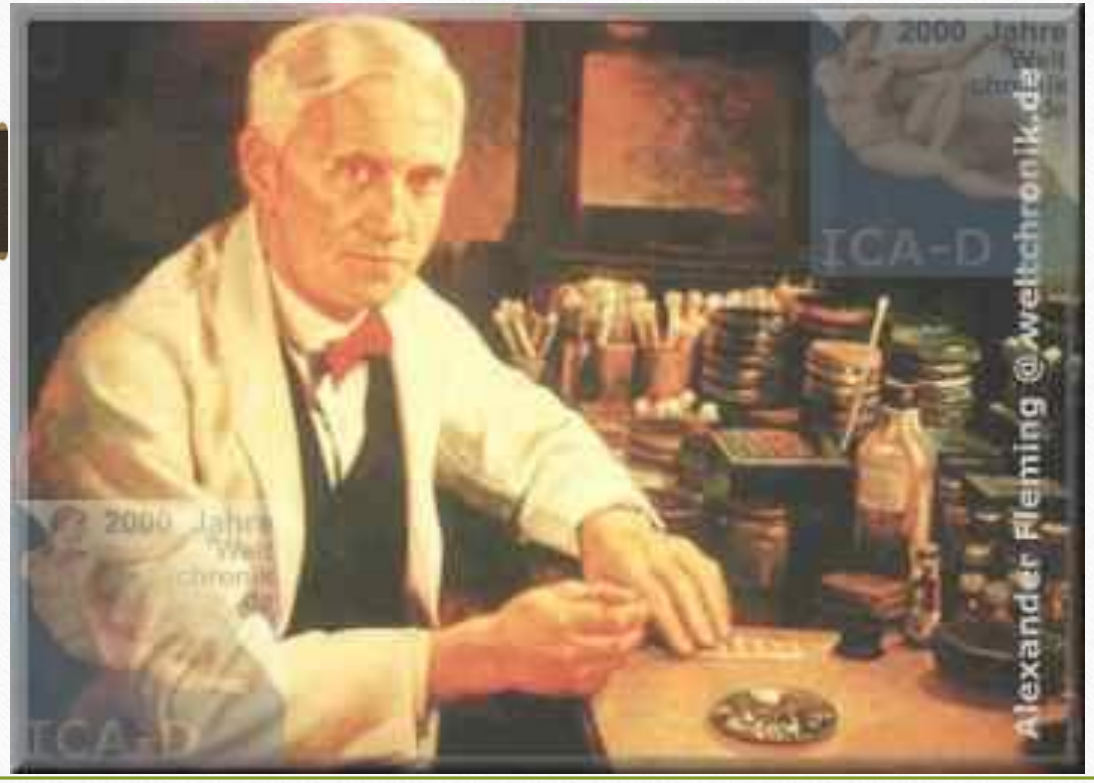
Estimated Annual Antibiotic Use in the United States.
Data are shown as approximate numbers of kilograms of antibiotics used per year.

A Commercial Pig-Farming Operation.
Antibiotics are fed to pigs to speed up growth and increase the efficiency of their digestion.

O sábio aviso de quem sabe…

- *"Existe claramente a necessidade de elevar esta problemática ao nível da decisão política porque constitui um problema económico e social e não só estritamente de saúde. Embora o compromisso dos políticos varie de região, deve existir um consenso global com uma abrangência planetária. Temos uma imperiosa necessidade de ter acesso não só à inovação tecnológica (nos âmbitos da prevenção, diagnóstico e tratamento), mas igualmente de inovação nos modelos de comercialização e fabrico. De preferência, deveríamos poder retroceder ao cenário onde existiam um confortável número de novos fármacos no "pipeline" e, simultaneamente, racionalidade na sua utilização. Para que isso possa acontecer, é vital envolver as faculdades de gestão, os economistas e ainda outros profissionais"*

… e a profetização de quem inventou!



