O Desafio das EPC:
Que papel para o PAPA?

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Centro Hospitalar e Universitário São João
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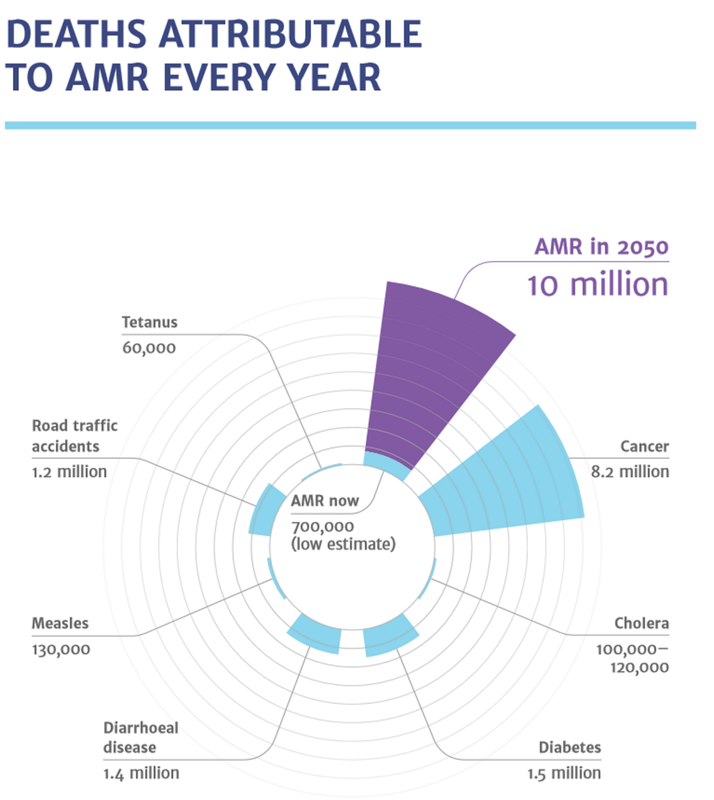
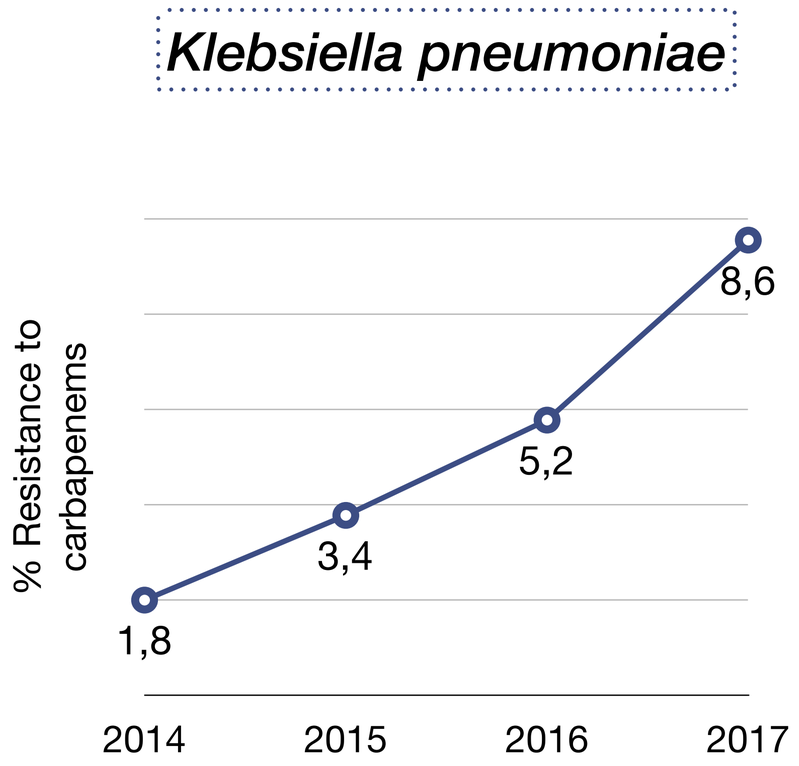
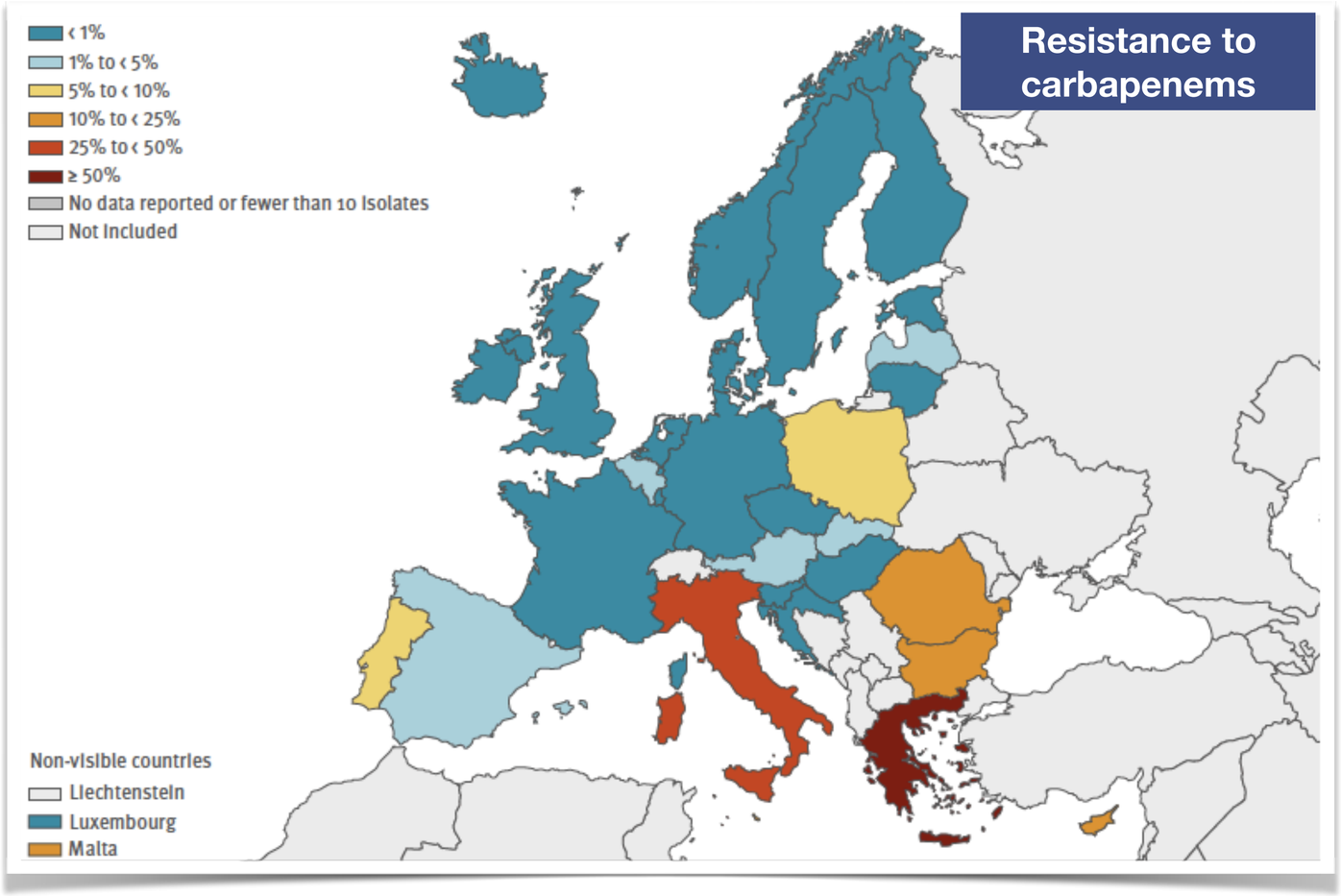
Introdução


00:00:03
By 2050, the death toll could be a staggering
one person every three seconds
if AMR is not tackled now.


DEATHS ATTRIBUTABLE TO AMR EVERY YEAR
AMR in 2050
10 million
Tetanus
60,000
Road traffic accidents
1.2 million
Cancer
8.2 million
AMR now
700,000
(low estimate)
Measles
130,000
Cholera
100,000–120,000
Diarrhoeal disease
1.4 million
Diabetes
1.5 million

Introdução

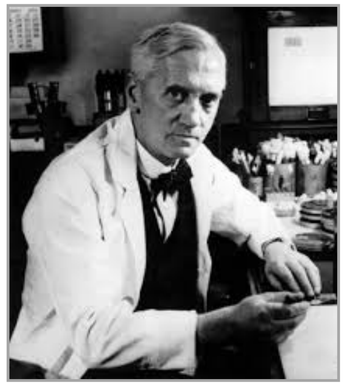




European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe – Annual report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2017. Stockholm: ECDC; 2018.

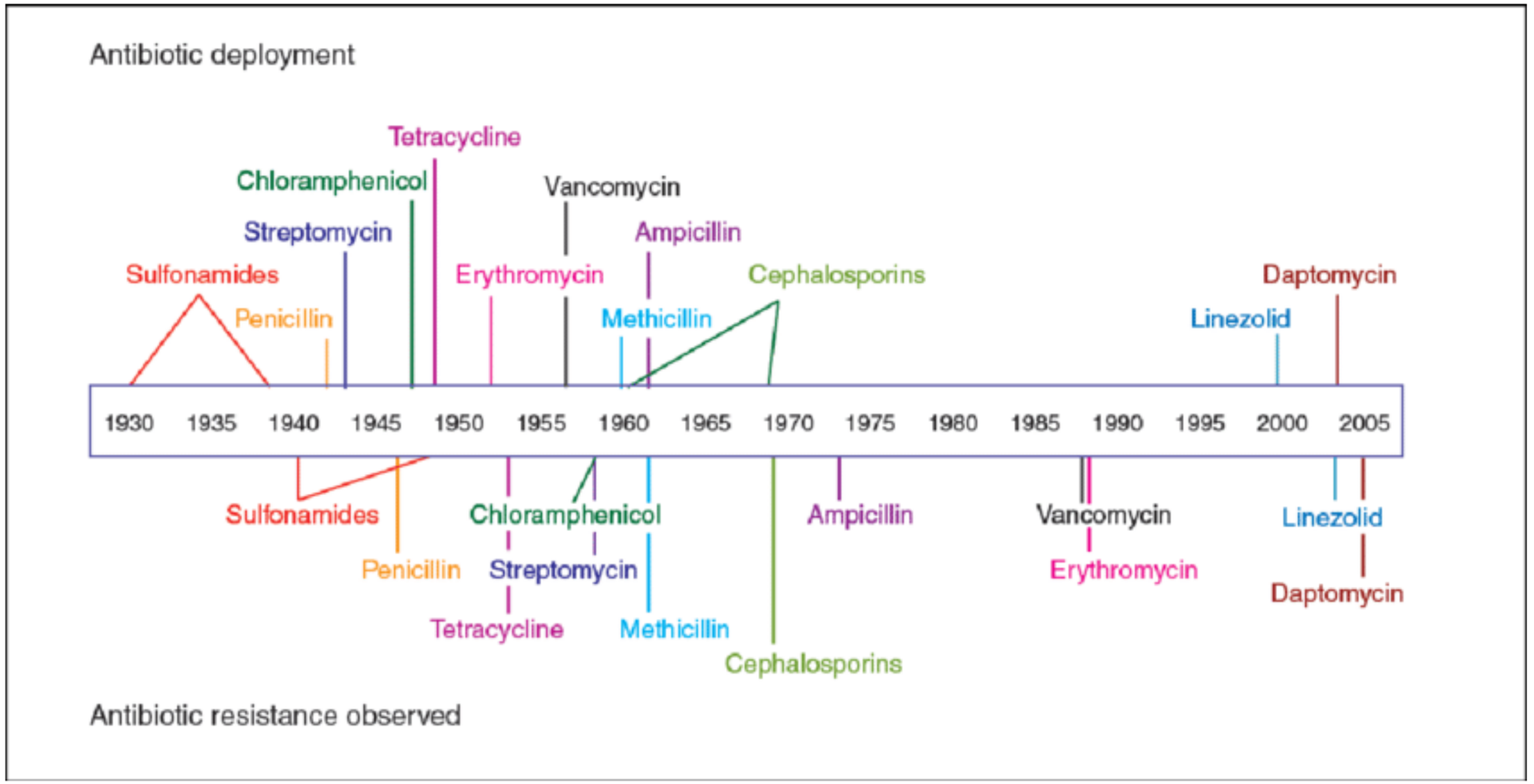
Introdução

"But I would like to sound one note of warning. Penicillin is to all intents and purposes non-poisonous so there is no need to worry about giving an overdose and poisoning the patient. There may be a danger, though, in underdosage. **It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body.**"



