

The Challenge of Antimicrobial Resistance in Human Health

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Disclosures

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Thanks to **PENICILLIN**
...He Will Come Home!



FROM ORDINARY MOLD—
the Greatest Healing Agent of this War!

On the gentle, green and yellow mold above, called *Penicillium notatum* in the laboratory, grows the miraculous substance first discovered by Professor Alexander Fleming in 1928. Named penicillin by its discoverer, it is the most potent weapon ever developed against many of the deadliest infectious diseases. It is because research on molds was already a part of Schenley's occupation, Schenley Laboratories were well able to meet the problem of large scale production of penicillin, when the great need for it arose.

When the thousands of miles of this war have added to pages of silent pain in a bitter hour, the greatest news event of World War II may well be the discovery and development — not of some vicious insect weapon that destroys — but of a weapon that saves lives. That weapon, of course, is penicillin.

Every day, penicillin is performing some unbelievable act of healing on some far battlefield. Thousands of men will remain hale and whole who otherwise would have had a chance. Better still, more and more of this precious drug is now available for civilian use — to save the lives of patients of every age.

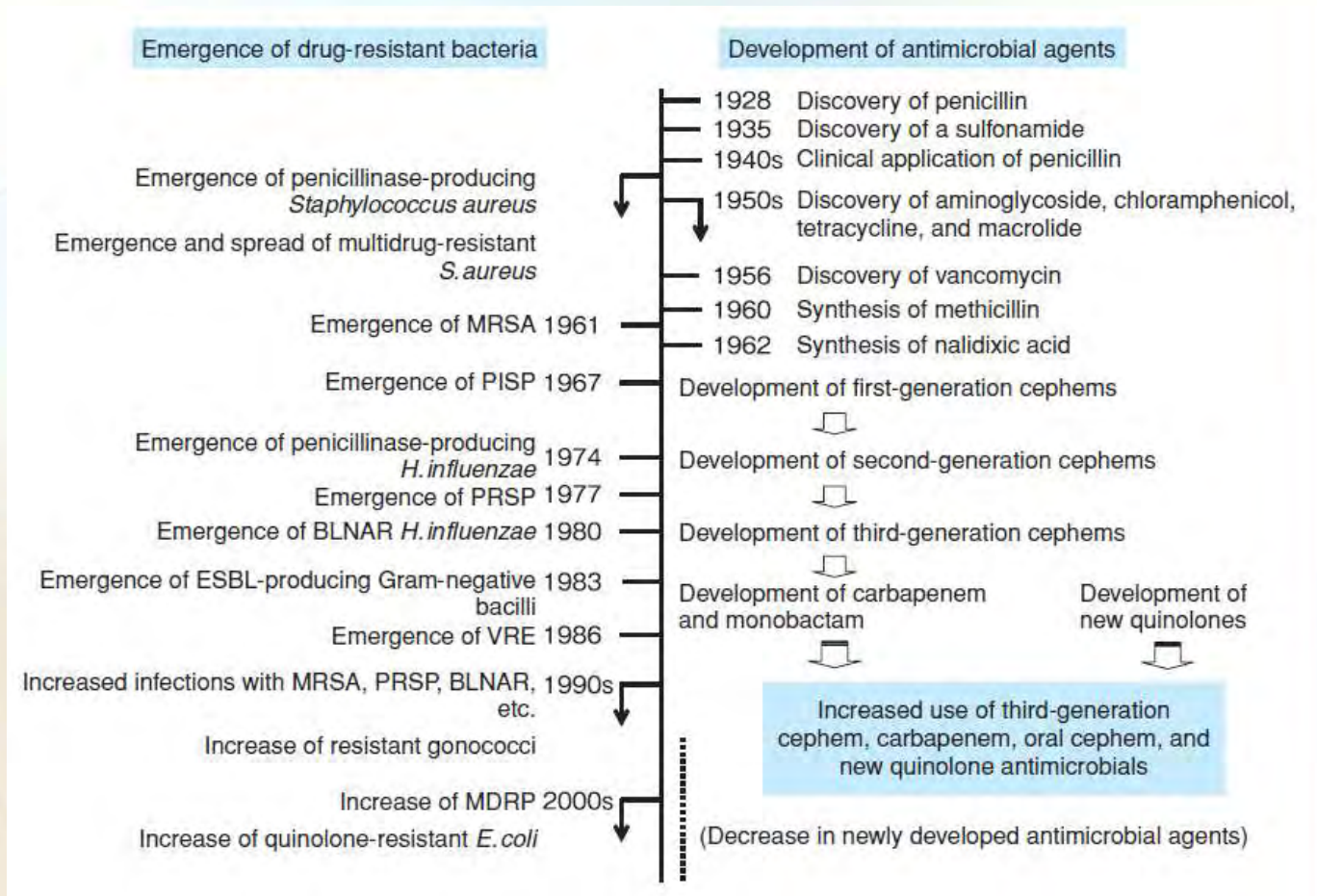
A year ago, production of penicillin was difficult, costly. Today, due to specially devised methods of mass-production, as set by Schenley Laboratories, Inc. and the 70 other firms designated by the government to make penicillin, it is available in ever-increasing quantity, at progressively lower cost.

Shown in "THE DOCTOR FIGHTS" showing RAYMOND JAMES' "Vagabond" exhibition.
U.S.S. has just paper for this and others.

SCHENLEY LABORATORIES, INC.
Producers of **PENICILLIN-Schenley**



Trend of Development of Antimicrobial Agents and Emergence of Drug-Resistant Bacteria



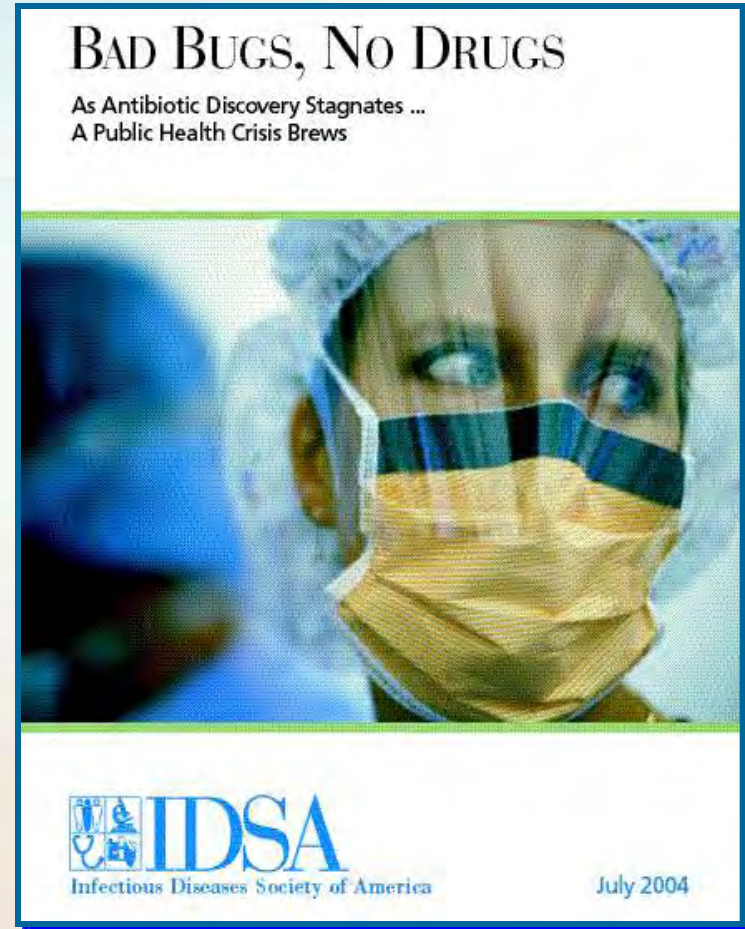
The Challenge of Antimicrobial Resistance in Human Health

- **Markedly increasing resistance development (novel mechanisms) and rates since 1975**
- **Reduced interest in anti-infective development by pharmaceutical companies**
- **Diminished infection control and public health infrastructure**
- **Limited treatment options**
- **Urgent need for action (example: ASM Task Force on Antibiotic Resistance, 1995) = SURVEILLANCE**

(also EDUCATION and RESEARCH)

Bad Bugs, No Drugs¹

- Declining research investments in antimicrobial development^{2,3}
- The Antimicrobial Availability Task Force of the IDSA identified problematic pathogens including gram-negative bacteria²
- Problematic pathogens can “escape” the activity of antibacterial drugs³
 - “ESKAPE” pathogens include
 - *Enterococcus faecium*
 - *Staphylococcus aureus*
 - *Klebsiella pneumoniae*
 - *Acinetobacter baumannii*
 - *Pseudomonas aeruginosa*
 - *Enterobacter spp*



The Infectious Diseases Society of America's (IDSA)

Efforts

- **2004**

- IDSA published whitepaper “Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates a Public Health Crisis Brews,” and launched an advocacy campaign to spur government solutions.

