



WEBINAR
**Semana Mundial de Conscientização
sobre o Uso de Antimicrobianos 2020**



Uso Racional de Antimicrobianos na Saúde Humana

Ana Cristina Gales



Organização das Nações Unidas
para a Alimentação
e a Agricultura



ORGANIZACIÓN MUNDIAL DE SANIDAD ANIMAL
Proteger a los animales, preservar nuestro futuro



União Europeia



ANVISA

Agência Nacional de Vigilância Sanitária

MINISTÉRIO DA
SAÚDE

MINISTÉRIO DA
AGRICULTURA, PECUÁRIA
E ABASTECIMENTO



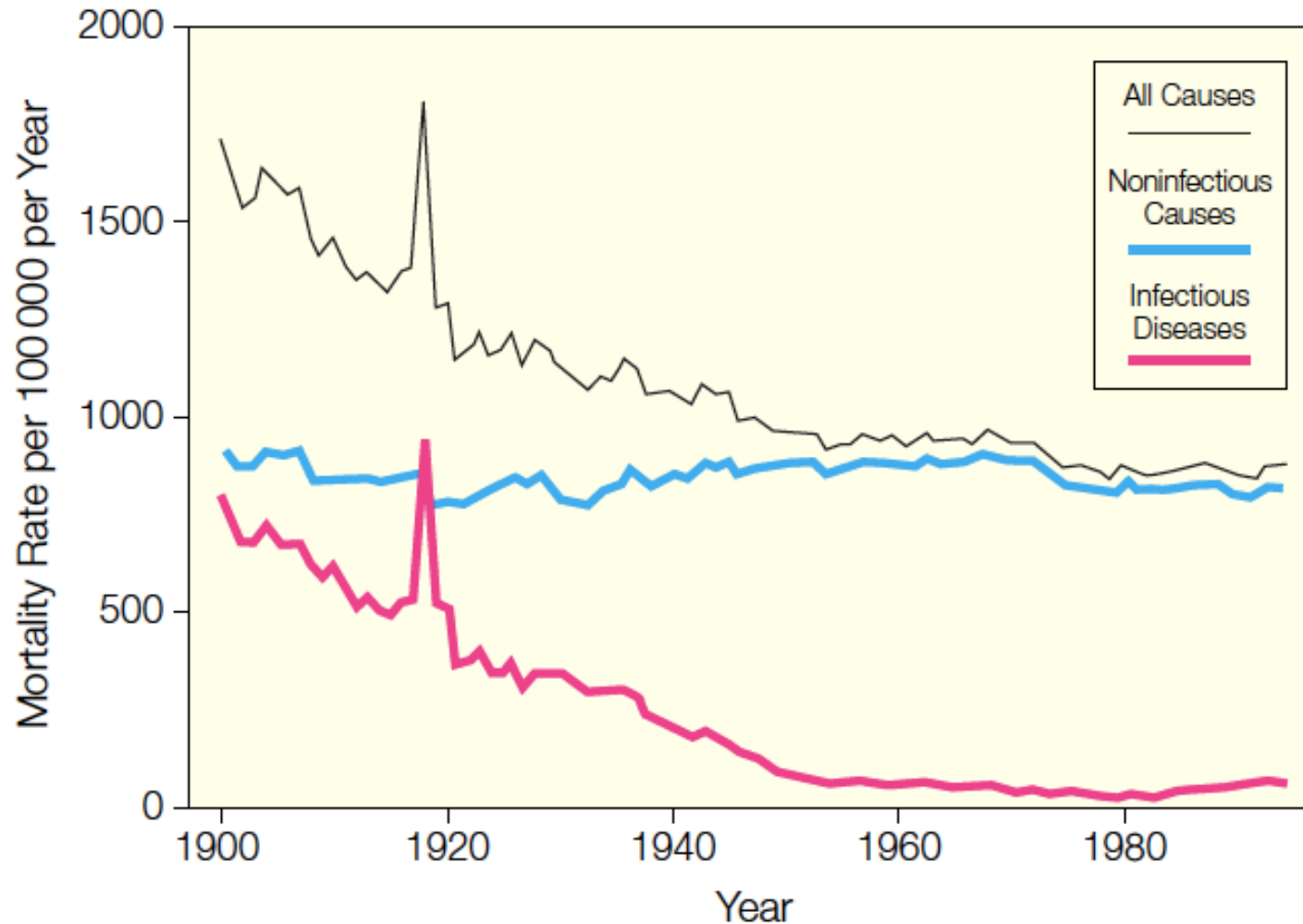
**PÁTRIA AMADA
BRASIL**
GOVERNO FEDERAL

Declaração de Conflitos de Interesse

- De acordo com a Norma 1595/2000 do Conselho Federal de Medicina e a Resolução 96/2008 da Agência Nacional de Vigilância Sanitária, declaro que:
- **Prestei consultoria para:**
WHO, PAHO, Ministério da Saúde (CGLAB, SCTIE), ANVISA, BrCAST, CNPq, CAPES e FAPESP
- **Participei em *Advisory boards*:**
Bayer, Cristália, Entasis Therapeutics, Eurofarma, MSD, Pfizer, Zambon
- **Fui Palestrante para:**
 - Eurofarma, InfectoPharm, MSD, Pfizer, Zambon

Trends in Infectious Disease Mortality in the United States During the 20th Century

Figure 2. Crude Mortality Rates for All Causes, Noninfectious Causes, and Infectious Diseases



Vacinas

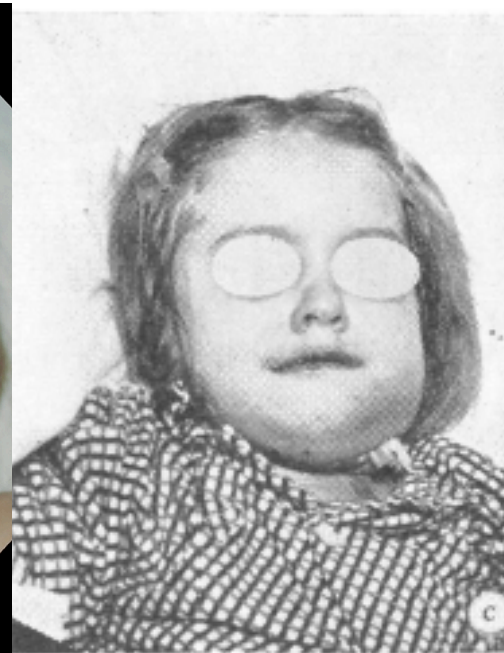
Saneamento
básico

REVIEW PAPERS

(Papers appearing in this section are invited reviews of subjects of wide current interest.)

PENICILLIN: A POTENT NEW CHEMOTHERAPEUTIC AGENT

WM. G. MYERS, Ph.D., M.D.,
The Ohio State University



Na admissão hospitalar

96h depois

Após 9 dias de tratamento

FIG. 1, a and b, front and side views of patient at onset of penicillin therapy. Extensive facial cellulitis and edema of both eyes may be noted; patient moribund; c, appearance of child ninety-six hours later.

A Resistência a Antimicrobianos é um Risco para Tratamentos mais complexos



Desinfetantes
e
antissépticos



CAUSES OF ANTIBIOTIC RESISTANCE

Antibiotic resistance happens when bacteria change and become resistant to the antibiotics used to treat the infections they cause.