Alexander Fleming. Penicillin.
Nobel Lecture, December 11, 1945

Introdução


Antibiotic deployment
Tetracycline
Chloramphenicol
Vancomycin
Streptomycin
Ampicillin
Sulfonamides
Erythromycin
Cephalosporins
Daptomycin
Penicillin
Methicillin
Linezolid
1930
1935
1940
1945
1950
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
Sulfonamides
Chloramphenicol
Ampicillin
Vancomycin
Linezolid
Penicillin
Streptomycin
Erythromycin
Daptomycin
Tetracycline
Methicillin
Cephalosporins
Antibiotic resistance observed

Introdução

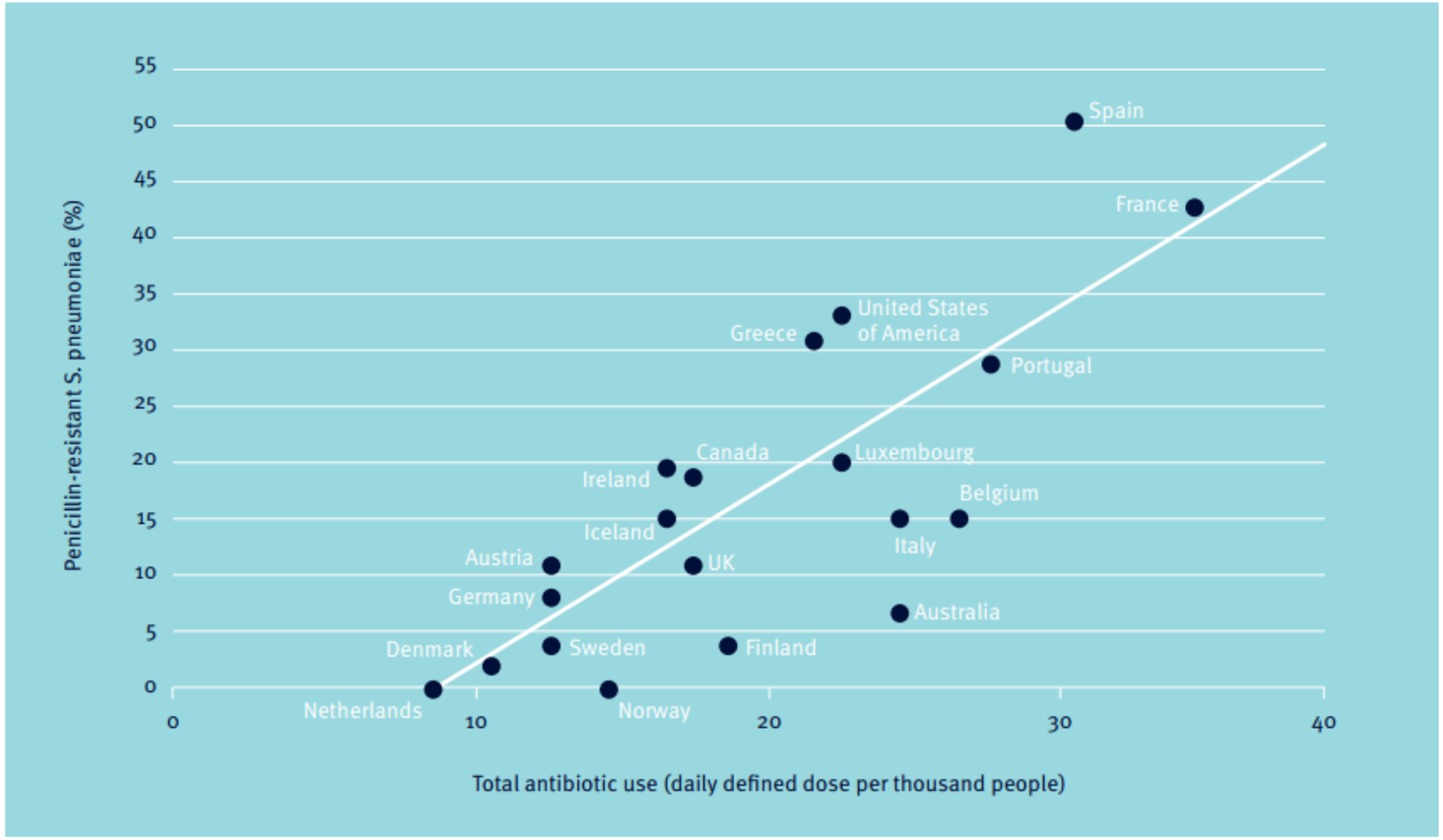


EXHIBIT 6: Correlation between antibiotic use and resistance[55]

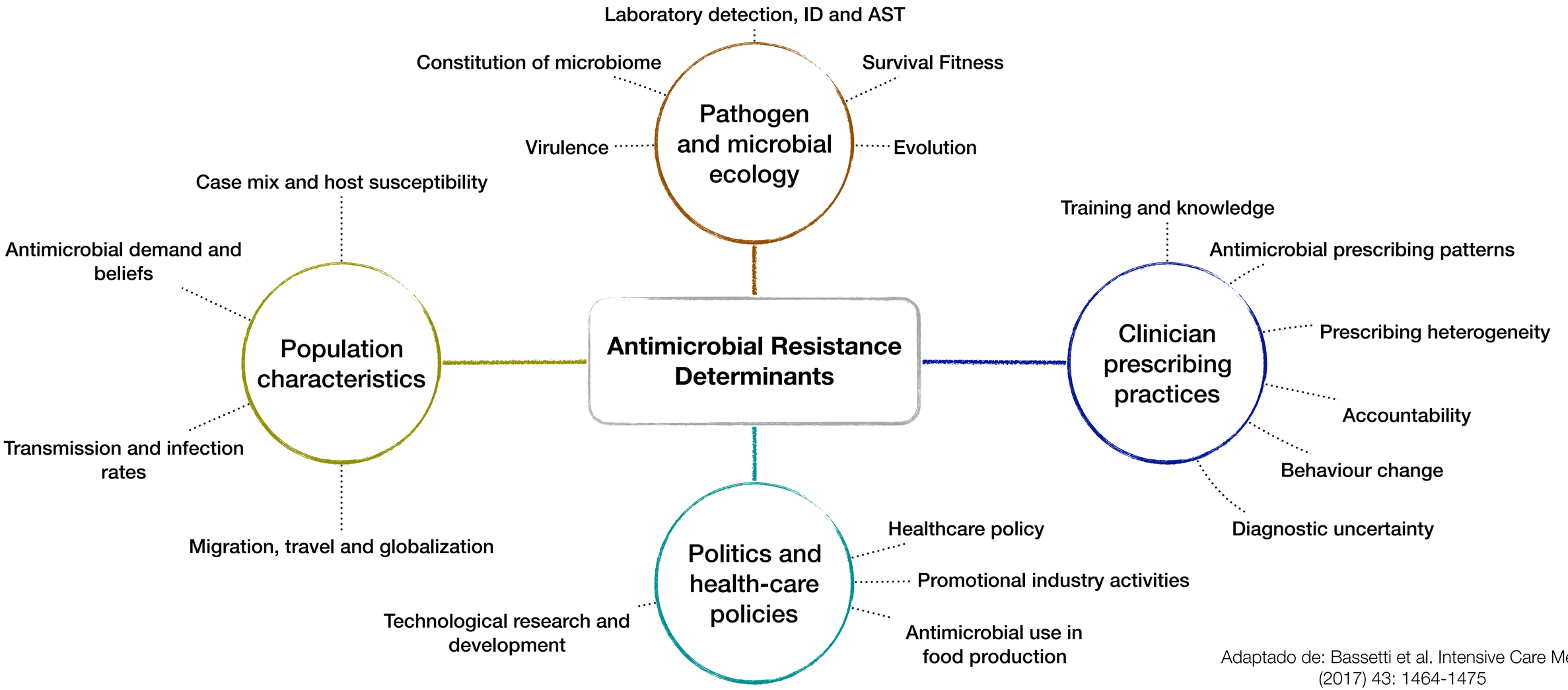
Introdução

Factors that promote antibiotic resistance:

- Bacterial population density in health care facilities
- Inadequate adherence to best infection control practices
- Increase of high risk patient populations
- **Antibiotic overuse in agriculture**
- Global travel and tourism (including medical tourism)
- Poor sanitation and contaminated water systems
- **Improper antibiotic prescribing in human medicine**
- **Overprescription of broad-spectrum antibiotics**
- **Paucity of rapid diagnostic tests to guide proper antibiotic prescribing**
- Lack of approved vaccines for drug resistant pathogens