- **2009**

- IDSA published an update on “Bad Bugs, No Drugs...”

- Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America. Helen W. Boucher, George H. Talbot, John S. Bradley, John E. Edwards, Jr, David Gilbert, Louis B. Rice, Michael Scheld, Brad Spellberg, and John Bartlett. *Clinical Infectious Diseases* 2009; 48:1–12.

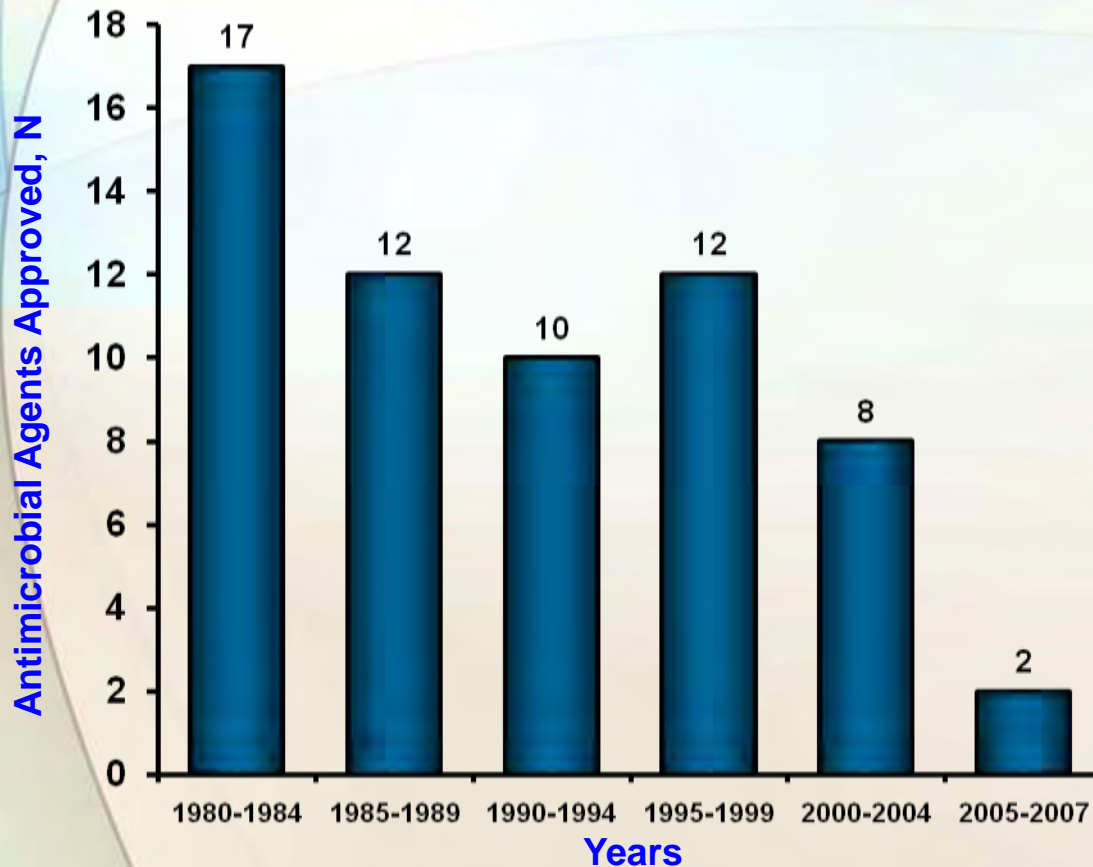
- **2010**

- IDSA statement before the House Committee on Energy and Commerce Subcommittee on Health June 9, 2010

- “Six years later, the drug pipeline and resistance problems have only grown worse as more companies have withdrawn from antibiotic research and development (R&D) and ever-more resistant “bad bugs” have spread across the United States in health care settings and communities, devastating the lives of the young and the old, the healthy and the frail.”

A Changing Landscape for Approval of Antibacterial Agents: FDA Approvals Over Time¹

Bars represent number of new antimicrobial agents approved by the FDA during each time frame.



“The number of antibacterials in Phase 2 or 3 of clinical development remains disappointing, and the absence of agents designed to treat infection due to resistant gram-negative bacilli places patients with these infections in danger”²

– Boucher, et al. *CID* 2009

1. Adapted from Colson. *Resources for the Future*. 2008.

http://www.extendingthecure.org/downloads/policy_briefs/Policy_Brief6_May08_newdrugs.pdf. Accessed May 1, 2009. 2. Boucher HW, et al. *Clin Infect Dis*. 2009;48:1-12.

Infectious Diseases Society of America 10 x 20 Initiative

“We seek a global commitment by the United States Government, particularly the Department of Health and Human Services (HHS), and other governments to create a sustainable antibiotic R&D enterprise, which in the short-term can produce 10 new safe and effective antibiotics by 2020. The antibiotics we seek are those that can treat the most serious and life-threatening pathogens against which most approved antibiotics are not effective.”

Public Perception: NY Times

Well



Tara Parker-Pope on Health

April 13, 2009, 7:56 PM

A Deadly Germ Unleashed by Antibiotics

By TARA PARKER-POPE

For years, health officials have sounded the alarm about overuse of antibiotics and the emergence of so-called “superbugs” that resist treatment. But the spread of a deadly germ linked with antibiotic use shows just how immediate the threat really is.

The culprit is *Clostridium difficile*, a bacteria that can cause life-threatening infection, diarrhea and stomach pain. What is so frightening about *C. difficile* is that it is typically triggered by a round of antibiotic use. In addition to killing the targeted infections, antibiotics wipe out beneficial bacteria, which can make a body more vulnerable to *C. difficile* infection.

To learn more about *C. difficile* read the full story, “[Stomach Bug Crystallizes a Threat From Antibiotics.](#)”

And please, join the discussion below. Have you or any one you know been diagnosed with *C. difficile*?

- Are Free Antibiotics Good for You?
- Resistant Bacteria Meet Reality Television
- Worries About a Gonorrhea ‘Superbug’
- Pets Get MRSA Infections Too
- Resistant Bacteria, Football Players and Gay Men

Public Perception

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Press Release

Moms Across America Uniting to Preserve Effectiveness of Antibiotics

Poll of 800+ Moms Shows More than Three Out of Four Concerned about Use of Antibiotics in Food Animal Production, Support Government Action to Limit Such Use

May 3, 2011

Contact: [Josh Wenderoff](#), 202.540.6542

WASHINGTON -- The [Pew Campaign on Human Health and Industrial Farming](#) today launched "Moms for Antibiotic Awareness," a grassroots movement of moms working to preserve the effectiveness of antibiotics for their children and families.

The campaign also released the results of an online poll of 804 American mothers who are registered voters and have children aged 16 or younger. Eighty percent of the respondents were concerned about giving antibiotics to animals that are being produced for meat and poultry, with 42 percent saying they are "very concerned" about this practice.

Each year, tens of thousands Americans die and hundreds of thousands more fall seriously ill from infections resistant to antibiotics. Newborns, children and seniors are particularly vulnerable to these diseases.

"Seven years ago, my one-and-a-half-year-old son, Simon, died from an infection because the antibiotics we relied on had become useless," said Everly Macario, founder of the MRSA Research Center at the University of Chicago and one of the first mothers to join Moms for Antibiotic Awareness. "Simon's death sounded an alarm that my fellow moms across this country need to hear: antibiotics are increasingly ineffective against life-threatening infections, and the lives of our children and loved ones are at stake. I am asking my fellow moms and their family members to honor Mother's Day by visiting www.SaveAntibiotics.org and joining Moms for Antibiotic Awareness."