Over-prescribing
of antibiotics



Patients not finishing
their treatment



Over-use of antibiotics in
livestock and fish farming



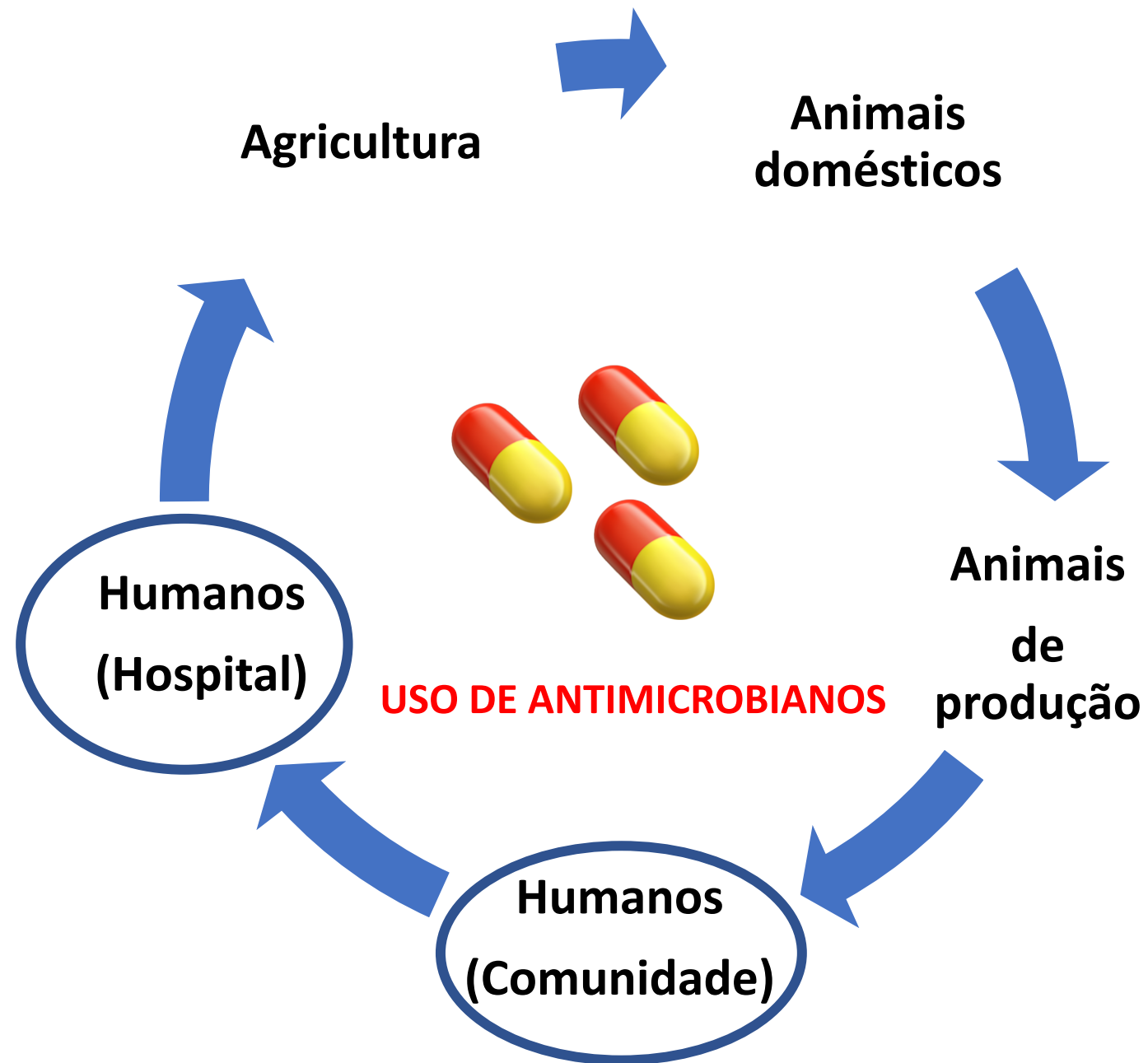
Poor infection control
in hospitals and clinics



Lack of hygiene and poor
sanitation

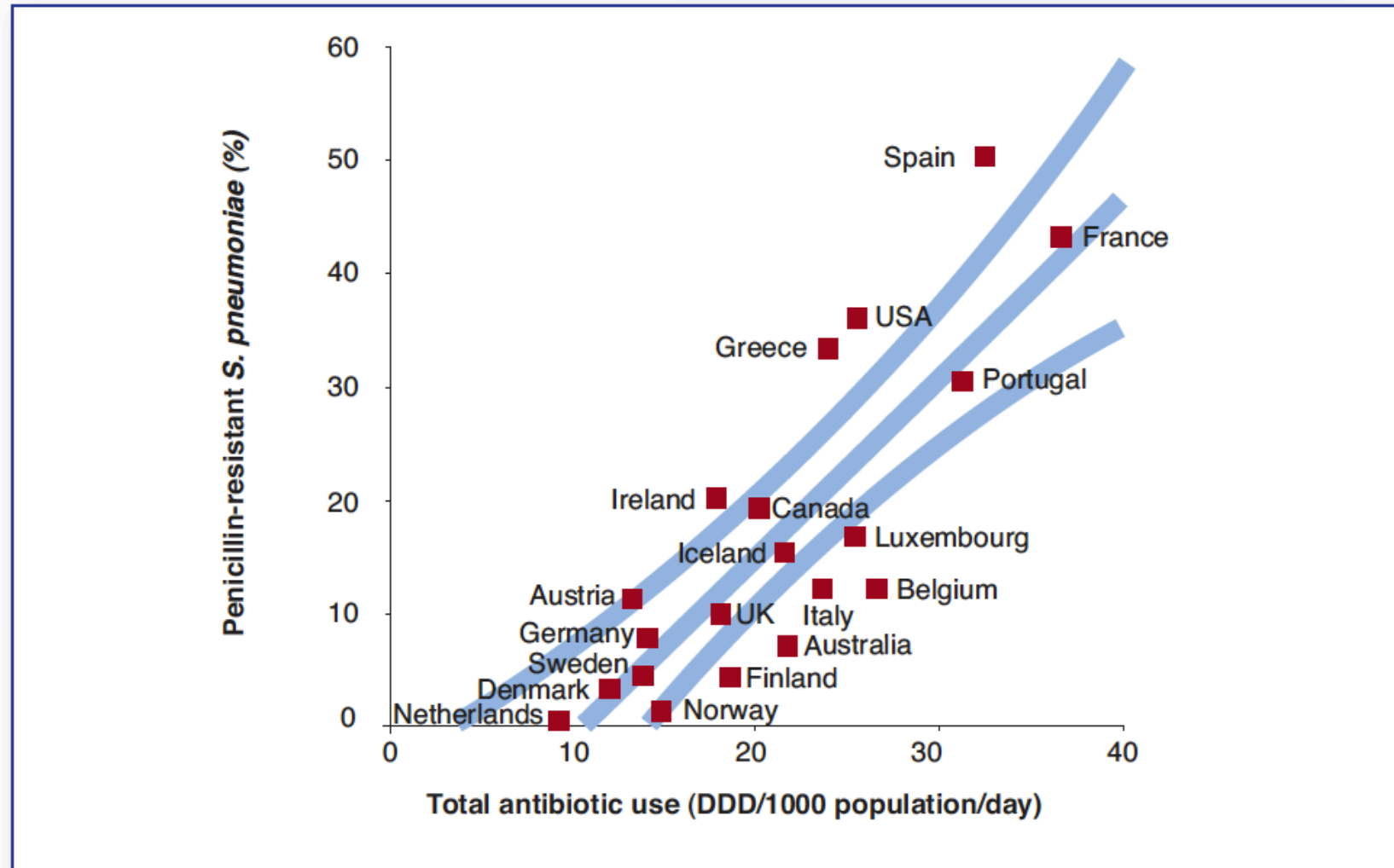


Lack of new antibiotics
being developed



Correlação entre Consumo de Penicilina e a Porcentagem de *S. pneumoniae* Resistente à Penicilina

Figure 2.6 Antibiotic use and AMR from 1990–2000 in selected countries



Large Nosocomial Outbreak of Colistin-Resistant, Carbapenemase-Producing *Klebsiella pneumoniae* Traced to Clonal Expansion of an *mgrB* Deletion Mutant

Tommaso Giani,^a Fabio Arena,^a Guendalina Vaggelli,^b Viola Conte,^a Adriana Chiarelli,^a Lucia Henrici De Angelis,^a Rossella Fornaini,^c Maddalena Grazzini,^d Fabrizio Niccolini,^d Patrizia Pecile,^b Gian Maria Rossolini^{a,b,e,f}

Department of Medical Biotechnologies, University of Siena, Siena, Italy^a; Clinical Microbiology and Virology Unit,^b Hospital Pharmacy Unit,^c and Hospital Medical Direction,^d Florence Careggi University Hospital, Florence, Italy; Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy^e; Don Carlo Gnocchi Foundation, Florence, Italy^f

TABLE 1 Observed BSI caused by *K. pneumoniae* during the study period^a

Yr	No. of <i>K. pneumoniae</i> BSI	No. (%) of <i>K. pneumoniae</i> isolates that were:			Colistin consumption ^d
		Carbapenemase sensitive	Carbapenemase resistant ^b	COL ^r CRKP ^{b,c}	
2009	29	28 (97)	1 (3)	0 (0; 0)	0.004
2010	49	38 (78)	11 (22)*	1 (3; 9)	0.013
2011	76	44 (58)	32 (42)*	4 (5; 12)	0.018
2012	128	46 (36)	82 (64)*	53 (41; 65)*	0.014
2013	93	32 (34)	61 (66)	35 (38; 57)	0.015
Total	375	188 (50)	187 (50)	93 (25; 50)	

^a Numbers and proportions of BSI cases caused by carbapenem-susceptible, carbapenem-resistant, and carbapenem- and colistin-resistant (COL^r CRKP) strains. For patients with recurrent BSI episodes, only the first episode was considered.

