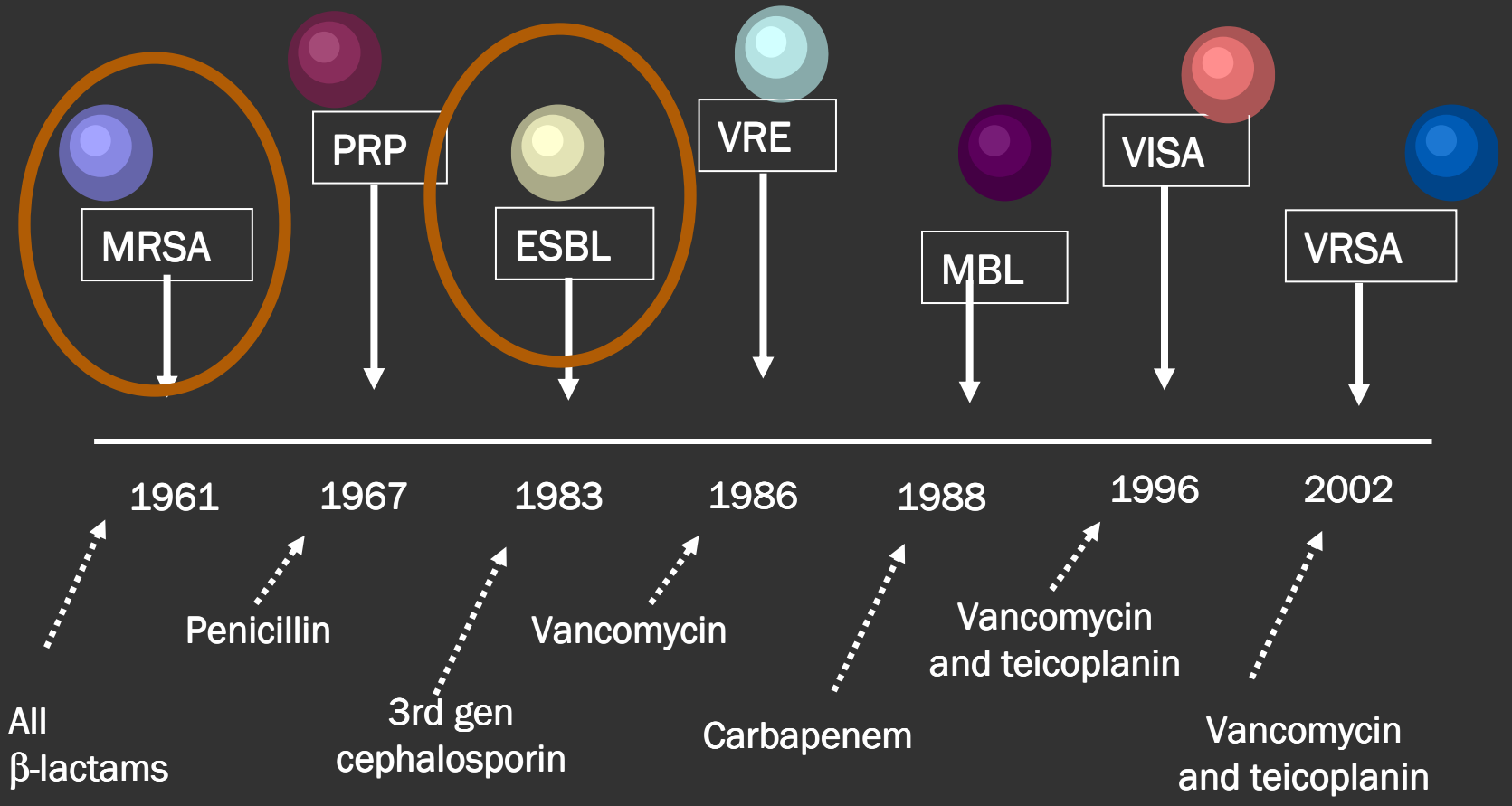
BAD BUGS IN MOTION: MRSA AND ESBL-PRODUCING ORGANISMS

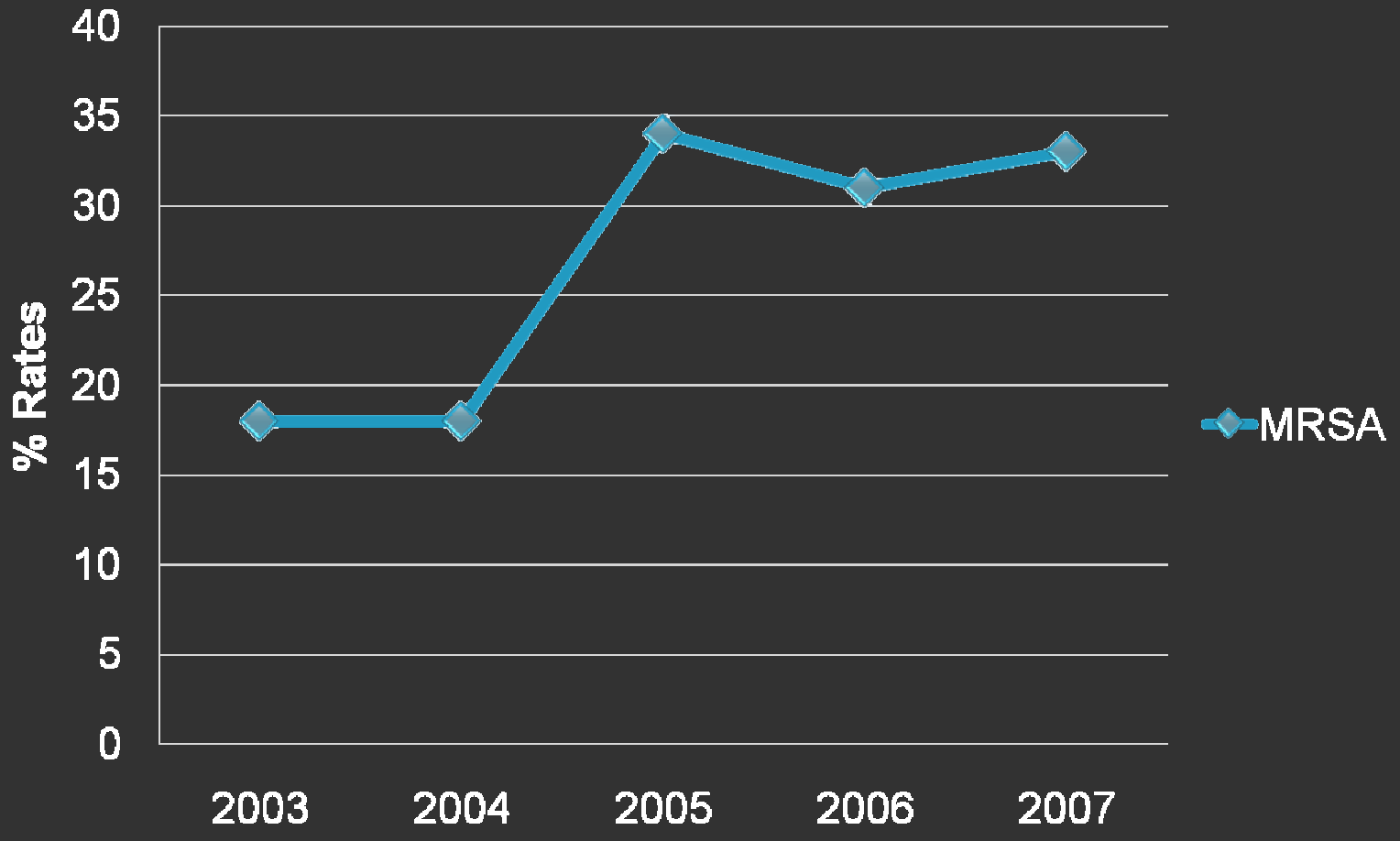
Jaime A. Santos