Last year, the U.S. Food and Drug Administration (FDA), the U.S. Department of Agriculture and the Centers for Disease Control and Prevention testified before Congress that there was a definitive link between the non-therapeutic uses of antibiotics on industrial farms and the crisis of antibiotic resistance in humans. In addition, many medical organizations including the American Medical Association, American

History of Medicine



2000 B.C.

Here, eat this root.

1000 A.D.

That root is heathen. Here, say this prayer.

1850 A.D.

That prayer is superstition. Here, drink this

potion.



1920 A.D.

That potion is snake oil. Here, swallow this

pill.

1945 A.D.

That pill is ineffective. Here, take this

penicillin.



1955 A.D.

Oops....bugs mutated. Here, take this

tetracycline.

1960-2010 A.D. 50 more “oops” ...Here, take this powerful antibiotic.

2011 A.D.

The bugs have won! Here, eat this root.

Examples of Antimicrobial Resistance Surveillance Programs

Human pathogens

Global programs

Alexander Project (1992-2001)
MYSTIC Program (1999-2008)
PROTEKT (1999-2008)
SENTRY Program (1997-present)

National/Regional programs

TSN (USA)
EARSS (EUROPE)
CANWARD (CANADA)

Veterinary pathogens

Global programs

WHO GSS (WHO, CDC)

National programs

JVARM (JAPAN)
NARMS (CDC, USDA, FDA)
FoodNet (CDC, USDA, FDA)

SENTRY Program Description

- **Global (four regions, 35 countries, 100-140 sites)**
 - North America
 - Latin America
 - Europe
 - Asia Pacific (Asia, Australia, South Africa)
- **Objectives (prevalence design)**
 - Infection site (BSI, CARTI, HAP, UTI, SSSI, etc.)
 - Genus or species
 - Special needs (resistance phenotype, etc)
- **Central reference laboratory processing**
 - Completely available organism collection
- **35 to 50 antimicrobials each year**
 - Investigational agents are selectively monitored

List of Most Common Pathogens from SENTRY 2010

Bloodstream Infections

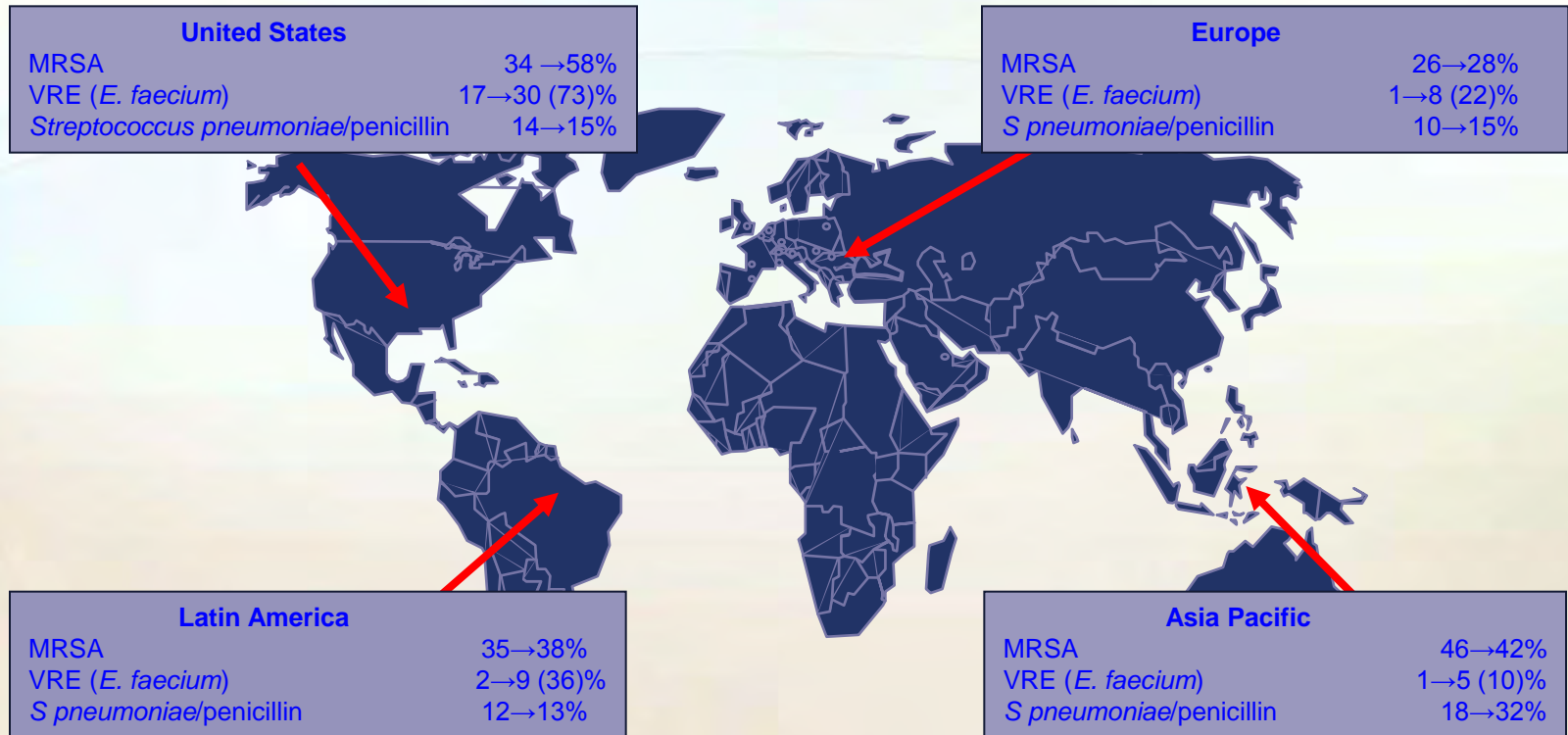
<i>Escherichia coli</i> (approx 23%)	<i>Beta-haemolytic streptococci</i>	<i>Citrobacter</i> spp.
<i>Staphylococcus aureus</i> *	<i>Streptococcus pneumoniae</i>	<i>Haemophilus</i> spp.
<i>Klebsiella</i> spp.*	<i>Viridans group streptococci</i>	<i>B. fragilis</i> group
<i>Enterococcus</i> spp.*	<i>Proteus mirabilis</i>	<i>Bacillus</i> spp.
<i>Coagulase-negative staphylococci</i>	<i>Serratia</i> spp.	<i>Aeromonas</i> spp.
<i>Pseudomonas</i> spp.*	<i>Salmonella</i> spp. (<1%)	<i>Listeria</i> spp.
<i>Enterobacter</i> spp.*	<i>Stenotrophomonas maltophilia</i>	<i>Corynebacterium</i> spp.
<i>Acinetobacter</i> spp.*	<i>Indole-positive Proteus</i> spp.	

* ESKAPE pathogens; "Bad Bugs, No Drugs"