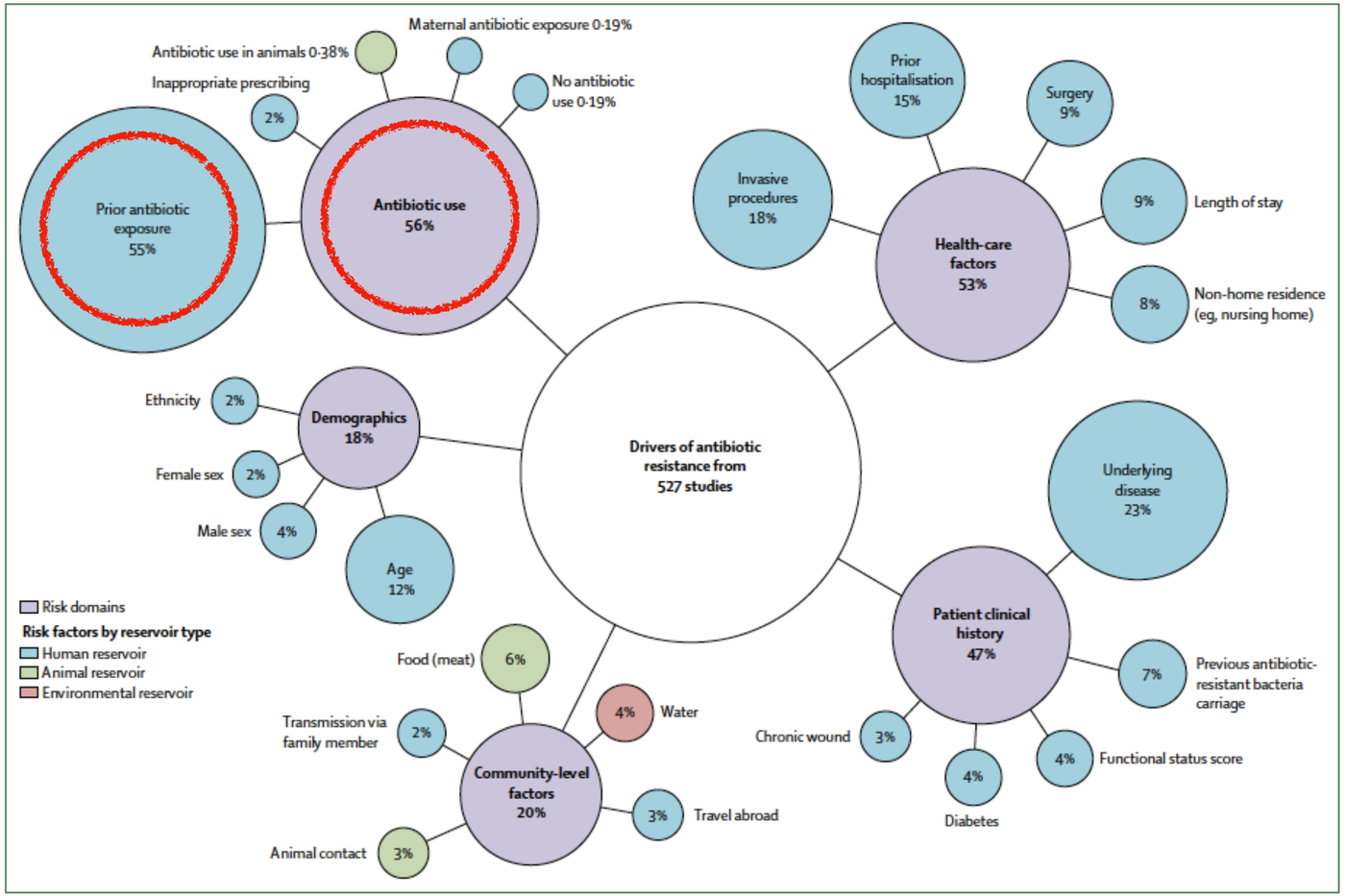
Watkins RR, Bonomo RA. Infect Dis Clin N Am 30 (2016) 313-322

Introdução



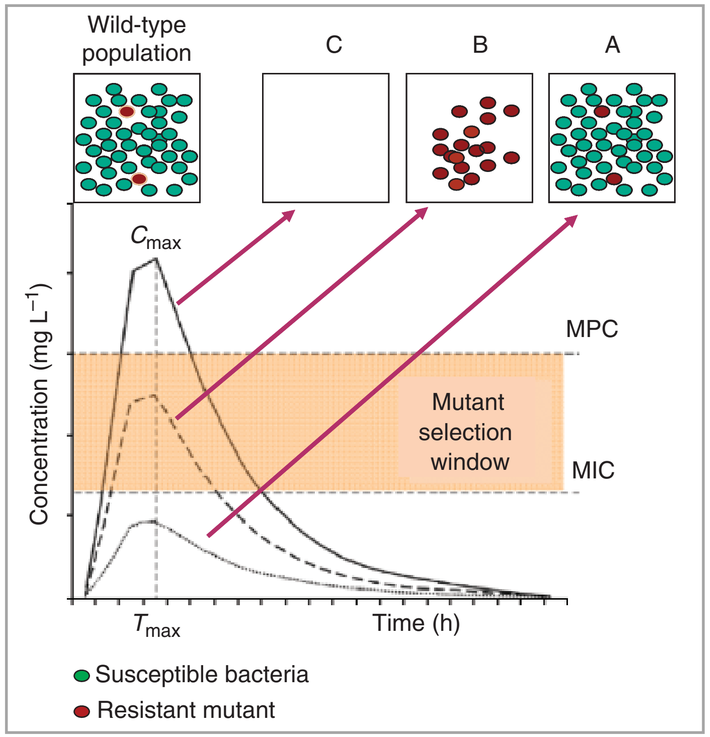
Adaptado de: Bassetti et al. Intensive Care Med (2017) 43: 1464-1475

Introdução



Chatterjee A et al. Lancet Inf Dis 2018 DOI: 10.1016/ S1473-3099(18)30296-2

Introdução



Cantón R, Morosini MI. Emergence and spread of antibiotic resistance following exposure to antibiotics. FEMS Microbiol Rev. 2011, 35: 977-91

Introdução

Does antibiotic restriction prevent resistance?

McGowan JE Jr, Gerding DN.
Emory University School of Medicine, Atlanta, GA, USA.
New Horiz. 1996 Aug;4(3):370-6.

Antimicrobial resistance among some hospital organisms has increased to a stage where it can no longer be tolerated. The need for preventive and corrective measures is urgent. **There is an association between the use of antimicrobial agents and resistance that is likely causal. Alterations in antimicrobial usage have been shown to affect antimicrobial resistance rates**, particularly with use of aminoglycosides. Efforts to improve antimicrobial use through educational efforts alone have been largely ineffective, even when coupled with quality management or clinical guideline aspects. Thus, further work is urgently needed to determine the impact of antimicrobial-use controls. Additional large-scale, well controlled trials of antimicrobial-use regulation employing sophisticated epidemiologic methods, molecular biological organism typing, and precise resistance mechanism analysis will be required to determine the best methods to prevent and control this problem and ensure our optimal **antimicrobial-use "stewardship." Consideration of the long-term effects of antimicrobial selection, dosage, and duration of treatment on resistance development should be a part of every antimicrobial treatment decision.**

Introdução

Table 1. Recommendations (with ratings[a]) for management of antimicrobial agent resistance

Problem	Useful solution	Rating	References
1. High level[b] of carbapenem-resistant *P. aeruginosa*	Reduce[c] fluoroquinolone and/or carbapenem use	BIII	[2,9,35,69–72]
2. High level of fluoroquinolone-resistant *P. aeruginosa*	Reduce fluoroquinolone use and change primary drug to ciprofloxacin	AI	[9,16,67,69,75–78]
3. High level of carbapenem-resistant *A. baumannii*	Reduce carbapenem use and assess for clonal problem	AII	[31–33]
4. High level of β-lactam resistance in *P. aeruginosa*	Reduce extended-spectrum cephalosporin use and replace with piperacillin–tazobactam	BIII	[35]
5. High level of ESBL-producing Enterobacteriaceae	Reduce extended-spectrum cephalosporin use and replace with piperacillin–tazobactam or imipenem–cilastatin or ampicillin–sulbactam	AI	[29,53,55–61]
6. High level of gentamicin–tobramycin resistance in Enterobacteriaceae	Replace with amikacin	AI	[25–27]
7. Concern over presence of VRE	Reduce cephalosporin and fluoroquinolone use and replace with piperacillin–tazobactam	AI	[43–45,62,63]
8. Concern over presence of MRSA	Reduce cephalosporin and fluoroquinolone use, and replace with a β-lactamase inhibitor drug	BIII	[50,53,54,81–84]
9. Concern over presence of *C. difficile*	Reduce cephalosporin, clindamycin and fluoroquinolone use and replace with: (a) piperacillin–tazobactam or (b) ticarcillin–clavulanate	AI and BIII, respectively, for (a) or (b)	[49,64–66,85–87]

L.R. Peterson. Clin Microbiol Infect 2005; 11 (Suppl.5):4-16

Antimicrobial stewardship

- **O que é?**

"…we suggest viewing antimicrobial stewardship as a **strategy, a coherent set of actions which promote using antimicrobials responsibly**. We stress the continuous need for 'responsible use' to be defined and translated into context-specific and time-specific actions."

"Antimicrobial stewardship programes are a set of interventions that aim to ensure the **judicious use of antimicrobials** by preventing their unnecessary use, and by providing targeted and limited therapy in situations where they are wanted… refers to how the **judicious use of antibiotics can maximize both their current effects and the chances of their being available for future generations**"

O.J. Dyar, Clin Microbiol Infect 2017;23:793

Antimicrobial stewardship

- **Que objectivos?**

✓ Melhoria dos outcomes para o tratamento e prevenção de infecção

✓ Minimizar efeitos adversos e toxicidade da terapêutica antimicrobiana

✓ **Minimizar o impacto na resistência e outros efeitos ecológicos adversos (ex: *C. difficile*)**

Nathwani D. Hospital Epidemiology and Infection Control, 4th ed. 2012
Doernberg SB et al. Infect Dis Clin N Am 31 (2017) 513–534

Antimicrobial stewardship

Formulary-related Strategies	Structural/Process Strategies	Clinical Strategies	Prescribing Guidance Strategies	Microbiology-related Strategies
• Formulary automatic substitution/therapeutic interchange policies • Formulary restriction • **Formulary restriction with preauthorization** • Formulary review/streamlining	• **Automatic stop orders** • Checklists • Clinical decision support systems/computerized physician order entry • Drug use evaluation/medication use evaluation • Facilitation of appropriate and timely antimicrobial administration in severe sepsis/septic shock • General antimicrobial order forms • Improved antimicrobial documentation • Scheduled antimicrobial reassessments ("antibiotic time-outs") • Surgical antibiotic prophylaxis optimization • Systematic antibiotic allergy verification	• De-escalation and streamlining • Dose optimization • Identification of inappropriate pathogen/antimicrobial combinations ("bug-drug mismatch") • Preventing treatment of non-infectious conditions • **Prospective audit with intervention and feedback** • Scheduled antimicrobial reassessments ("antibiotic time-outs") • Targeted review of patients with Clostridium difficile infection • **Targeted review of patients with bacteremia/fungemia** • Targeted review of redundant therapy or therapeutic duplication • Therapeutic drug monitoring (with feedback)	• Clinical decision support systems/computerized physician order entry • **Disease-specific treatment guidelines/pathways/algorithms and/or associated order forms** • **Empiric antibiotic prescribing guidelines** • Facilitation of appropriate and timely antimicrobial administration in severe sepsis/septic shock • Intravenous to oral conversion • **Prescriber education**	• **Antibiograms** • Cascading microbiology susceptibility reporting • Improved diagnostics • Promotion of timely and appropriate microbiologic sampling • Strategic microbiology results reporting

Adaptado de: http://www.publichealthontario.ca/en/BrowseByTopic/InfectiousDiseases/AntimicrobialStewardshipProgram/Pages/ASP-Strategies.aspx

Antimicrobial stewardship

Prevenção da emergência de resistências

O Desafio das EPC:
Que papel para o PAPA?

Limitação da disseminação de resistências

Diminuição das resistências existentes

Antimicrobial stewardship

Prevenção da emergência de resistências

O Desafio das EPC:
Que papel para o PAPA?

