

Reflexões sobre Bactérias Multiresistentes:-o que funciona ?!

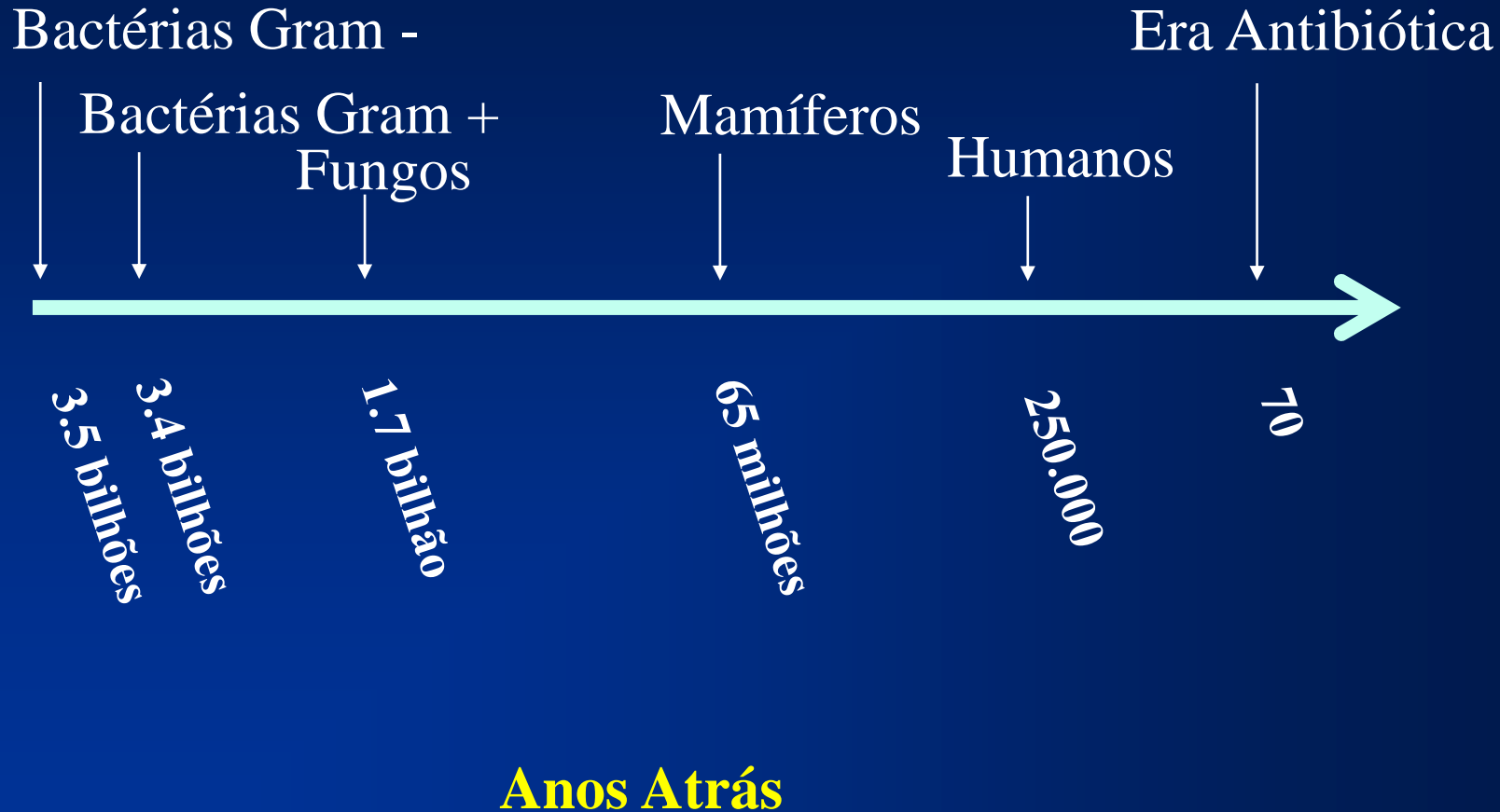
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Sem conflito de interesse
relacionado ao tema

Perspectiva Evolucionária da Era Antibiótica



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graph TD; A[ADERÊNCIA] --> B[COLONIZAÇÃO]; B --> C[INFECÇÃO];
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ADERÊNCIA

COLONIZAÇÃO

INFECÇÃO

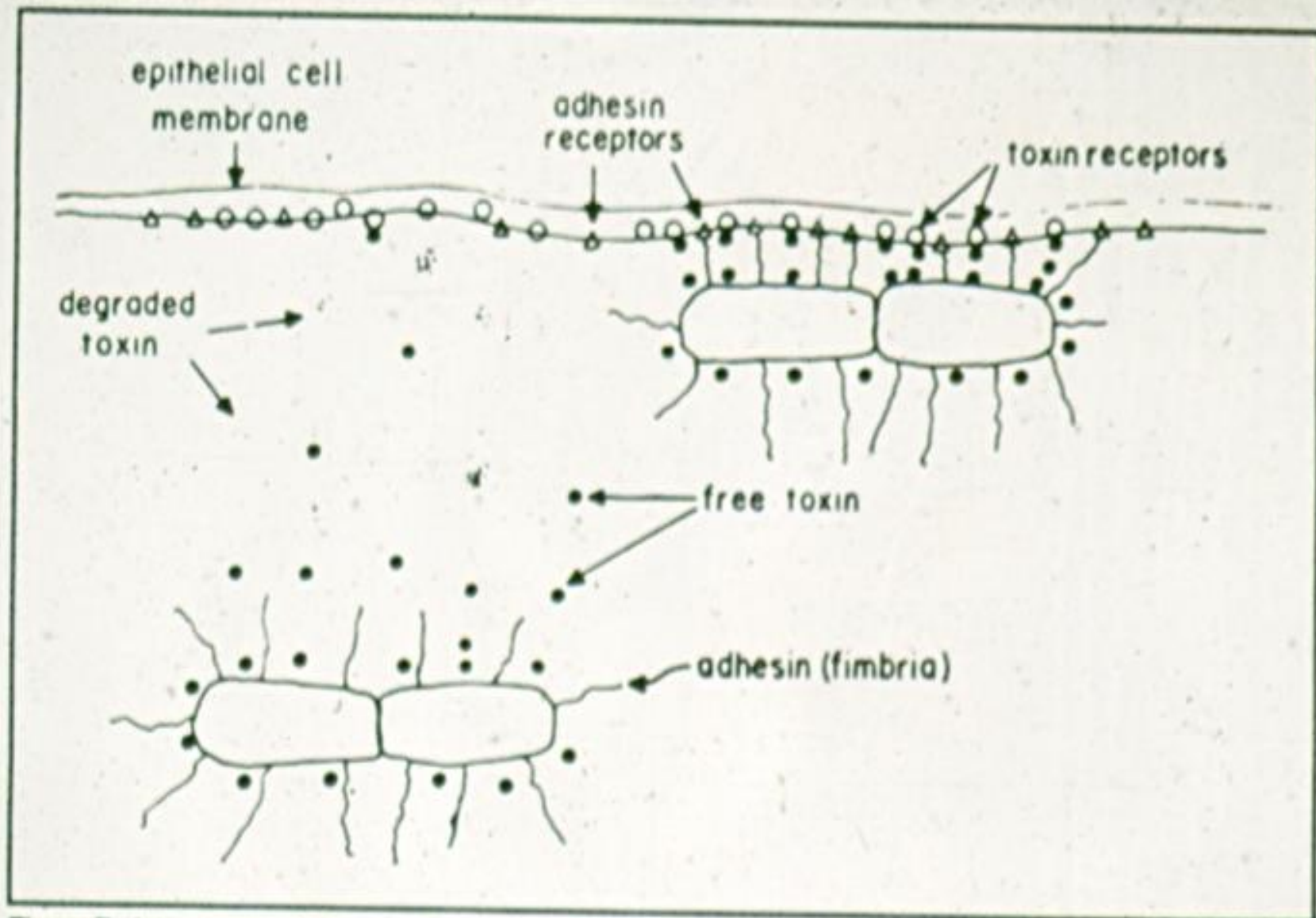
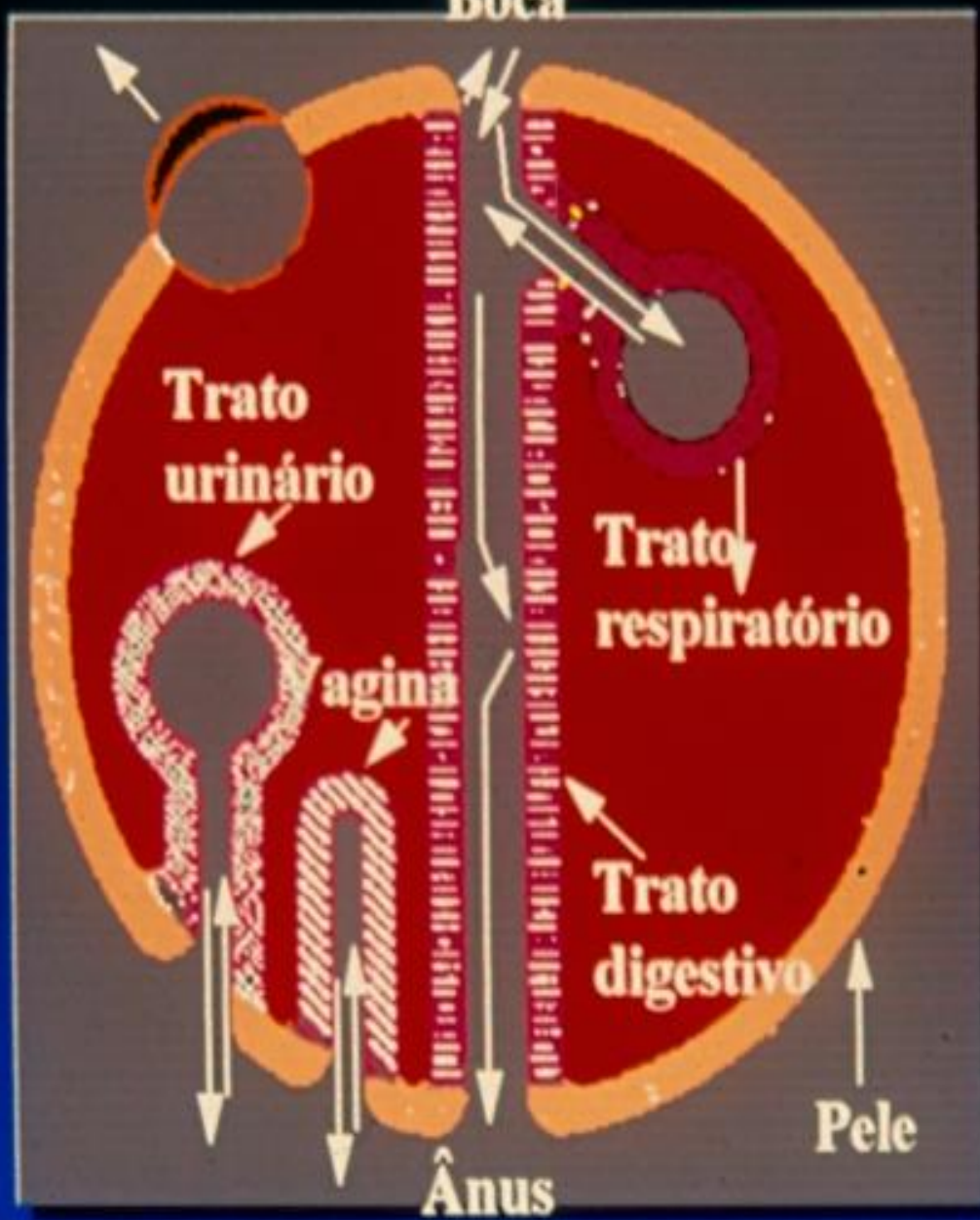


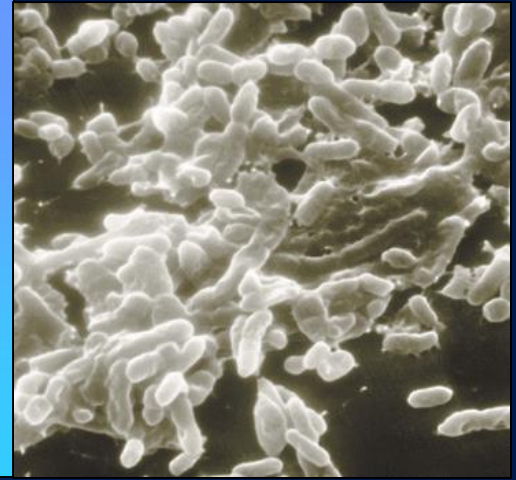
Figure 7. Advantage of bacterial adherence for efficient delivery of toxin to membrane receptors of host cells. The close association of the organism to the epithelial membrane prevents degradation of toxin in the extracellular milieu and allows toxin to be delivered to receptors at a higher concentration. (From Beachey EH. *J Infect Dis* 1981;143:325-345, reproduced with permission).

Conjuntiva

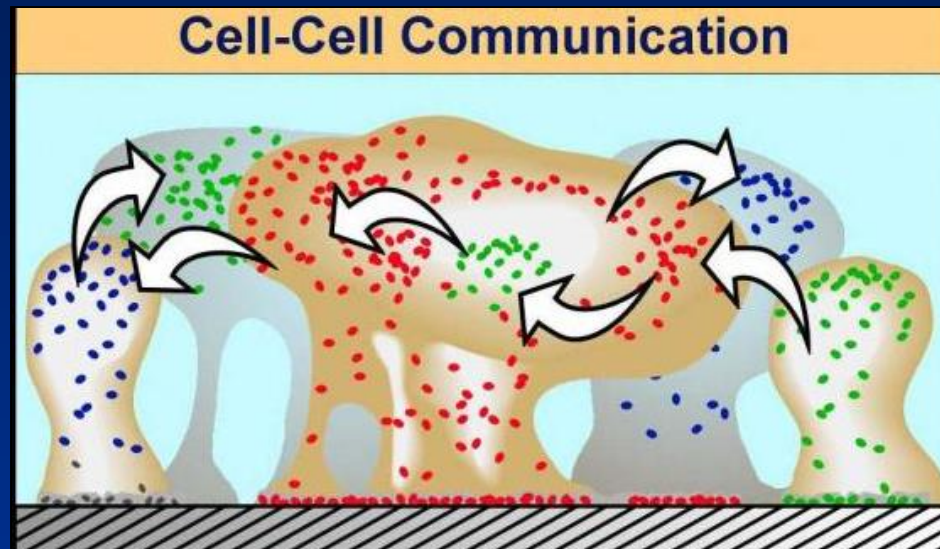
Boca



Biofilme: populações de microrganismos que se concentram na interface sólido-líquido e tipicamente estão envolvidos por uma matriz.

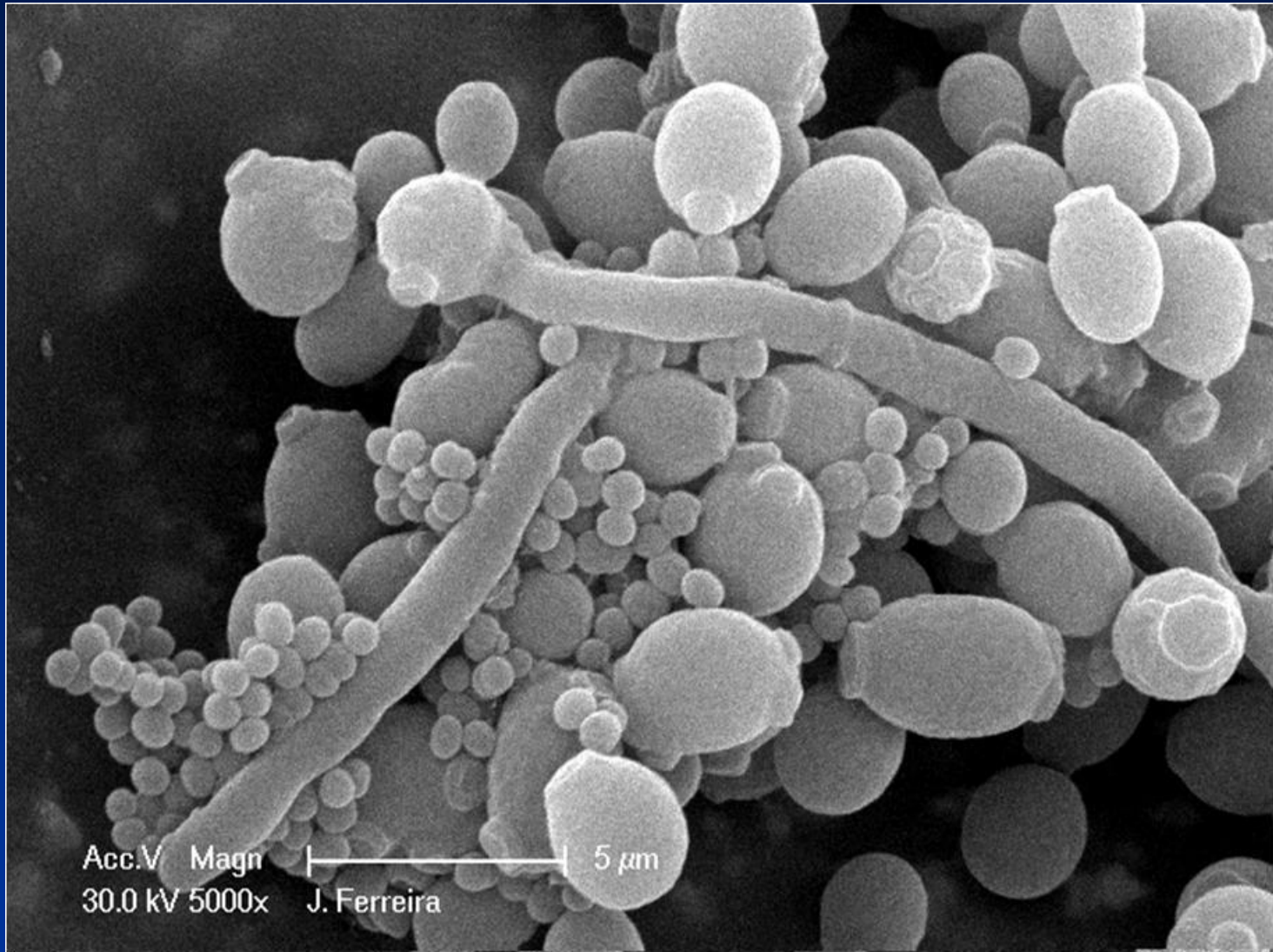


Sinalização célula -célula: multicelularidade bacteriana e o comportamento das comunidades.