Trend and Current Status of Resistance

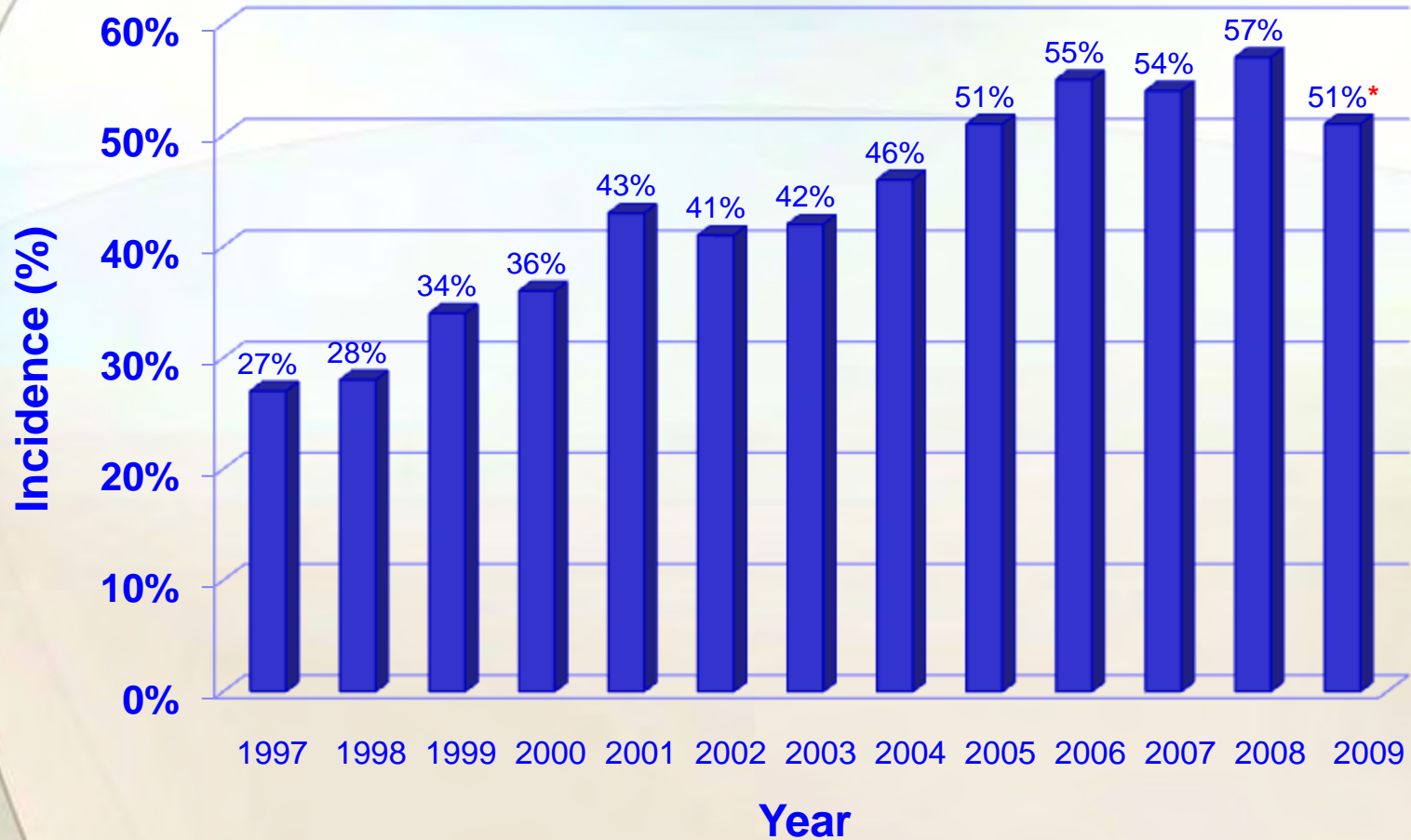
- **Gram-positive pathogens**
 - *S. aureus* (MRSA)
 - Enterococci (VRE)
 - *S. pneumoniae* (PenR)
- **Gram-negative pathogens**
 - Enterobacteriaceae
 - *E. coli* (CipR, ESBL)
 - *Klebsiella* spp. (CipR, ESBL, CarbR)
 - *Enterobacter* spp. (CazR, ESBL)
 - Non-fermentative pathogens
 - *P. aeruginosa* (CarbR, MBL)
 - *Acinetobacter* spp. (CarbR, MDR)

Worldwide Resistance to Selected Antimicrobials (1997-1999) Compared to (2007-2009)



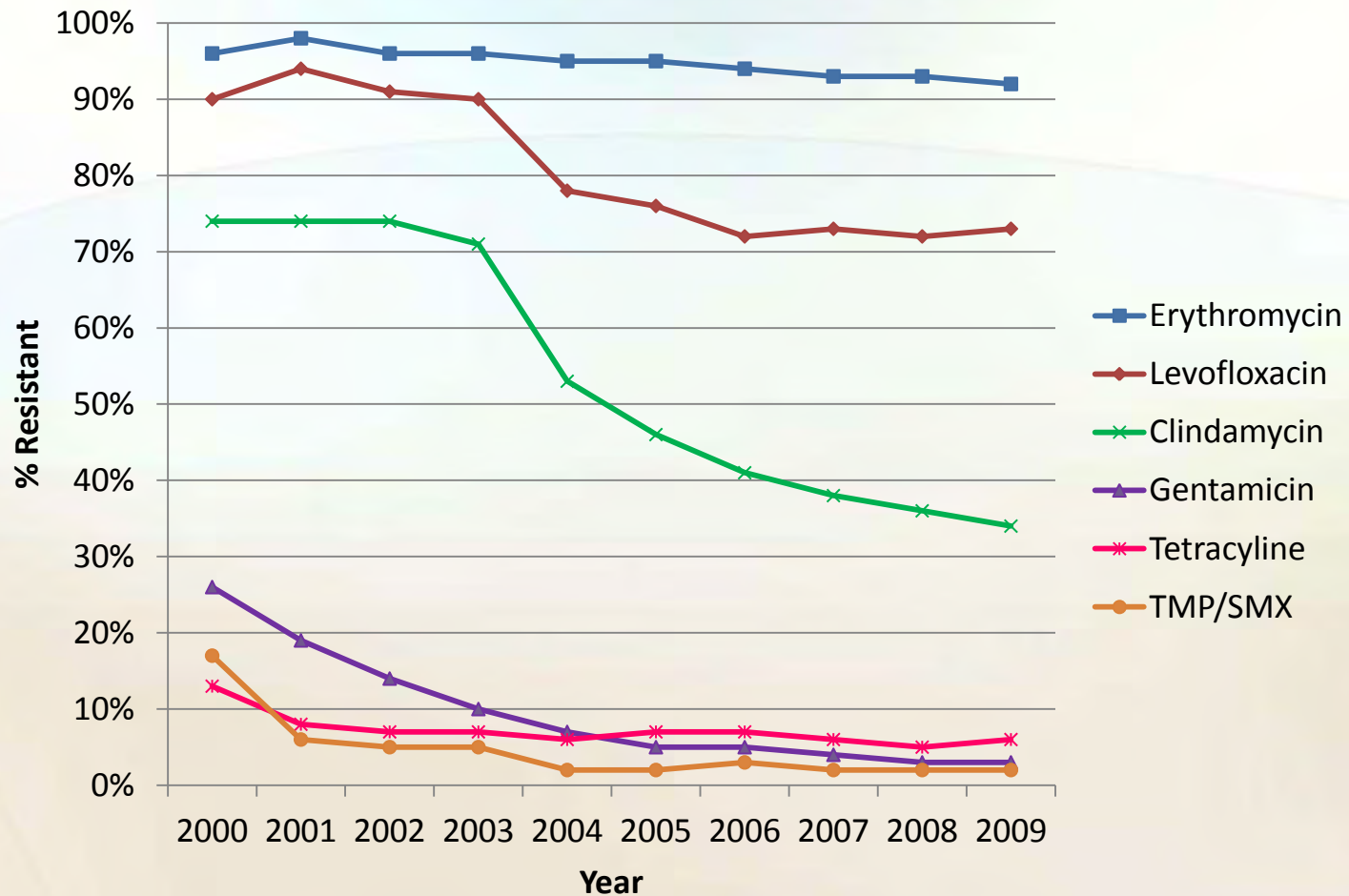
MRSA indicates methicillin-resistant *Staphylococcus aureus*; PIP-TAZO, piperacillin-tazobactam; VRE, vancomycin resistant enterococci; ESBL, extended spectrum β -lactamases. Jones *et al.* SENTRY Antimicrobial Surveillance Program 1997-2009. JMI Laboratories (www.jmilabs.com)

Trends in MRSA Rates in SENTRY Program Medical Centers (Bacteremias in USA, 1997–2009)



* = MRSA rate declined in 2009

Trends in Erythromycin, Levofloxacin, Clindamycin, Gentamicin, Tetracycline, and TMP/SMX Resistance Rates among 20,049 MRSA in USA (SENTRY Program, 2000-2009)^a



a. Modified from Jones et al., *Diagn. Microbiol. Inf. Disease* 71: (in press), 2011.