ANTIBIOTIC RESISTANCE – A GLOBAL PROBLEM



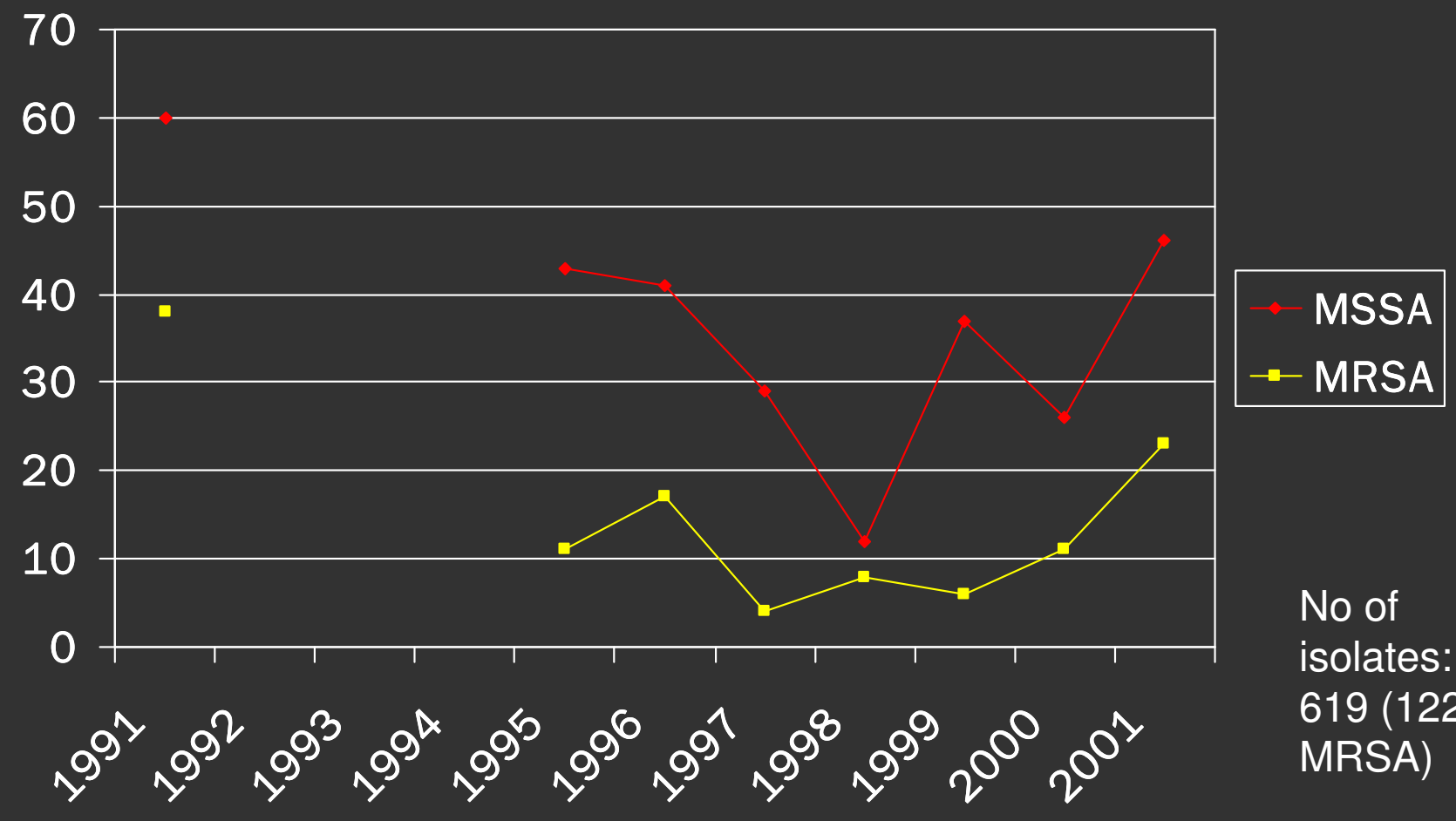
Emergence → Spread

MRSA SURVEILLANCE RATES 2003-2007: ANTIMICROBIAL RESISTANCE SURVEILLANCE PROGRAM (ARSP)