O biofilme é um ecossistema altamente dinâmico, que atua de maneira coordenada.

Biofilmes polimicrobianos



Associated Microbiota

Total Body cells 10^{13}

Total Microbial cells 10^{14}

Intestines

1.2 Kg
Metabolic
activity=
liver

40% faecal
weight

200 - 300 species

30 - 40 genera



Skin

10^{12}

Qual o papel dos microorganismos em nosso corpo?

- Estimulo antigênico
- Metabólico
- Proteção
- Limpeza...

Quando deixá-los fazer o seu papel ?!!

- Aspectos Clínicos
- Psicológicos
- Éticos
- Legais
- Religiosos
- Políticos

Níveis de Resistência

Código	Classificação	Definição
MDR	Microorganismo Multirresistente (MMR)	1. Não sensível a ≥ 1 agente em ≥ 3 categorias antimicrobianas
XDR	Microorganismo extensivamente resistente (MER)	2. Não sensível a pelo menos 1 agente nas categorias antimicrobianas, porém permanecendo sensível a 1 ou 2 categorias antimicrobianas (sensível a pelo menos 1 agente)
PDR	Microorganismo Pan-resistente(MPR)	3. Não sensível a todos os agentes listados em todas as categorias de antimicrobianos (é necessário testar todos os agentes listados para caracterizar um microorganismo como Pan-resistente).

RESISTÊNCIA BACTERIANA



UM GRANDE PROBLEMA DE SAÚDE PÚBLICA

↑ Morbi/mortalidade

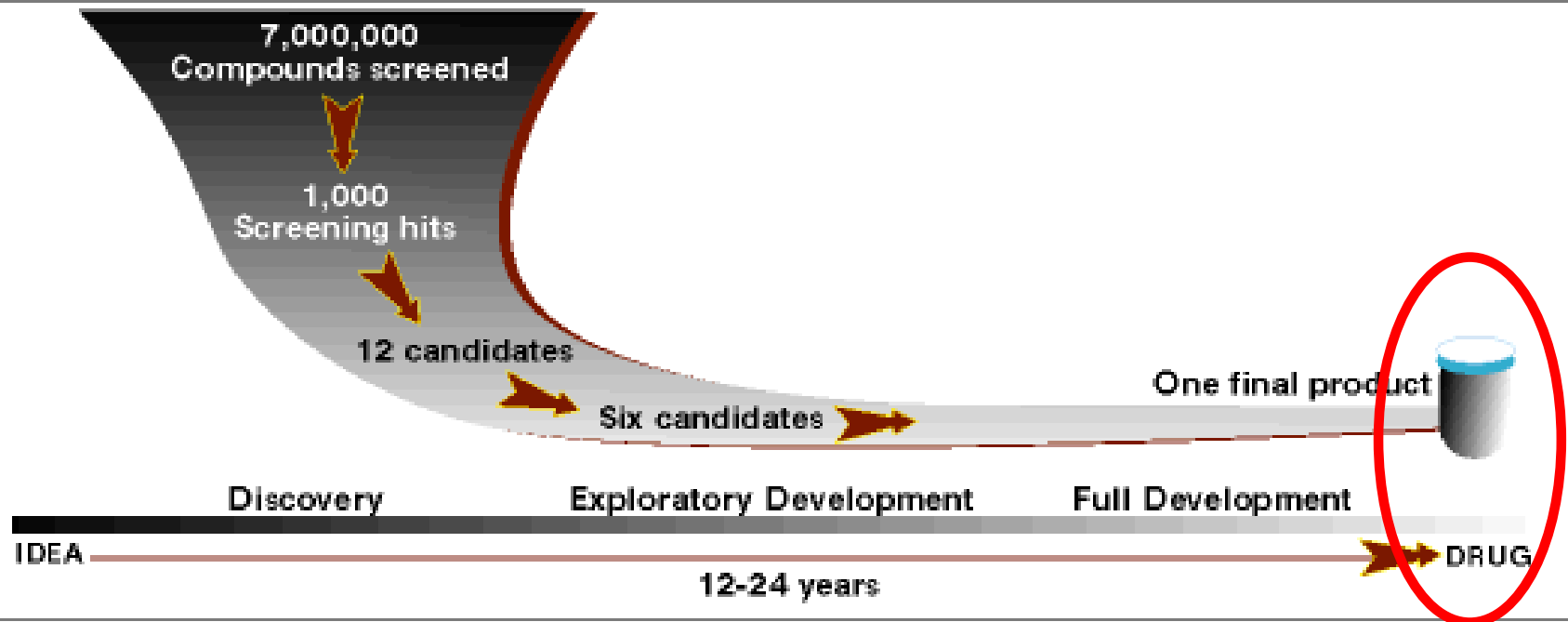
Menos opções terapêuticas

↑ Custos

Ocorrência de surtos

Novas opções terapêuticas??!

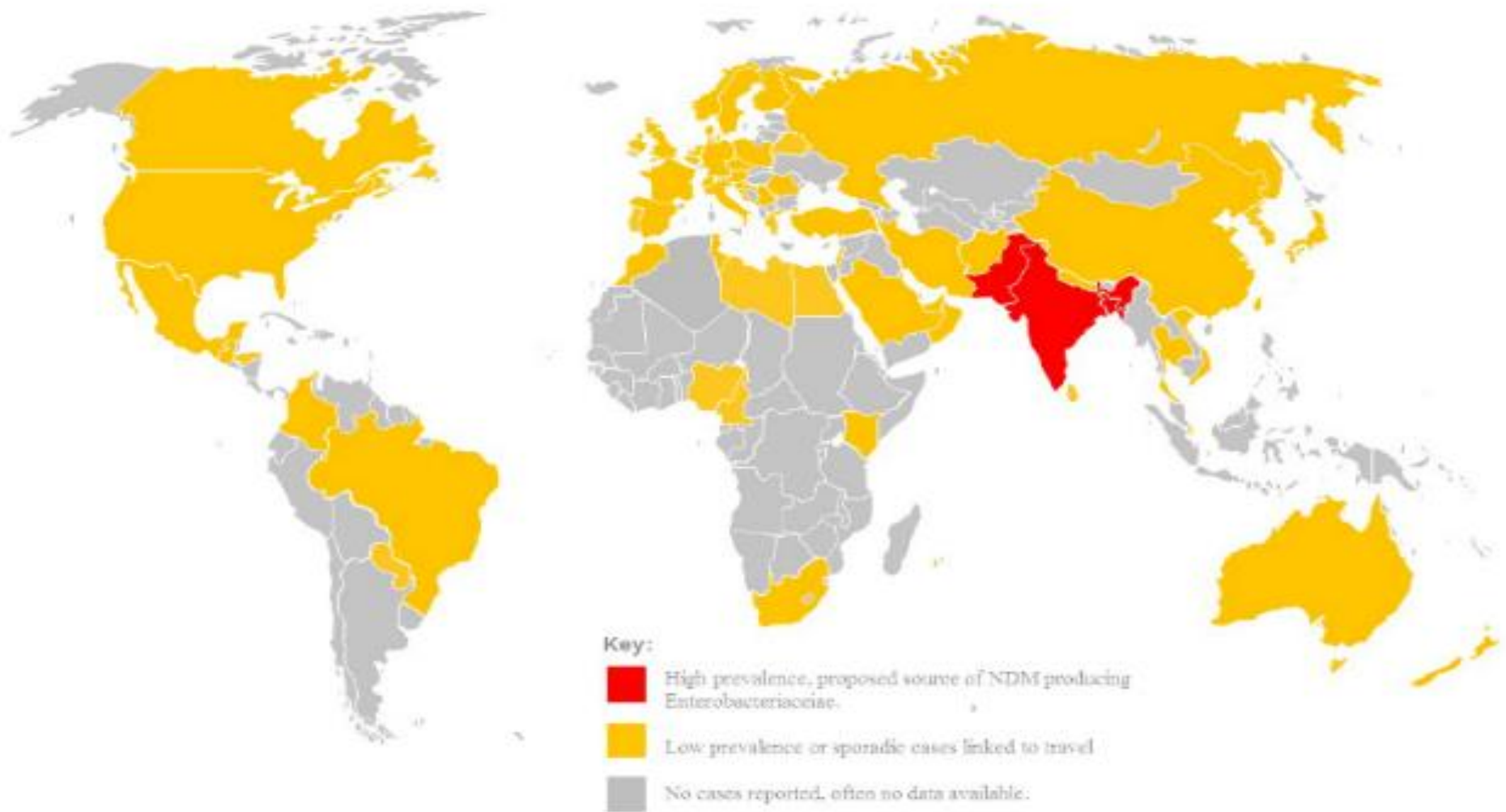
ATTRITION ON THE ROAD: Research and development of new drugs



Source: Pfizer Inc.

USO RACIONAL!!!

Global spread of NDM producing Enterobacteriaceae

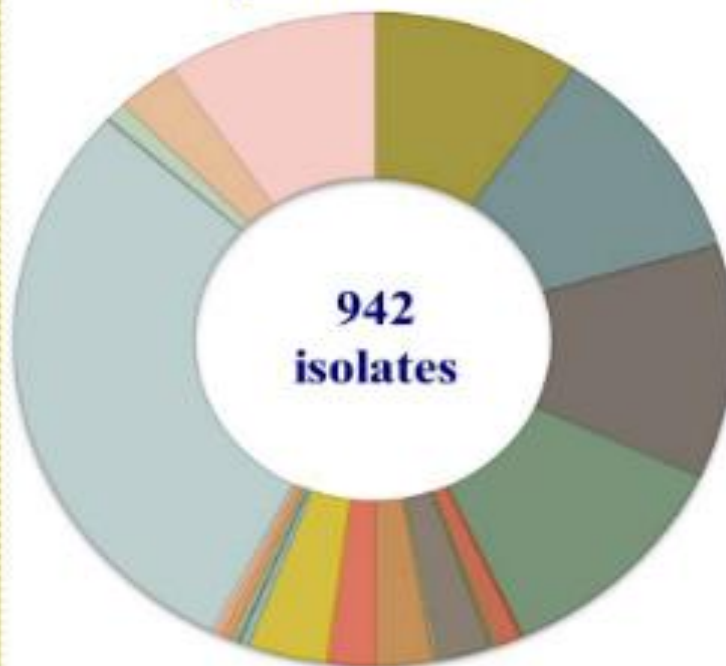






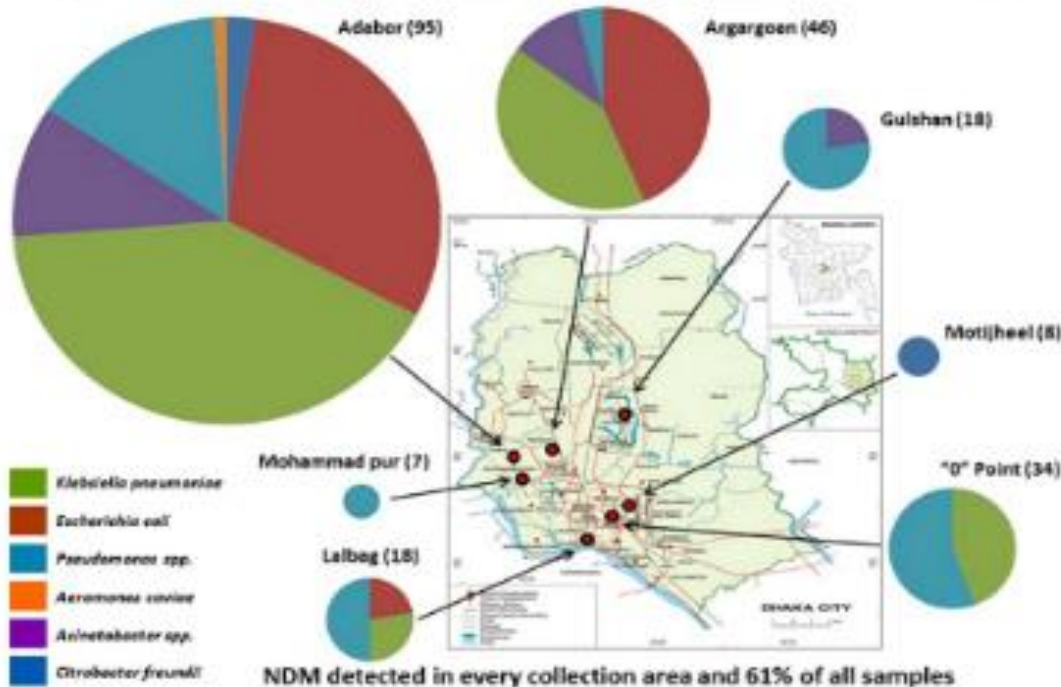
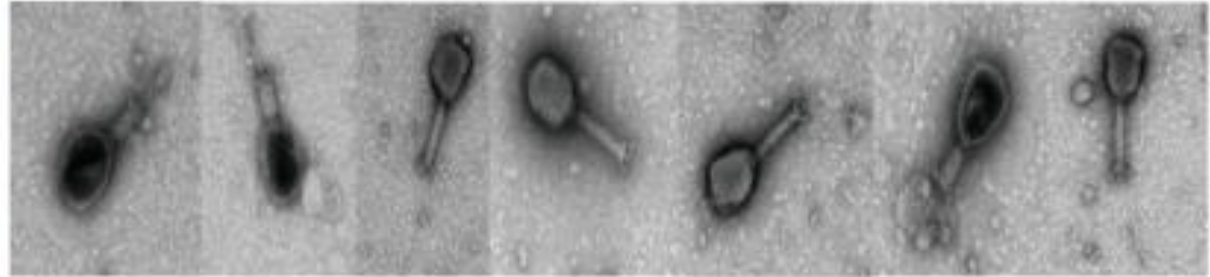
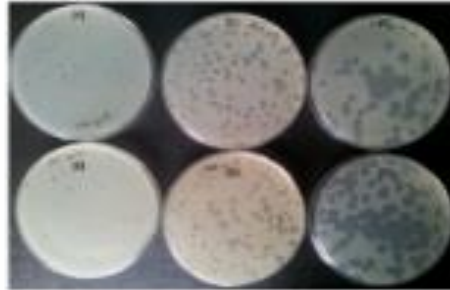
with such sanitary conditions...