Six-year Trends in Linezolid Resistance Rates Observed in the USA LEADER Program (2004 to 2009; 33,378 Isolates)

Organism (no. tested)	% of isolates nonsusceptible or resistant to linezolid ^a					
	2004	2005	2006	2007	2008	2009
<i>S. aureus</i> (18,537)	0.00	0.03	0.03	0.06	0.10	0.15
CoNS (4,526)	0.20	1.13	1.61	1.76	1.64	1.47
Enterococci (4,577)	0.80	0.64	1.83	1.13	0.55	0.49
<i>S. pneumoniae</i> (3,292)	0.00	0.00	0.00	0.00	0.00	0.00
Other streptococci ^b (2,446)	NT	NT	0.00	0.00	0.00	0.00
All organisms (33,378)	0.14	0.24	0.45	0.44	0.36	0.34

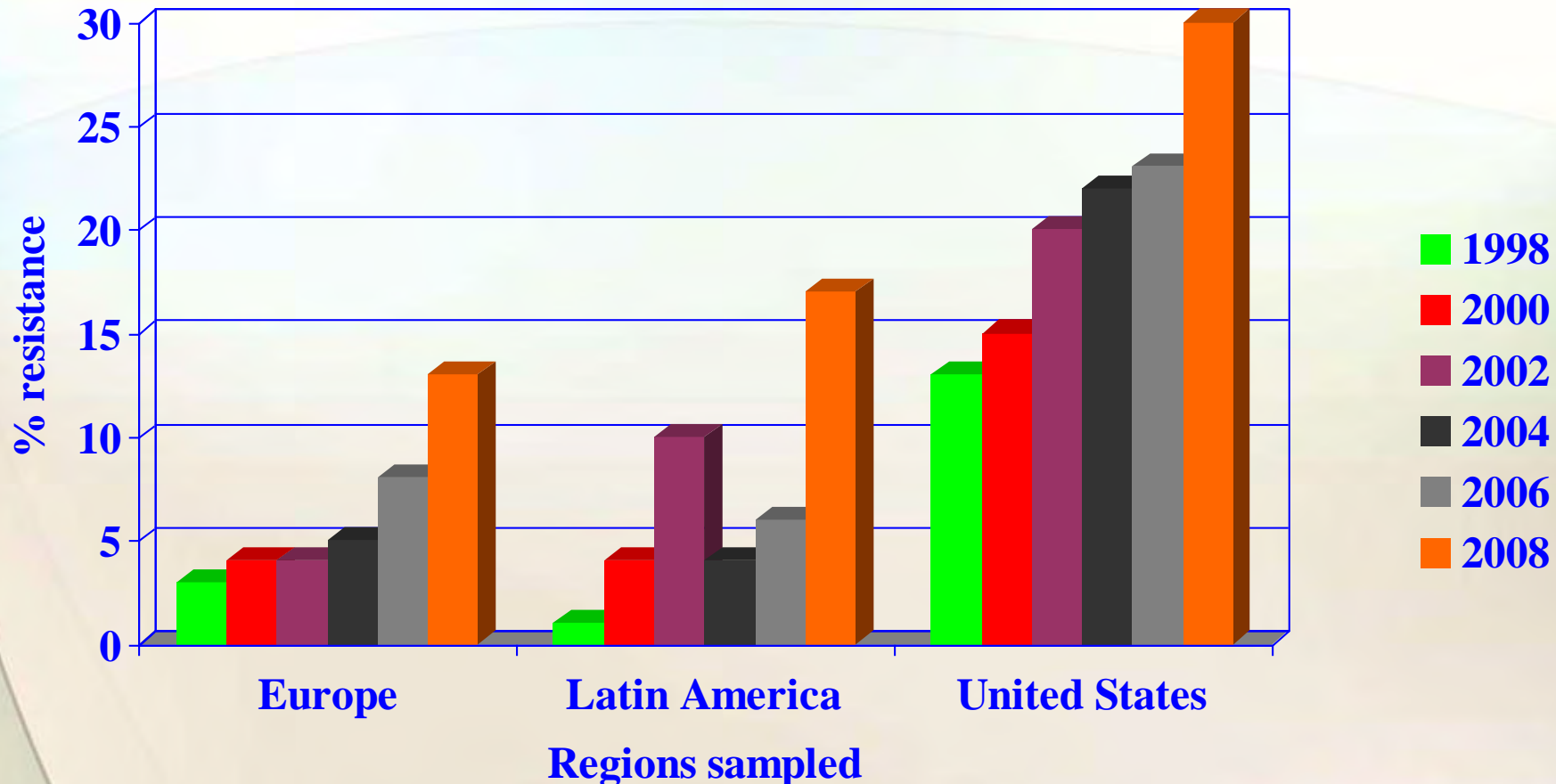
a. Modified from Farrell et al., Antimicrob. Agents Chemother. 55: 3684-3690, 2011.

b. Viridans group and β -haemolytic streptococci.

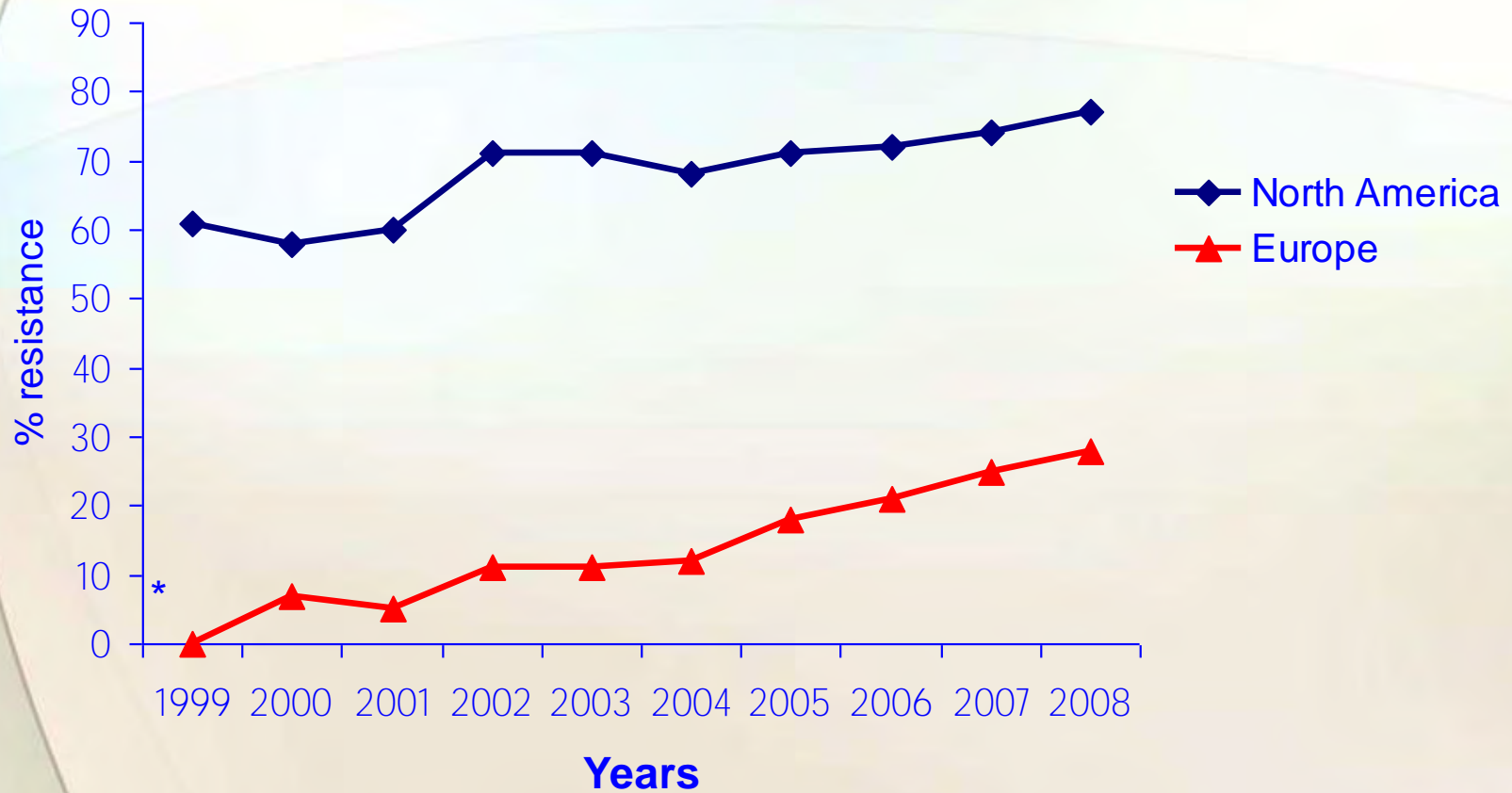
S. aureus Identified as Linezolid-Resistant in the 2009
LEADER Program (MIC, $\geq 8 \mu\text{g/ml}$) in the USA, only 5 of
3,257 Isolates or 0.15%