- ***"Existe o perigo que alguém, por ignorância, possa vir a diminuir as o nº de tomas, a encurtar o tempo de tratamento, ou mesmo a reduzir as doses, expondo os microrganismos a quantidades não letais do antibiótico, e desse modo induzir a sua resistência".***
  (Discurso da cerimónia de atribuição do Prémio Nobel da Medicina, Estocolmo, 1945)

Policies and incentives for promoting innovation in antibiotic research

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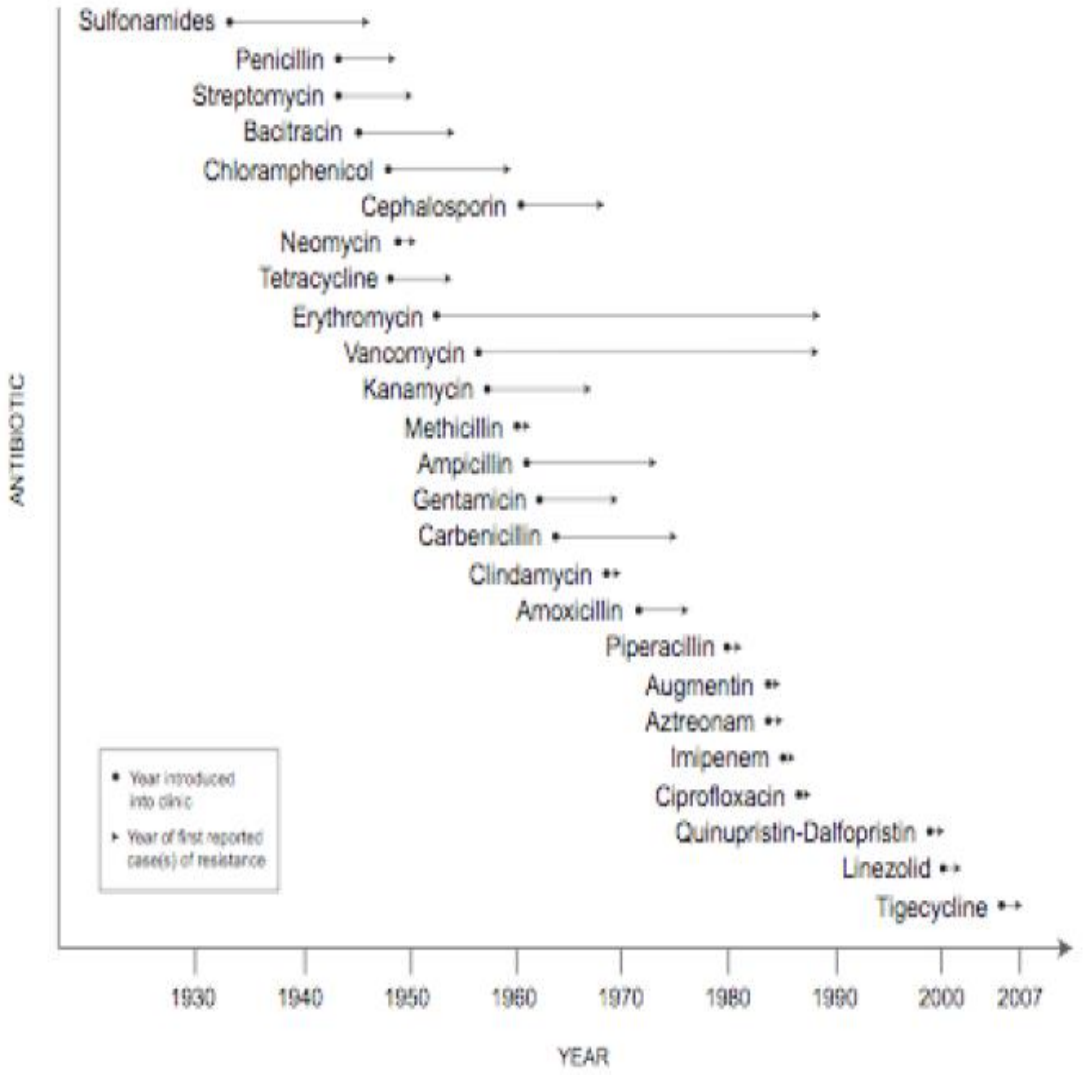
Figure 4.4.1 Timeline of the Rapid Rate of Resistance [38`#202,70].



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The risk/benefit of predicting a post-antibiotic era: Is the alarm working?

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There have been concerns about antimicrobial resistance since the first widespread use of antibiotics in humans. More recently, this concern has grown and become the focus of clinical, scientific, and political activity. In part, the political interest is a consequence of publicizing a bleak picture of a post-antibiotic world. There are, however, dangers in using a discourse of fear. In this article, we discuss whether the evidence base is available to justify such claims and, more importantly, put this in the policy context with which it is used. Many governments now use a risk assessment approach to identify security concerns, based on reasonable worst-case scenarios. There is no doubt that for effective policy-based action to occur, antimicrobial resistance needs to be seen as a national and international security priority, particularly as the major cost of inaction will mostly be felt in the future. We conclude that presenting the evidence in a manner that is used to encourage prioritization of security policy is not only justified, it is essential to drive action in this area.