Identification of *bla*_{NDM} positive isolates



- Alishewanella* sp. n= 1
 - Citrobacter* sp. n= 88
 - Enterobacter* sp. n= 103
 - Escherichia* sp. n= 109
 - Klebsiella* sp. n= 106
 - Khuyvera* sp. n= 1
 - Leclercia* sp. n= 11
 - Morganella* sp. n= 1
 - Proteus* sp. n= 1
 - Raoultella* sp. n= 23
 - Achromobacter* sp. n= 2
 - Acinetobacter* sp. n= 25
 - Aeromonas* sp. n= 20
 - Alcaligenes* sp. n= 33
 - Brevundimonas* sp. n= 4
 - Chryseobacterium gleum* n=1
 - Comamonas* sp. n= 3
 - Delftia* sp. n=4
 - Ochrobactrum* sp. n= 3
 - Pseudochrobactrum* sp. n= 1
 - Pseudomonas* sp. n= 276
 - Rhizobium* sp. n= 1
 - Shewanella* sp. n=9
 - Stenotrophomonas* sp. n=26
 - No reliable ID n=89
- Enterobacteriaceae

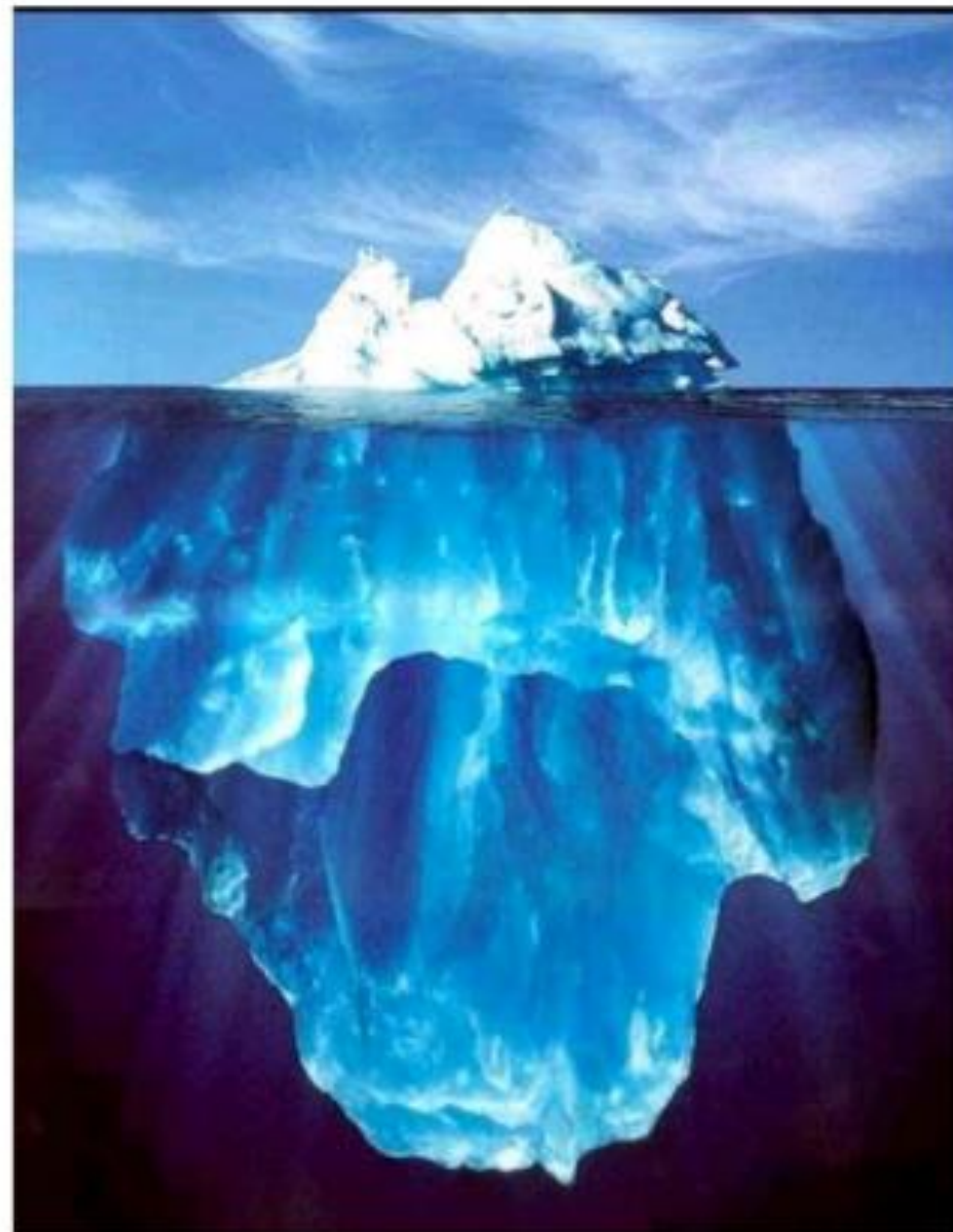
E. coli ST-405, ST-648 and ST-101 in the Bangladesh environment modulated by specific environmental bacteriophages [P-1173].



The prevalence of specific bacteriophage and *E. coli* ST's in the environment is inversely related suggesting that phage modulate strain prevalence in the environment and in the clinic.

Porque no Sul da Ásia (India)??

	INDIA	PAKISTAN	BANGLADESH	SRI LANKA	AFGANISTAN	NETHERLANDS
^a Nosocomial Resistance rates	+++++	+++++	+++	+++	+++	+
^b Community Resistance rates	+++++	+++++	+++	+++	ND	++
^c Public health expenditure as a % of total Health expenditure	*31%	27%	37%	45%	16%	87%
^d Total Health expenditure as a % of GDP	1.2%	0.7%	1.4%	1.5%	1.5%	10.2%
^e GDP PPP	3rd	27th	42nd	65th	104th	23 rd
^f GDP per capita	139rd	143rd	157th	124th	165th	14 th
^g National Antibiotic Production	+++++	+	+	+/-	+/-	+/-
^h Ranking in Medical Tourism Popularity	4th	>50	>50	>50	>50	>50
ⁱ World Sanitation Ranking	145th	133rd	120th	73rd	136th	16 th
^j International export in foods	+++	+	++	+	+	++





J Med Microbiol. 2012 Jun;61(Pt 6):864-7. doi: 10.1099/jmm.0.043190-0. Epub 2012 Mar 1.

Abdominal abscess due to NDM-1-producing *Klebsiella pneumoniae* in Spain.

Oteo J¹, Domingo-García D, Fernández-Romero S, Saez D, Guiu A, Cuevas O, Lopez-Brea M, Campos J.

 **Author information**

Abstract

We describe a clinical case of an abdominal abscess due to NDM-1-producing *Klebsiella pneumoniae* in a 35-year-old Spanish patient after hospitalization in India for perforated appendicitis and peritonitis. The strain belonged to the MLST type 231 and had multiple additional antibiotic resistance genes such as bla(CTX-M-15), armA methylase, aac(6')-Ib-cr, dfrA12, sul1 and qnrB and lack of porin genes ompK35 and ompK36. The patient was cured after abscess drainage.

Scand J Infect Dis. 2012 Apr;44(4):312-4. doi: 10.3109/00365548.2011.633549. Epub 2011 Nov 29.

Successful treatment of NDM-1 *Klebsiella pneumoniae* bacteraemia in a neutropenic patient.

Chien JM¹, Koh TH, Chan KS, Chuah TH, Tan TT.

Infect Control Hosp Epidemiol. 2014 Apr;35(4):390-7. doi: 10.1086/675607.

Carbapenem-resistant *Klebsiella pneumoniae* producing New Delhi metallo- β -lactamase at an acute care hospital, Colorado, 2012.

Epson EE¹, Pisnev LM, Wendt JM, MacCannell DR, Janelle SJ, Kitchel B, Rasheed JK, Limbago BM, Gould CV, Kallen AJ, Barron MA, Bamberg WM.

Antimicrob Agents Chemother. 2012 Nov;56(11):6062-3. doi: 10.1128/AAC.00838-12. Epub 2012 Aug 20.

Isolation of *Klebsiella pneumoniae* producing NDM-1 metallo- β -lactamase from the urine of an outpatient baby boy receiving antibiotic prophylaxis.

Mirovic V, Tomanovic B, Lepsanovic Z, Jovcic B, Kolic M.



Table 1. Carbapenem-resistant organisms cultured from skin sites or blood cultures from patient during admission.

ORGANISM	SITE	CO.AMO	CEFTAZ	CETFTRIAX	CIPRO	PIP.TAZ	ERTAPEN	MEROPEN	COTRIMOX	GENT	AMIK	COLISTIN	TIGECYL	RESISTANCE ENZYME(S)
<i>Vibrio cholera</i>	BC	R	R	R	R	R	R	R	S	R	R	R	S	NDM-1
<i>Enterobacter cloacae</i>	SS	R	R	R	R	R	R	R	R	R	R	S	I	NDM-1 & AmpC
<i>Acinetobacter baumannii</i>	SS	R	R	R	R	R	R	R	R	R	R	S	R	OXA 23-like OXA 51-like
<i>Acinetobacter lwoffii</i>	SS	R	R	R	R	R	R	R	R	R	R	S	S	OXA 23-like OXA 51-like
<i>Acinetobacter baumannii</i>	BC,SS	R	R	R	R	R	R	R	R	R	R	S		OXA 23-like OXA 51-like
<i>Citrobacter koseri/freundii</i>	SS	R	R	R	R	R	R	R	S	R	R	S	-	NDM-1
<i>Escherichia coli</i>	SS	R	R	R	R	R	R	R	S	R	S	S	S	NDM-1
<i>Pseudomonas aeruginosa</i>	BC,SS	-	R	-	R	R	-	R	-	R	-	S		VIM-2
<i>Klebsiella pneumoniae</i>	SS	R	R	R	R	R	R	R	R	R	R	S	I	NDM-1

Key:

Site BC: blood culture SS: skin site

Antibiotic abbreviations: co.amox: co-amoxiclav, ceftaz: ceftazidime, ceftriax: ceftriaxone, piptaz: piperacilin-tazobactam, ertapen: ertapenem,

meropen:meropenem, cotrimox: cotrimoxazole, gent:gentamicin, amik:amikacin, tigecyl tigecycline

S = Susceptible, I = Intermediate, R = Resistant

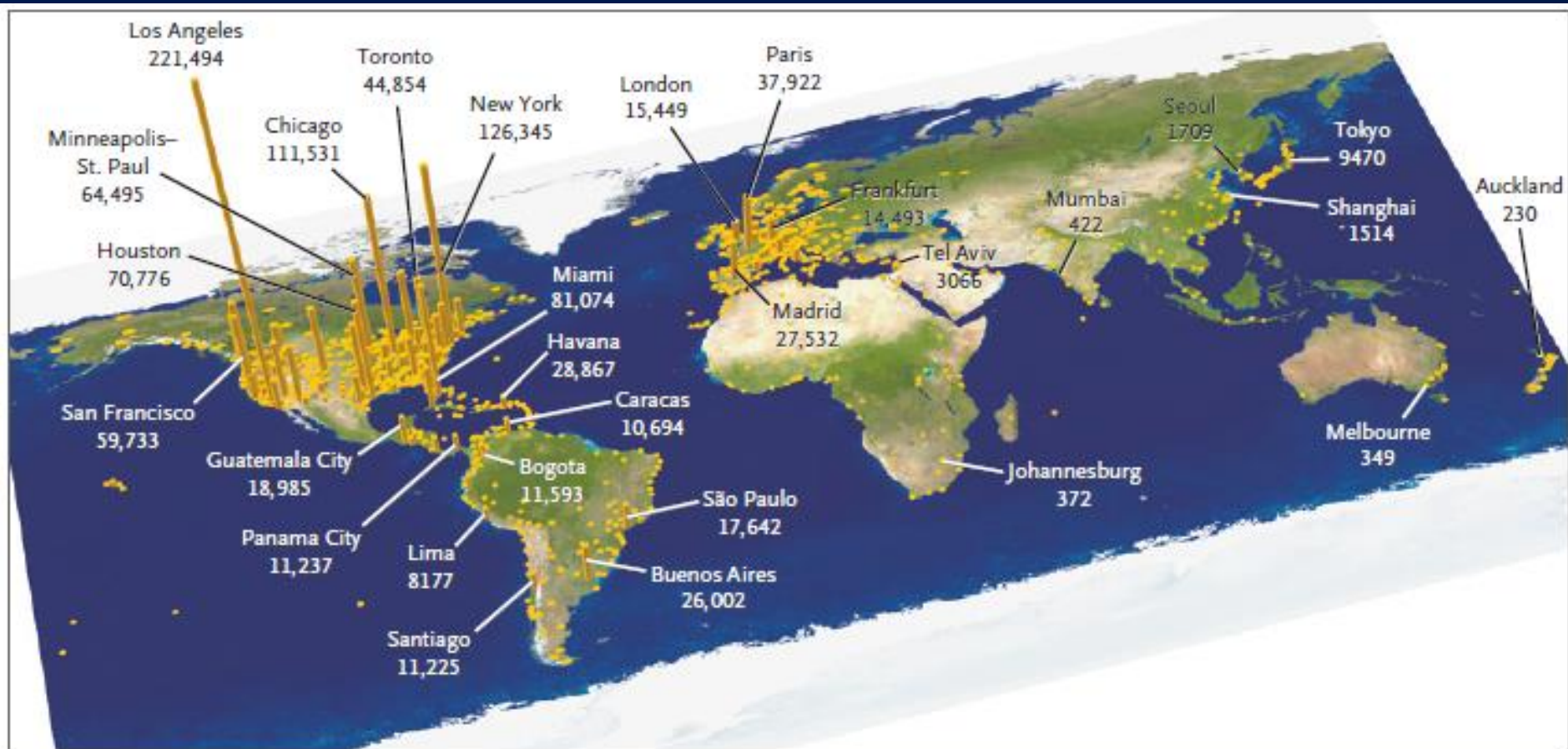


Figure 1. Destination Cities and Corresponding Volumes of International Passengers Arriving from Mexico between March 1 and April 30, 2008.

2, 35 M passageiros do México 1.018 cidades em 164 países

Watch a Patient Interview



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M Beckett

"I cannot say enough good about the hospital. Actually, it has been a great experience."
M Ballantine

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[Liposuction](#)

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Estrume de vaca comumente contaminado com novos genes de resistência

- 25/04/2014



O estrume de vaca é comumente empregado para fins agrícolas. No entanto, o estrume de vacas leiteiras contém uma quantidade notável de novos genes de resistência a antibióticos (RA) provenientes de bactérias do intestino dos animais. Com isso, há um possível risco de transferência de genes de resistência para as bactérias do solo, de acordo com um estudo realizado por pesquisadores norte-americanos da Universidade de Yale e apresentado na "mBio".

KPC epidemiologia

- Primeiro relato em 2001 EUA(NC- 3)
- Espécies envolvidas:
 - Gram-negativos entéricos:
K. pneumoniae, *K. oxytoca*, *Citrobacter freundii*,
Enterobacter sp, *E. coli*, *Salmonella* sp, *Serratia* sp ²
 - Não fermentadores:
P. aeruginosa ² e *Acinetobacter* sp ³

1. P. Nordmann, et al. CID 2002 and Lancet Infect Dis, 2009;
2. V. Miriagou, et al. CMI, 2010; 3. IE. Robledo, et al. AAC, 2010

KPC

- Resistência a beta-lactâmicos: penicilinas, cefalosporinas de amplo espectro, monobactams e carbapenemas¹
- Gen bla_{KPC}: localização plasmidial¹
 - Potencial para disseminação entre espécies diferentes^{1,2}
 - Multirresistência: ESBL; R a fluoroquinolonas e aminoglicosídeo¹

1. P. Nordmann, et al. *Lancet Infect Dis*, 2009;

2. V. Miriagou, et al. *CMI*, 2010

Table 1. Geographic origin and structure of Tn4401 and other β -lactamases of *Klebsiella pneumoniae* isolates*

			PCR result								
Isolate no.	Isolate type	Origin	Tn4401					Other β -lactamases			
			KPC-2	TnpA	ISKPN7	ISKPN6	Deletion, bp	SHV	TEM	CTX-M	OXA
1	YC	USA	+	+	+	+	−100	SHV-11	TEM-1	−	OXA-9
2	GR	Greece	+	+	+	+	−100	SHV-11	TEM-1	−	OXA-9
3	K271	Sweden	+	+	+	+	−100	SHV-11	TEM-1	−	OXA-9
4	KN2303	Colombia	+	+	+	+	None	SHV-11	−	−	−
5	KN633	Colombia	+	+	+	+	None	OKP-A	TEM-1	CTX-M-12	−
6	INC H1521-6	Colombia	+	+	+	+	None	SHV-1	TEM-1	CTX-M-15	−
7	INC H1516-6	Colombia	+	+	+	+	None	SHV-1	TEM-1	CTX-M-15	−
8	HPTU 27635	Colombia	+	+	+	+	None	OKP-B	−	−	−
9	HPTU 2020532	Colombia	+	+	+	+	None	OKP-A	TEM-1	CTX-M-12	−
10	A28006	Brazil	+	+	+	+	None	SHV-11	TEM-1	CTX-M-2	−
11	A28008	Brazil	+	+	+	+	None	SHV-11	TEM-1	CTX-M-2	−
12	A28009	Brazil	+	+	+	+	None	SHV-11	TEM-1	CTX-M-2	−
13	A28011	Brazil	+	+	+	+	None	SHV-11	TEM-1	CTX-M-2	OXA-9
14	A33504	Brazil	+	+	+	+	None	SHV-11	TEM-1	CTX-M-2	OXA-9
15	475	Israel	+	+	+	+	−200	SHV-11	−	CTX-M-15	−
16	588	Israel	+	+	+	+	−200	SHV-11	TEM-1	−	OXA-9

*KPC, *K. pneumoniae* carbapenemase.