Location (State)	Age/Sex	MIC ($\mu\text{g/ml}$)	Mechanism
Connecticut	68/M	8	L3 (S145 deletion)
California	14/F	16	G2576T
Kansas	17/M	16	G2576T
Ohio	52/M	16	<i>cfr</i>
Kentucky	52/M	16	<i>cfr</i>

Regional Trends in Blood Culture VRE Rates (SENTRY Program, 1997-2008 [12 years]; >35,000 Isolates)

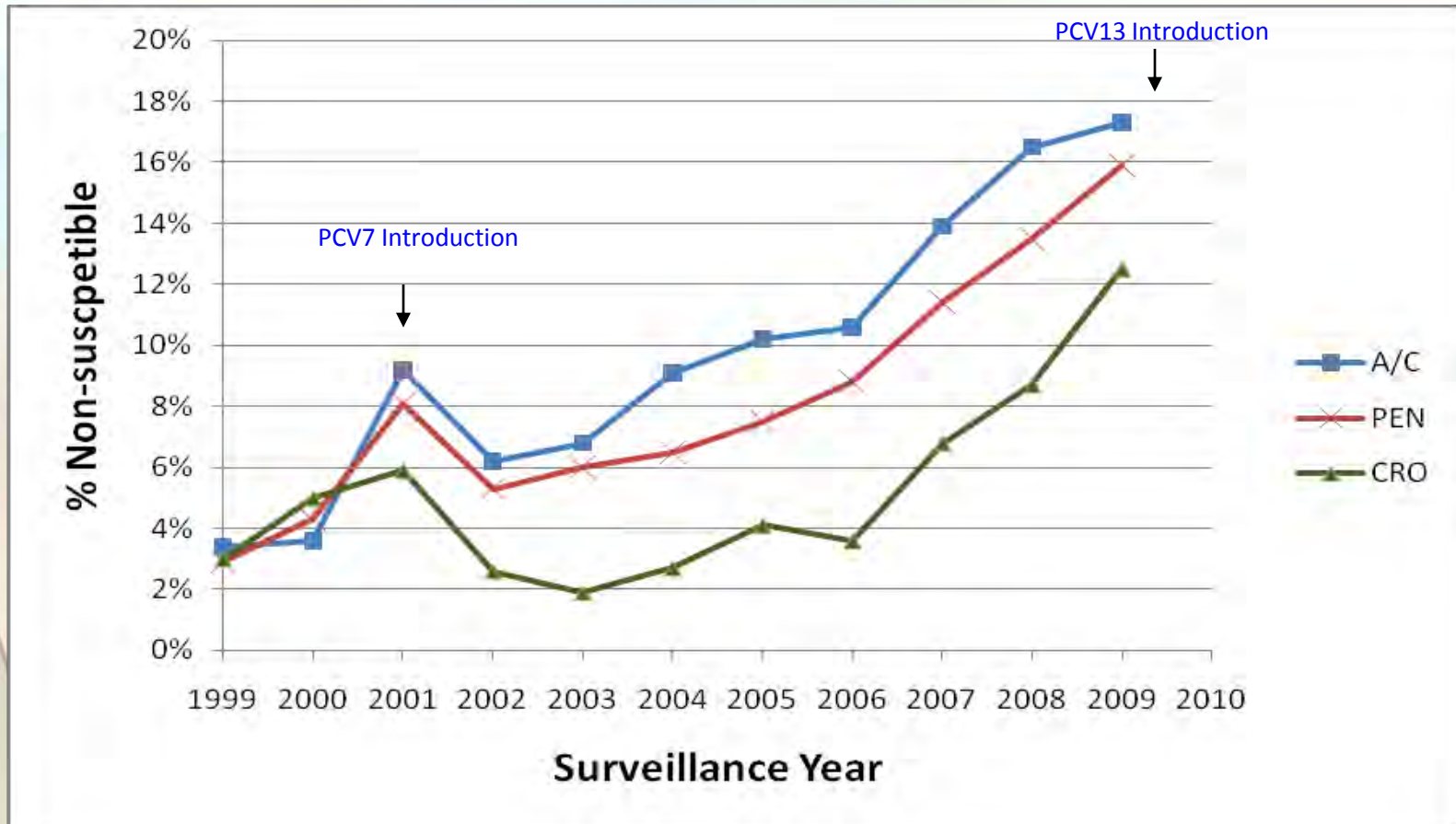


Progression of Vancomycin Resistance Among *E. faecium* Bacteremias in North America and Europe (1999-2008 SENTRY Program)



*withdrawal of animal growth promoters eg. avoparcin

Profile of Nonsusceptibility Rates for 3 Commonly Used β -lactams (A/C=amoxicillin/clavulanate, PEN=penicillin, high-dose, and CRO=ceftriaxone) Tested against 14,384 *S. pneumoniae* Isolates from the USA SENTRY Program (1998-2009)



a. From Jones et al., J. Antimicrob. Chemother. 66 (Suppl. 3): 69-80, 2011.

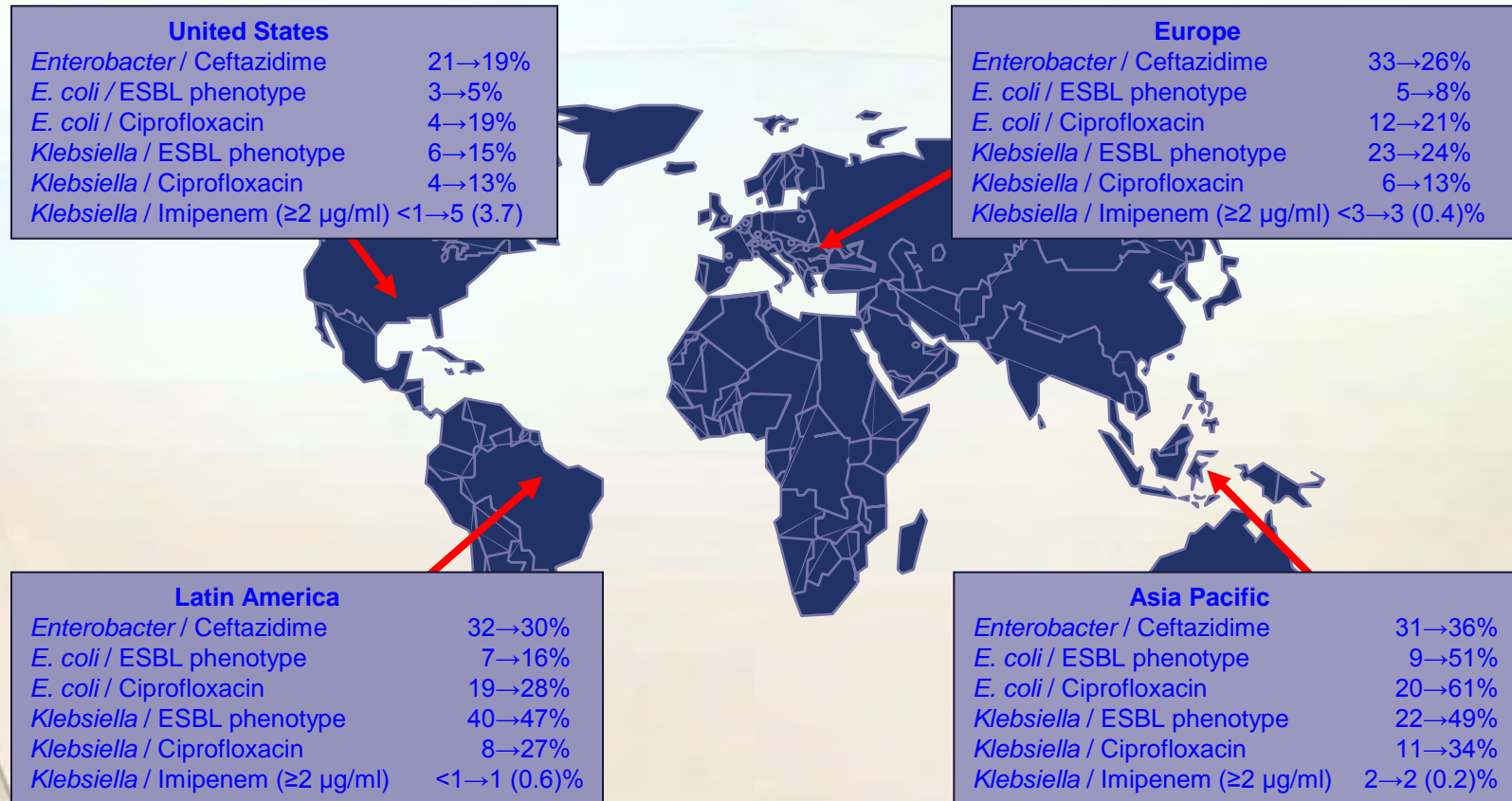
Trends in Susceptibility for Five Antimicrobial Classes Tested against 14,394 *S. pneumoniae* (1998-2009)^a