Carlos C, ARSP

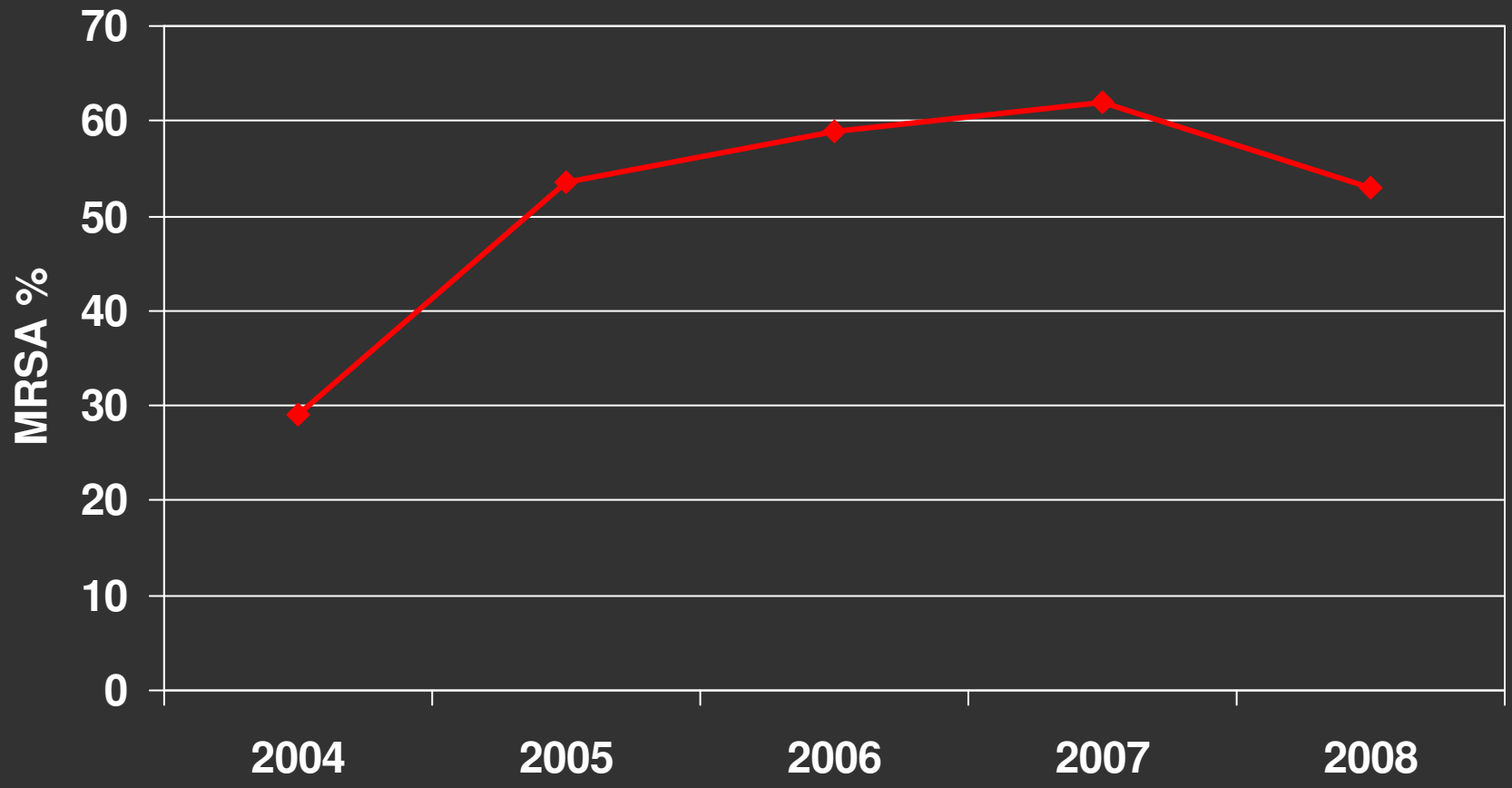
PCMC DATA: SELECTED YEARS



No of isolates: 619 (122 MRSA)

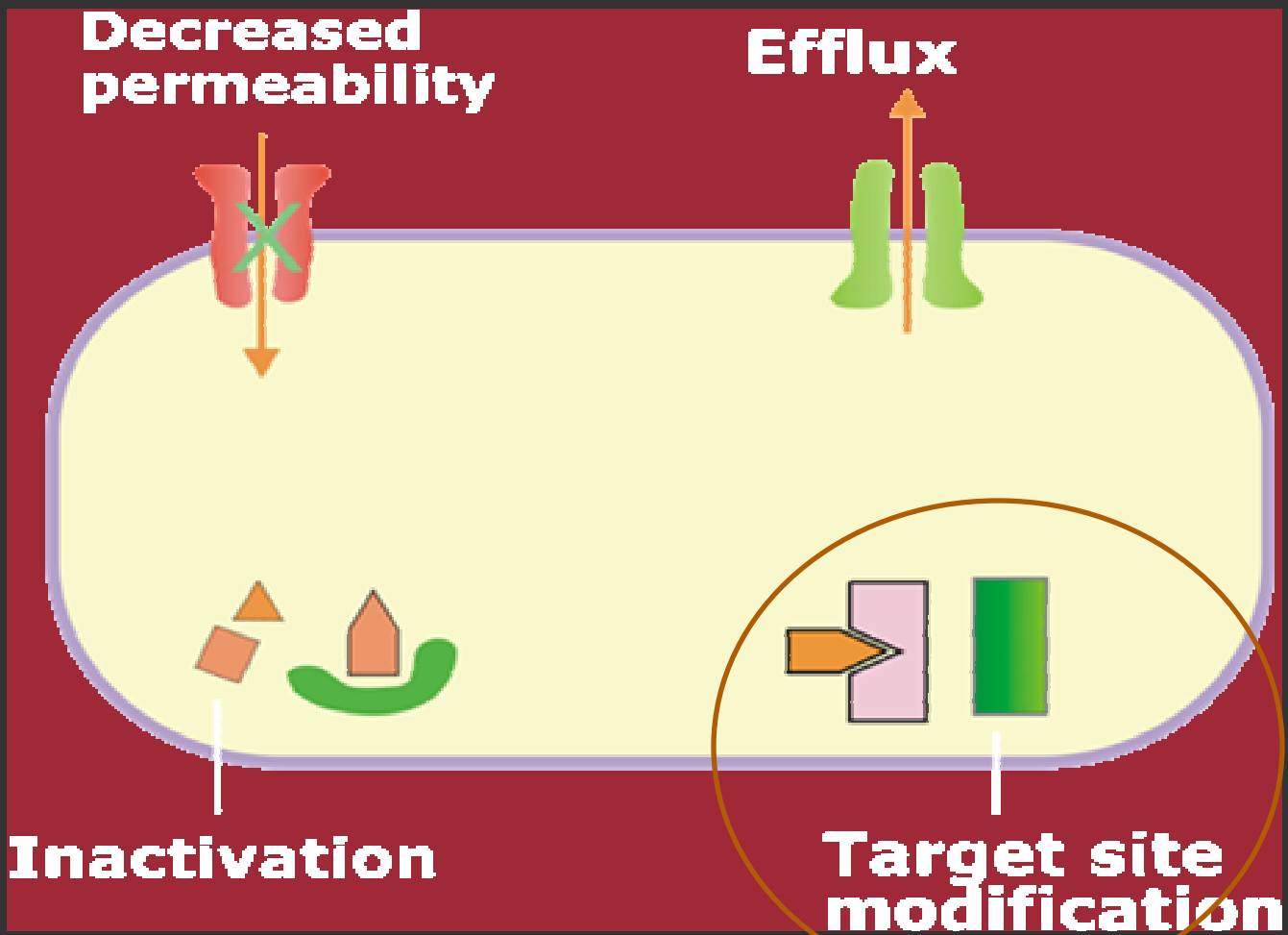
Manahan-Soriano C, Samulde-Ressurreccion, Santos J, MD, MRSA in Children, 2003