Limitação da disseminação de resistências

Diminuição das resistências existentes

Otimização do tratamento das infeções por EPC

Antimicrobial stewardship

Prevenção da emergência de resistências

O Desafio das EPC:
Que papel para o PAPA?

Limitação da disseminação de resistências

Diminuição das resistências existentes

Será que funciona?

Antimicrobial stewardship e resistência

Consumo ATBs

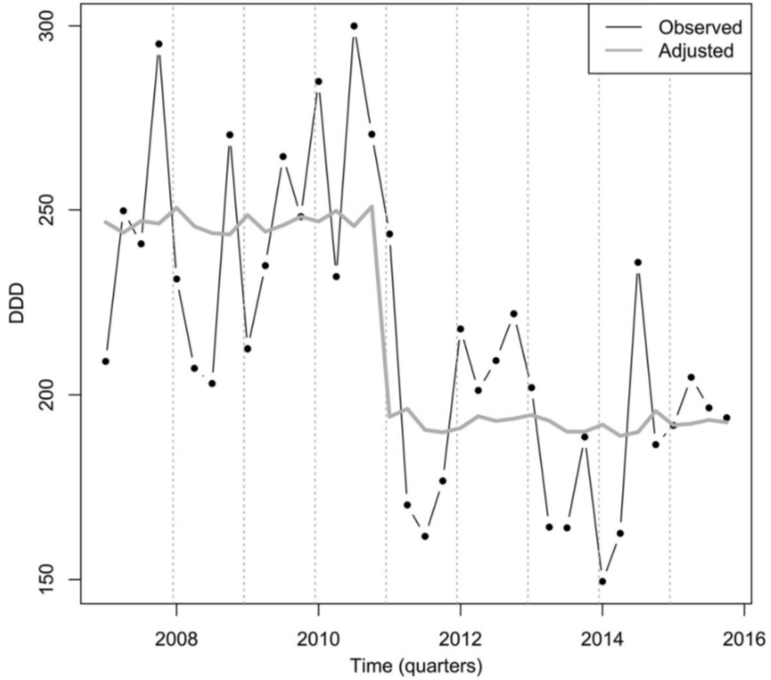


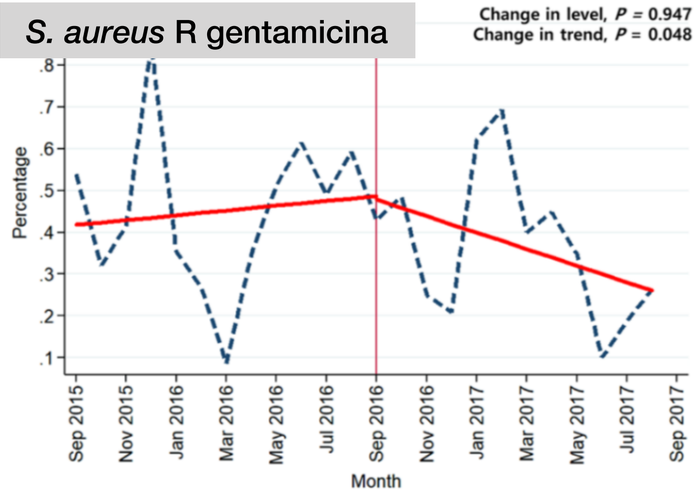
FIG 1 Defined daily doses (DDDs) of antimicrobials used in the ICU per 100 occupied beds before and after implementation of an antimicrobial stewardship program in 2011 (quarterly data).

	Before AMS program				After AMS program					
Parameter	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	***P*[b]**
Patients analyzed (April to June)	120	108	107	131	126	130	141	144	153	
Men (%)	70	72.2	60.8	63.4	65.9	66.2	63.8	63.2	60.1	0.353
Mean age in yrs (SD)	57.9 (17.5)	59.4 (17.4)	57.5 (19.8)	61.7 (15.9)	56.7 (17.9)	59.4 (19.4)	59.5 (19.7)	60.6 (17.9)	60.9 (16.2)	0.366
Mean APACHE II score on ICU admission (SD)	16.3 (9.0)	16.9 (9.5)	16.7 (8.6)	18.3 (9.0)	17.1 (9.6)	14.6 (8.0)	16.3 (9.6)	15.5 (9.8)	16.9 (10.2)	0.109
Mean ICU stay in days (SD)	11.5 (12.4)	13.4 (14.3)	11.8 (12.5)	9.5 (9.4)	8.7 (8.3)	8.4 (10.8)	8.7 (9.6)	8.3 (11.3)	8.0 (9.5)	<0.001
ICU mortality (% patients)	12.5	16.7	12.2	13.7	11.1	11.5	14.9	10.4	12.4	0.468
ICU-acquired MDROs (% patients)	15.8	32.4	27.1	22.1	12.7	14.6	18.4	2.8	3.3	<0.001

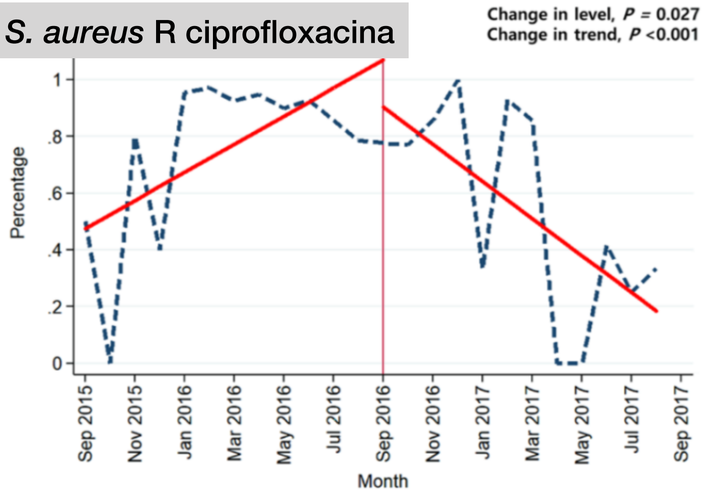
lvarez-Lerma F et al A Before-and-After Study of the Effectiveness of an Antimicrobial Stewardship Program in Critical Care. Antimicrob Agents Chemother. 2018 Mar 27;62(4).

Antimicrobial stewardship e resistência

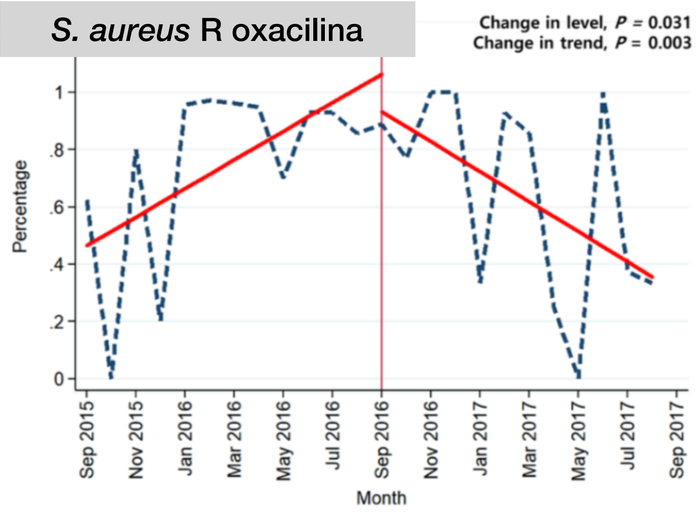
S. aureus R gentamicina



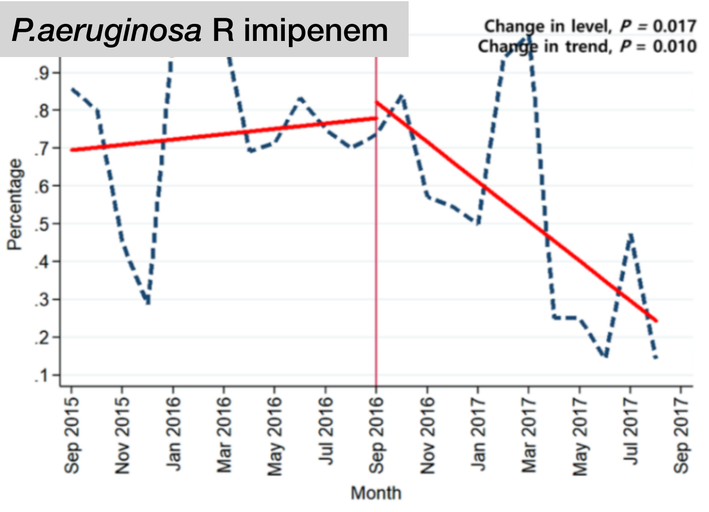
S. aureus R ciprofloxacina



S. aureus R oxacilina

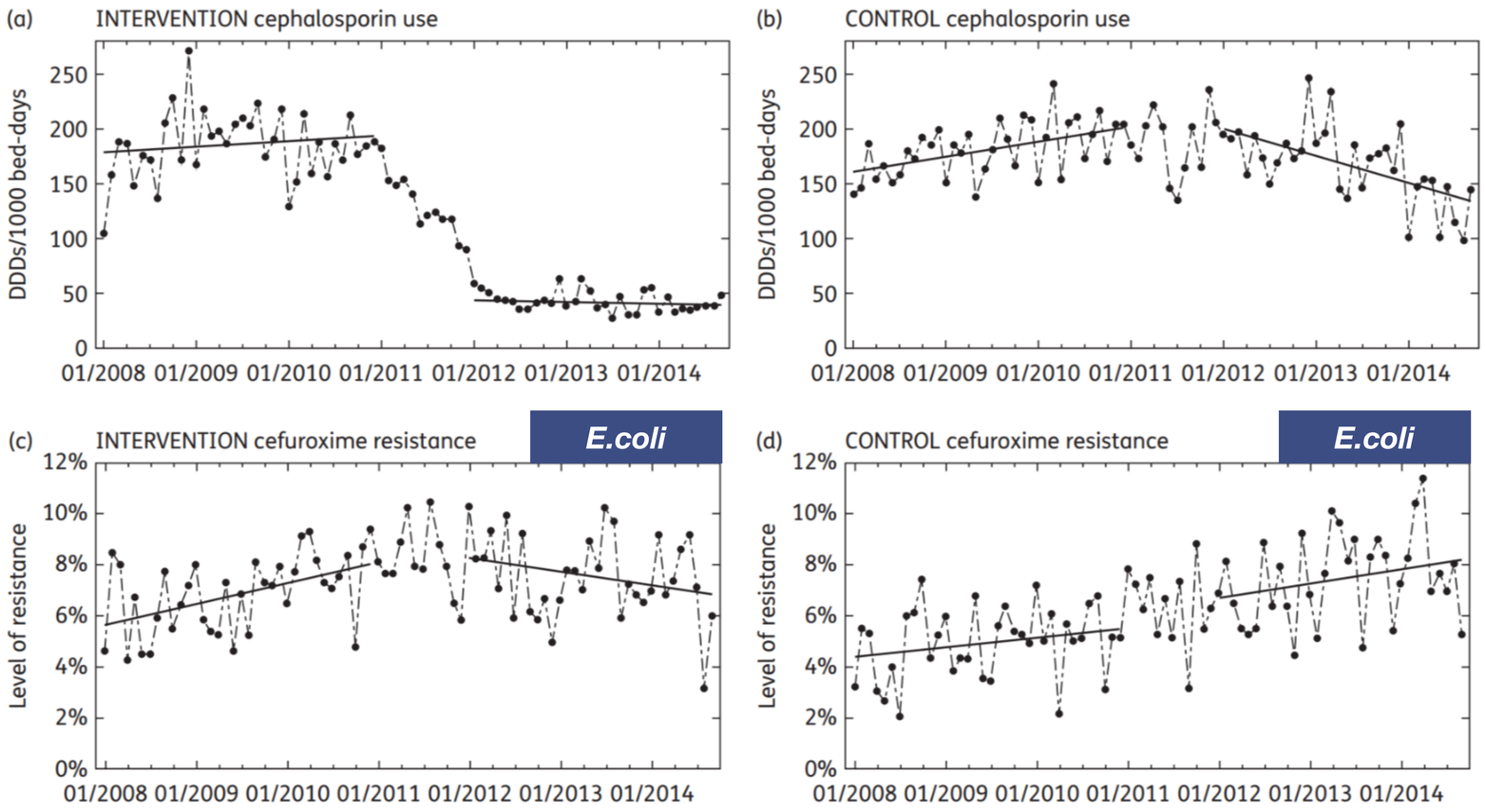


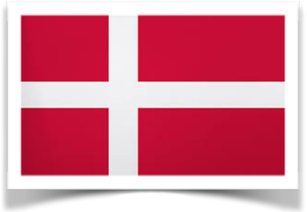
P.aeruginosa R imipenem



Hwang H, Kim B. Sci Rep. 2018 Oct 3;8(1):14757.