Antimicrobial agent	Susceptibility rate (%)		
	1998	2009	Variation
Erythromycin	82.2	60.8	-21.4
Clindamycin	96.2	79.1	-17.1
Tetracycline	88.8	75.5	-13.3
TMP/SMX	73.8	65.7	-8.1
Levofloxacin	99.8	99.2	-0.6
(Ciprofloxacin) ^b	(2.2) ^b	(3.3) ^b	-

a. From the SENTRY Program. Modified from Jones and Sader. *Diagn. Microbiol. Inf. Dis.* 68: 334-336, 2010.

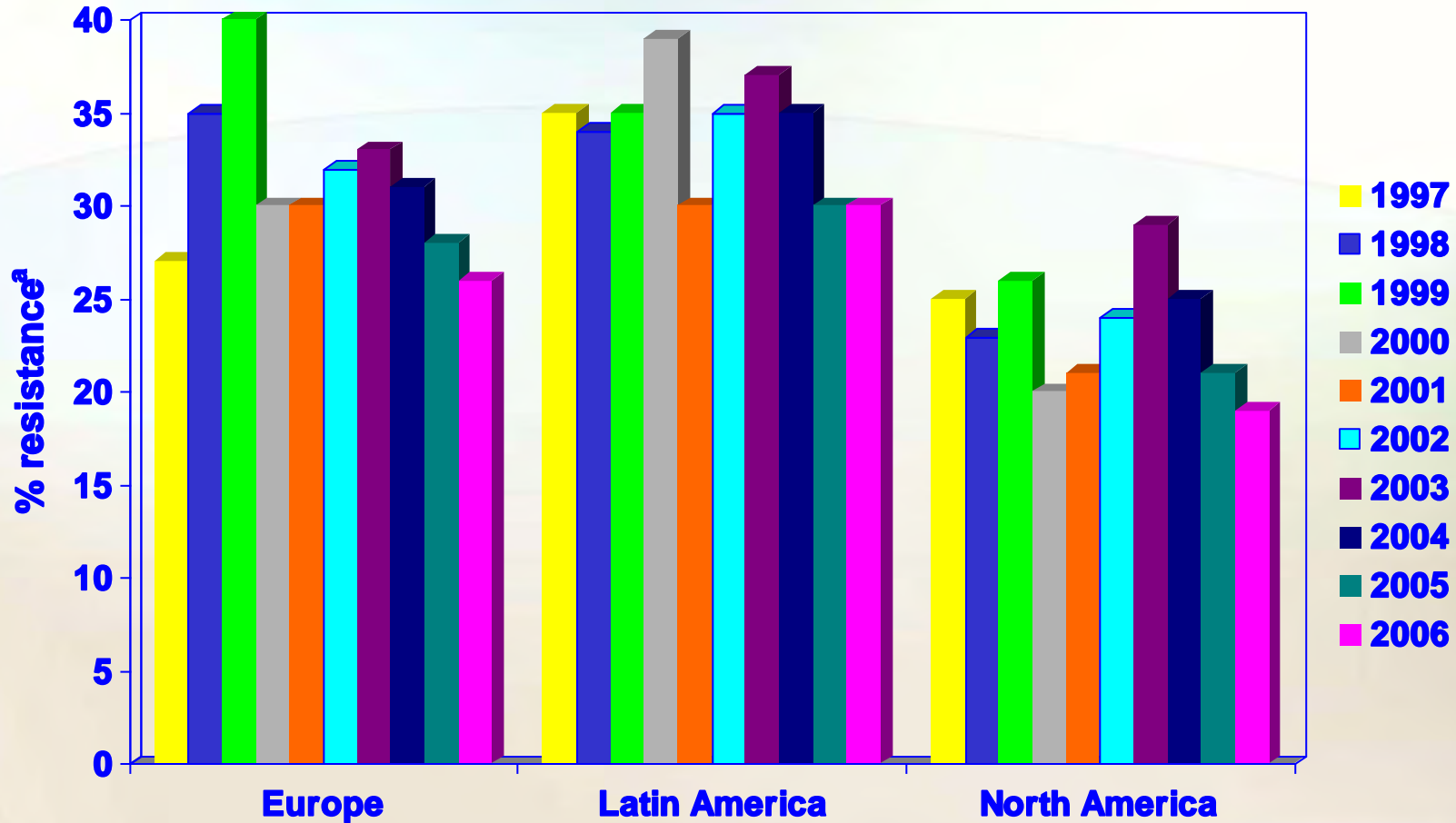
b. Ciprofloxacin MICs at ≥ 4 $\mu\text{g/ml}$ = % with mutational events in QRDR (Chen et al., 1999).

Worldwide Resistance to Selected Antimicrobials (1997-1999) Compared to (2007-2009)



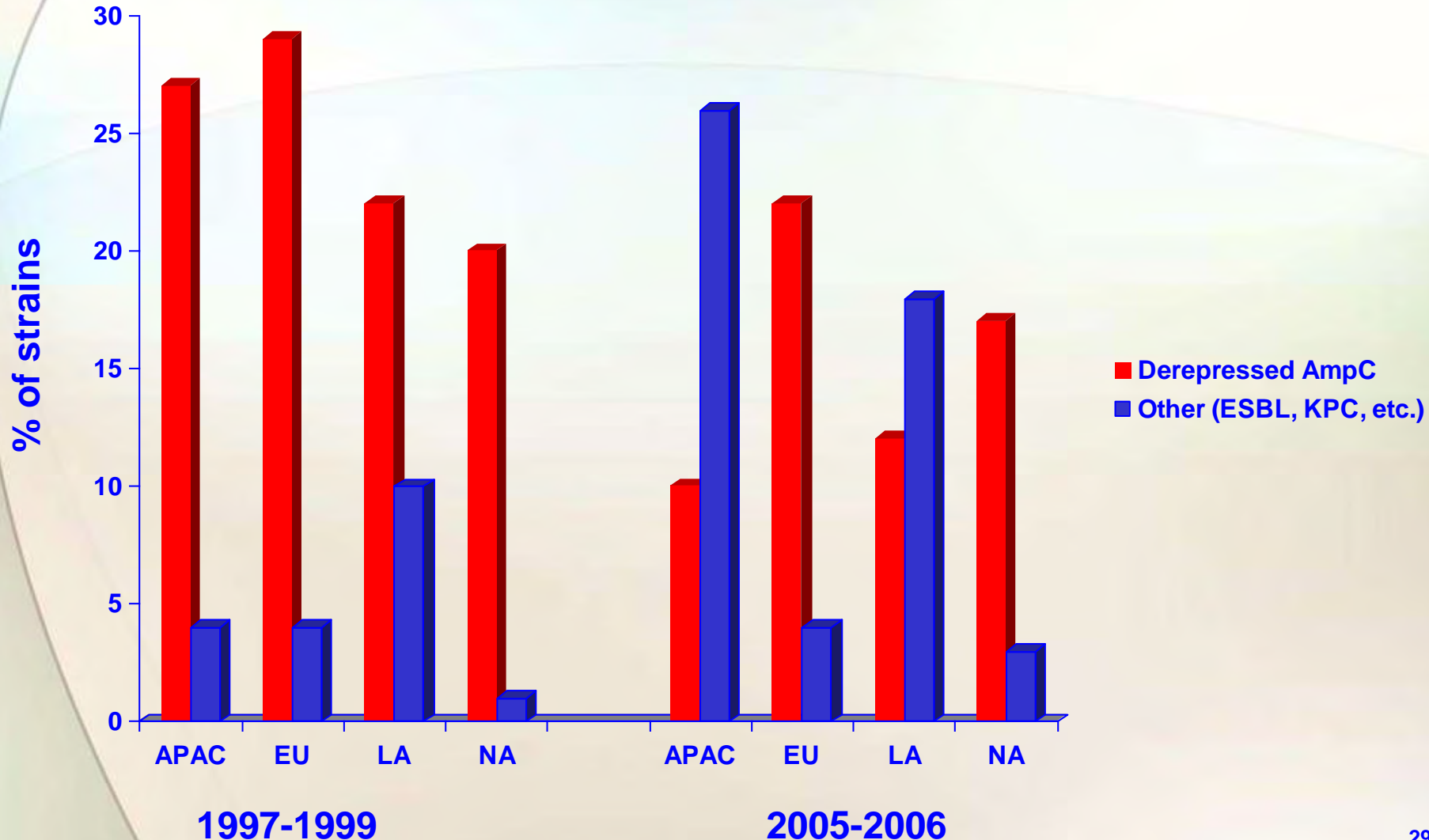
ESBL, extended spectrum β -lactamases
 Jones *et al.* SENTRY Antimicrobial Surveillance Program 1997-2009. JMI Laboratories (www.jmilabs.com)