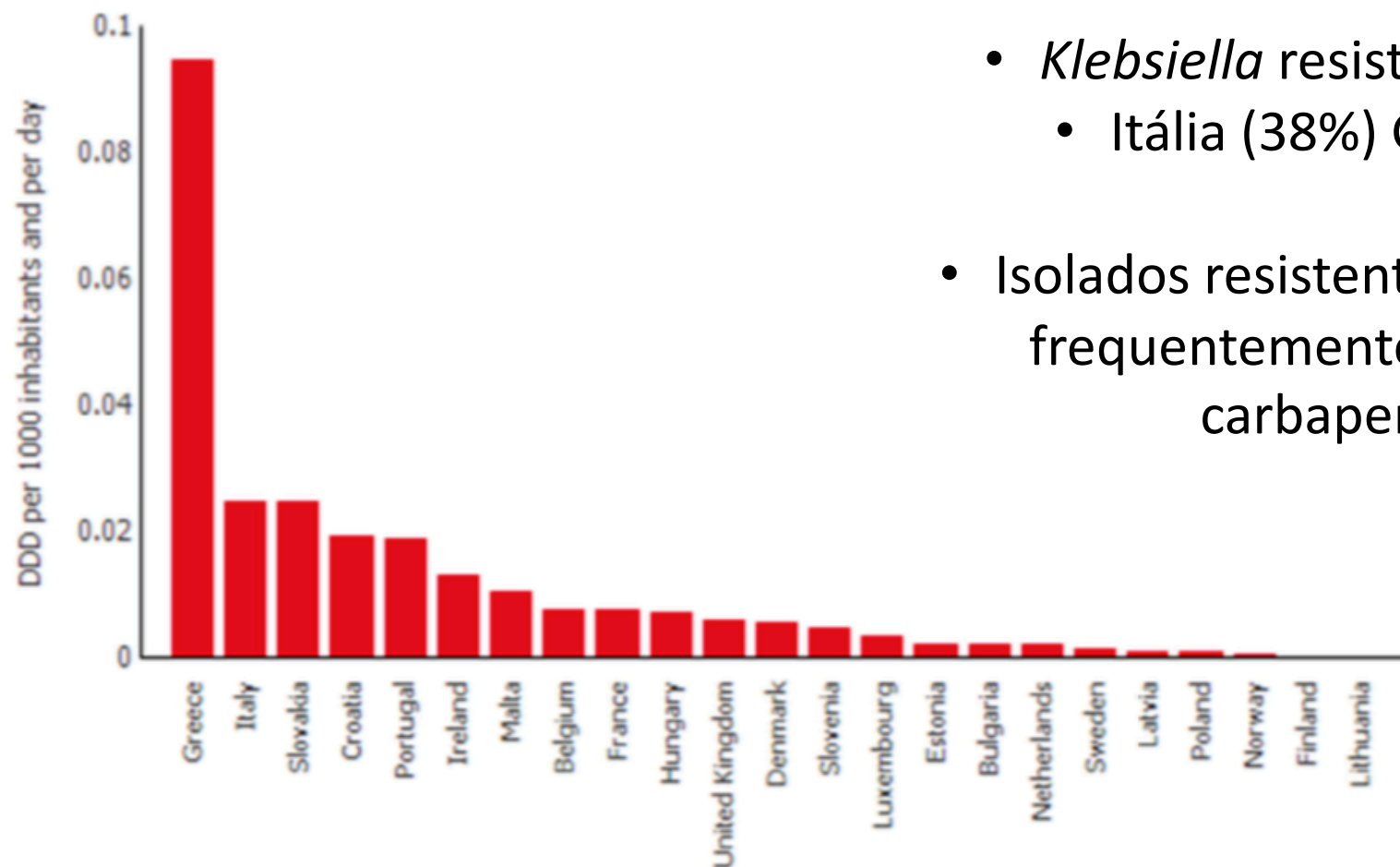
^b An asterisk indicates that the difference in the proportion of resistant isolates was statistically significantly different ($P < 0.05$) from that for the previous year. For statistical analysis, the chi-squared test with Yates' correction or Fisher's exact test (as appropriate) was used.

^c Proportions are reported in relation to both *K. pneumoniae* BSI and CRKP BSI. (Values are shown in parentheses and separated by semicolons.) COL^r *K. pneumoniae* was only observed among CRKP cases.

^d Data on colistin consumption in the hospital during the study period, expressed as the defined daily dose per 1,000 inhabitants per day, are also reported.

Consumo de Polimixina na Europa

Consumption of Polymyxins (ATC group J01XB) in the hospital sector in Europe, reporting year 2014



- *Klebsiella* resistente à colistina
 - Itália (38%) Grécia (26%)
- Isolados resistentes à colistina são frequentemente produtores de carbapenemases

Fig. 2. Trends in consumption of polymyxins from several European countries, reporting year 2014. ATC, Anatomical Therapeutic Chemical classification system; DDD, defined daily doses. Reproduced from the European Centre for Disease Prevention and Control (ECDC) [5].

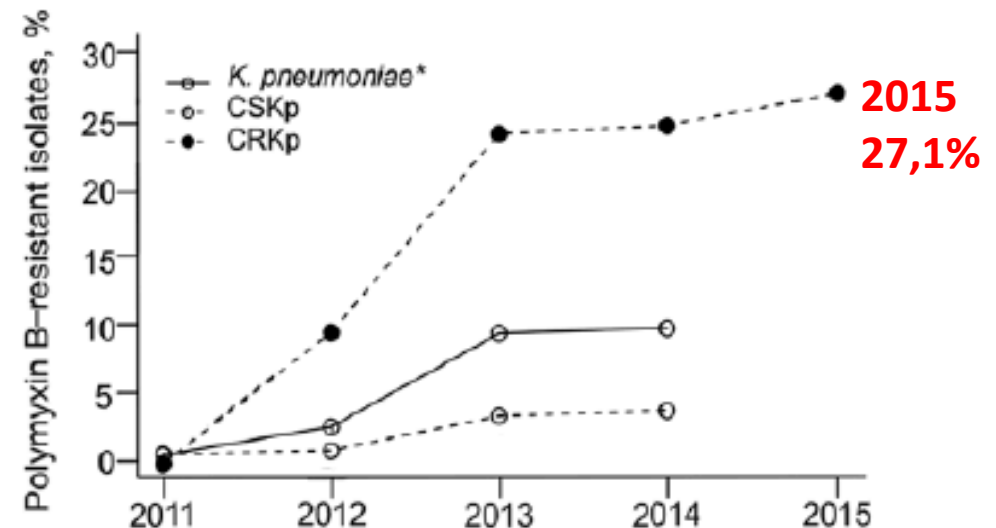
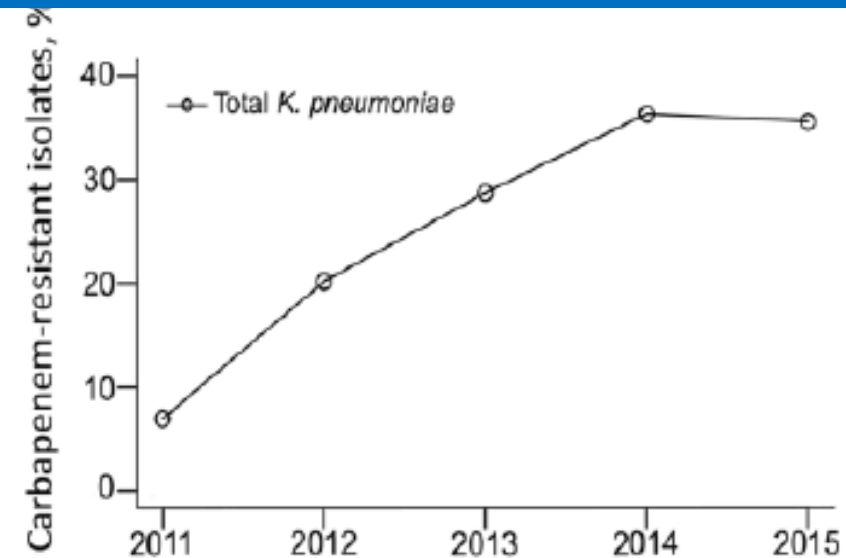
Resistência à Polimixina na Cidade de São Paulo

Polymyxin B Resistance in Carbapenem-Resistant *Klebsiella pneumoniae*, São Paulo, Brazil