Antimicrobial Resistance in Intensive Care Units from Seven Brazilian Hospitals

Carlos EF STARLING, Estevão U Silva,
Edna M Meireles, Adriana Cunha,
Bráulio RGM COUTO

Hospitals Vera Cruz, Life Center, Universitário São José,
São Francisco, Vila da Serra, Universitário Risoleta Neves
and Baleia, Belo Horizonte, Brazil

Belo Horizonte, Brazil

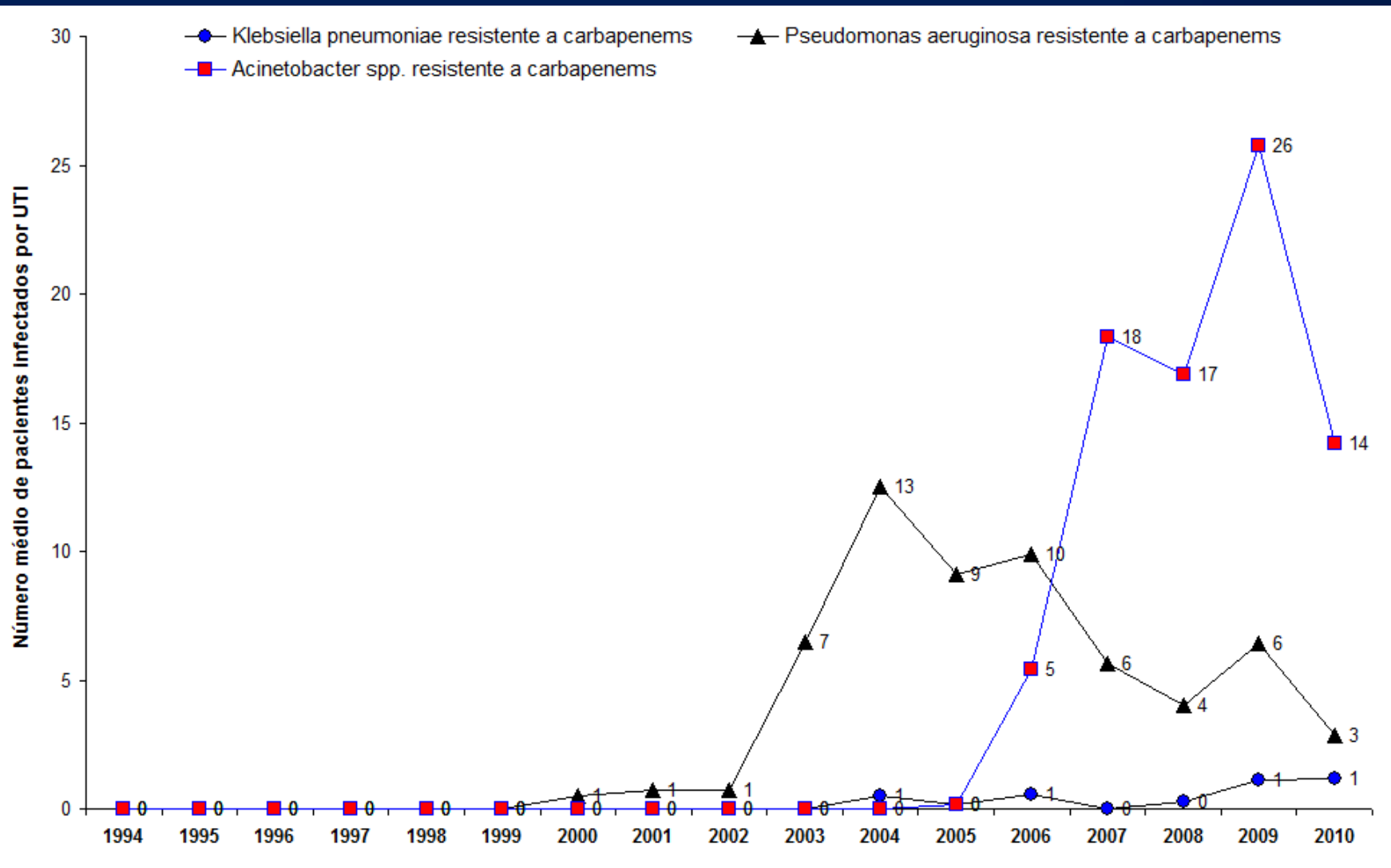
Results

- Nine pathogens were responsible for 81% of all NIs:
 - *Pseudomonas aeruginosa* (15%);
 - *Staphylococcus aureus* (12%);
 - *Acinetobacter* spp. (12%);
 - *Coagulase-negative staphylococci* (9%);
 - *Escherichia coli* (8%);
 - *Klebsiella pneumoniae* (8%);
 - *Enterobacter* spp. (7%);
 - *Candida* spp. (6%);
 - 35 • *Enterococci* spp. (4%).

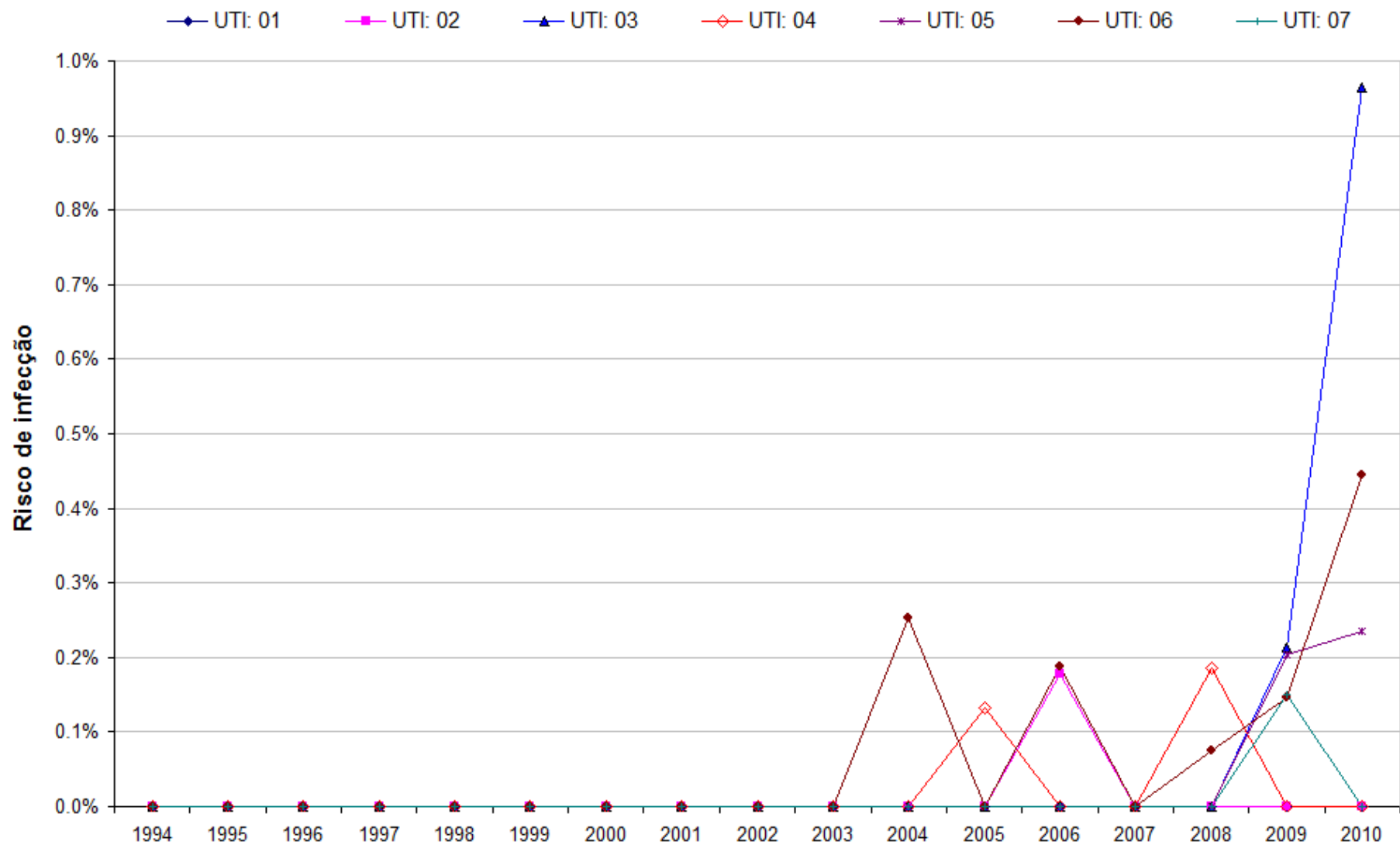
Antimicrobial-resistant pathogens that cause healthcare-associated infections in ICUs from seven Brazilian hospitals. Jan/1994 to Dec/2008.

Pathogen	Antimicrobial Resistance	Period			
		1994-2001		2002-2009	
		n	Resistance	n	Resistance
Acinetobacter spp.	Aminoglicosideos	68	56%	1,398	66%
Acinetobacter spp.	Carbapenems	84	6%	1,390	53%
Acinetobacter spp.	Third-generation cephalosporins	69	84%	1,342	84%
Acinetobacter spp.	Ciprofloxacin/ofloxacin	62	68%	1,386	88%
Coagulase-negative staphylococci	Methicillin	196	60%	497	83%
E. coli	Carbapenems	32	0%	132	1%
Enterobacter spp.	Third-generation cephalosporins	121	38%	333	67%
Enterobacter spp.	Carbapenems	55	2%	162	4%
Enterococci spp.	Vancomycin	9	0%	94	13%
Klebsiella pneumoniae	Third-generation cephalosporins	88	44%	439	48%
Klebsiella pneumoniae	Carbapenems	32	0%	242	2%
Klebsiella spp.	Carbapenems	39	0%	265	2%
Pseudomonas aeruginosa	Imipenem	142	4%	819	44%
Pseudomonas aeruginosa	Third-generation cephalosporins	124	33%	767	67%
Pseudomonas aeruginosa	Ciprofloxacin/ofloxacin	119	20%	857	52%
Staphylococcus aureus	Methicillin	320	53%	590	51%

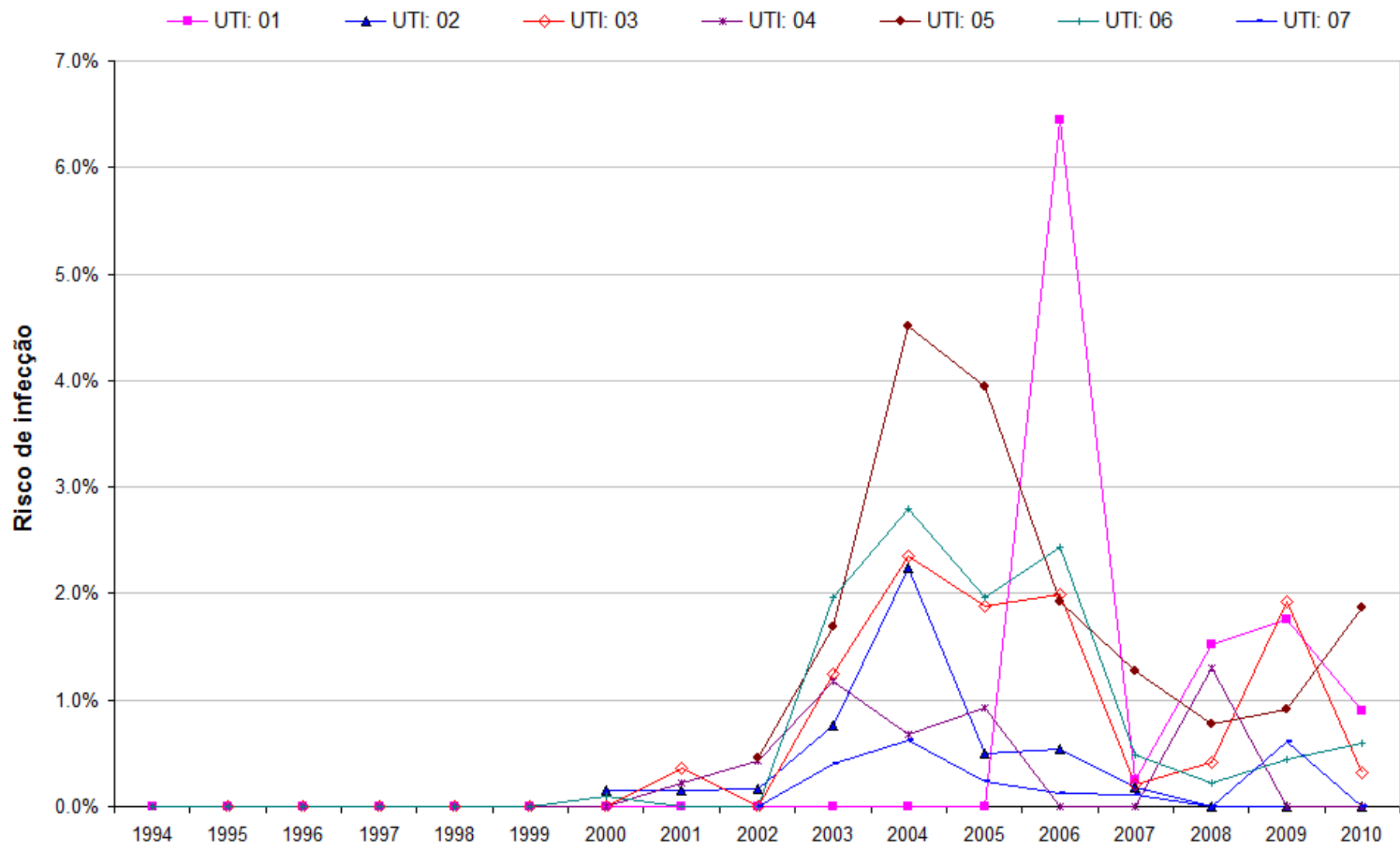
Número médio de pacientes com infecções causadas por microorganismos multirresistentes: 1994-2010



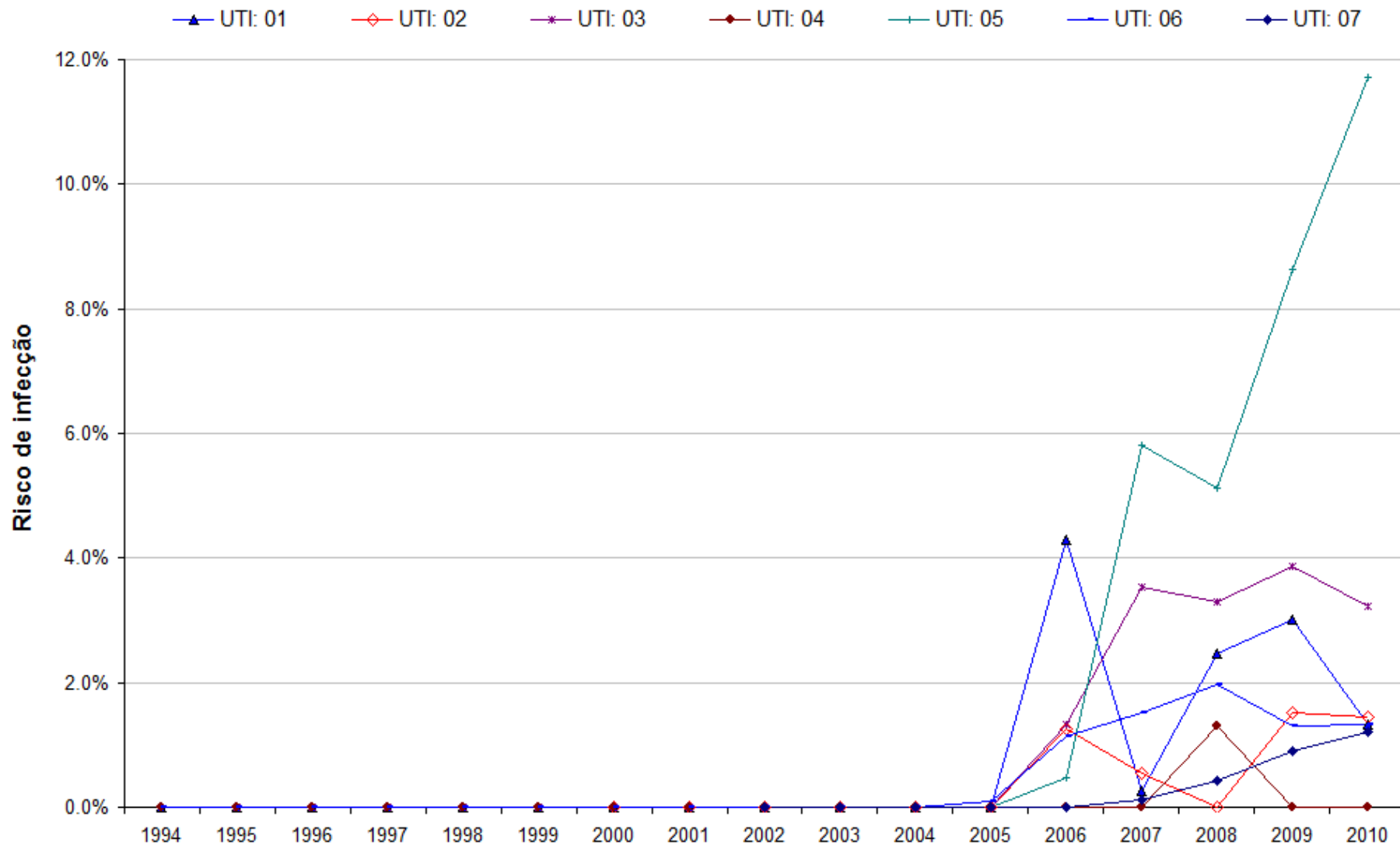
Risco de infecções por *Klebsiella pneumoniae* resistente a carbapenems: 1994-2010



Risco de infecção por *Pseudomonas aeruginosa* resistente a carbapenems : 1994-2010



Risco de infecção por *Acinetobacter spp.* resistente a carbapenems: 1994-2010



Risco de infecção causadas por microorganismos multirresistentes: 1994-2010

Risco de um paciente de CTI evoluir com infecção pelo microorganismo: casos de IH por 1.000 pacientes

Microorganismo

<i>Klebsiella pneumoniae</i> resistente a carbapenems	0.4
<i>Pseudomonas aeruginosa</i> resistente a carbapenems	6.9
<i>E. coli</i> resistente a carbapenems	0.1
<i>Acinetobacter spp.</i> resistente a carbapenems	9.9
MRSA	8.5

Letalidade das infecções causadas por microorganismos multirresistentes: 1994-2010

Microorganismo	Total de casos	Total de óbitos	Letalidade
<i>Klebsiella pneumoniae</i> resistente a carbapenems	39	19	49%
<i>Pseudomonas aeruginosa</i> resistente a carbapenems	567	276	49%
<i>E. coli</i> resistente a carbapenems	17	7	41%
<i>Acinetobacter spp.</i> resistente a carbapenems	785	278	35%
MRSA	1104	368	33%

Figura 1 – Classificação da KPC em infecção ou colonização. Hospital Regional Público de Betim, julho de 2011 a setembro de 2012. Mais da metade das KPCs (52%) referem-se a casos de colonização.