PERCENTAGE OF MRSA OVER TOTAL S.AUREUS ISOLATES AT PCMC FROM 2004-2008



Source: ICC, PCMC

MECHANISMS OF RESISTANCE

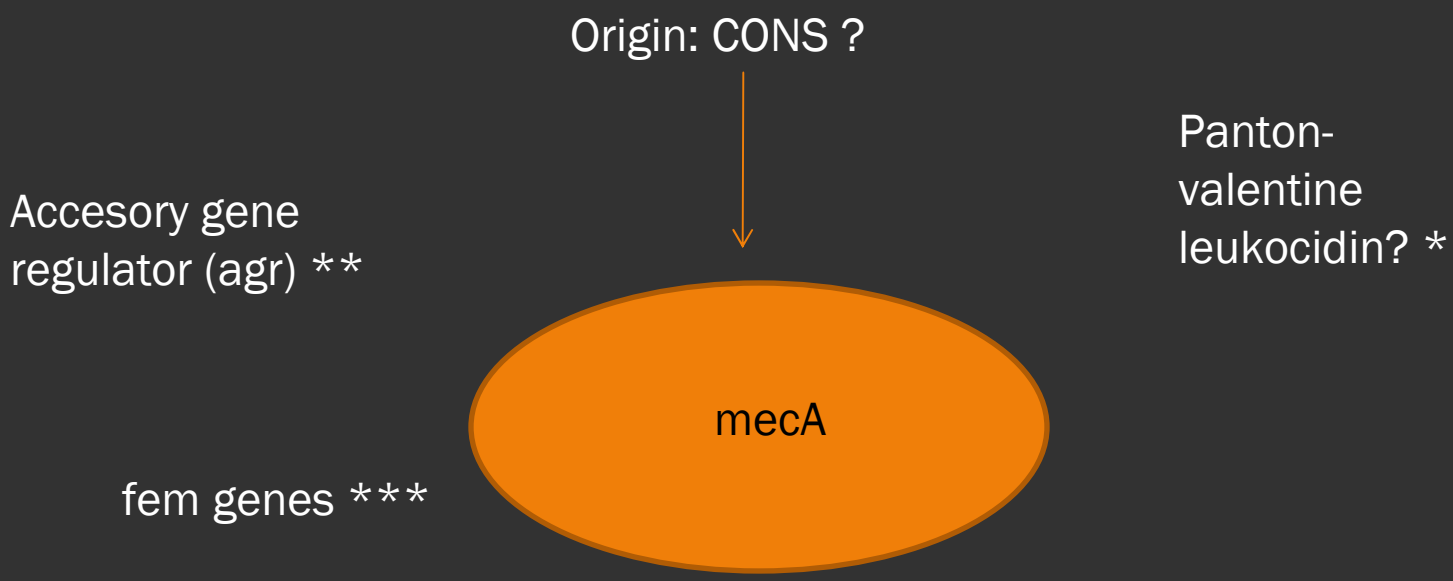


WHAT ARE MRSA'S?

- oxacillin MIC ≥ 4 mcg/mL*
- MIC's of 4 to 8 mcg/mL : borderline or low level resistance
- resistant to all beta-lactams, including cephalosporins
- mediated by mecA gene, found in all resistant strains, which codes for PBP2a**
- mecA is part of mobile SCCmec (5 types)***

*Clinical and Laboratory Standards Institute 2006
**Inglis et al, J Gen Microbiol 1988 ; Tesch et al, Antimicrob Agents Chemother 1988
***Oliveira et al , Microb Drug Resist 2001 ; Ito et al, Antimicrob Agents Chemother 2004

FACTORS INFLUENCING EXPRESSION



* Moran et al, N Engl J Med 2006; Voyich et al, J Infect Dis 2006; Boyle-Vavra et al, Lab Invest2007

**Moise-Broder et al, Clin Infect Dis2004; Sakoulas et al, Antimicrob Agents Chemother2002

***Berger-Bachi, Trends Microbiol 1994

CLASSIFICATION OF MRSA

- HA-MRSA*

  -presence of an invasive device at the time of admission

  -history of MRSA infection or colonization

  -history of surgery, hospitalization, dialysis, or residence in a long-term care facility in the 12 months preceding culture