Antimicrobial stewardship e resistência





Jonas Boel, et al. Journal of Antimicrobial Chemotherapy, Volume 71, Issue 7, 1 July 2016, Pages 2047–2051

Antimicrobial stewardship e resistência

C. difficile

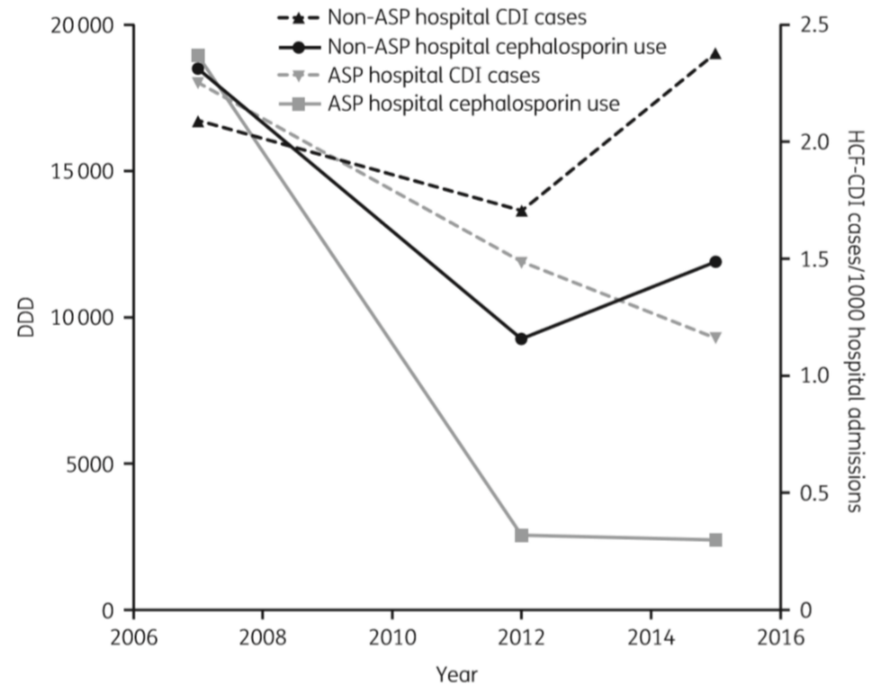


Figure 1. Cephalosporin use and incidence of HCF-CDI. Left *y*-axis shows use of cephalosporins and right *y*-axis shows incidence of HCF-CDI.

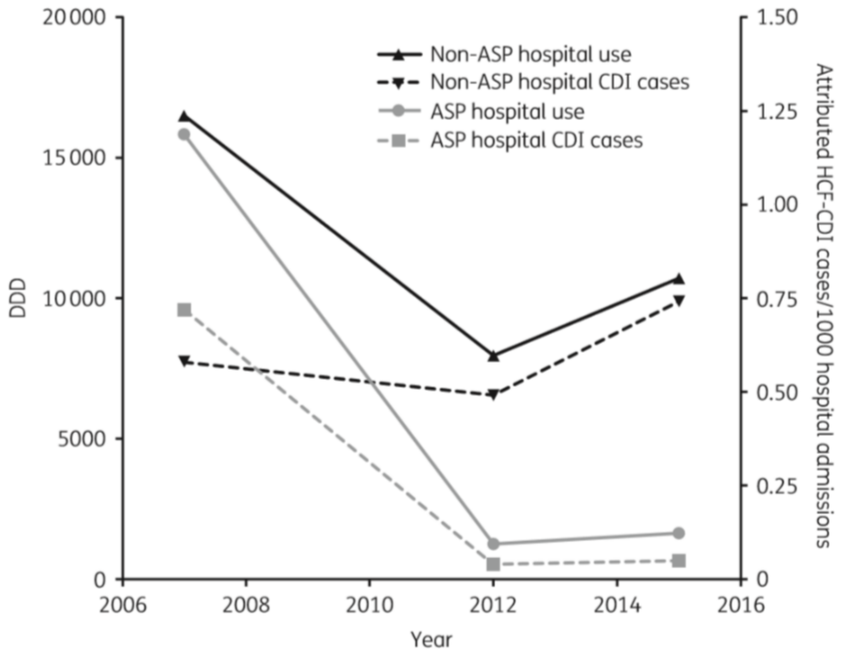
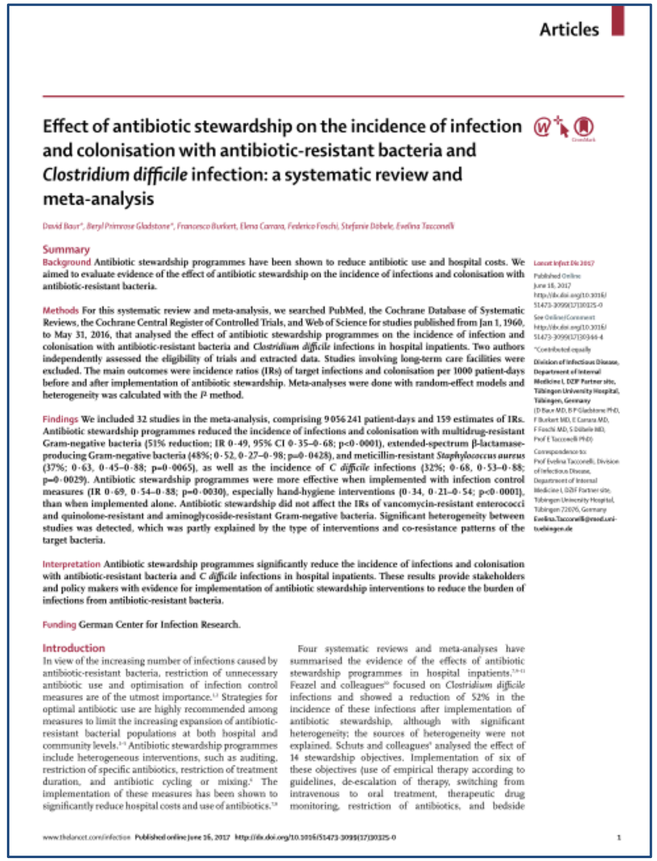


Figure 2. Use of iv cephalosporins and HCF-CDI cases attributed to iv cephalosporins. Left *y*-axis shows use of iv cephalosporins and right *y*-axis shows HCF-CDI cases attributed to iv cephalosporins.

Johan Karp et al. J Antimicrob Chemother 2018

Antimicrobial stewardship e resistência

- 32 estudos observacionais incluídos
- **51%** de redução na incidência Gram neg MDR (IR 0,49; IC 95% 0,35–0,68; p<0,0001)
- **48%** de redução na incidência de ESBL (IR 0,52; IC 95% 0,27–0,98; p=0,0428)
- **37%** de redução na incidência de MRSA (IR 0,63; IC 95% 0,45–0,88; p=0,0065)
- **32%** de redução na incidência de Clostridium difficile (IR 0,68; IC 95% 0,53–0,88; p=0,0029)



Articles

Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infection: a systematic review and meta-analysis

David Baur*, Beryl Primrose Gladstone*, Francesco Burkert, Elena Carrara, Federico Foschi, Stefanie Döbele, Evelina Tacconelli

Summary

Background Antibiotic stewardship programmes have been shown to reduce antibiotic use and hospital costs. We aimed to evaluate evidence of the effect of antibiotic stewardship on the incidence of infections and colonisation with antibiotic-resistant bacteria.

Methods For this systematic review and meta-analysis, we searched PubMed, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and Web of Science for studies published from Jan 1, 1960, to May 31, 2016, that analysed the effect of antibiotic stewardship programmes on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infections in hospital inpatients. Two authors independently assessed the eligibility of trials and extracted data. Studies involving long-term care facilities were excluded. The main outcomes were incidence ratios (IRs) of target infections and colonisation per 1000 patient-days before and after implementation of antibiotic stewardship. Meta-analyses were done with random-effect models and heterogeneity was calculated with the I^2 method.

Findings We included 32 studies in the meta-analysis, comprising 9 056 241 patient-days and 159 estimates of IRs. Antibiotic stewardship programmes reduced the incidence of infections and colonisation with multidrug-resistant Gram-negative bacteria (51% reduction; IR 0·49, 95% CI 0·35–0·68; p<0·0001), extended-spectrum β-lactamase-producing Gram-negative bacteria (48%; 0·52, 0·27–0·98; p=0·0428), and meticillin-resistant *Staphylococcus aureus* (37%; 0·63, 0·45–0·88; p=0·0065), as well as the incidence of *C difficile* infections (32%; 0·68, 0·53–0·88; p=0·0029). Antibiotic stewardship programmes were more effective when implemented with infection control measures (IR 0·69, 0·54–0·88; p=0·0030), especially hand-hygiene interventions (0·34, 0·21–0·54; p<0·0001), than when implemented alone. Antibiotic stewardship did not affect the IRs of vancomycin-resistant enterococci and quinolone-resistant and aminoglycoside-resistant Gram-negative bacteria. Significant heterogeneity between studies was detected, which was partly explained by the type of interventions and co-resistance patterns of the target bacteria.

Interpretation Antibiotic stewardship programmes significantly reduce the incidence of infections and colonisation with antibiotic-resistant bacteria and *C difficile* infections in hospital inpatients. These results provide stakeholders and policy makers with evidence for implementation of antibiotic stewardship interventions to reduce the burden of infections from antibiotic-resistant bacteria.

Funding German Center for Infection Research.