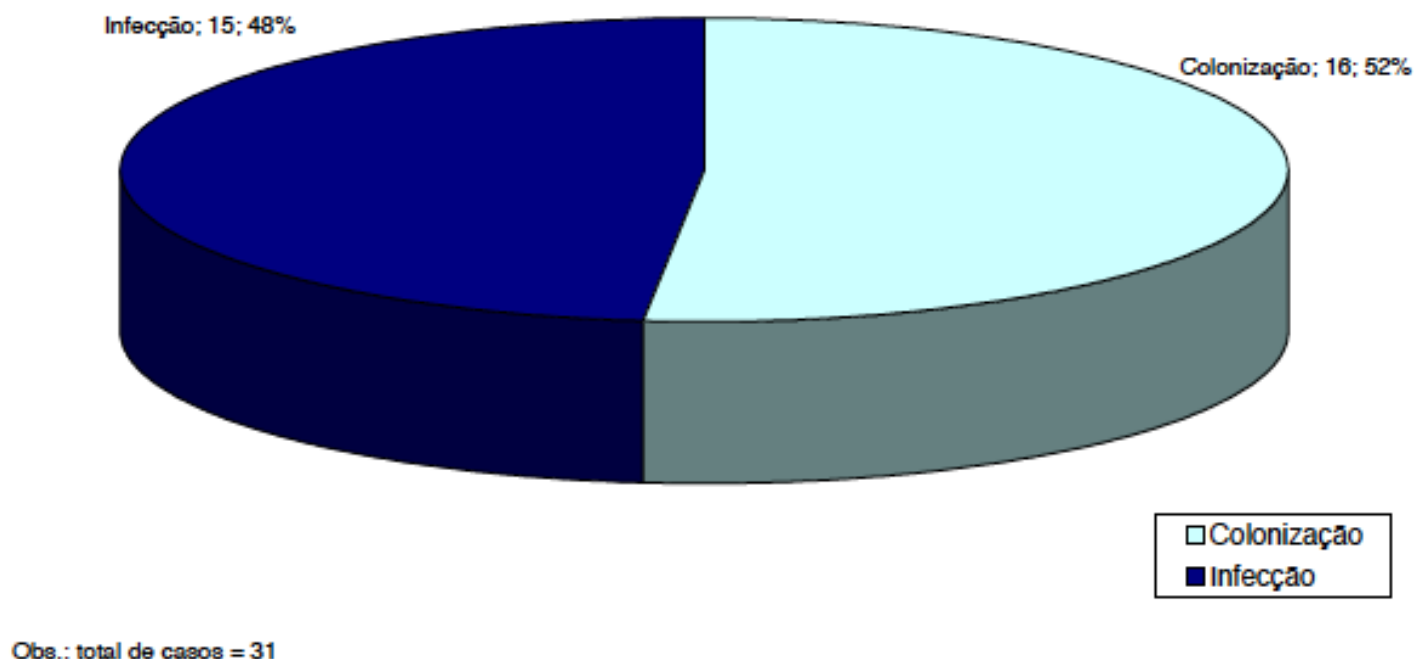
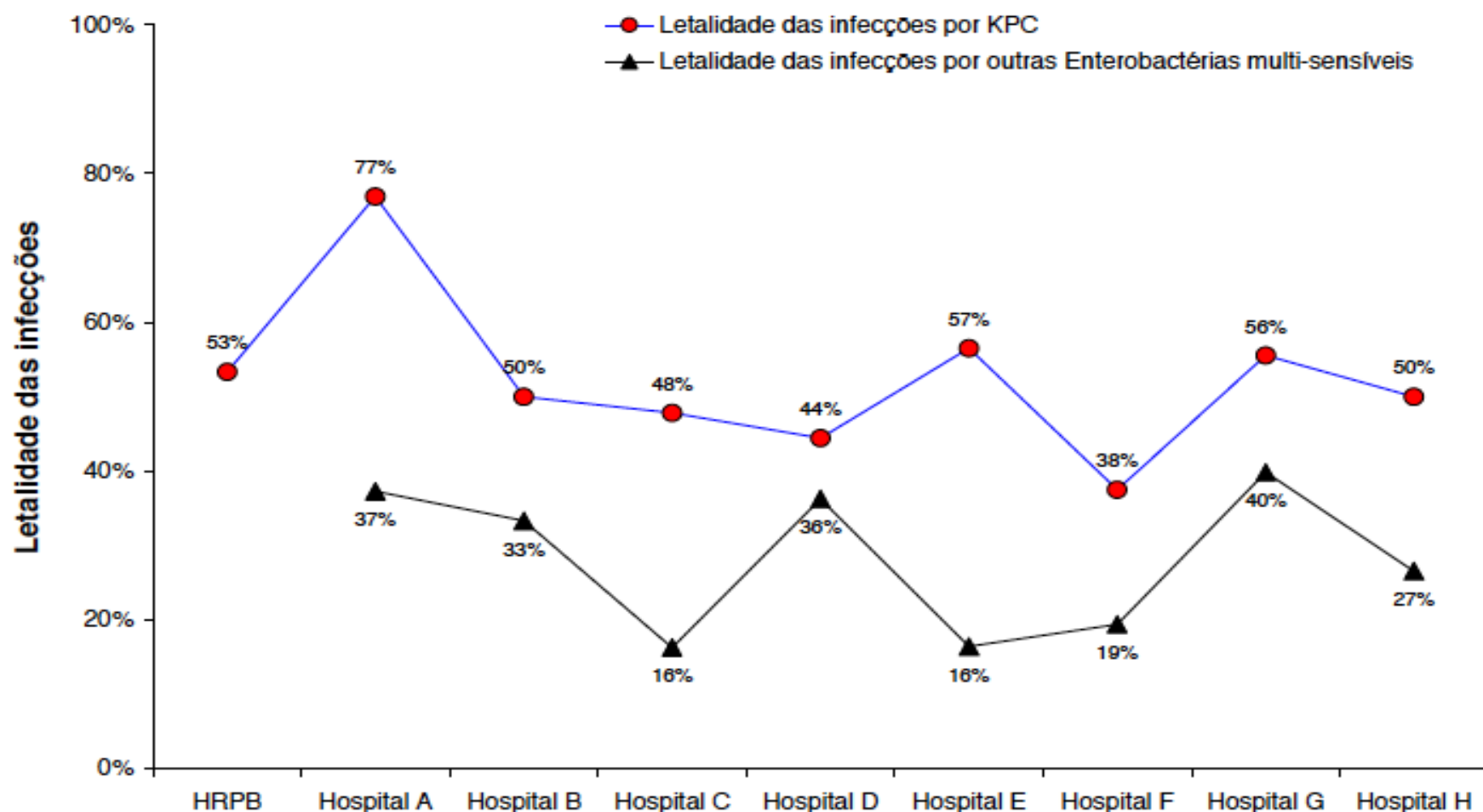


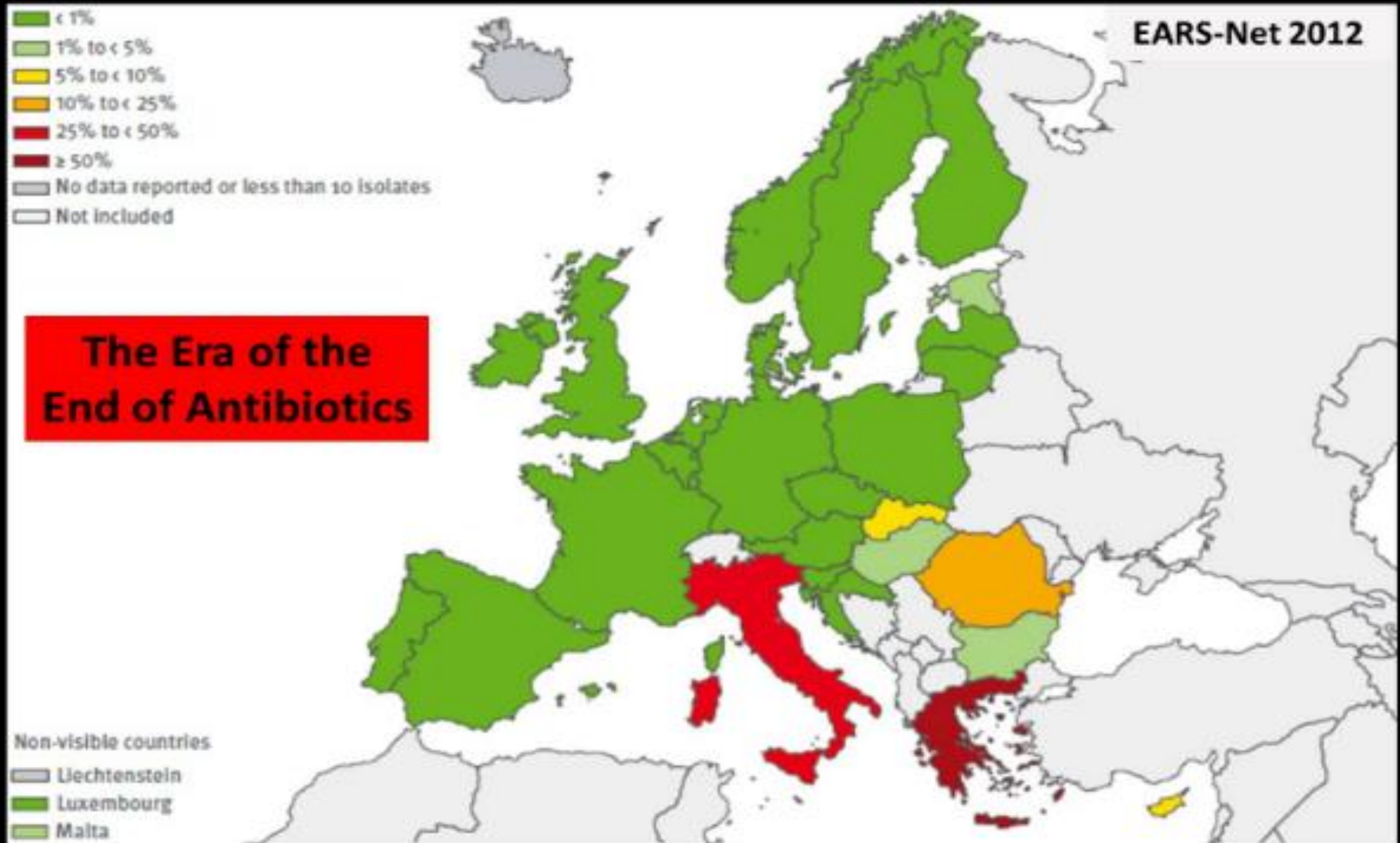
Tabela 3 – Fatores comuns aos pacientes do Hospital Regional Público de Betim infectados ou colonizados por KPC, julho de 2011 a setembro de 2012 (continuação).

Variável	Categorias	Frequência	Percentual
Setor de internação	UCM	12	39%
	CTI-1	8	26%
	CTI-2	7	23%
	UCIR	2	6%
	CTI-PED	1	3%
	OS	1	3%
Evolução do paciente	Óbito	16	52%
	Internado	8	26%
	Alta	6	19%
	Transferência	1	3%
Uso prévio de antimicrobiano antes do isolamento da KPC	Carbapenem	11	35%
Sonda vesical de demora antes do isolamento da KPC	Sim	15	48%
	Não	16	52%
Cateter venoso central antes do isolamento da KPC	Sim	13	42%
	Não	18	58%
Ventilação mecânica antes do isolamento da KPC	Sim	15	48%
	Não	16	52%
Outro microorganismo multirresistente	Sim	24	77%
	Não	7	23%
	Acinetobacter MR	19	61%
	VRE	13	42%
	ESBL	13	42%
	Outro MR	12	39%
	MRSA	6	19%
	Pseudomonas MR	6	19%

Figura 7 – Letalidade das infecções causadas por Enterobactérias: comparação entre o risco de óbito de pacientes com KPC versus pacientes com infecções por bactérias multissensíveis. Análise dos dados do Hospital Regional Público de Betim e de outros hospitais de Belo Horizonte.



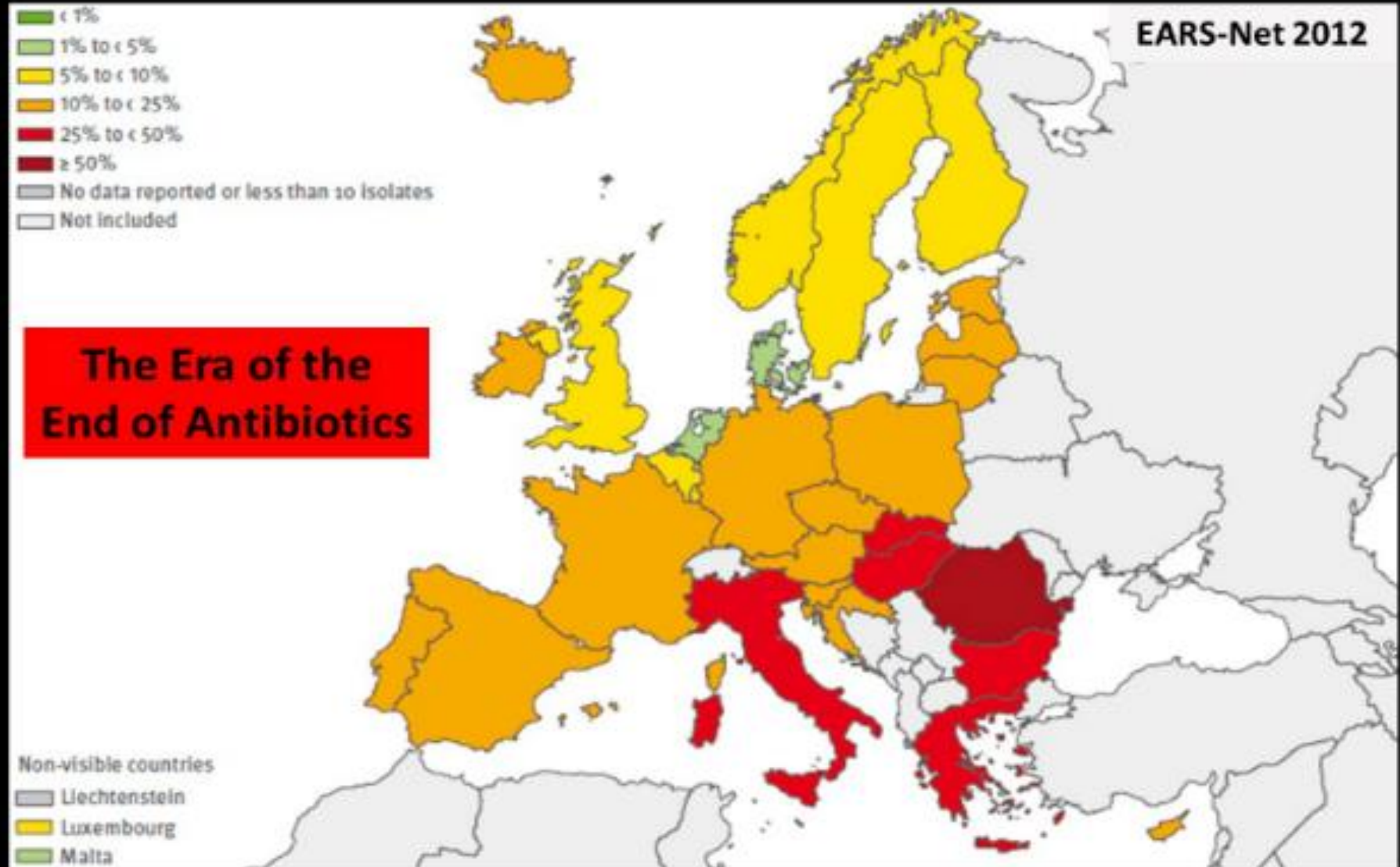
Klebsiella pneumoniae: Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2012