- CA-MRSA**

  onset in the community in a patient who is without risk factors for HA-MRSA

*Klevens et al, JAMA 2007; Fridkin et al, N Engl J Med 2005

** Fridkin et al, N Engl J Med 2005; Gorwitz RJ, Pediatr Infect Dis J. 2008

MICROBIOLOGIC DIFFERENCES

HA-MRSA

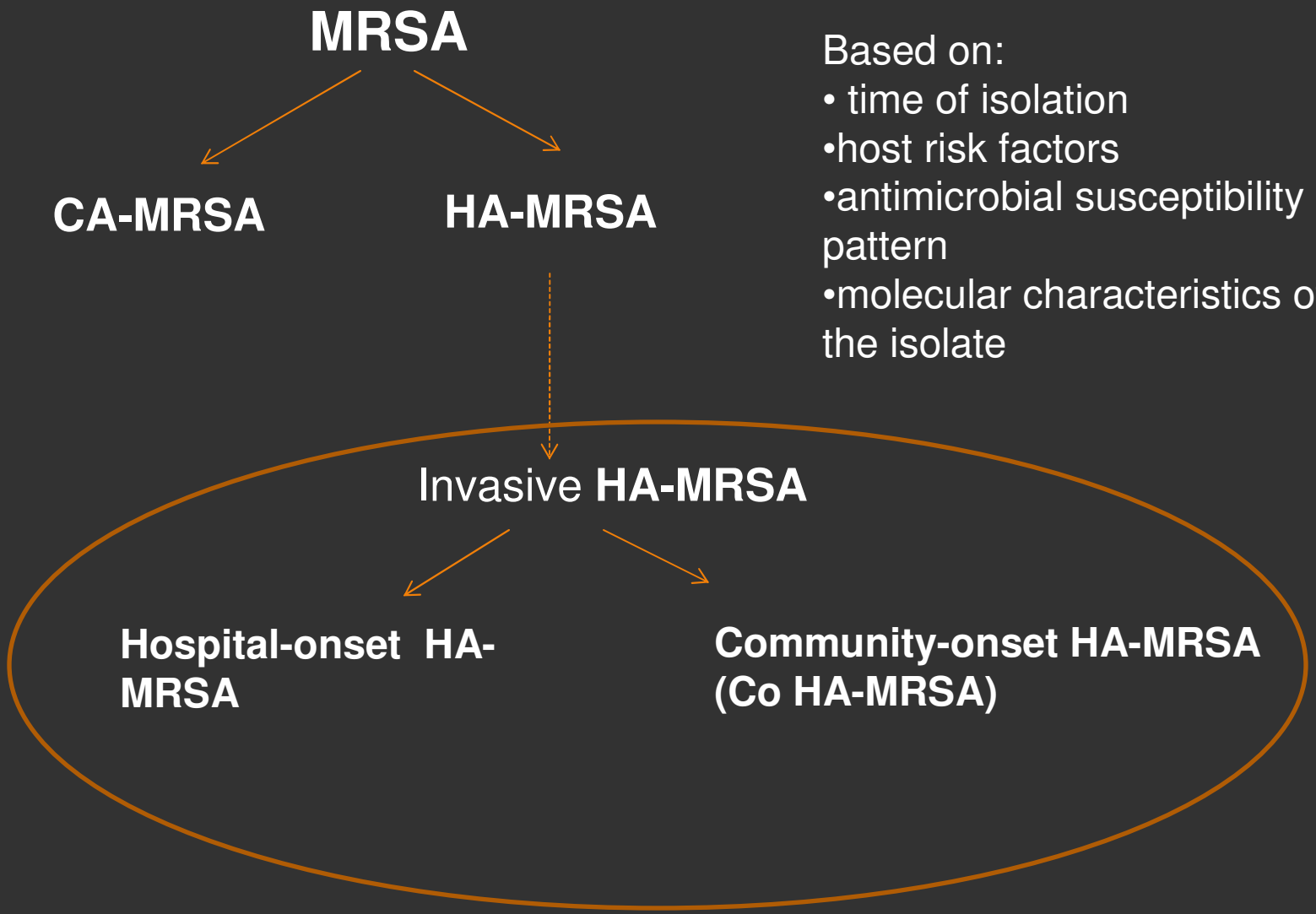
- mostly associated with SCCmec types I, II, and III
- *multidrug resistant* (usu. to 3 or more agents)*

CA-MRSA

- associated with SCCmec type IV and, sometimes, type V
- *often not multidrug resistant to non-beta lactam agents* e.g. clindamycin, fluoroquinolones, tetracyclines, mupirocin*
- many are PVL + : increased morbidity in children with osteomyelitis and mortality in in *S. aureus* pneumonia**
- *resistance increasing*

*Naimi et al, JAMA 2003; Deserinski, Clin Infect Dic 2005; Ma et al, Antimicrob Agents Chemother 2002; ** Baba, Lancet 2002; Diep et al, J Infect Dis 2006; Diep et al, Lancet 2006; ** Gillet et al, Lancet 2002; Martinez-Aguilar et al, Pediatr Infect Dis J 2004; Bocchini et al, Pediatrics 2006; ***Han et al, J Clin Microbiol. 2007; Styers et al, Ann Clin Microbiol Antimicrob. 2006

MRSA CLASSIFICATION



Based on:
- time of isolation
- host risk factors
- antimicrobial susceptibility pattern
- molecular characteristics of the isolate

HA-MRSA (US CDC ABC SURVEILLANCE)

- Invasive *Hospital-onset HA-MRSA :*

  positive culture result from normally sterile site obtained >48 hours after hospital admission

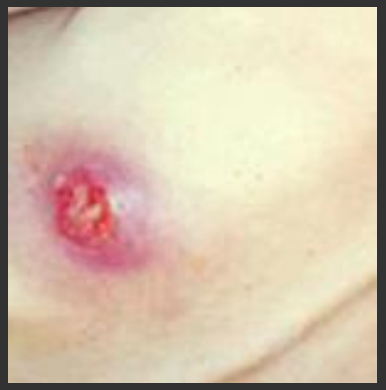
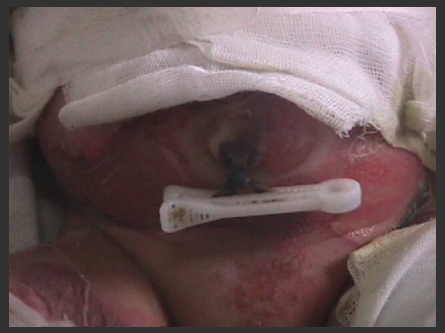
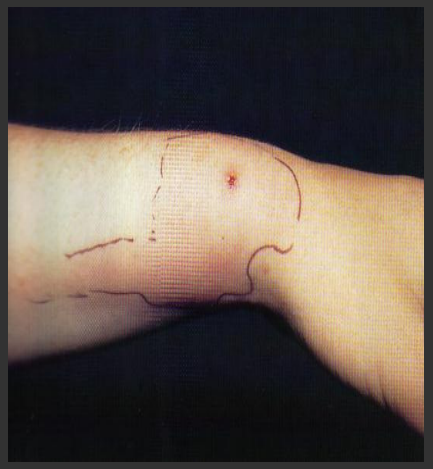
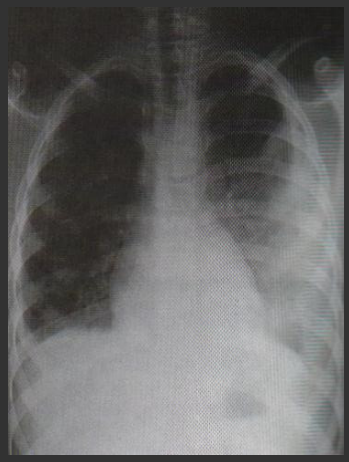
- Invasive *community-onset HA-MRSA* (*CO HA-MRSA*) :