Regional Trends in *Enterobacter* Derepressed AmpC Resistances (SENTRY Program, 1997-2006)



a. Ceftazidime resistance rates

Changes in Ceftazidime (CAZ) Resistance Mechanisms among CAZ-Resistant *Enterobacters* (SENTRY Program, 1997-1999 versus 2005-2006)



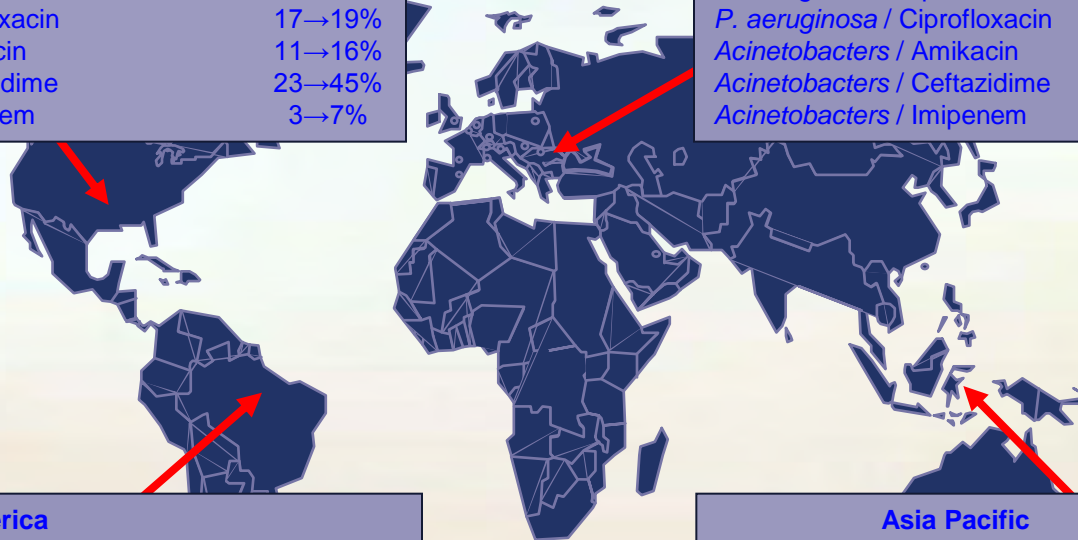
Worldwide Resistance to Selected Antimicrobials (1997-1999) Compared to (2007-2009)

United States

<i>P. aeruginosa</i> / Imipenem	9→8%
<i>P. aeruginosa</i> / Piperacillin-tazobactam	11→12%
<i>P. aeruginosa</i> / Ciprofloxacin	17→19%
<i>Acinetobacters</i> / Amikacin	11→16%
<i>Acinetobacters</i> / Ceftazidime	23→45%
<i>Acinetobacters</i> / Imipenem	3→7%

Europe

<i>P. aeruginosa</i> / Imipenem	16→16%
<i>P. aeruginosa</i> / Piperacillin-tazobactam	16→17%
<i>P. aeruginosa</i> / Ciprofloxacin	26→23%
<i>Acinetobacters</i> / Amikacin	47→51%
<i>Acinetobacters</i> / Ceftazidime	48→55%
<i>Acinetobacters</i> / Imipenem	22→27%



Latin America

<i>P. aeruginosa</i> / Imipenem	18→21%
<i>P. aeruginosa</i> / Piperacillin-tazobactam	25→20%
<i>P. aeruginosa</i> / Ciprofloxacin	35→36%
<i>Acinetobacters</i> / Amikacin	66→65%
<i>Acinetobacters</i> / Ceftazidime	67→71%
<i>Acinetobacters</i> / Imipenem	11→25%

Asia Pacific

<i>P. aeruginosa</i> / Imipenem	9→24%
<i>P. aeruginosa</i> / Piperacillin-tazobactam	11→28%
<i>P. aeruginosa</i> / Ciprofloxacin	12→38%
<i>Acinetobacters</i> / Amikacin	22→54%
<i>Acinetobacters</i> / Ceftazidime	30→61%
<i>Acinetobacters</i> / Imipenem	5→37%

Resistance Mechanisms Occurring in 50 Meropenem-Resistant *P. aeruginosa* Isolates^a

Mechanism patterns

AmpC hyperproduction	OprD reduction	Efflux upregulation		MβL	No. isolates
		mexXY	mexCD		
+		+			25
+	+	+			10
+	+				5
+					5
+		+	+		2
	+		+		1
		+			1
				IMP-15	1

a. Morita et al. Abstract LB-13 (late breaker), 2006 IDSA, Toronto, Canada.

Acinetobacter

- ***Acinetobacter* stands out in NNIS survey since 2003**
- **Rapidly increasing in prevalence (especially pneumonia)**
- **At ICAAC 2006, carbapenem resistance rates reported as high as 40% ²**
- ***A. baumannii* Resistant to Carbapenems (USA MYSTIC Program, 2007)**
 - **Nine of 15 centers had epidemic clusters (60%)**
 - **Five centers had OXA-type carbapenemases**
 - **OXA-23 (10) and OXA-24 (5)**
 - **Arkansas, Colorado, Kentucky, New Jersey and New York**
 - **30% of carbapenem-resistant isolates**
- **Multidrug-resistant phenotypes were routine, 2 to 5 organism clonal occurrences**

¹ Gaynes R et al. *Clin Infect Dis*. 2005;41:848-854.

² Carey RB et al. Presented at: 46th ICAAC; Sept 27-30, 2006; San Francisco, CA. Poster K-1495

Conclusions

- **Resistance to antimicrobials continues to evolve**
- **Resistance mechanisms are diverse and often multiple**
 - **MRSA**
 - **VRE**
 - **DRSP**
 - **Target alterations (OMP, porins)**
 - **ESBLs**
 - **MβLs**
 - **Inactivating enzymes**
 - **Access changes**
- **Therapeutic options may vary**
 - **More acceptable for Gram-positive cocci**
 - **Limited for MDR Gram-negative bacilli**
 - **Major pharmaceutical industry is generally disinterested (recent excitement!)**
 - **Regulatory approval intervals have actually increased**

Conclusions

- **Management of AMR requires a multi-disciplinary approach**
 - **Formulary controls**
 - **Infection control**
 - **Microbiology laboratory resistance detection systems and epidemiologic typing methods**
 - **Interested medical staff with institutional commitment of resources**
 - **Local and global surveillance systems are needed**
 - **Public education**
 - **Increased drug development**

Social Context^a

- **Concern about resistance is used as ammunition for other agendas, most obviously including marketing by the pharmaceutical industry and cost containment within managed or socialized health care.**
- **This argument assumes a vacuum in which no new drugs are developed.**
- **Concerns about resistance have led to the banning of most agricultural growth promoters in Europe.**
- **Less is said on the other aspects of modern life that potential exacerbate resistance: Large hospitals; the concentration of the very young and very old in socialized care; and increasing travel. Action on these would be socially and politically impossible, even if they are more pertinent to the sum total of resistance than the use of zinc bacitracin as a agricultural growth promoter!!!**

a. Livermore. Clin. Infect. Dis. 36:S11-23, 2002.

Acknowledgements

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