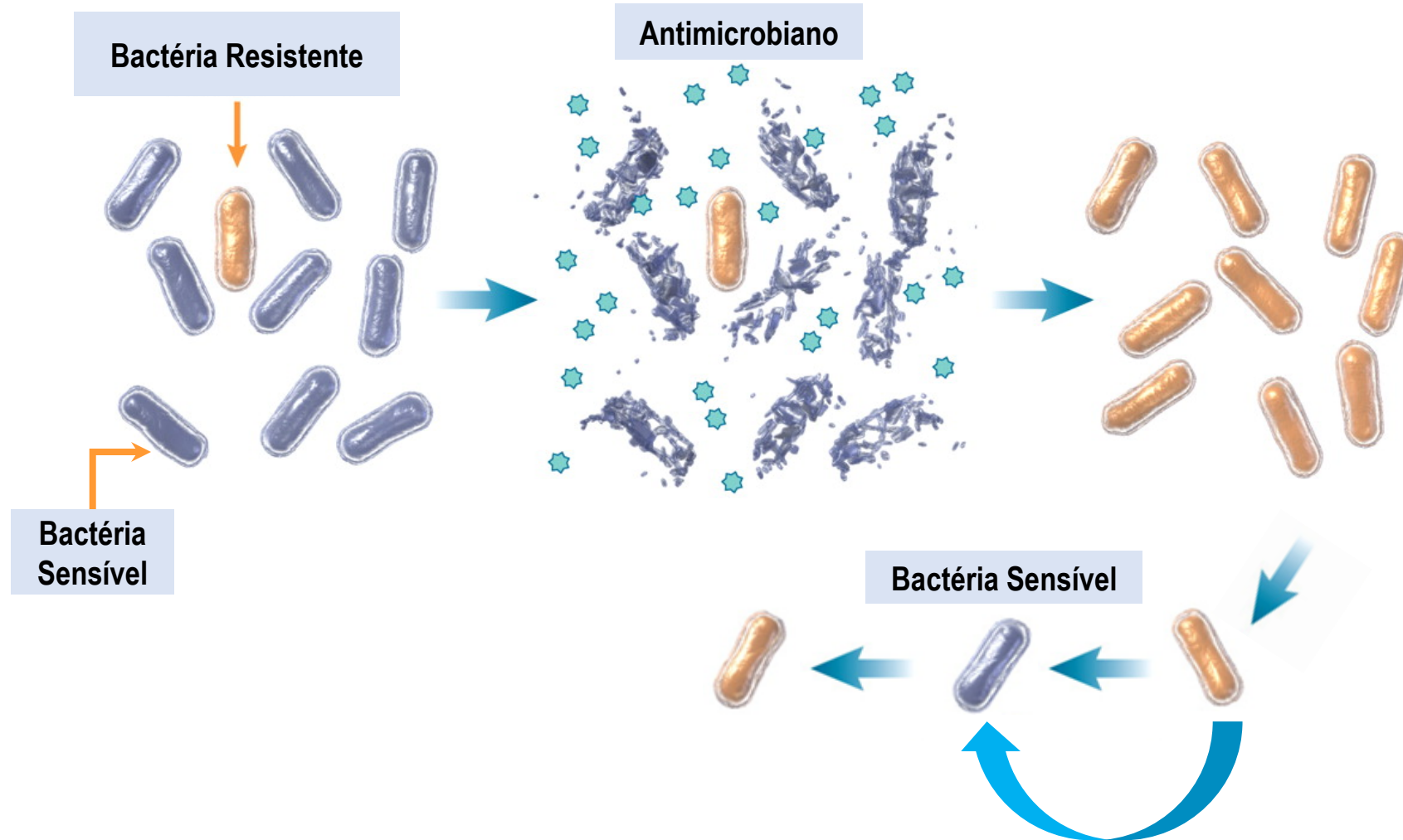
Flávia Bartolleti, Bruna Mara Silva Seco,
Carla Capuzzo dos Santos,
Carolina Bragança Felipe,
Mara Elisa Borsato Lemo,
Tatiane da Silva Alves, Lilian F. Passadore,
Marcelo J. Mimica, Suely Carlos Ferreira Sampaio,
Alexandre Prehn Zavascki,
Jorge Luiz Mello Sampaio

Author affiliations: University of São Paulo School of
Pharmaceutical Sciences, São Paulo, Brazil (F. Bartolleti,

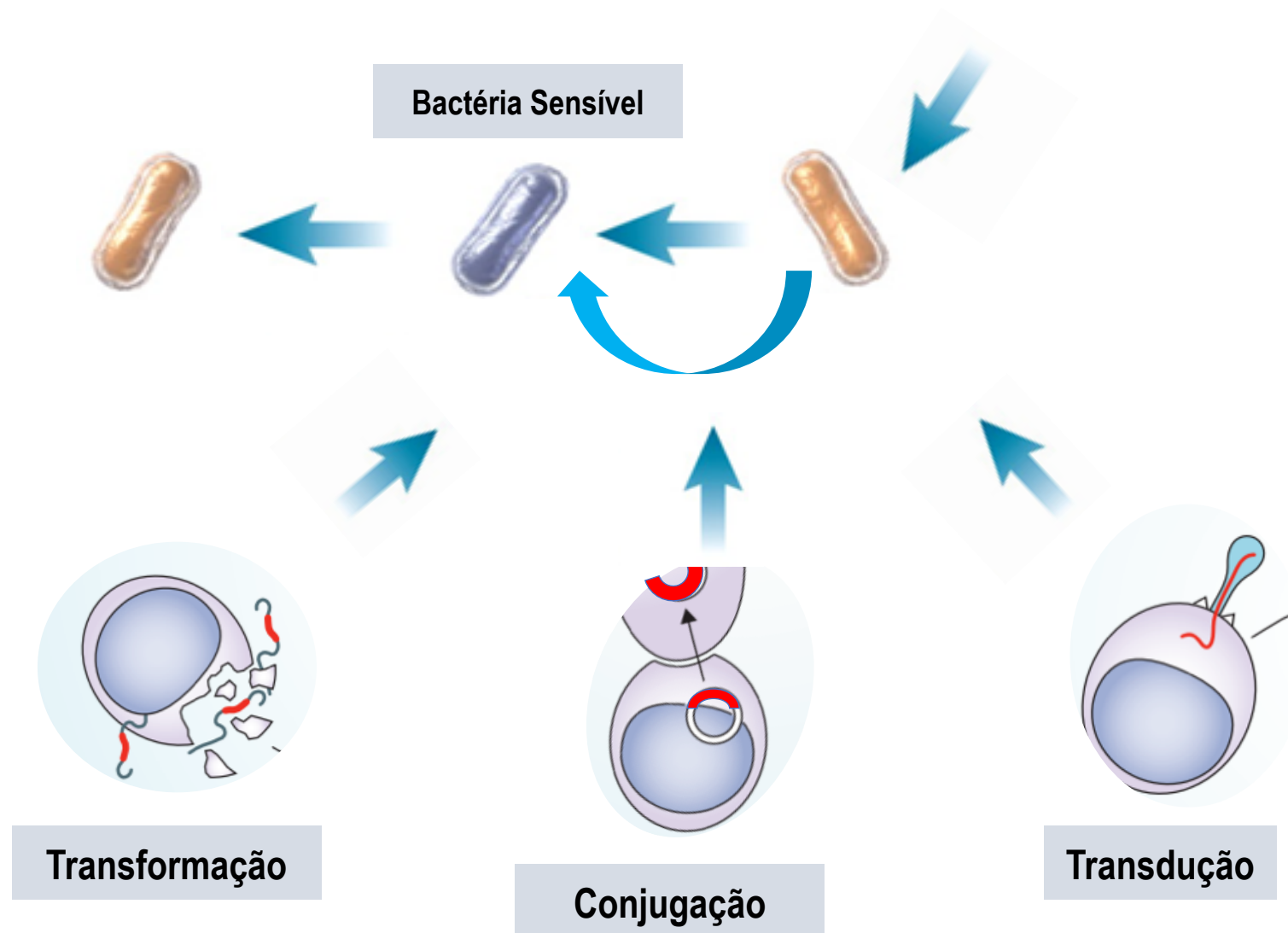
Bartolleti et al., 2016, EID, v.22:1849-50.



Efeito da Pressão Seletiva Exercida pelos Antimicrobianos



Transferência Horizontal dos Genes de Resistência



Concentrações subinibitórias de quinolonas aumentam a taxa de conjugação por \uparrow a expressão de genes associados à conjugação (mecanismo independente de SOS)

Shun-Mei et al. Microb Pathog. 2018 Jan;114:57-62.