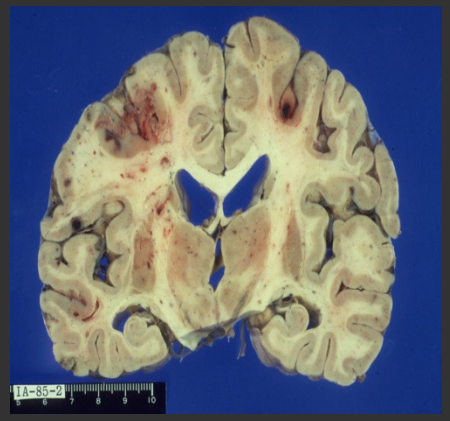
  cases with onset in the community and at least 1 of healthcare risk factors for HA-MRSA;

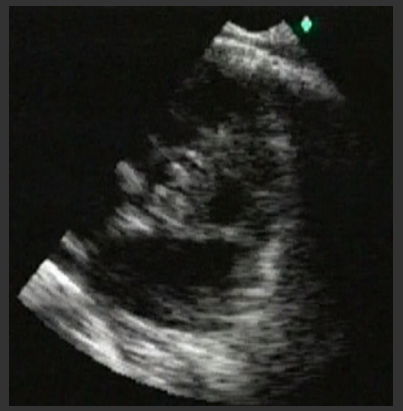
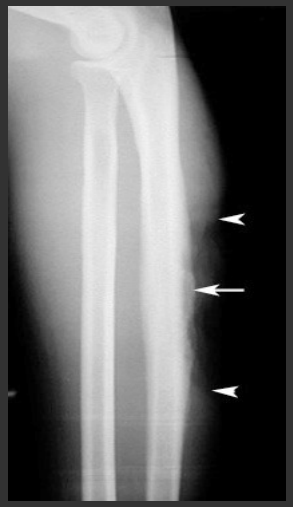
  underlying illness predisposing to frequent confinement/visits to medical facilities *

*Zaoutis et al, Pediatr Infect Dis J. 2006; Hulten et al, Pediatr Infect Dis J 2006

CLINICAL PRESENTATION



Mandell, Atlas of Infectious Diseases; cases from Phil. Children's Medical Center

CLINICAL PRESENTATION*

- asymptomatic
- skin and soft tissue
- Invasive
- pneumonia
- UTI, sinusitis, endocarditis, pyomyositis and others
- Morbidity and mortality greater in invasive disease and in young infants

* Wisplinghof et al, Clin Infect Dis 2004; National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control 2004; Zaoutis et al, Pediatr Infect Dis J. 2006

CA-MRSA VS HA-MRSA: PCMC DATA (1991-2001, N=691, MRSA=122)

- Affects all age group
- Skin: most common site of infection
- Profile, clinical presentation, co-morbid conditions, risk factors and outcome for development of MRSA are the same for both community and nosocomial acquired infections

Manahan-Soriano C, Samulde-Ressurreccion, Santos J, MD, MRSA in Children, 2003

CA-MRSA VS HA-MRSA : PCMC DATA, 2004-2006

- wound, pleural fluid, tracheal aspirate, blood
- Community-acquired isolate: isolate obtained from OPD or isolated within 48 hours of hospitalization
- superficial and deep seated infections in both MRSA (51.6%) and MSSA (42.8%) groups
- Difficulty of breathing and cough more frequent in MRSA
- No significant risk factors differences

Avendano-Coronel A, Banez M, dela Cruz , Santos J, Risk factors, Demographic, clinical Characteristics and Outcomes of Patients Diagnosed to have CA-MRSA October 2006

EMPIRIC THERAPY OF LIFE-THREATENING *S. AUREUS* INFECTIONS (SEPTIC SHOCK, CNS, ENDOCARDITIS)

Drugs of choice	vancomycin + oxacillin, ± gentamicin	40 to 60 mg/kg/day in 4 doses; maximum daily dose 2-4 g 150 to 200 mg/kg per day in 4 to 6 doses; maximum daily dose 4 to 12 g 3 mg/kg per day in 3 doses
Alternative	linezolid ± gentamicin	<12 years: 30 mg/kg per day in 3 doses 12 years: 20 mg/ per day in 2 doses; maximum daily dose 1200 mg