Introduction

In view of the increasing number of infections caused by antibiotic-resistant bacteria, restriction of unnecessary antibiotic use and optimisation of infection control measures are of the utmost importance.[1,2] Strategies for optimal antibiotic use are highly recommended among measures to limit the increasing expansion of antibiotic-resistant bacterial populations at both hospital and community levels.[1,3] Antibiotic stewardship programmes include heterogeneous interventions, such as auditing, restriction of specific antibiotics, restriction of treatment duration, and antibiotic cycling or mixing.[3] The implementation of these measures has been shown to significantly reduce hospital costs and use of antibiotics.[3,4] Four systematic reviews and meta-analyses have summarised the evidence of the effects of antibiotic stewardship programmes in hospital inpatients.[3,5–11] Feazel and colleagues[10] focused on *Clostridium difficile* infections and showed a reduction of 52% in the incidence of these infections after implementation of antibiotic stewardship, although with significant heterogeneity; the sources of heterogeneity were not explained. Schuts and colleagues[5] analysed the effect of 14 stewardship objectives. Implementation of six of these objectives (use of empirical therapy according to guidelines, de-escalation of therapy, switching from intravenous to oral treatment, therapeutic drug monitoring, restriction of antibiotics, and bedside

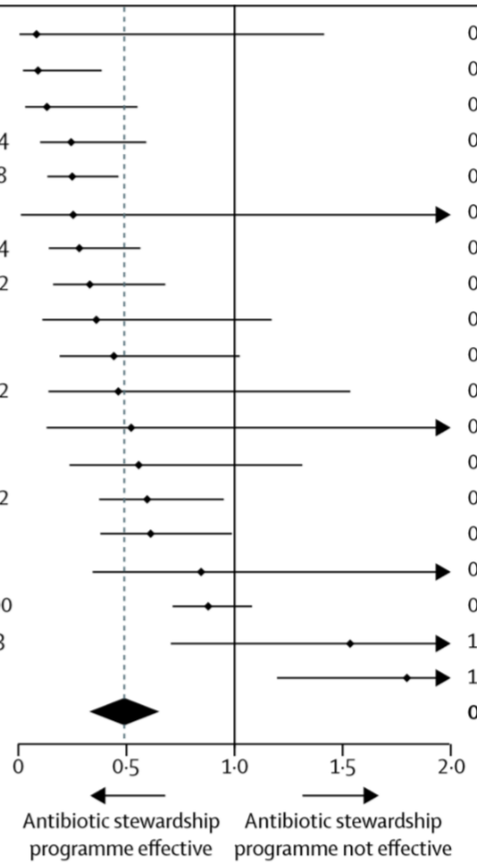
www.thelancet.com/infection Published online June 16, 2017 http://dx.doi.org/10.1016/S1473-3099(17)30325-0 1

Baur et al. Lancet Infect Dis 2017 Published online

Antimicrobial stewardship e resistência

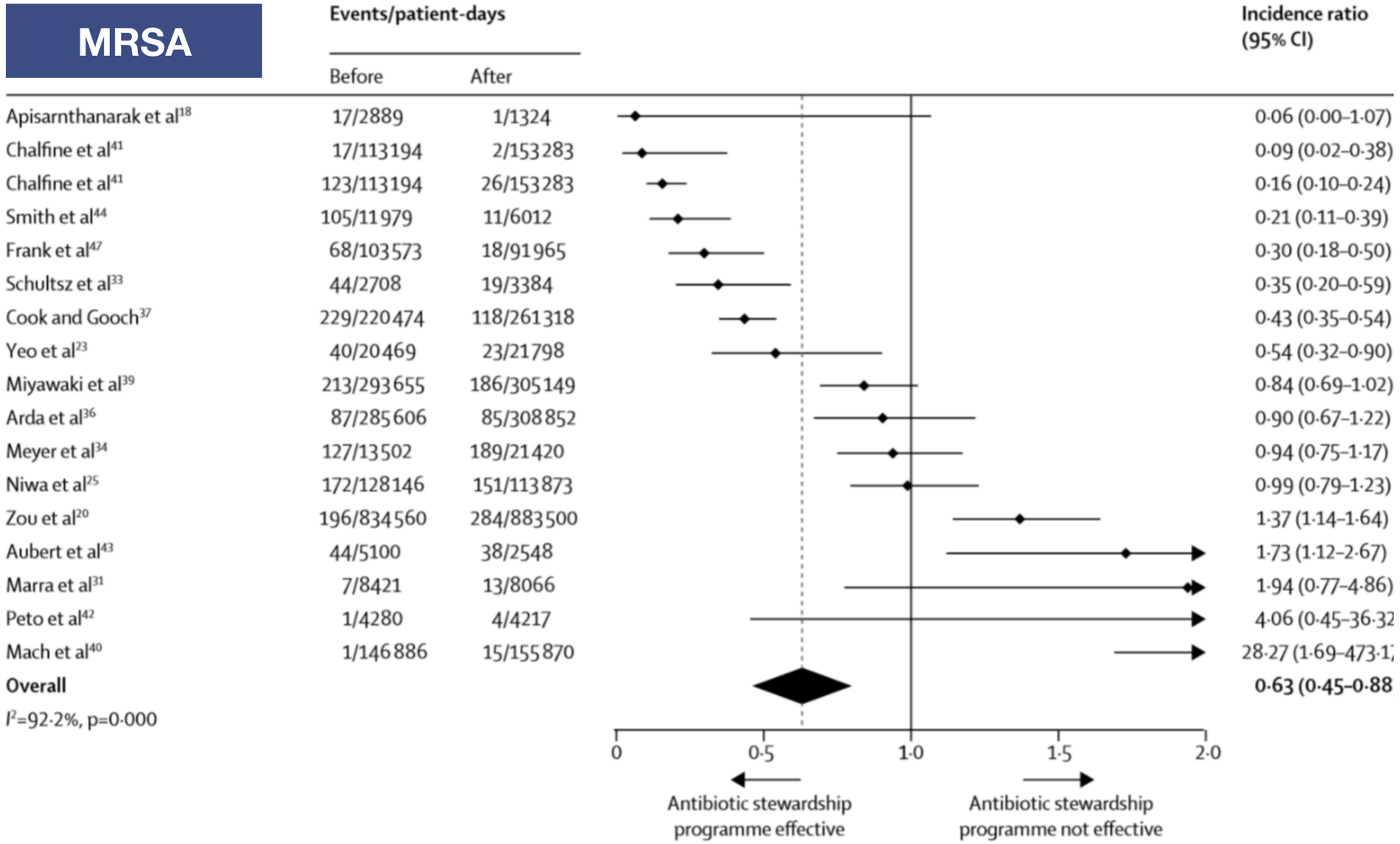
GNB MDR

		Events/patient-days		Incidence ratio (95% CI)
		Before	After	
Apisarnthanarak et al[18]	MDR *Pseudomonas aeruginosa*	13/2889	1/1324	0·08 (0·00–1·41)
Marra et al[31]	Imipenem-resistant *Acinetobacter baumannii*	23/8421	2/8066	0·09 (0·02–0·39)
Apisarnthanarak et al[18]	XDR *A baumannii*	33/2889	2/1324	0·13 (0·03–0·55)
Takesue et al[32]	Metallo-β-lactamase GNB	27/698794	6/635794	0·24 (0·10–0·59)
Cook and Gooch[37]	Carbapenem-resistant *P aeruginosa*	44/220474	13/261318	0·25 (0·13–0·46)
Peto et al[42]	MDR *P aeruginosa*	2/4280	1/4217	0·25 (0·01–5·63)
Takesue et al[32]	MDR GNB	39/698794	10/635794	0·28 (0·14–0·56)
Arda et al[36]	Meropenem-resistant *Acinetobacter* spp	28/285606	10/308852	0·33 (0·16–0·68)
Leverstein-van Hall et al[45]	MDR Enterobacteriaceae	9/19142	4/23583	0·36 (0·11–1·17)
Yeo et al[23]	Carbapenem-resistant *P aeruginosa*	17/20469	8/21798	0·44 (0·19–1·02)
Arda et al[36]	Meropenem-resistant *P aeruginosa*	8/285606	4/308852	0·46 (0·14–1·54)
Marra et al[31]	Imipenem-resistant *Klebsiella pneumoniae*	6/8421	3/8066	0·52 (0·13–2·09)
Marra et al[31]	Imipenem-resistant *P aeruginosa*	15/8421	8/8066	0·56 (0·24–1·31)
Arda et al[36]	Meropenem-resistant *A baumannii*	45/285606	29/308852	0·60 (0·37–0·95)
Meyer et al[34]	Imipenem-resistant *P aeruginosa*	34/13502	33/21420	0·61 (0·38–0·99)
Yeo et al[23]	Carbapenem-resistant *A baumannii*	10/20469	9/21798	0·85 (0·34–2·08)
Zou et al[20]	Meropenem-resistant *P aeruginosa*	185/834560	172/883500	0·88 (0·71–1·08)
Niwa et al[25]	Imipenem-resistant *P aeruginosa*	11/128146	15/113873	1·53 (0·70–3·34)
Aubert et al[43]	Imipenem-resistant *P aeruginosa*	49/5100	44/2548	1·80 (1·20–2·70)
Overall				**0·49 (0·35–0·68)**
I^2=76·2%, p=0·000				



Baur et al. Lancet Infect Dis 2017 Published online

Antimicrobial stewardship e resistência



Baur et al. Lancet Infect Dis 2017 Published online

Antimicrobial stewardship e resistência

“In conclusion:
…**Antibiotic stewardship programmes have an essential role in combating the development of antibiotic resistance**, especially for MDR Gram-negative bacteria…

…**Co-implementation of hand-hygiene improvement interventions with antibiotic stewardship programmes** has a **synergistic effect** and is thus recommended for future antibiotic stewardship planning…

…Good quality intervention studies are needed to **help prioritise the various antibiotic stewardship programmes for each specific resistance scenario”**

Antimicrobial stewardship e resistência

- 221 estudos incluídos **(58 RCT's)**
- Risco de morte semelhante em ambos os grupos (11%) (RD 0%; IC 95% -1% a 0%; 28 RCT's; 15827 doentes)
- Duração de internamento diminuída em **1,12 dias** (IC 95% 0,7-1,54 dias; 15 RCT's; 3834 doentes)
- Diminuição do tratamento antimicrobiano em **1,95 dias** (IC 95% 1,67 a 2,22 dias; 14 RCT's; 3318 doentes)
- **Redução de infecções** por Clostridium difficile (-48,6%; IC 95% -80,7% a -19,2%; 7 estudos)
- Não demonstrado impacto nas resistências

Antimicrobial stewardship e resistência

- Revisão sistemática (26 estudos):
  - **27%** (7) com resultados positivos
  - 12% (3) com resultados positivos limitados
  - 27% (7) com resultados dúbios
  - **15%** (4) com resultados negativos
  - 19% (5) com resultados não interpretáveis

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American Journal of Infection Control ▬ (2018) ▬–▬

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State of the Science Review

Are antimicrobial stewardship programs effective strategies for preventing antibiotic resistance? A systematic review

Leandro G. Bertollo *, Diego S. Lutkemeyer, Anna S. Levin PhD

Department of Infectious Diseases and Infection Control, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil

Key Words:
Antimicrobial stewardship
infection control
antibiotic resistance, bacterial
review, systematic

Background: Antimicrobial stewardship programs (ASPs) have been proposed as a solution for the global burden of antibiotic resistance, despite the lack of evidence on the subject.
Objective: To analyze the role of ASPs in reducing bacterial resistance to antibiotics in hospital settings.
Data sources: A review in PubMed, Scopus, LILACS, and SciELO databases was performed. The period analyzed was January 1, 2012-January 4, 2017.
Eligibility criteria: Studies that related ASPs to bacterial resistance.
Data extraction: All studies that did not focus on ASPs were removed. Antifungal and antiviral programs were excluded.
Results: Only 8 studies had quasi-experimental designs, and none were controlled trials. ASP strategies and microorganism-antibiotic pairs evaluated varied widely. Seven studies were classified as presenting clearly positive results, 3 had limited positive results, 7 had doubtful results, 4 had negative results, and 5 had noninterpretable results. The implementation of new infection control practices occurred in 7 studies.
Limitations: There are yet few studies on this matter, and most of them have inadequate study designs. Great heterogeneity between study features was detrimental to drawing evidence-based conclusions.
Conclusions: There is no solid evidence that ASPs are effective in reducing antibiotic resistance in hospital settings. We uphold the need for more studies with appropriate study designs, standardized ASP interventions targeting common microorganism-antibiotic pairs, and avoiding simultaneous implementation of infection control practices.