Table A5.2 Consumption of antibiotics (DDD per 1000 inhabitants per day) and proportion (%) of total consumption by AWARe categorization in six countries of the Region of the Americas (2015)

Country	DDD per 1000 Inhabitants per day (% of total)				
	Access	Watch	Reserve	Other	Total
Bolivia (Plurinational State of)^{a,b,c}	15.12 (77.3%)	4.41 (22.5%)	0.00 (0.0%)	0.03 (0.2%)	19.57 (100.0%)
Brazil^b	14.72 (64.7%)	6.72 (29.5%)	0.08 (0.4%)	1.23 (5.4%)	22.75 (100.0%)
Canada	10.02 (58.7%)	5.21 (30.5%)	0.02 (0.1%)	1.80 (10.6%)	17.05 (100.0%)
Costa Rica^{b,c}	11.82 (83.3%)	2.25 (15.9%)	0.00 (0.0%)	0.11 (0.8%)	14.18 (100.0%)
Paraguay^{a,b,c}	8.69 (44.8%)	10.29 (53.1%)	0.00 (0.0%)	0.39 (2.0%)	19.38 (100.0%)
Peru^{a,b,c}	7.19 (70.1%)	2.95 (28.7%)	0.00 (0.0%)	0.12 (1.1%)	10.26 (100.0%)

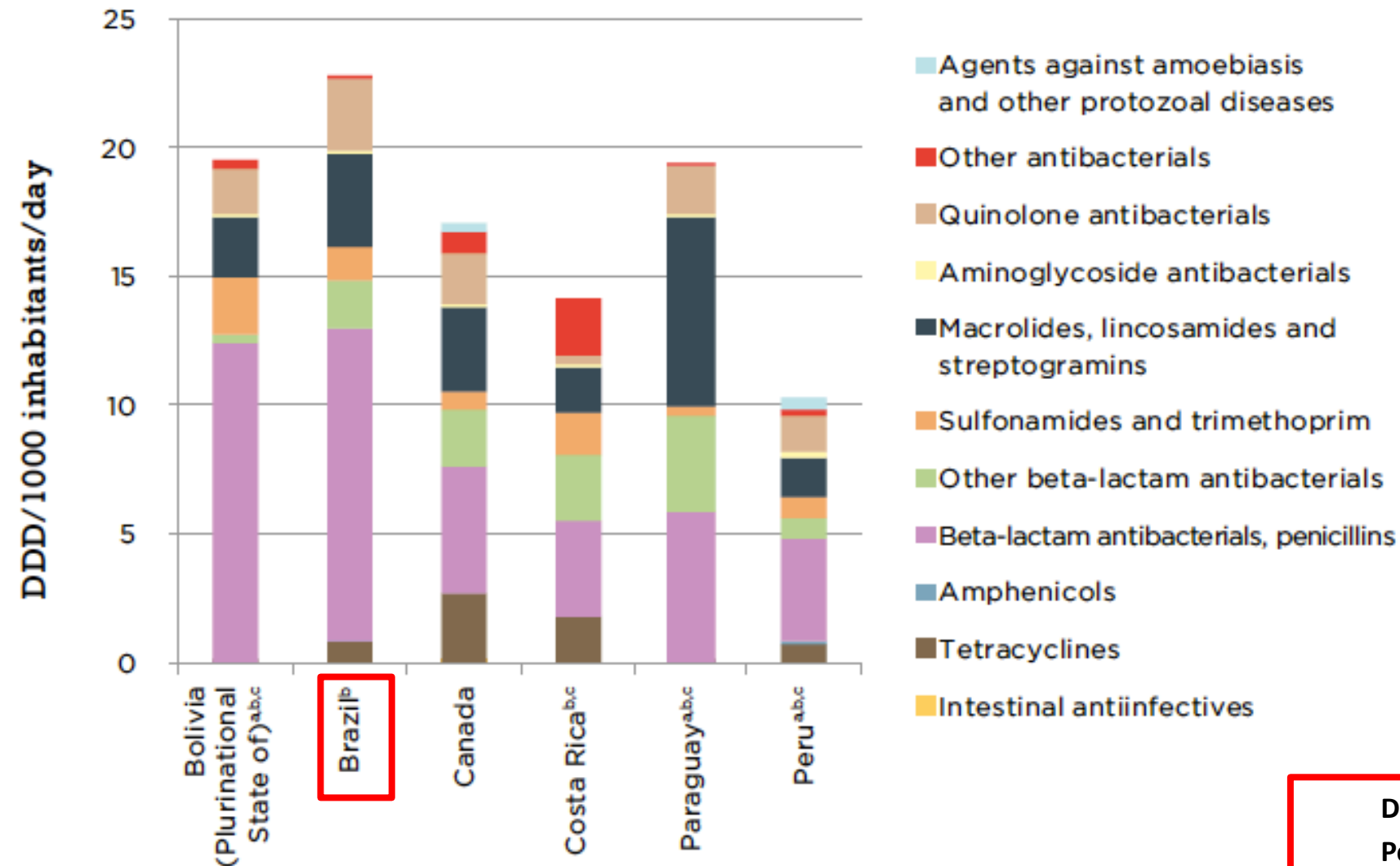
^a Coverage of antimicrobial consumption estimated to be 70% or less, population-adjusted.

^b Data from 2016.

^c Only public sector reported.

to improve access (Access),
to monitor important antibiotics (Watch)
preserve 'last resort' antibiotics (Reserve)

Fig. 4.4 Consumption of antibiotics (DDD per 1000 inhabitants per day) by pharmacological subgroup in six countries of the Region of the Americas (2015)



DDD/1000hab/dia
 Penicilinas = 12,15
 MLS = 3,69
 Quinolonas = 2,83

^a Coverage of antimicrobial consumption estimated to be 70% or less, population-adjusted.

^b Data from 2016.

^c Only public sector reported.

Pressão Seletiva Exercida pelo Uso de Antimicrobianos

- Exposição às fluoroquinolonas, cefalosporinas de amplo espectro ou penicilinas anti-pseudomonas foram fatores de risco independentes para infecção por *K. pneumoniae* resistente aos carbapenêmicos^{1,2}
- Duração da exposição antimicrobiana³
 - Risco de *Klebsiella* produtora de ESBL ou resistente aos carbapenêmicos aumentou com a exposição mais prolongada ao β -lactâmico/inibidor de β -lactamase
 - O uso de fluoroquinolona amplificou o impacto da exposição aos carbapenêmicos ao risco de infecção por ESBL e CRE
- Número cumulativo de exposições foram fatores de risco independentes para CRE⁴

1. Falagas et al. J Antimicrob Chemother 2007; 60:1124-30.

2. Gasink et al. Infect Control Hosp Epidemiol 2009; 30:1180-5.

3. Kritsotakis et al. J Antimicrob Chemother 2011; 66:1383-91.

4. Patel et al. J Antimicrob Chemother 2011; 66:1600-8

Programa de Gerenciamento de Antimicrobianos*: Objetivos

Melhoria na Assistência

Terapia Eficaz (4Rs)

“O ATB certo para o paciente correto, no momento certo, na dose e na via corretas, causando o menor prejuízo para o paciente e futuros pacientes.”

Redução dos danos colaterais

< toxicidade / Infecções por *C. difficile* / CVC-ICS/LOS ATB Resistência

Antimicrobial Stewardship Program

=

AMS ou ASP

Impacto nos custos

< Danos colaterais - < custo

< Custo com ATBs

Curto prazo (dias)

Médio Prazo (semanas/meses)

Longo Prazo (anos)

Uso Responsável de Antimicrobianos

- **Restrição do uso de cefalosporinas para uso profilático e fluoroquinolonas para choque séptico¹**
 - A proporção mensal de *K. pneumoniae* produtora de ESBL diminuiu de 37% para 10% ($P < 0,001$).
 - Incidência anual de colonização por *K. pneumoniae* produtora de ESBL por 1.000 leitos-ocupado/dia diminuiu significativamente de $>1,00$ para $<0,5$ ($P < 0,001$)
- **Educação e medidas de controle semi-restritivas na prescrição de antimicrobianos²**
 - Maio 2014 a April 2016
 - Redução SS no consumo de antimicrobianos (-1,45 DDD/1000 pacientes/dia mensalmente, 95% IC -2,38 a -0,52, $P = 0,004$)
 - Tendência SS na redução da incidência de infecção de corrente sanguínea por *K. pneumoniae* resistente aos carbapenêmicos (taxa de incidência de 0,96, 95% CI 0,92-0,99, $P = 0,013$).



World Health
Organization

ANTIMICROBIAL STEWARDSHIP PROGRAMMES

IN HEALTH-CARE FACILITIES IN LOW- AND

MIDDLE-INCOME COUNTRIES

A WHO PRACTICAL TOOLKIT



National Quality Partners Playbook: Antibiotic Stewardship in Acute Care

NATIONAL QUALITY FORUM
NATIONAL QUALITY PARTNERS
ANTIBIOTIC STEWARDSHIP ACTION TEAM

Part I

Strategies for implementing
and sustaining antimicrobial
stewardship



Implementation of
Antibiotic Stewardship Core Elements
at Small and Critical Access Hospitals



ANTIMICROBIAL STEWARDSHIP FROM PRINCIPLES TO PRACTICE



BRITISH SOCIETY FOR
ANTIMICROBIAL
CHEMOTHERAPY



Centers for Disease
Control and Prevention
National Center for Emerging and
Zoonotic Infectious Diseases

Cover photo courtesy of Galesinger Jersey Shore Hospital



Agência Nacional de Vigilância Sanitária

Diretriz Nacional para Elaboração de Programa de Gerenciamento do Uso de Antimicrobianos em Serviços de Saúde

Gerência de Vigilância e Monitoramento em Serviços de Saúde - GVIMS

Gerência Geral de Tecnologia em Serviços de Saúde - GGTS

Brasília, 28 de dezembro de 2017.