Keywords: antimicrobial resistance; policy; post-antibiotic era; raising the alarm

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VIEWPOINT

Beginning and possibly the end of the antibiotic era

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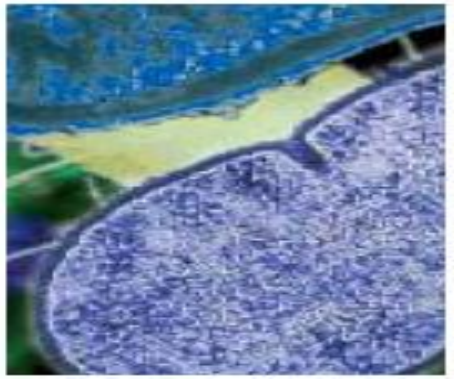
Quand le miracle antibiotique vire au cauchemar

François Trémolières



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A new strategy to fight antimicrobial resistance: the revival of old antibiotics

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The increasing prevalence of hospital and community-acquired infections caused by multidrug-resistant (MDR) bacterial pathogens is limiting the options for effective antibiotic therapy. Moreover, this alarming spread of antimicrobial resistance has not been paralleled by the development of novel antimicrobials. Resistance to the scarce new antibiotics is also emerging. In this context, the rational use of older antibiotics could represent an alternative to the treatment of MDR bacterial pathogens. It would help to optimize the armamentarium of antibiotics in the way to preserve new antibiotics and avoid the prescription of molecules known to favor the spread of resistance (i.e., quinolones). Furthermore, in a global economical perspective, this could represent a useful public health orientation knowing that several of these cheapest "forgotten" antibiotics are not available in many countries. We will review here the successful treatment of MDR bacterial infections with the use of old antibiotics and discuss their place in current practice.

Keywords: multi-drug-resistant pathogens, MRSA and VRE, ESBLs, colistin, fosfomycin, trimethoprim-sulfamethoxazole combination, tetracyclins, MDR-tuberculosis

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'Old' antibiotics for emerging multidrug-resistant bacteria

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Abstract

Purpose of review—Increased emergence of bacterial resistance and the decline in newly developed antibiotics have necessitated the reintroduction of previously abandoned antimicrobial agents active against multidrug-resistant bacteria. Having never been subjected to contemporary drug development procedures, these 'old' antibiotics require redevelopment in order to optimize therapy. This review focuses on colistin as an exemplar of a successful redevelopment process and briefly discusses two other old antibiotics, fusidic acid and fosfomycin.

Recent findings—Redevelopment of colistin led to an improved understanding of its chemistry, pharmacokinetics and pharmacodynamics, enabling important steps towards optimizing its clinical use in different patient populations. A scientifically based dosing algorithm was developed for critically ill patients, including those with renal impairment. As nephrotoxicity is a dose-limiting adverse event of colistin, rational combination therapy with other antibiotics needs to be investigated.

Summary—The example of colistin demonstrated that state-of-the-art analytical, microbiological and pharmacokinetic/pharmacodynamic methods can facilitate optimized use of 'old' antibiotics in the clinic. Similar methods are now being applied to fosfomycin and fusidic acid in order to optimize therapy. To improve and preserve the usefulness of these antibiotics rational approaches for redevelopment need to be followed.