The antibiotic era began in 1923 with the discovery of penicillin by Alexander Fleming. Antimicrobial resistance was already a problem of global public health in the 1940s, a few years after the introduction of antibiotics into clinical practice. The World Health Organization, together with member states and collaborators, produced in 2014 for the first time a document that portrays the exact magnitude of the situation concerning bacterial resistance in the world.[1] The study clearly states that resistance to common bacteria has reached alarming levels. According to the World Health Organization report, groups of key antibiotics no longer work for half of the patients in several countries: carbapenems, which are administered to treat infections caused by *Klebsiella pneumoniae*, and fluoroquinolones, indicated for treatment of urinary infections, have been proven ineffective against pathogens in >50% of patients.[1] The emergence of antimicrobial resistance is a threat to public health.[2,3]

Behind this scenario lies the extraordinary genetic ability of these microorganisms. A wide range of biochemical and physiologic mechanisms may be involved in the development of bacterial resistance,[4] and the lack of knowledge about the complex relationship between pathogen exposure to drugs and the development of resistance justifies the few advances in resistance prevention and control. The most obvious and probably most costly example regarding public health (morbidity and mortality) concerns bacteria. In 2009, databases[5] listed >20,000 potential resistance genes of 400 different types.

The development of bacterial resistance to antimicrobial agents is triggered by the selection of resistant organisms[6] during individual or populational antibiotic-based treatments.[7,8] Another form of contact of individuals with resistant species is through agriculture: because antibiotics are used as growth supplements in livestock,[9,10] resistant bacteria of these animals may reach consumers through consumed animal products.[10]

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E-mail address: bertolloleandro@gmail.com (L.G. Bertollo).
Conflicts of interest: None to report.

0196-6553/
https://doi.org/10.1016/j.ajic.2018.01.002

Antimicrobial stewardship e resistência

“Conclusion:

There is no solid evidence that ASPs are effective in reducing antibiotic resistance in hospital settings… need for more studies with appropriate study designs and standardized ASP interventions… Implementing new infection control measures simultaneously with ASPs should be avoided because it may be a major confounding factor that was present in a substantial proportion of studies.”

???

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Conflicts of interest: None to report.

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Antimicrobial stewardship

Prevenção da emergência de resistências

O Desafio das EPC:
Que papel para o PAPA?

Limitação da disseminação de resistências

Diminuição das resistências existentes

Será que funciona?

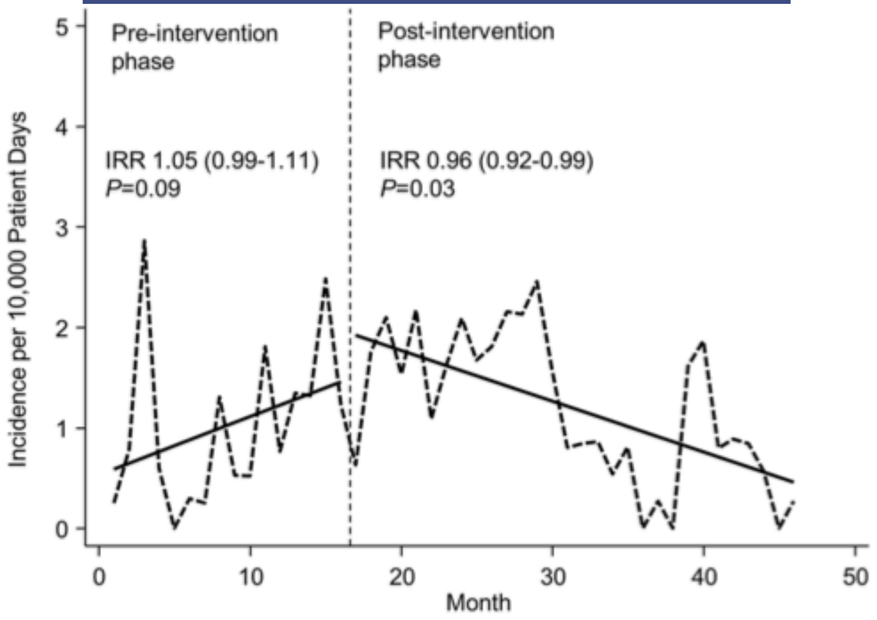
Antimicrobial stewardship e resistência

Estratégias implementadas:

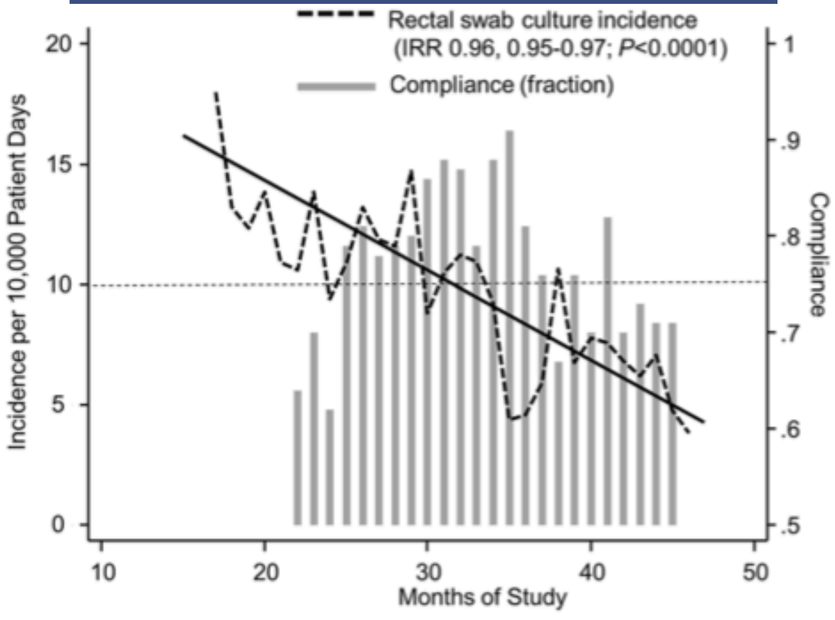
- Coorte de doentes
- Intensificação de educação
- Optimização de higiene de mãos e limpeza

- Promoção de regimes “poupadores de carbapenemos
- Revisão de todas as prescrições de carbapenemos em 48h

KPC Bloodstream infection



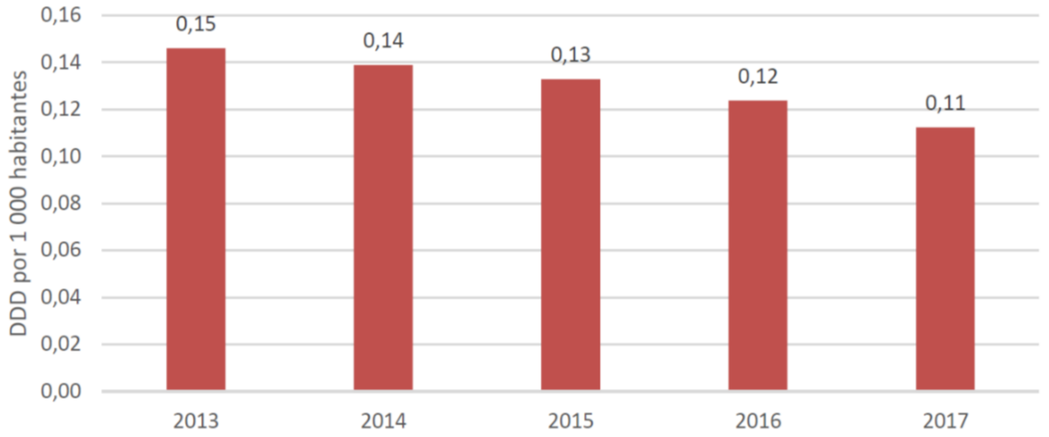
KPC colonization



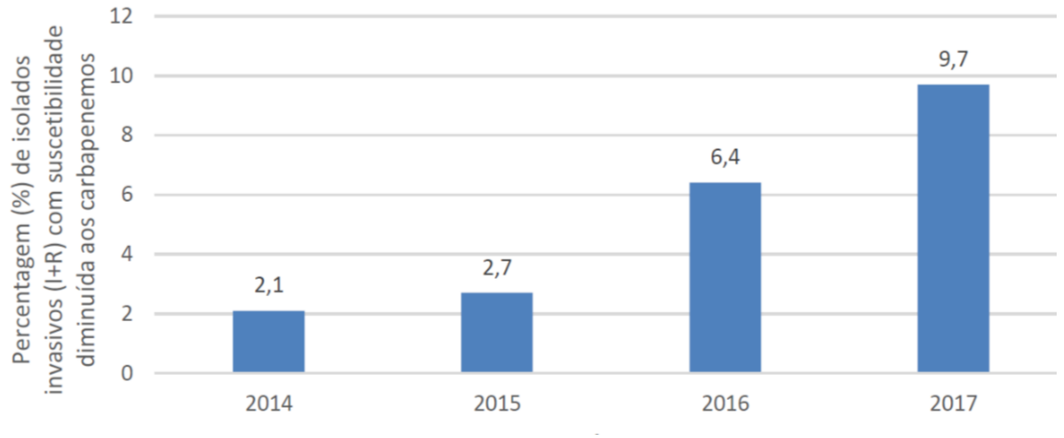
Viale P et al. Infect Dis Ther (2015) 4 (Suppl 1):S65–S83