Diretriz Nacional para Elaboração de Programa de Gerenciamento do
Uso de Antimicrobianos em Serviços de Saúde.

GVIMS/GGTES/ANVISA

2. OBJETIVO

Orientar os profissionais de saúde na elaboração e implementação de programas de gerenciamento do uso de antimicrobianos nos serviços de saúde.

Constituem elementos essenciais para a criação, implantação e execução desse Programa nos hospitais:

- Apoio da alta direção do hospital;
- Definição de responsabilidades de todos os profissionais envolvidos;
- Educação;
- Desenvolvimento de ações para melhorar a prescrição de antimicrobianos;
- Monitoramento do programa e
- Divulgação de resultados.

- ✓ Alta gestão institucional;
- ✓ CCIH;
- ✓ Equipe médica;
- ✓ Equipe de enfermagem;
- ✓ Farmácia clínica;
- ✓ Laboratório de microbiologia;
- ✓ Tecnologia da informação e
- ✓ Coordenações de setores estratégicos para o gerenciamento do uso de antimicrobianos como, por exemplo, unidades clínicas e assistências (UTI, Centro Cirúrgico e obstétrico, clínica médica, emergência, Centro de oncologia, etc.) e as unidades de apoio (farmácia, laboratório de análises clínicas, núcleo de qualidade, gerenciamento de risco ou segurança do paciente, entre outros)¹⁵.

Diretriz Nacional para Elaboração de
Programa de Gerenciamento do Uso de
Antimicrobianos em Serviços de Saúde

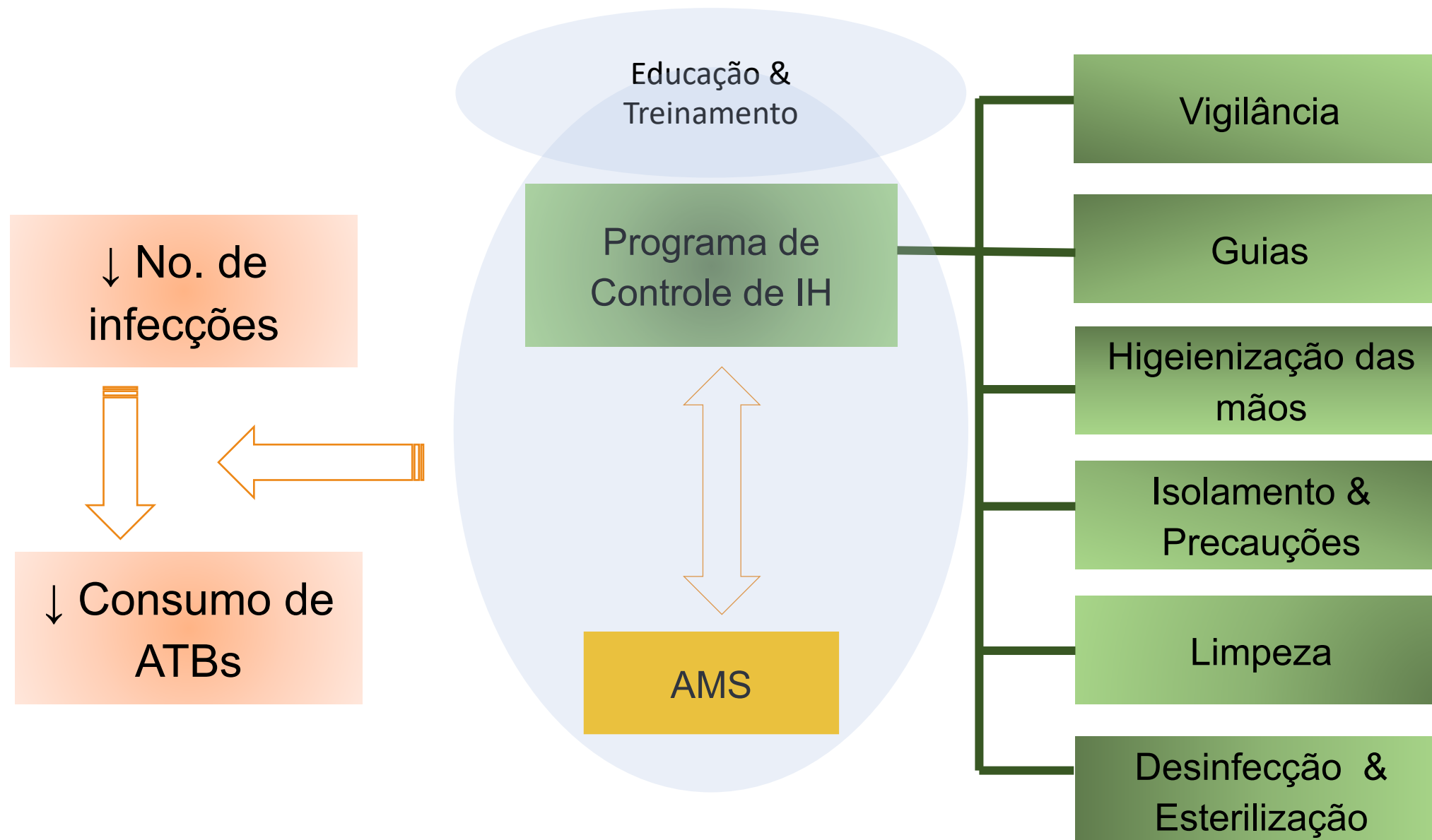
Gerência de Vigilância e Monitoramento em Serviços de Saúde - GVIMS

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GVIMS/GGTS/ANVISA

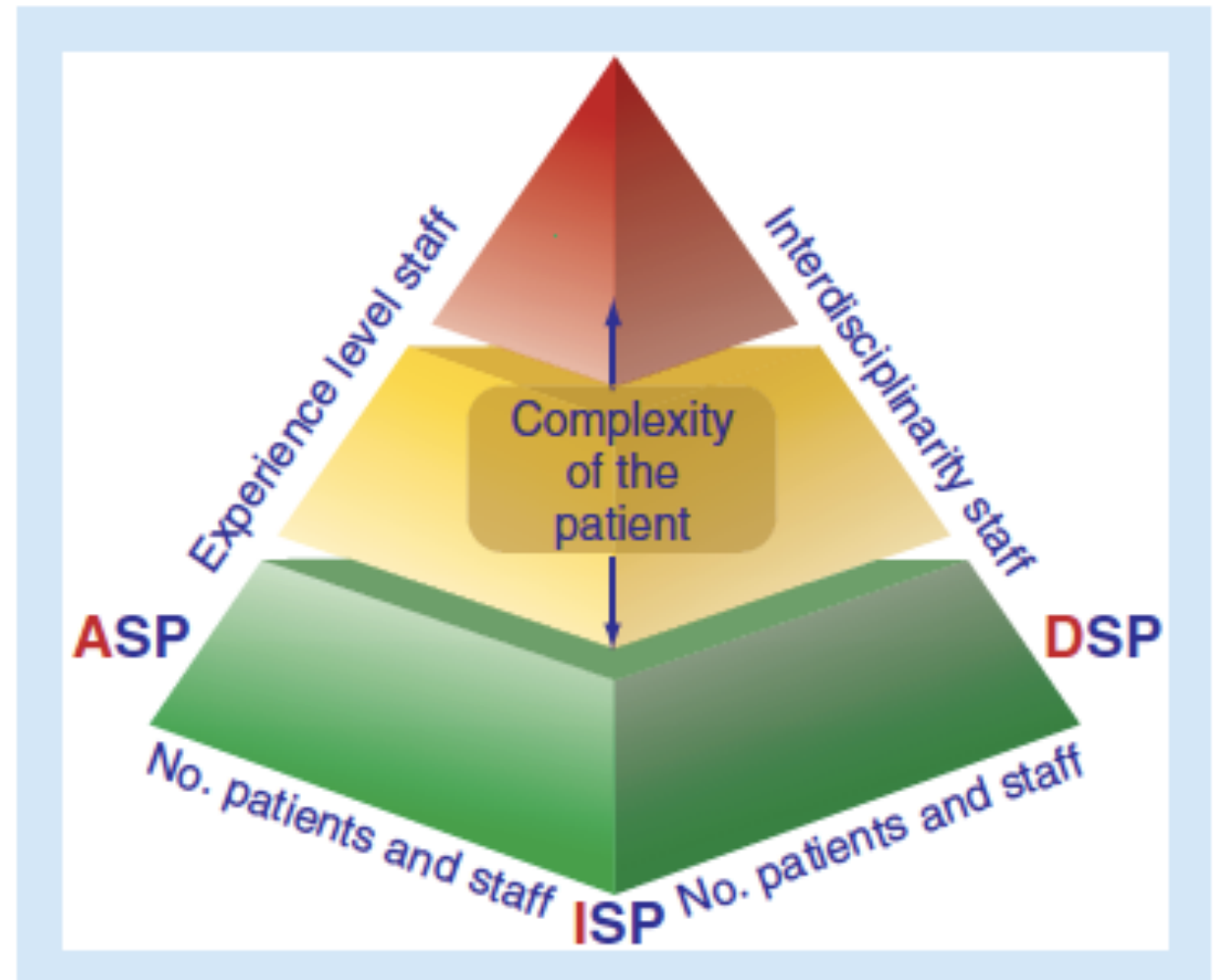
Relação entre os Programas de CIH e AMS



Cooperação entre Alemanha e a Holanda

EurSafety Health-net project (>8 milhões de habitantes).