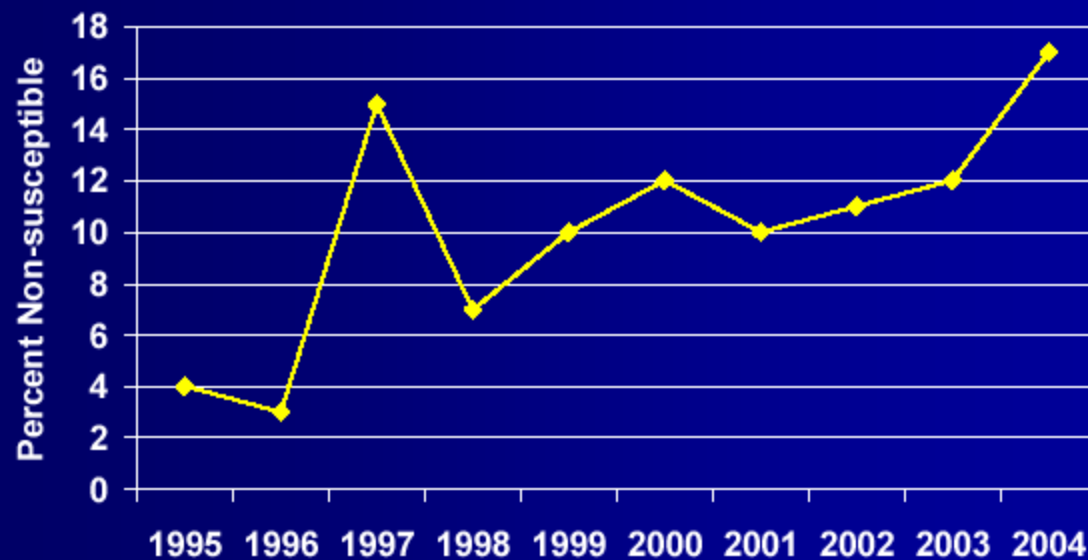
Acinetobacter spp: Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2012



Pseudomonas aeruginosa: Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2012



***Acinetobacter* spp. Non-susceptible to all
tested aminoglycosides, beta-lactams,
carbapenams and quinolones-
NNIS 1995-2004**



Copyright 2007 Society for Healthcare Epidemiology of America

Multivariable Analysis of Risk Factors for the Occurrence of *A. baumannii*

Imipenem-resistant <i>A. baumannii</i> (n = 104)	
Age	OR, 1.03
ICU stay	OR, 21.54
3G-Ceph	OR, 2.11
Imipenem	OR, 9.18

Imipenem-susceptible <i>A. baumannii</i> (n = 387)	
Age	OR, 1.02
ICU stay	OR, 8.05
Imipenem	—
3G-Ceph	OR, 2.07

Risk Factors for MDR *P. aeruginosa*

Predictive variables

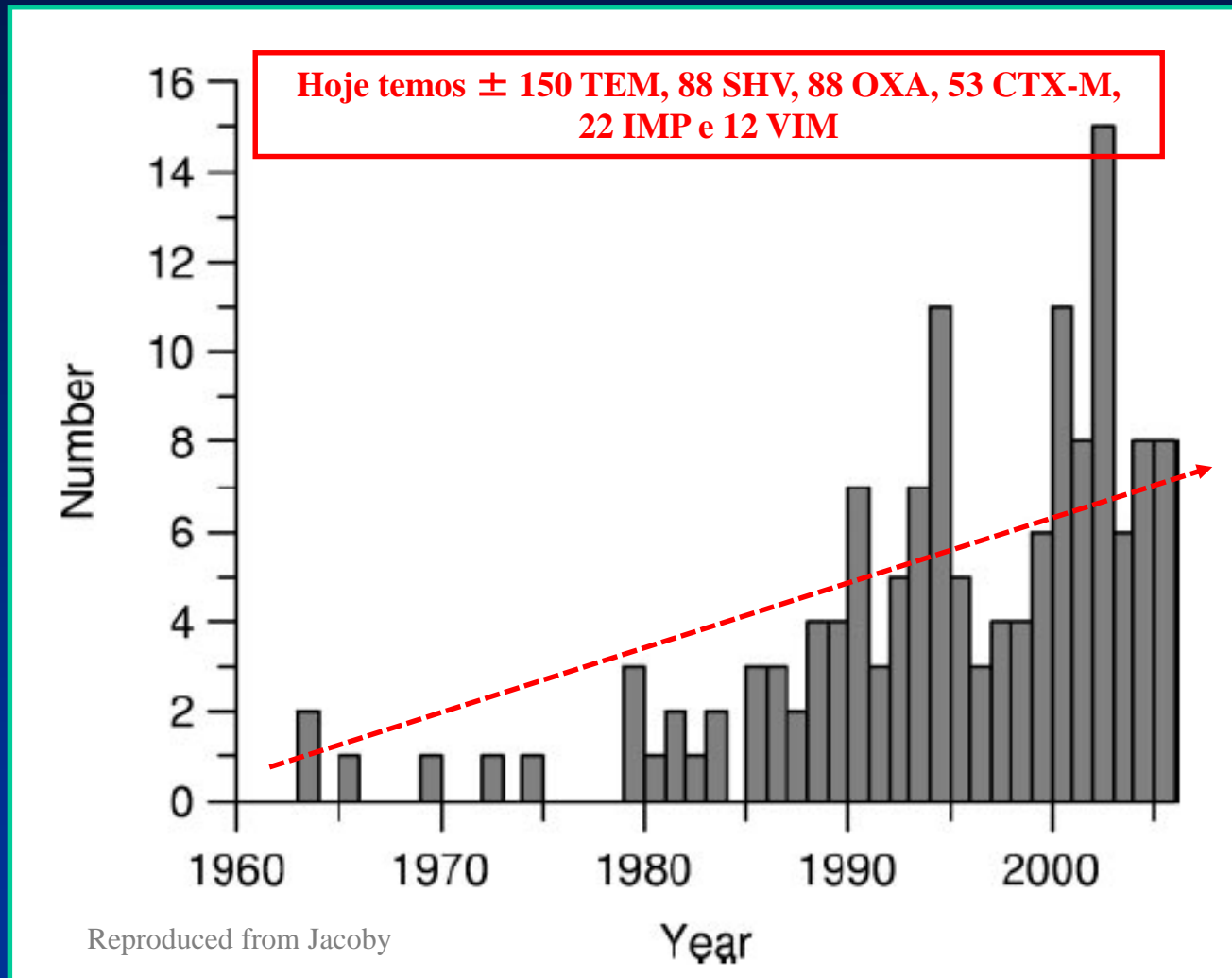
Variables	<i>P</i> value	OR	95% CI
Mechanical ventilation	0.010 ^a	8.19	1.65 – 40.7
Exposure to fluoroquinolones	0.188	2.749	0.61 – 12.4
Exposure to imipenem/meropenem	<0.001^a	44.8	9.16 – 219

Tigecycline has decreased in vitro activity against, and is not appropriate therapy for, known *P. aeruginosa* infection.

^a*P* < 0.05.

Reprinted with permission. Cao B, et al. *J Hosp Infect.* 2004;57:112-118.

β -Lactamase Discovery



Number of new β -lactamases reported per year

Como Enfrentar a Resistência bacteriana ?

- ➔ Monitorar a prevalência e a resistência dos microrganismos isolados em cada setor do hospital
- ➔ Evitar a disseminação dos MMR entre pacientes do hospital (Precauções, limpeza, desinfecção ambiental, etc.)
- ➔ Usar racionalmente os antibióticos
 - Escolha empírica e pós-cultura
 - Posologia
 - Tempo de uso

Focusing on the 4 “Ds” of Optimal Antimicrobial Therapy

Right Drug



Right Dose



De-escalation



Right Duration of Therapy

Joseph J, Rodvold KA. Expert Opin Pharmacother. 2008;9:561-75

One hundred years ago...

Address in Pathology,
ON
CHEMIO THERAPY.

DELIVERED BEFORE THE SEVENTEENTH INTERNATIONAL
CONGRESS OF MEDICINE.

BY

HIS EXCELLENCY WIRKLICHER GEHEIMER RAT

PROFESSOR DR. PAUL EHRLICH,

DIRECTOR OF THE ROYAL INSTITUTE FOR EXPERIMENTAL THERAPY,
FRANKFORT-ON-MAIN.



“Frapper fort et frapper vite”
“Hit hard and hit fast”

Paul Ehrlich

The British Medical Journal 1913;2:353

While Facing the Era of the End of Antibiotics We Should Think **The Prediction of a Prophet**



“Penicillin should only be used if there is a properly diagnosed reason and, if it needs to be used, use the highest possible dose for the shortest time necessary. Otherwise antibiotic resistance will develop.”

Alexander Fleming

12 Steps to Prevent Antimicrobial Resistance: Hospitalized Adults

12 Contain your contagion

Prevent Transmission

11 Isolate the pathogen

10 Stop treatment when cured

Use Antimicrobials Wisely

9 Know when to say “no” to vanco

8 Treat infection, not colonization

7 Treat infection, not contamination

6 Use local data

5 Practice antimicrobial control

4 Access the experts

Diagnose and Treat Effectively

3 Target the pathogen

2 Get the catheters out

Prevent Infection

1 Vaccinate

Antibioticoterapia no Paciente Grave

Escolha empírica adequada

Determinantes dos prováveis patógenos

- Padrão etiológico e de resistência locais
- Duração da hospitalização
- Tipo e duração de dispositivos invasivos
- Uso prévio recente de antibiótico
- Comorbidade

The Appropriate Duration of Antimicrobial Therapy

Why Short Duration of Therapy?

Is Short Duration the Optimal Therapy?

Optimal Duration of Short Therapy

Failure
Relapse
(Death)



- Shorter length of hospital stay
- Reduction of side effects
- Reduction of costs
- Reduction of “selective pressure” on normal floras
- **Control of antimicrobial resistance**

Rubinstein E, Int. J Ant. Agents 2007

Duration of Antibiotic Therapy for Bacteraemia: A Systematic Review and Meta-analysis

- A total of 24 trials met inclusion criteria and 155 patients had documented bacteremia: 69 primary neonatal bacteraemia and 86 secondary to pyelonephritis, intrabdominal infections and pneumonia, caused by Gram-negatives in 126pts (81%)
- Outcomes in bacteremic patients receiving 5 to 7 days versus 7 to 21 days antibiotic therapy:

No significant difference was detected with respect to rates of

- Clinical cure: 86% versus 95%
- Microbiologic cure: 100% versus 94% or
- Survival: 88% versus 90%

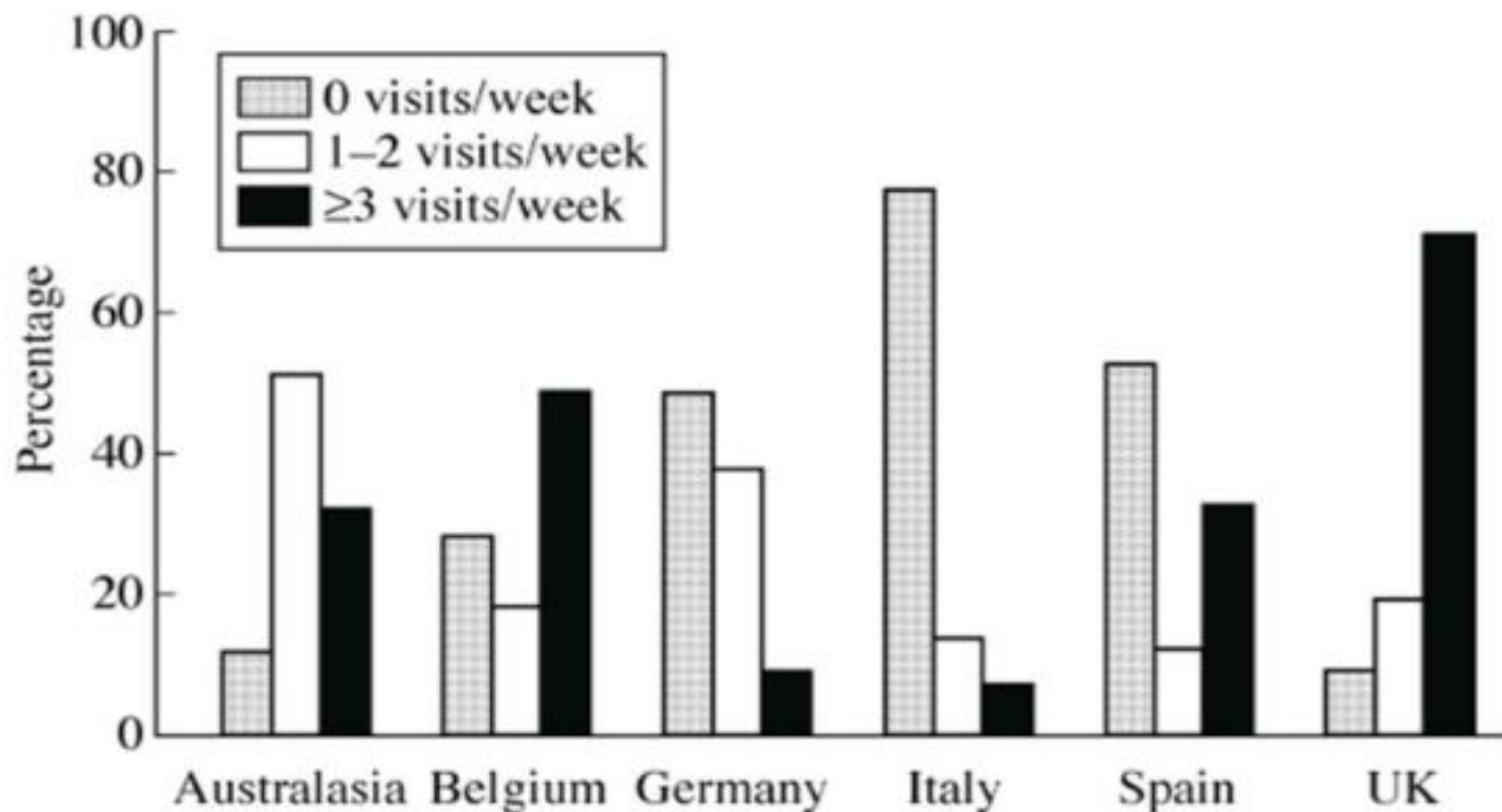
Havey TC, et al. Critical Care 2011;15:R267

Variability of Treatment Duration for Bacteraemia in the Critically Ill: a Multinational Survey

- A questionnaire was sent to membership lists of national and international intensive care societies.
- Responses from 254 intensive care units in 34 worldwide countries revealed a wide variation in antibiotic strategy ranging from short course (≤ 5 days) therapy with restricted-spectrum antibiotics, to long course (≥ 10 days) use of broad-spectrum combinations.
- Two factors were significantly associated with antibiotic prescribing practice, the country of origin and the level of microbiologist and/or infectious diseases specialist input: **The greater the specialist input, the shorter the duration of therapy ($P < 0.0001$)**

Corona A, et al. JAC 2003; 52: 849

Variation in infectious diseases/microbiology specialist input among countries with ≥ 10 responding ICUs



Corona A, et al. JAC;2003:849

Short Antibiotic Treatment Courses or How Short is Short?

- ⊙ In an international survey of the use of short-term therapy in hospital bacteraemias it was found that:

Short therapy in critically ill patients was related, among other factors, to the presence of an Infectious Diseases Consultant

Corona et al. IJAA 2003; 52: 849

Reducing Treatment Duration in Bacteraemia: How Could the Clinician Feel Safe?

The Correct Timing of Antibiotic Discontinuation Which is the Role of Biomarkers?

Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial



Lila Bouadma, Charles-Edouard Luyt, Florence Tubach, Christophe Cracco, Antonio Alvarez, Carole Schwebel, Frédérique Schortgen, Sigismond Lasocki, Benoît Veber, Monique Dehoux, Maguy Bernard, Blandine Pasquet, Bernard Régnier, Christian Brun-Buisson, Jean Chastre, * Michel Wolff, * for the PRORATA trial group†

Summary

Background Reduced duration of antibiotic treatment might contain the emergence of multidrug-resistant bacteria in intensive care units. We aimed to establish the effectiveness of an algorithm based on the biomarker procalcitonin to reduce antibiotic exposure in this setting.

Lancet 2010; 375: 463-74

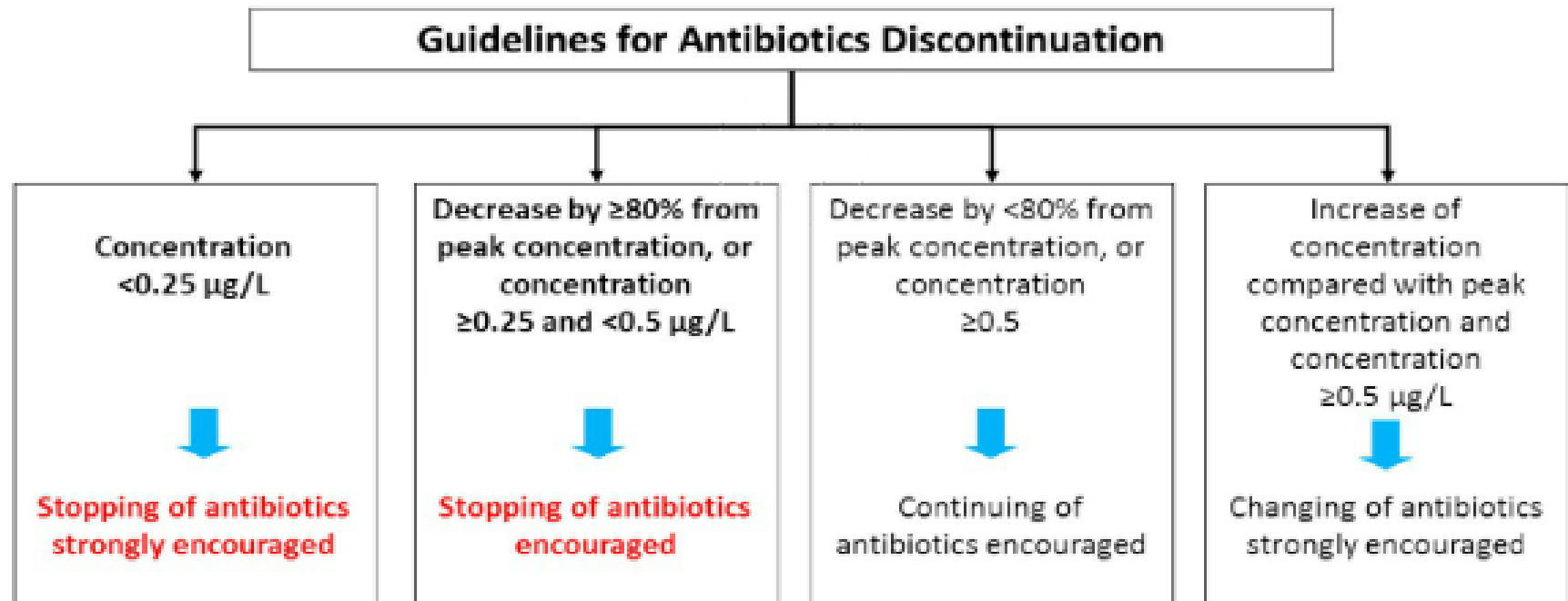
Published Online

January 23, 2010

<http://www.thelancet.com>

The Duration of Therapy

Use of Procalcitonin in the ICU



Bouadma, et al. Lancet 2010;375:463

Risk factors

- Long hospital stay •
- ICU stay •
- Mechanical ventilation •
- Invasive devices •
- Immunesuppression •
- Combat injuries –
- or multiple casualties trauma –

Screening for Acinetobacter

TABLE 1. Sensitivities of surveillance cultures from different body sites among patients with recent clinical culture of MDR *A. baumannii* (≤ 10 days)

Culture site	No. of patients sampled	No. with MDR <i>A. baumannii</i>	Sensitivity (%)
Surveillance sites			
Nostrils	22	4	18
Pharynx	22	5	23
Skin	22	3	13.5
Rectum	21	3	14
Clinical sites			
Wounds ^a	9	2	22
Endotracheal aspirates ^b	7	2	29

^a Only discharging wounds were cultured.

^b Endotracheal aspirates were obtained only from intubated patients.

Environmental control

- The roll of the environmental control clear for *Acinetobacter baumannii*

TABLE 1. Results of environmental culture in the MICU and SICU

Location	No. of samples	No. (%) positive for <i>A. baumannii</i>	
		Imipenem-susceptible	Imipenem-resistant
Room surfaces	168	25 (15)	31 (18)
Windowsills	40	7 (17)	7 (17)
Furniture	50	9 (18)	8 (16)
Patient care items	24	2 (8)	6 (25)
Handwashing sinks	21	2 (9)	2 (9)
Soil	17	4 (23)	7 (41)
Miscellaneous	16	1 (6)	1 (6)
Air	12	1 (8)	0 (0)
ICU personnel	45	4 (9)	2 (4)
Gowns	28	2 (7)	2 (7)
Hands	17	2 (12)	0 (0)

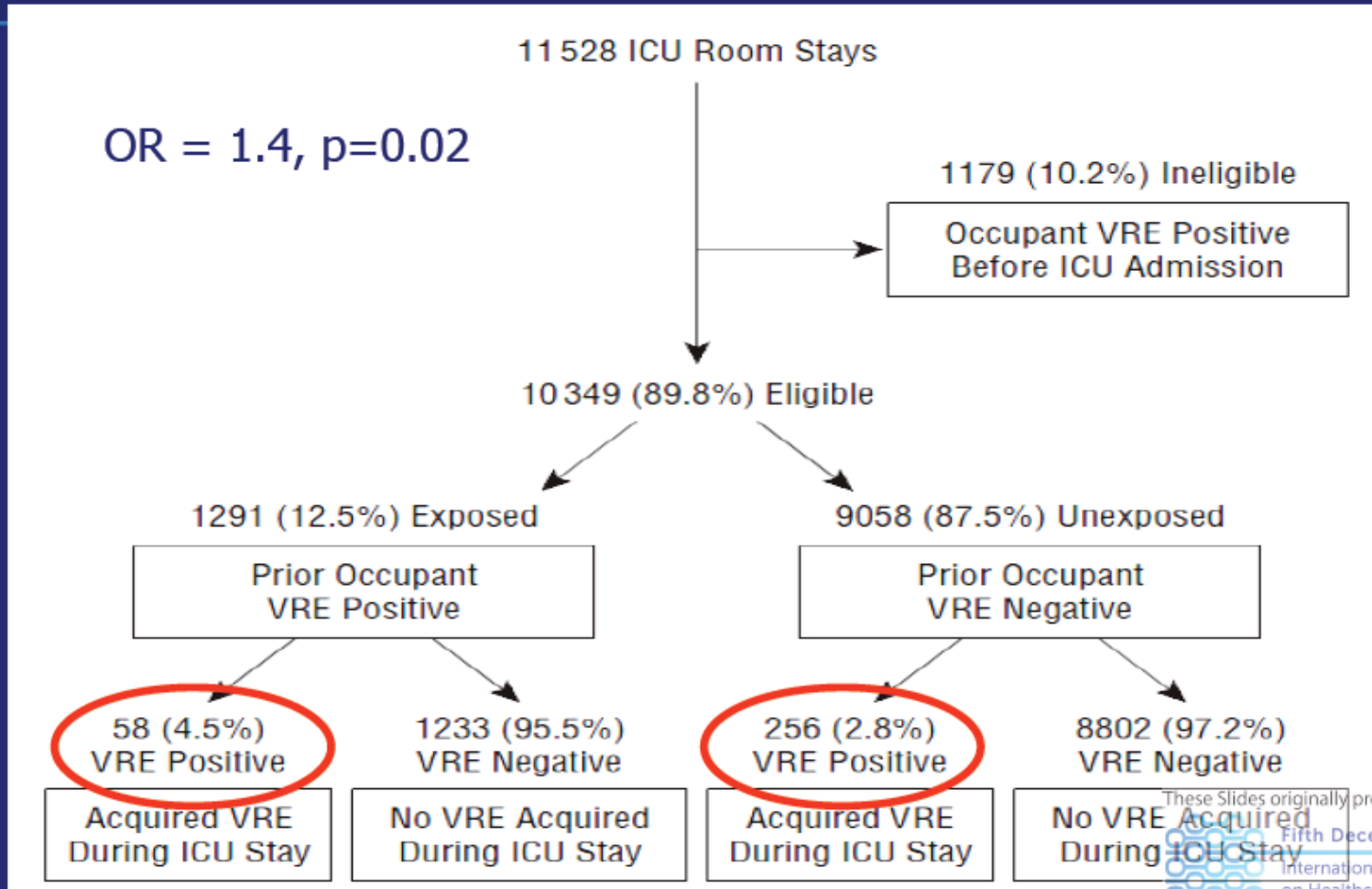
ICU outbreak by 2 clones ended only when ICU closed, cleaned and disinfected with formaldehyde

Table 1: Persistence of clinically relevant bacteria on dry inanimate surfaces.

Type of bacterium	Duration of persistence (range)
<i>Acinetobacter</i> spp.	3 days to 5 months
<i>Bordetella pertussis</i>	3 – 5 days
<i>Campylobacter jejuni</i>	up to 6 days
<i>Clostridium difficile</i> (spores)	5 months
<i>Chlamydia pneumoniae</i> , <i>C. trachomatis</i>	≤ 30 hours
<i>Chlamydia psittaci</i>	15 days
<i>Corynebacterium diphtheriae</i>	7 days – 6 months
<i>Corynebacterium pseudotuberculosis</i>	1–8 days
<i>Escherichia coli</i>	1.5 hours – 16 months
<i>Enterococcus</i> spp. including VRE and VSE	5 days – 4 months
<i>Haemophilus influenzae</i>	12 days
<i>Helicobacter pylori</i>	≤ 90 minutes
<i>Klebsiella</i> spp.	2 hours to > 30 months
<i>Listeria</i> spp.	1 day – months
<i>Mycobacterium bovis</i>	> 2 months
<i>Mycobacterium tuberculosis</i>	1 day – 4 months
<i>Neisseria gonorrhoeae</i>	1 – 3 days
<i>Proteus vulgaris</i>	1 – 2 days
<i>Pseudomonas aeruginosa</i>	6 hours – 16 months; on dry floor: 5 weeks
<i>Salmonella typhi</i>	6 hours – 4 weeks
<i>Salmonella typhimurium</i>	10 days – 4.2 years
<i>Salmonella</i> spp.	1 day
<i>Serratia marcescens</i>	3 days – 2 months; on dry floor: 5 weeks
<i>Shigella</i> spp.	2 days – 5 months
<i>Staphylococcus aureus</i> , including MRSA	7 days – 7 months
<i>Streptococcus pneumoniae</i>	1 – 20 days
<i>Streptococcus pyogenes</i>	3 days – 6.5 months
<i>Vibrio cholerae</i>	1 – 7 days

Risk of VRE from Prior Room Occupant

20 month study, 10 ICUs



OU SEJA....

BACTERIA DEIXA RASTRO...

DAZO Solution (AKA – Goo)





BIOQUELL implant in the US – side room bio-decon

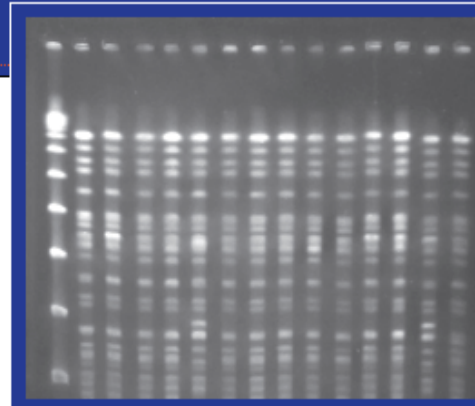
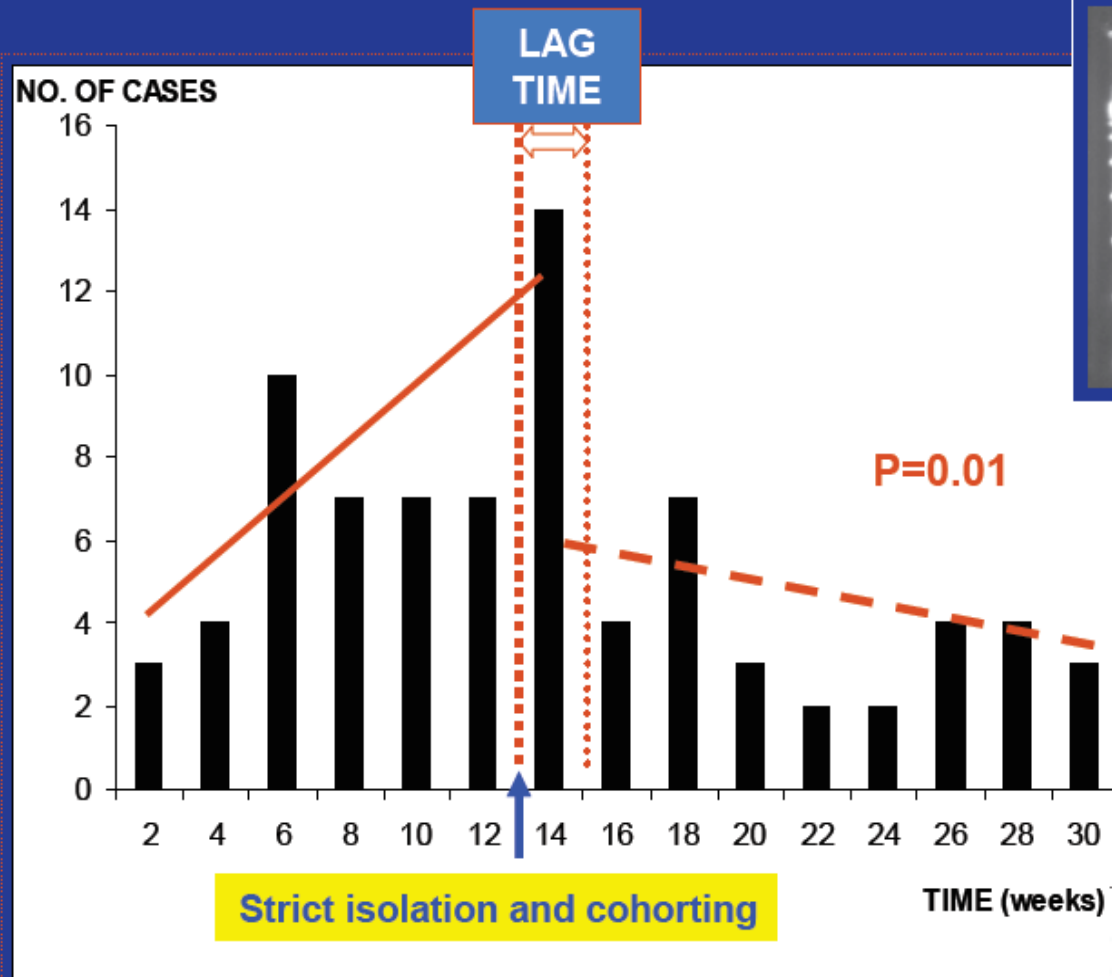


BIOQUELL implant in the US – side room bio-decon





Infection control-when person to person transmission is the main issue



Incidence of KPC-producing *Klebsiella* spp.



May 29, 2013

Screening Inpatients for MRSA — Case Closed !

Michael B. Edmond, M.D., M.P.H., and Richard P. Wenzel, M.D.

« *The lack of effectiveness of active detection and isolation should prompt hospitals to discontinue the practice for control of endemic MRSA.* »

...but to use universal decolonization ?

SDD: Case still open?