AMS e ERC em Portugal…

Consumo de carbapenemos

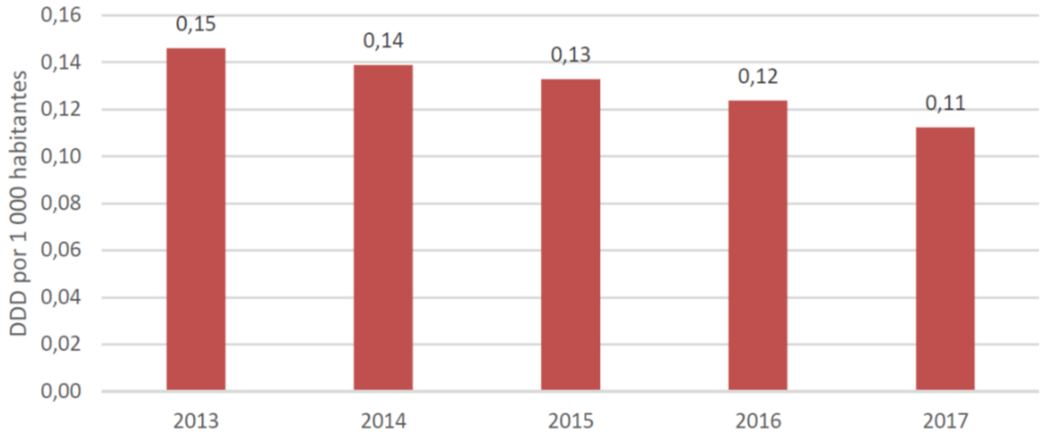


***K. pneumoniae* susc. reduzida a carbapenemos**



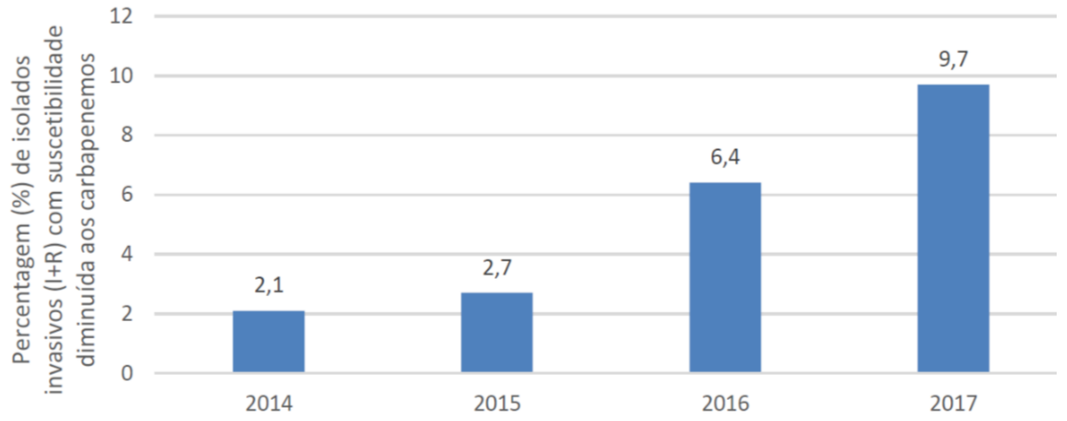
AMS e ERC em Portugal…

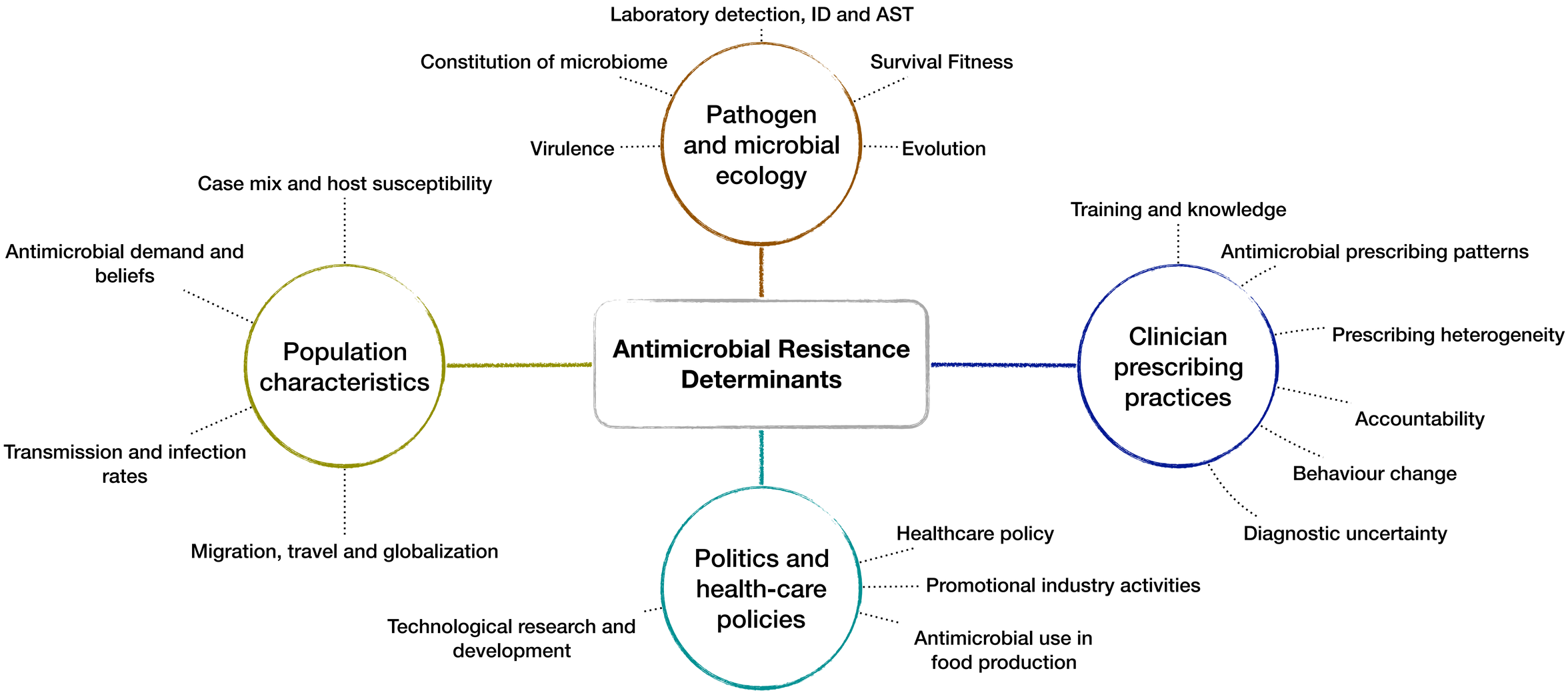
Consumo de carbapenemos



Porquê?

***K. pneumoniae* susc. reduzida a carbapenemos**





Adaptado de: Bassetti et al. Intensive Care Med (2017) 43: 1464-1475

Determinantes da resistência

	Effect on resistance rate of 1 SD increase in each explanatory variable (logit)	p value
Usage (standardised)	−0·88	0·64
Governance index	−7·89	0·025
Health expenditure index	−5·54	0·093
GDP per capita (standardised)	6·62	0·030
Education index	7·93	0·058
Infrastructure index	−16·84	0·014
Climate index	2·01	0·33
R^2	0·54	..

GDP=gross domestic product. R^2=coefficient of determination.

***Table 2*: Effect of changes in indices on the resistance of *Escherichia coli* to third-generation cephalosporins and fluoroquinolones**

	Effect on resistance rate of 1 SD increase in each explanatory variable (logit)	p value
Usage (standardised)	2·36	0·070
Governance index	−11·18	<0·0001
Health expenditure index	−6·34	0·0065
GDP per capita index (standardised)	3·36	0·11
Education index	8·59	0·0035
Infrastructure index	−13·24	0·0052
Climate index	−0·25	0·86
R^2	0·75	..

GDP=gross domestic product. R^2=coefficient of determination.

***Table 3*: Effect of changes in indices on the aggregate resistance rate**

Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis

Peter Collignon, John J Beggs, Timothy R Walsh, Sumanth Gandra, Ramanan Laxminarayan

Summary

Background Understanding of the factors driving global antimicrobial resistance is limited. We analysed antimicrobial resistance and antibiotic consumption worldwide versus many potential contributing factors.

Methods Using three sources of data (ResistanceMap, the WHO 2014 report on antimicrobial resistance, and contemporary publications), we created two global indices of antimicrobial resistance for 103 countries using data from 2008 to 2014: *Escherichia coli* resistance—the global average prevalence of *E coli* bacteria that were resistant to third-generation cephalosporins and fluoroquinolones, and aggregate resistance—the combined average prevalence of *E coli* and *Klebsiella* spp resistant to third-generation cephalosporins, fluoroquinolones, and carbapenems, and meticillin-resistant *Staphylococcus aureus*. Antibiotic consumption data were obtained from the IQVIA MIDAS database. The World Bank DataBank was used to obtain data for governance, education, gross domestic product (GDP) per capita, health-care spending, and community infrastructure (eg, sanitation). A corruption index was derived using data from Transparency International. We examined associations between antimicrobial resistance and potential contributing factors using simple correlation for a univariate analysis and a logistic regression model for a multivariable analysis.

Findings In the univariate analysis, GDP per capita, education, infrastructure, public health-care spending, and antibiotic consumption were all inversely correlated with the two antimicrobial resistance indices, whereas higher temperatures, poorer governance, and the ratio of private to public health expenditure were positively correlated. In the multivariable regression analysis (confined to the 73 countries for which antibiotic consumption data were available) considering the effect of changes in indices on *E coli* resistance (R^2 0·54) and aggregate resistance (R^2 0·75), better infrastructure (p=0·014 and p=0·0052) and better governance (p=0·025 and p<0·0001) were associated with lower antimicrobial resistance indices. Antibiotic consumption was not significantly associated with either antimicrobial resistance index in the multivariable analysis (p=0·64 and p=0·070).

Interpretation Reduction of antibiotic consumption will not be sufficient to control antimicrobial resistance because contagion—the spread of resistant strains and resistance genes—seems to be the dominant contributing factor. Improving sanitation, increasing access to clean water, and ensuring good governance, as well as increasing public health-care expenditure and better regulating the private health sector are all necessary to reduce global antimicrobial resistance.

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Lancet Planet Health 2018; 2: e393–405

See Comment page e376

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Introduction

Antimicrobial resistance is a substantial global problem across countries regardless of income level and imposes a large clinical and financial burden.[1–4] Multidrug-resistant bacteria that develop in any country or region have been shown to spread rapidly,[4,5] and antimicrobial resistance is recognised as a so-called One Health problem.[6,7] Although the use and overuse of antibiotics are primary drivers of the emergence and maintenance of antimicrobial resistance, other factors contribute to its increased prevalence.[4,5,7,8] The observation of higher antimicrobial resistance rates in several low-income countries and middle-income countries (LMICs), in which per-person consumption of antibiotics is much lower than in high-income countries, supports this idea.[8,9,11] Quality of governance, public spending on health, poverty (ie, gross domestic product [GDP] per person), education, and community infrastructure are known to affect health outcomes.[12–14] However, previous studies have been limited in their assessment of antimicrobial resistance and have not been extrapolated to a global scale. Similarly, little is known about the effect of climate on the prevalence of antimicrobial resistance.

The dissemination of antimicrobial resistance can be described as a two-step process. First, de-novo mutations

Collignon P et al. Lancet Planet Health 2018; 2: e398–405

O Desafio das EPC:
Que papel para o PAPA?

✓ Prevenção da emergência de resistência

✓ Limitação da disseminação de resistências

✓ Diminuição do nível de resistências atuais

Importante

O Desafio das EPC:
Que papel para o PAPA?

- Prevenção da emergência de resistência
- Limitação da disseminação de resistências
- Diminuição do nível de resistências atuais

Decisivo
Fundamental

- Contexto de estratégias multimodais
- Integração com estratégias de prevenção e controlo de infeção
- Reconhecimento da complexidade das resistências

Knowing is not enough; we must apply.
Willing is not enough; we must do.

Goethe

O Desafio das EPC:
Que papel para o PAPA?

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Faculdade de Medicina da Universidade do Porto