115 hospitais, + 200 LTCF e outras instituições de saúde trabalhando em conjunto para o controle de infecção.



- ✓ Utilização de protocolos clínicos para as principais síndromes clínicas;
- ✓ Adoção das boas práticas de prescrição, como documentação de dose, duração e indicação do antimicrobiano;
- ✓ Auditoria prospectiva de prescrição com intervenção e divulgação dos dados;
- ✓ Readequação da terapia, conforme resultados microbiológicos;
- ✓ Análise técnica das prescrições pela farmácia;
- ✓ Restrição com uso de formulário terapêutico e pré-autorização de antimicrobianos.

Regras de ouro para prescrição de antimicrobianos¹:

- Guiada por resultados microbiológicos, sempre que possível;
- Indicação de uso baseada em evidência científica;
- Espectro restrito, se possível;
- Dose apropriada, de acordo com sítio e tipo de infecção;
- Quando possível, priorizar a via oral;
- Minimizar a duração da terapia antimicrobiana;
- Monoterapia, sempre que possível;
- Reavaliação do paciente 48h após o início da terapia antimicrobiana.

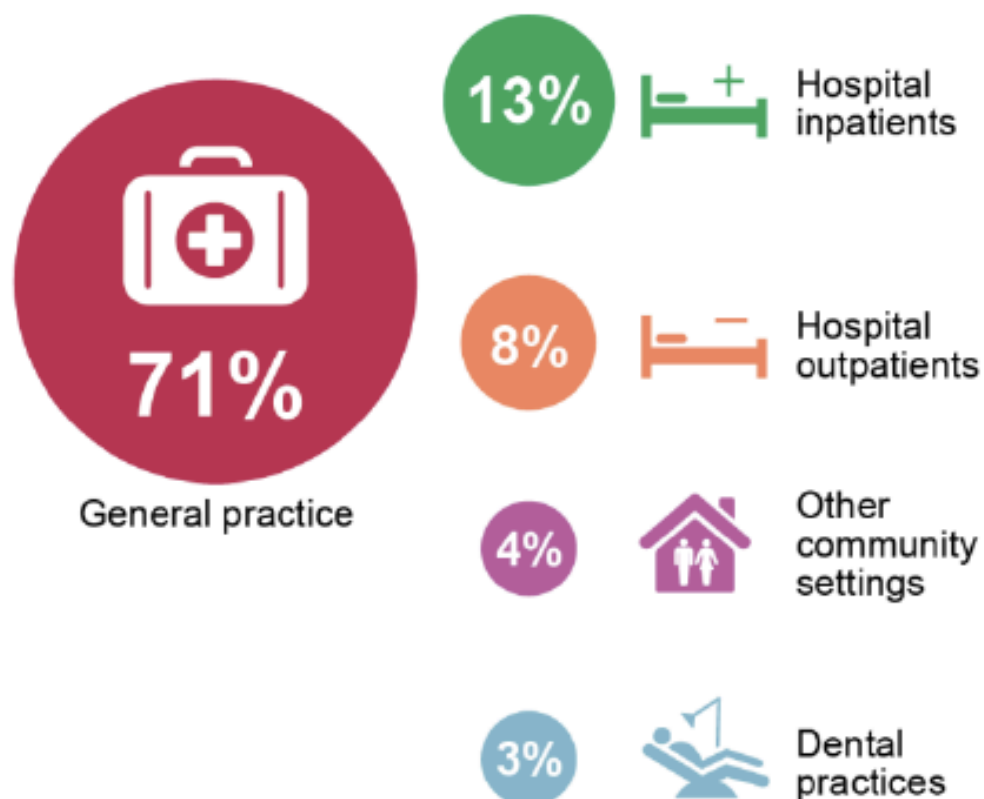
Como eu posso melhorar a prescrição de antimicrobianos?

- Uso de biomarcadores
- Diagnóstico rápido (ID e TSA)
- Terapia antimicrobiana inicial
 - Espectro de cobertura (pK/pD; terapia combinada)
 - Guias locais
- Terapia antimicrobiana definitiva (dirigida)
 - Descalonamento
 - Terapia sequencial
 - Tempo de tratamento
- Medidas de controle de infecção
- Comunicação
- Educação

Infographic 4. Total antibiotic consumption and trends by prescriber setting

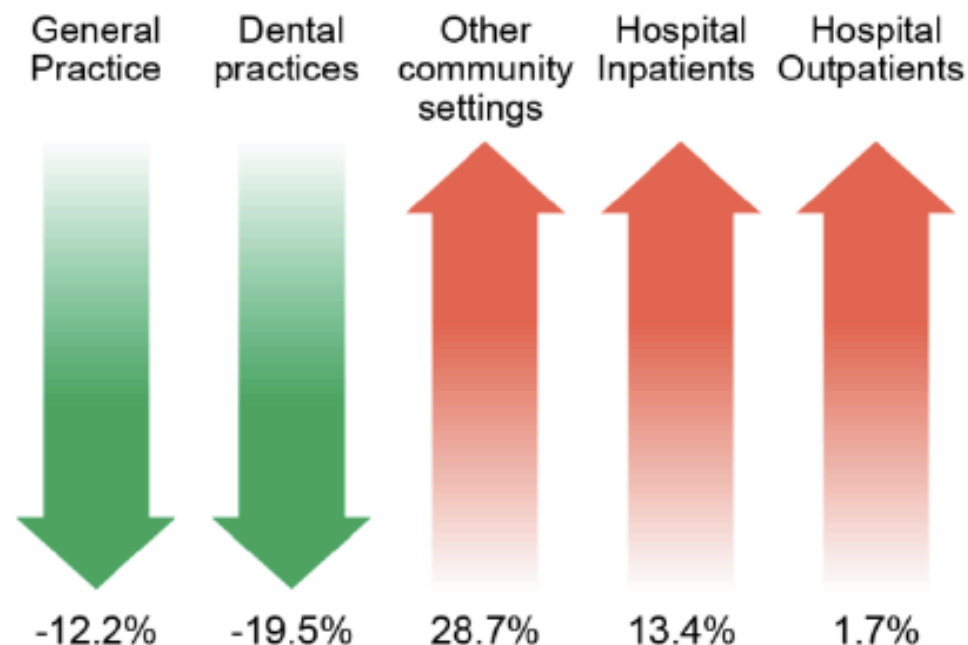
Total antibiotic consumption by prescriber setting as proportion of overall prescribing, England, 2019

Who is Prescribing?



Trends in total antibiotic consumption by prescriber setting, England, 2015-2019

% change



% change (DDDs per 1,000 inhabitants per day)

Uso de Antimicrobianos na Comunidade

- > 50% prescritos desnecessariamente para IVAS
- Baixa adesão aos guidelines

Infecção	% de Pacientes recebendo antibióticos recomendados como de primeira escolha		
	Austrália ¹	EUA ²	
	Adultos e crianças	Adultos	Crianças (0-19 a)
Faringite e/ou amigdalite	39%	37%	60%
Rinossinusite	27%	37%	52%
Otite Média Aguda	51%	-	67%

1. Aura 2017 Second Australian report on antimicrobial use and resistance in human Health

2. CDC Report on Antibiotic Use in United States:Progress and Opportunities.2017



The Core Elements of Outpatient Antibiotic Stewardship



National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion



CS289000-A

Entities that are intended audiences for this report are outpatient health care professionals and leaders of their respective clinics, departments, facilities, and health care systems.



Primary care clinics and clinicians

These clinics and clinicians prescribe approximately half of all outpatient antibiotics in the United States.* This includes clinicians specializing in family practice, pediatrics, and internal medicine, all of whom treat a wide variety of patients and conditions that might benefit from antibiotic treatment.