A 45-year record of R&D

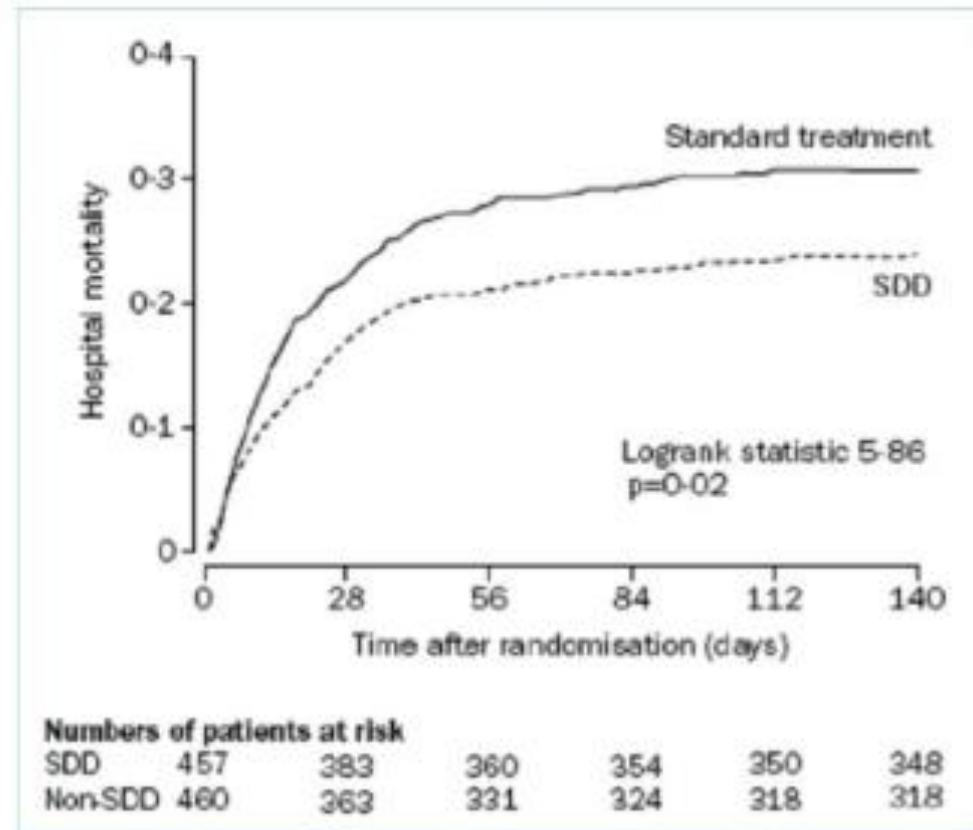
... but remains an experimental therapy !!

Does SDD reduce both mortality and resistance?

- ICU mortality:
 - 15% *vs.* 23%, $P = 0.002$
 - $RR = 0.65 (0.44 - 0.85)$
- Duration of ICU stay
 - 11,6 *vs.* 13,4 ($P < 0.01$)
- Hospital mortality:
 - 24% *vs.* 31%, $P = 0.02$
 - $RR = 0.78 (0.63 - 0.96)$

Larger effect than in MA !

Cumulative risk of mortality among the 2 treatment groups



E de Jonge & al, *Lancet* 2003; 362: 1011-16.



ORIGINAL ARTICLE

Decontamination of the Digestive Tract and Oropharynx in ICU Patients

A.M.G.A. de Smet, M.D., J.A.J.W. Kluytmans, M.D., Ph.D., B.S. Cooper, Ph.D., E.M. Mascini, M.D., Ph.D., R.F.J. Benus, M.D., T.S. van der Werf, M.D., Ph.D., J.G. van der Hoeven, M.D., Ph.D., P. Pickkers, M.D., Ph.D., D. Bogaers-Hofman, I.C.P., N.J.M. van der Meer, M.D., Ph.D., A.T. Bernards, M.D., Ph.D., E.J. Kuijper, M.D., Ph.D., J.C.A. Joore, M.D., M.A. Leverstein-van Hall, M.D., Ph.D., A.J.G.H. Bindels, M.D., Ph.D., A.R. Jansz, M.D., R.M.J. Wesselink, M.D., Ph.D., B.M. de Jongh, M.D., Ph.D., P.J.W. Dennesen, M.D., Ph.D., G.J. van Asselt, M.D., Ph.D., L.F. te Velde, M.D., I.H.M.E. Frenay, M.D., Ph.D., K. Kaasjager, M.D., Ph.D., F.H. Bosch, M.D., Ph.D., M. van Iterson, M.D., S.F.T. Thijsen, M.D., Ph.D., G.H. Kluge, M.D., Ph.D., W. Pauw, M.D., J.W. de Vries, M.D., Ph.D., J.A. Kaan, M.D., J.P. Arends, M.D., L.P.H.J. Aarts, M.D., Ph.D., P.D.J. Sturm, M.D., Ph.D., H.I.J. Harinck, M.D., Ph.D., A. Voss, M.D., Ph.D., E.V. Uijtendaal, Pharm.D., H.E.M. Blok, M.Sc., E.S. Thieme Groen, M.D., M.E. Pouw, M.D., C.J. Kalkman, M.D., Ph.D., and M.J.M. Bonten, M.D., Ph.D.

A cluster-randomised crossover trial in 13 Dutch ICUs

N ENGL J MED 360:1 NEJM.ORG JANUARY 1, 2009

Clinical endpoints (adjusted)

Adjusted outcomes			
	Standard Care N=1990 OR	SDD N=2045 OR(CI)	SOD N=1904 OR(CI)
Mortality at	1	0.83 (0.72-0.97)	0.86 (0.74-0.99)
At day 28 SDD and SOD were associated with:			
➤ Reduced mortality at day 28 of 17% and 14%			
➤ Absolute mortality reductions of 4.5% and 3.5%			
➤ Number needed to treat of 22 and 29			
SDD and SOD tended to reduce:			
➤ Duration of mechanical ventilation			
➤ Duration of ICU-stay			
➤ Duration of hospital stay			

Random effects logistic regression model with adjustment for age, gender, APACHE II score, ventilation, surgical/non-surgical and study center.

Conclusions (1)

- In the Netherlands
 - SDD / SOD recommended for routine use in all patients with expected length of ICU stay >2 days
 - Together with careful microbiological monitoring
 - May be more beneficial in patients with mid-range severity (*Krueger et al, AJRCCM 2002*), and in selected groups (*de la Cal, Ann Surg 2005*)

Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study

www.thelancet.com/infection Published online March 21, 2011

Anne Marie G A de Smet, Jan A J W Kluytmans, Hetty E M Blok, Ellen M Mascini, Robin F J Benus, Alexandra T Bernards, Ed J Kuijper, Maurine A Leverstein-van Hall, Arjan R Jansz, Bartelt M de Jongh, Gerard J van Asselt, Ine H M E Frenay, Steven F T Thijssen, Simon N M Conijn, Jan A Kaan, Jan P Arends, Patrick D J Sturm, Martin C J Bootsma, Marc J M Bonten

Incidence of MDR bacteremia

	SC n=1989	SOD n=1904	SDD n=2034
Frequency of obtaining blood cultures (per pt day)	0,11	0,13	0,11
MDRB ≤ 2 days in ICU	6	3	3
MDRB ≥ 3 days in ICU (%)	19 (1.7)	20 (1.4)	8 (1.0)

Four-year surveillance data in ICUs using or not SDD - Conclusions

- ❑ Resistance rates to 3GC increased over time in ICUs not using SOD/SDD
- ❑ Decreasing trend in all markers of antibiotic resistance in respiratory isolates in ICUs that continuously used SOD/SDD
- ❑ Significant decrease in resistance rates of respiratory isolates in ICUs that introduced SOD/SDD

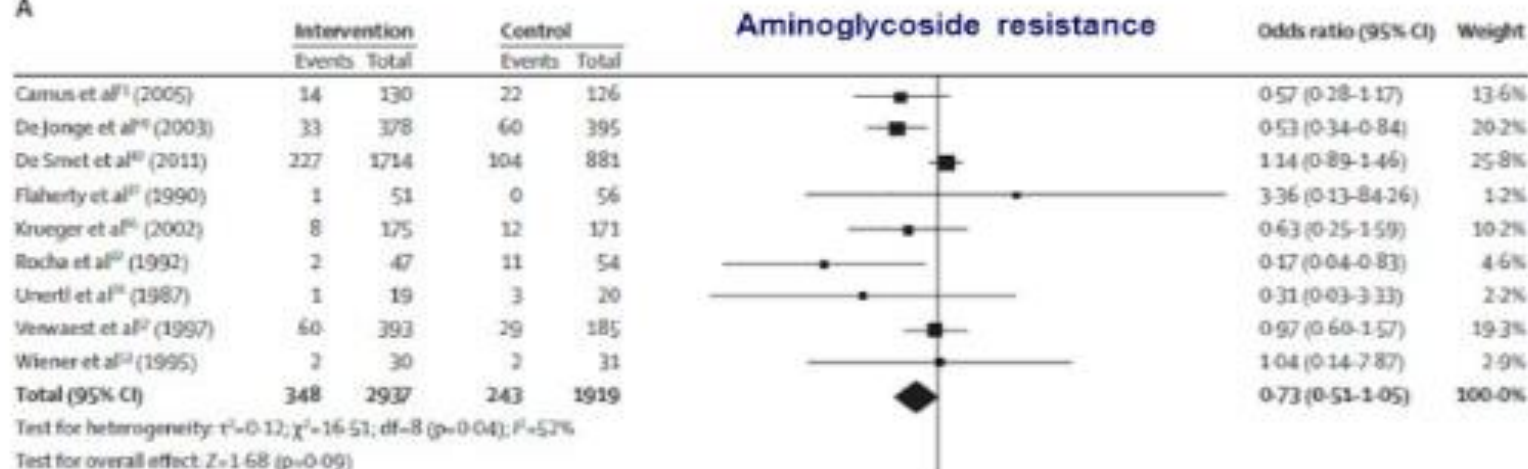
Houben & al, *J Antimicrob Chemother* 2014; 69: 797–804

Effect of selective decontamination on antimicrobial resistance in intensive care units: a systematic review and meta-analysis (64 studies)

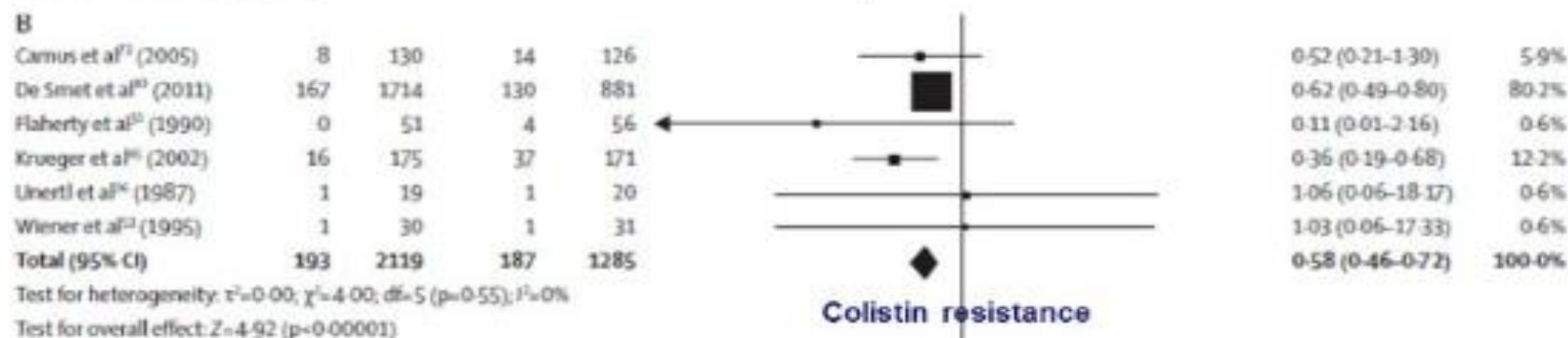
Lancet Infect Dis 2013;
13: 328-41

Nick Daneman, Syed Sarwar, Robert A Fowler, Brian H Cuthbertson, on behalf of the SuDDICU Canadian Study Group

A



B



Como Enfrentar a Resistência bacteriana ?

- 1) Melhora a Higienização das Mãos
- 2) Cultura de Vigilância e Isolamento
- 3) Banhos com Clorexidina
- 4) Luvas e Capote para cuidados universais
- 5) [1+2; 1+3, 1+4 2+3, 2+4, 3+4, 1+2+3, etc

What worked for MRSA-BSI?

	Screen/Isolate			CHX			Universal Gloving/Gowning
		Hand Hygiene	Mup/CHX		Mup	Hand Hygiene	
Cepeda Lancet 2005	NO						
Huskins NEJM 2011	NO						
Jain NEJM 2011	YES NO						
Climo NEJM 2013				NO			
Huang NEJM 2013							
Harris JAMA 2013							NO
Derde LID 2013	NO					NA	

What worked for MRGNB-BSI?

	Screen/Isolate			CHX			Universal Gloving/Gowning
		Hand Hygiene	Mup/CHX		Mup	Hand Hygiene	
Cepeda Lancet 2005	NO						
Huskins NEJM 2011	NO						
Jain NEJM 2011	YES NO						
Climo NEJM 2013				NO			
Huang NEJM 2013							
Harris JAMA 2013							NO
Derde LID 2013	NO					NO	

Screening and isolation in high-endemicity settings: Failures on a local level

Intervention to Reduce Transmission of Resistant Bacteria in Intensive Care

W. Charles Huskins, M.D., Charmaine M. Huckabee, M.S., Naomi P. O'Grady, M.D.,
Patrick Murray, Ph.D., Heather Kopetskie, M.S., Louise Zimmer, M.A., M.P.H.,
Mary Ellen Walker, M.S.N., Ronda L. Sinkowitz-Cochran, M.P.H.,
John A. Jernigan, M.D., Matthew Samore, M.D., Dennis Wallace, Ph.D.,
and Donald A. Goldmann, M.D., for the STAR*ICU Trial Investigators*

N ENGL J MED 364;15 NEJM.ORG APRIL 14, 2011

Isolation of patients in single rooms or cohorts to reduce spread of MRSA in intensive-care units: prospective two-centre study

Lancet 2005; 365: 295-304

Jorge A Cepeda, Tony Whitehouse, Ben Cooper, Janeane Hails, Karen Jones, Felicia Kwaku, Lee Taylor, Samantha Hayman, Barry Cookson,
Steve Shaw, Chris Kibbler, Mervyn Singer, Geoffrey Bellingan, A Peter R Wilson

CRISE? QUAL CRISE??



How to control MDRO, especially Carbapenem-Resistant Bacteria?

- Be aggressive!
- Hand Hygiene
- (True) Rapid screening and isolation (?)
- Environmental cleaning (?)
- Modulation of carriage (?)
 - Topical antibiotics (SDD) (?)
 - Probiotics (?)

ORIGINAL ARTICLE

Effect of Daily Chlorhexidine Bathing on Hospital-Acquired Infection

Michael W. Climo, M.D., Deborah S. Yokoe, M.D., M.P.H., David K. Warren, M.D.,
Trish M. Perl, M.D., Maureen Bolon, M.D., Loreen A. Herwaldt, M.D.,
Robert A. Weinstein, M.D., Kent A. Sepkowitz, M.D., John A. Jernigan, M.D.,
Kakotan Sanogo, M.S., and Edward S. Wong, M.D.

Climo et al. N Engl J Med 2013;368:533-42

Decolonization in Academic Adult ICUs

- Study Conduct

- 3 ICUs, 1 hospital dropped, low compliance
- 9 ICUs, 6 hospitals, 7,727 patients remained
- As-treated analysis

Climo et al. N Engl J Med 2013;368:533-42

Decolonization Success

	Intervention	Control	
MDRO acquisition			
No. of infections	127	165	0.03
Incidence rate (no./1000 patient-days)	5.10	6.60	
VRE acquisition			
No. of infections	80	107	0.05
Incidence rate (no./1000 patient-days)	3.21	4.28	
MRSA acquisition			
No. of infections	47	58	0.29
Incidence rate (no./1000 patient-days)	1.89	2.32	
Hospital-acquired bloodstream infection			
No. of infections	119	165	0.007
Incidence rate (no./1000 patient-days)	4.78	6.60	
Primary bloodstream infection			
No. of infections	90	131	0.006
Incidence rate (no./1000 patient-days)	3.61	5.24	
Central-catheter-associated bloodstream infection			
No. of infections	21	43	0.004
Incidence rate (no./1000 catheter-days)	1.55	3.30	

PRECAUÇÕES UNIVERSAIS

 **LAVAR AS MÃOS**
Antes e depois de todo contato com o paciente.

 **USAR LUVAS**
Manuseio direto do sangue e secreções corporais, material de risco de contaminação e de risco de lesão.

 **USAR AVENTAL**
Manuseio direto de todo o conteúdo de líquidos e materiais corporais.

 **USAR MÁSCARA E ÓCULOS PROTETORES**
Manuseio de todo o conteúdo de líquidos e materiais corporais.

 **DESCARTAR MATERIAIS PERFUNDO-CONTANTES**
De acordo com o tipo de material, descartar em local apropriado.

ANEXO 02/2006







CONCLUSÕES

- A resistência microbiana é um problema de saúde pública;
- Existe uma demanda local pela produção de conhecimento sobre a resistência microbiana;
- Os laboratórios, apesar das boas taxas de recuperação de agentes, carecem de uma padronização;
- Ausência de um grupo de referência para confirmação de padrões especiais de resistência em Minas Gerais;

... As bactérias refletem o
comportamento e a evolução
do homem, assim como a sua
postura diante da vida e da
morte ...

CARLOS STARLING