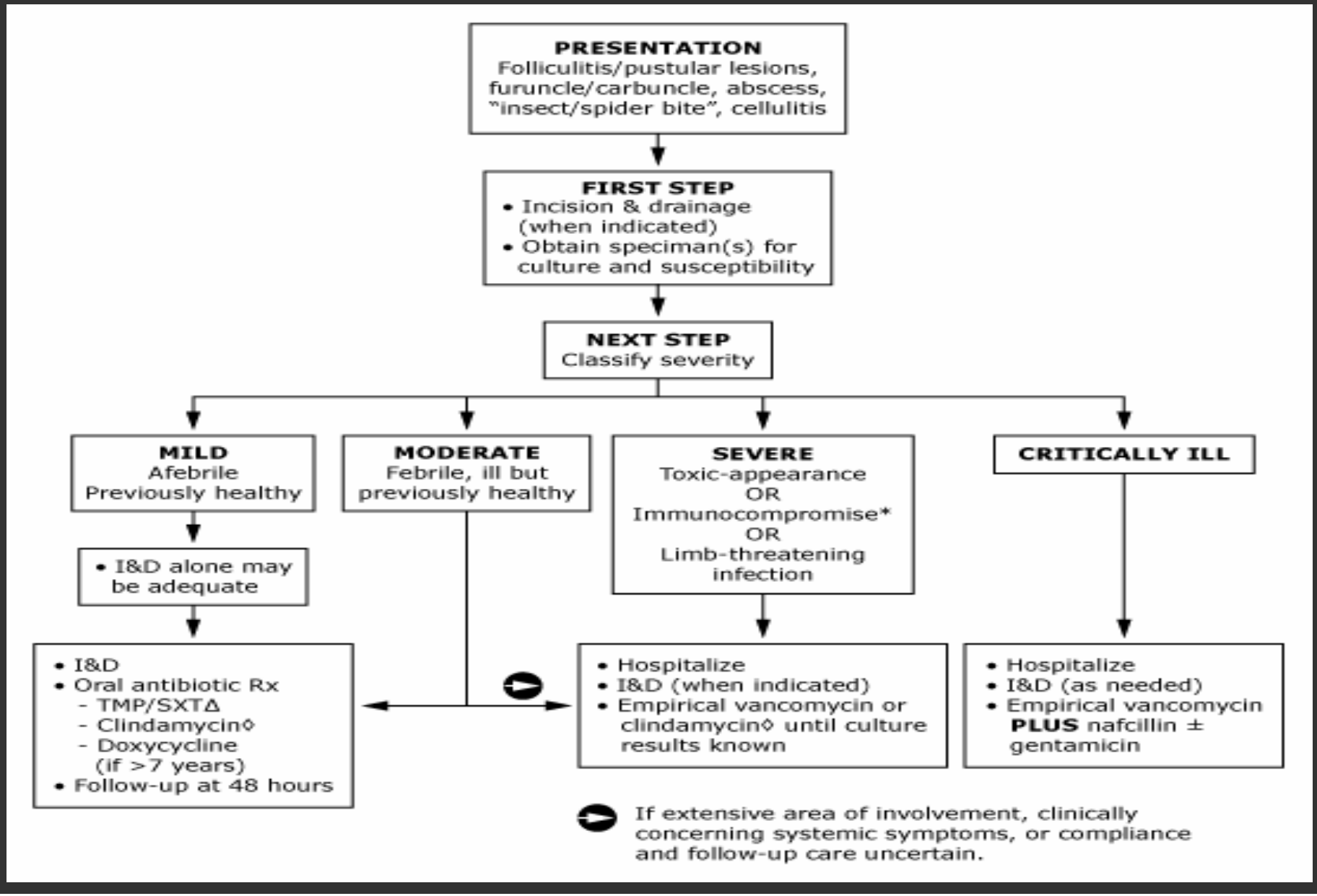
Red Book: 2006 Report of the Committee on Infectious Diseases, 27th ed, 2006

EMPIRIC THERAPY OF NON-LIFE-THREATENING *S. AUREUS* INFECTIONS

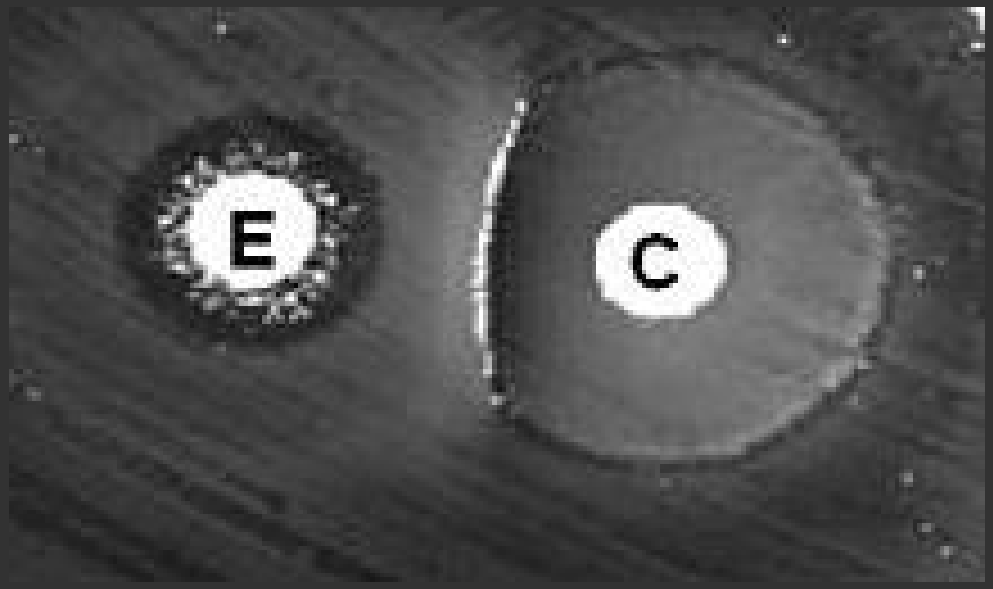
Prevalence of MRSA colonization and infection in community <5 to 10 percent	oxacillin	oxacillin: 150 to 200 mg/kg per day in 4 to 6 doses; maximum daily dose 4 to 12 g
Prevalence of MRSA colonization and infection in community >5 to 10 percent and prevalence of clindamycin resistance in community is low	clindamycin	30 to 40 mg/kg per day in 3-4 doses; maximum daily dose 1.2-2.7 g
Risk factors for healthcare-associated infection	vancomycin	40 to 60 mg/kg per day in 4 doses; maximum daily dose 2-4 g

Red Book: 2006 Report of the Committee on Infectious Diseases, 27th ed, 2006

APPROACH TO SUSPECTED MRSA SKIN AND SOFT TISSUE INFECTION (BAKER, CJAAP NEWS 2007; 28:1)



INDUCIBLE CLINDAMYCIN RESISTANCE: D TEST FOR MLS(B) RESISTANCE



S. aureus that appear susceptible to clindamycin and resistant to erythromycin by standard techniques may have induction of clindamycin resistance in the presence of clindamycin

TREATMENT OF MRSA INFECTIONS IN CHILDREN OLDER THAN 30 DAYS WHEN ANTIBIOTIC SUSCEPTIBILITIES ARE KNOWN

- *Life-threatening* (CNS, endocarditis, septic shock)

  drug of choice – vancomycin 40-60 mg/kg/day in 4 doses +/- gentamycin 3 mg/k/day (or +/- rifampin 20 mg/kg/day in 2 doses)

  alternative (excluding CNS and pneumonia) – daptomycin (6 mg/kg/day in 1 dose)

Red Book: 2006 Report of the Committee on Infectious Diseases, 27th ed, Pickering, LK (Ed), American Academy of Pediatrics, 2006

TREATMENT OF MRSA INFECTIONS IN CHILDREN OLDER THAN 30 DAYS WHEN ANTIBIOTIC SUSCEPTIBILITIES ARE KNOWN

- *Non-life-threatening* (e.g. Pneumonia, septic arthritis, osteomyelitis)