Outpatient specialty and subspecialty clinics and clinicians

These clinics and clinicians focus on treatment and management of patients with specialized medical conditions that sometimes benefit from antibiotic therapy. These specialties clinics include gastroenterology, dermatology, urology, obstetrics, otolaryngology, and others.



Emergency departments (EDs) and emergency medicine clinicians

EDs and emergency medicine clinicians are positioned between acute care hospitals and the community and encounter unique challenges, including lack of continuity of care and higher concentration of high-acuity patients, as well as unique opportunities for stewardship interventions, such as greater clinician access to diagnostic resources and the expertise of pharmacists and consultants.



Retail health clinics and clinicians

These clinics and clinicians provide treatment for routine conditions in retail stores or pharmacies and represent a growing category of health care delivery in the United States.



Urgent care clinics and clinicians

These clinics and clinicians specialize in treating patients who might need immediate attention or need to be seen after hours but might not need to be seen in EDs.



Dental clinics and dentists

Dental clinics and dentists use antibiotics as prophylaxis before some dental procedures and for treatment of dental infections.



Health care systems

Health care systems plan, deliver, and promote health care services and often involve a network of primary and specialty outpatient clinics, urgent care centers, EDs, acute care hospitals, and other facilities that provide health care services. Health care systems can use existing antibiotic stewardship programs or develop new ones to promote appropriate antibiotic prescribing practices in their outpatient facilities as well as across the system.



Nurse practitioners and physician assistants

These clinicians work in every medical specialty and subspecialty involved in antibiotic prescribing and should be included in antibiotic stewardship efforts.

*Source: CDC. Outpatient antibiotic prescriptions—United States, 2013. Atlanta, GA: US Department of Health and Human Services, CDC; 2013. http://www.cdc.gov/getsmart/community/pdfs/annual-reportsummary_2013.pdf

Reducing inappropriate antibiotic prescribing in the residential care setting: current perspectives

Áreas de potencial uso indevido de antibióticos

1. Profilaxia para ITU
2. Tratamento da bacteriúria assintomática
3. Prescrição empírica sem confirmação do diagnóstico (sem a coleta de exames, ex. quinolonas em ITUs)
4. Prescrição para IVAS, bronquite aguda
5. Duração prolongada do tratamento
6. Terapia de amplo espectro ou parenteral em idosos com doenças terminais.



The Core Elements of **Antibiotic Stewardship for Nursing Homes**





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

Few studies

Inappropriate design

Heterogeneous interventions

Distinct bug/drug combinations

Definition of resistance

Confounding variables

(infection control measures)

CONCLUSIONS

There is no solid evidence that ASPs are effective in reducing antibiotic resistance in hospital settings. There are still few studies analyzing this matter, most of them with inappropriate study designs. The studies put into practice very heterogeneous interventions targeting varied microorganism-antibiotic pairs, which makes it difficult to unify their results and conclusions and reach an evidence-based consensus. We uphold the need for more studies with appropriate study designs and standardized ASP interventions targeting common microorganism-antibiotic pairs. 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.

Epidemiologia da Resistência Bacteriana

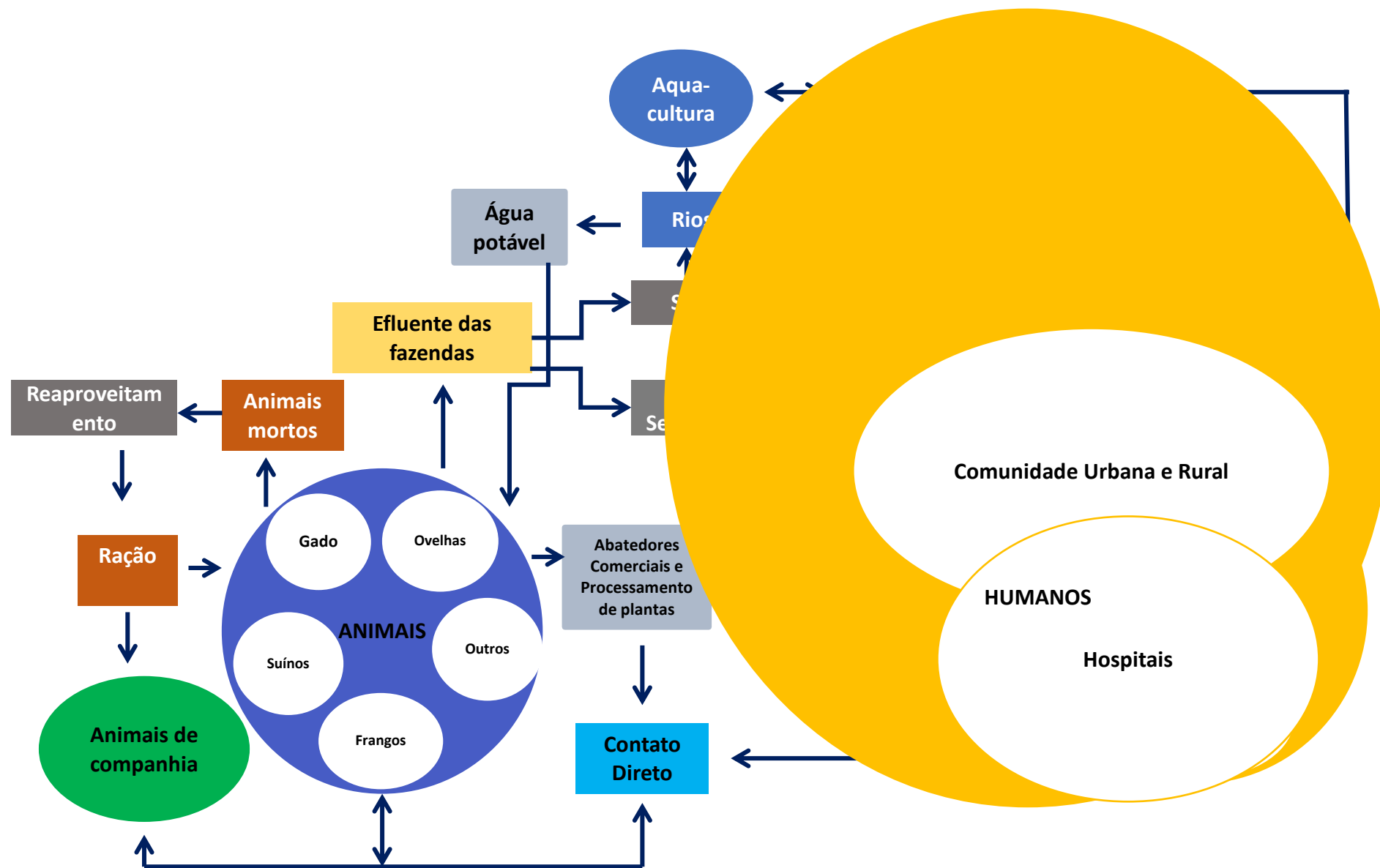
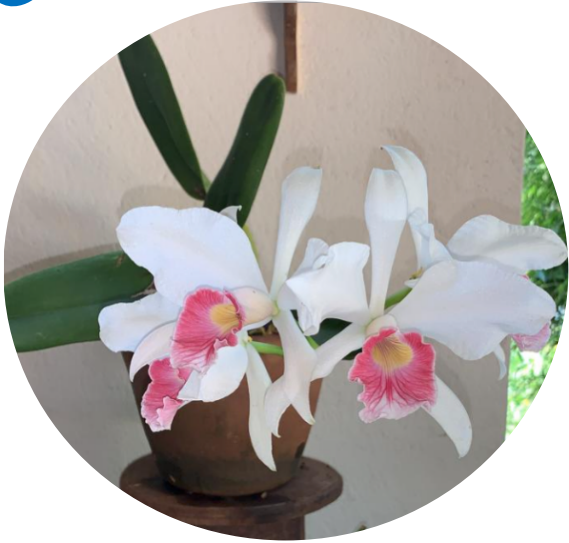


Figura adaptada http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/pubs/amr-ram_final_report-rapport_06-27-eng.pdf

Mensagem Final

- O uso de antimicrobianos tem sido fortemente associado à seleção e ao favorecimento do crescimento de bactérias resistentes;
- Porém, o uso responsável de antimicrobianos nem sempre tem sido associado à redução das taxas resistência bacteriana;
- A epidemiologia da resistência bacteriana é complexa, com várias interfaces e com necessidade de implementação de medidas simultâneas em vários setores.

Muito Obrigada!



O controle de bactérias MDR exige uma ação global e coordenada porque o contexto epidemiológico é complexo.

Exemplos de uso inadequado

MEDIDAS PARA POPULAÇÃO GERAL



State of the Science Review

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

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

CONCLUSIONS

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