Keywords:
colistin, fosfomycin, fusidic acid; pharmacodynamics, pharmacokinetics

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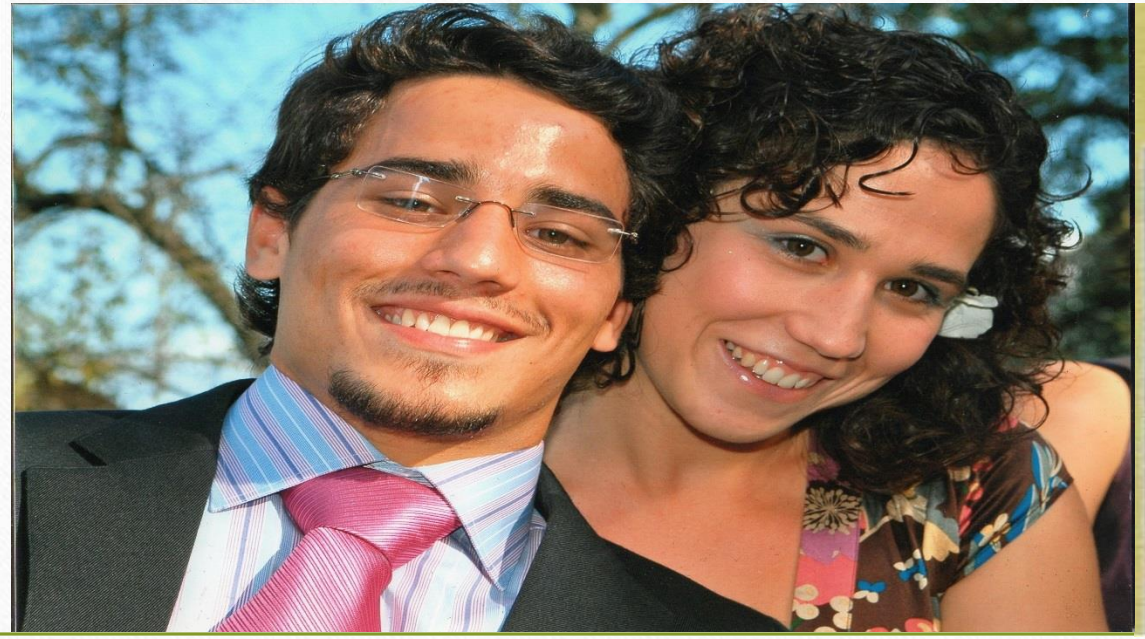
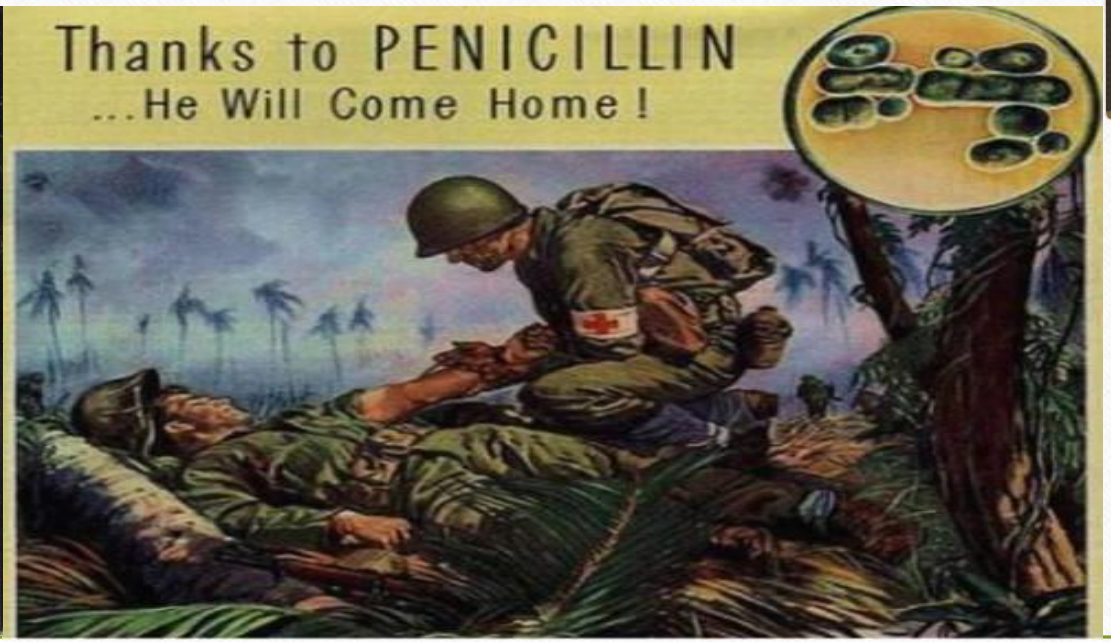
M. Liberdade / M. Responsabilidade



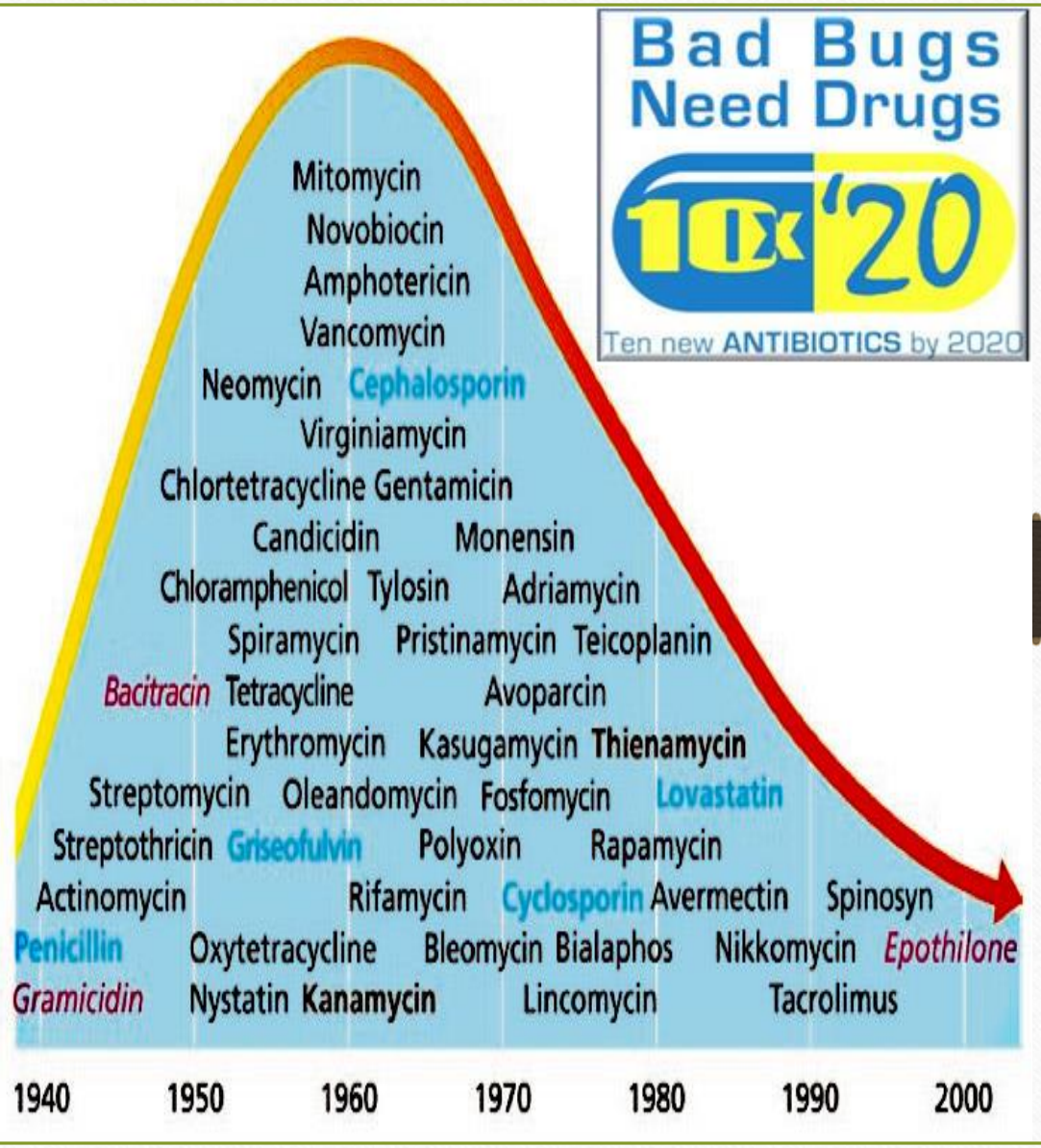
M. Disponibilidade / M. Adequação



Conclusions

Education is not enough….

- Create an antimicrobial stewardship programm
- Make it multidisciplinary and efficient
- Costumize it to your service and centre
- Define a AMS physician champion as the leader and increase the interaction with microbiology
- Faclitate access
- Make it persuasive and pedagogical
- Assure accountability, defining goals and metrics in 3 domains: decrease antibiotic consumption, hospital acquired infections and antimicrobial resistance
- Communicate results to the staff


Bad Bugs Need Drugs
10x'20
Ten new ANTIBIOTICS by 2020
Mitomycin
Novobiocin
Amphotericin
Vancomycin
Neomycin Cephalosporin
Virginiamycin
Chlortetracycline Gentamicin
Candicidin Monensin
Chloramphenicol Tylosin Adriamycin
Spiramycin Pristinamycin Teicoplanin
Bacitracin Tetracycline Avoparcin
Erythromycin Kasugamycin Thienamycin
Streptomycin Oleandomycin Fosfomycin Lovastatin
Streptothricin Griseofulvin Polyoxin Rapamycin
Actinomycin Rifamycin Cyclosporin Avermectin Spinosyn
Penicillin Oxytetracycline Bleomycin Bialaphos Nikkomycin Epothilone
Gramicidin Nystatin Kanamycin Lincomycin Tacrolimus
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