  Drug of choice: clindamycin (if susceptible) 30-40 mg/kg/day in 3 – 4 doses

  Alternatives:

  vancomycin

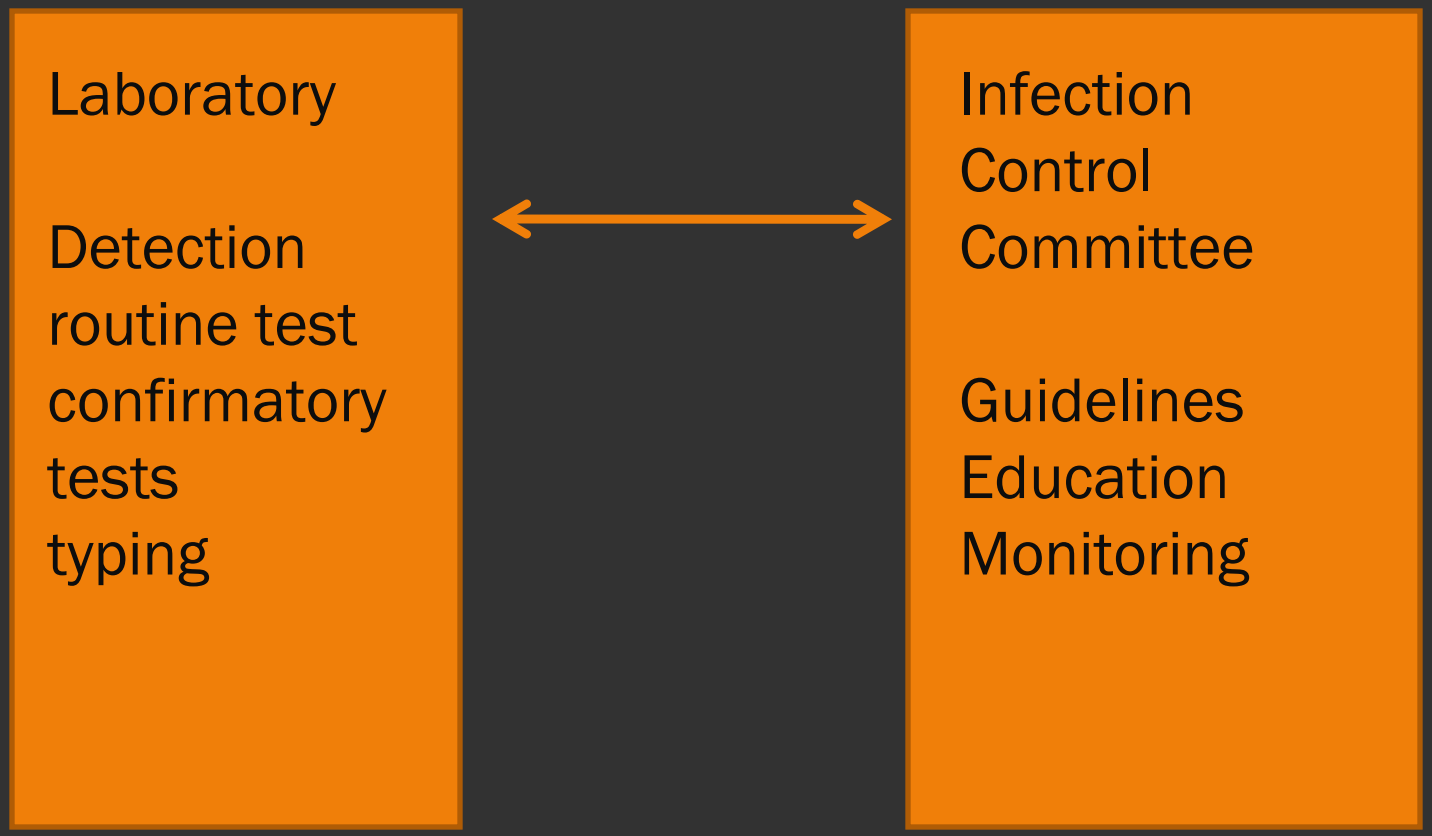
  linezolid (pneumonia, septic arthritis, osteomyelitis) <12 years: 30 mg/kg per day in 3 doses > or =12 years: 20 mg/kg per day in 2 doses; maximum daily dose 1200 mg

  daptomycin (septic arthritis, osteomyelitis, persistent bacteremia >4 days) 6 mg/kg/day in 1 dose

  - duration of treatment: site, ~4 weeks for endocarditis, osteomyelitis, necrotizing pneumonia, or disseminated infection

Red Book: 2006 Report of the Committee on Infectious Diseases, 27th ed, Pickering, LK (Ed), American Academy of Pediatrics, 2006

PREVENTION OF MRSA



TRANSMISSION

- Colonized individuals : Skin and nares -most commonly anterior nares (<1 to 22%)*
- Contaminated surfaces and equipment, e.g.,Blood pressure cuffs, torniquets, stethoscopes **(17% MRSA in 1 study***, 1.3% in another****)

*Davis et al, Clin Infect Dis 2004; Kuehnert et al, J Infect Dis. 2006; Kenner et al, Infect Control Hosp Epidemiol 2003 ; Heininger et al, Pediatr Infect Dis J. 2007; Alfaro et al, Pediatr Infect Dis J. 2006; Gorwitz et al, J Infect Dis. 2008

** Boyce et al, Infect Control Hosp Epidemiol 1997

*** Smith et al, Arch Intern Med 1996; ****Guinto et al, Am J Infect Control 2002

GUIDELINES IN CARE OF MRSA PATIENTS

- private room or cohort
- clean, nonsterile gloves
- wash hands with an antimicrobial soap or waterless antiseptic agent
- gown if substantial contact with the patient or environmental surfaces in the room is anticipated, or if the patient has wound drainage
- mask when caring for MRSA patients may reduce nasal acquisition of MRSA by healthcare workers.

Boyce & Pittet, MMWR Recomm Rep 2002 (HICPAC); Muto et al, Infec Control Hosp Epidemiol 2003 (SHEA Guidelies)

GUIDELINES IN CARE OF MRSA PATIENTS

- limit transport
- when possible, dedicate the use of noncritical equipment to a single patient or cohort of patients
- *More timely institution of appropriate contact precautions have been shown to control the spread of MRSA more effectively than standard precautions*.
- Surveillance cultures of the anterior nares and open wounds for patients at high risk of MRSA colonization or infection

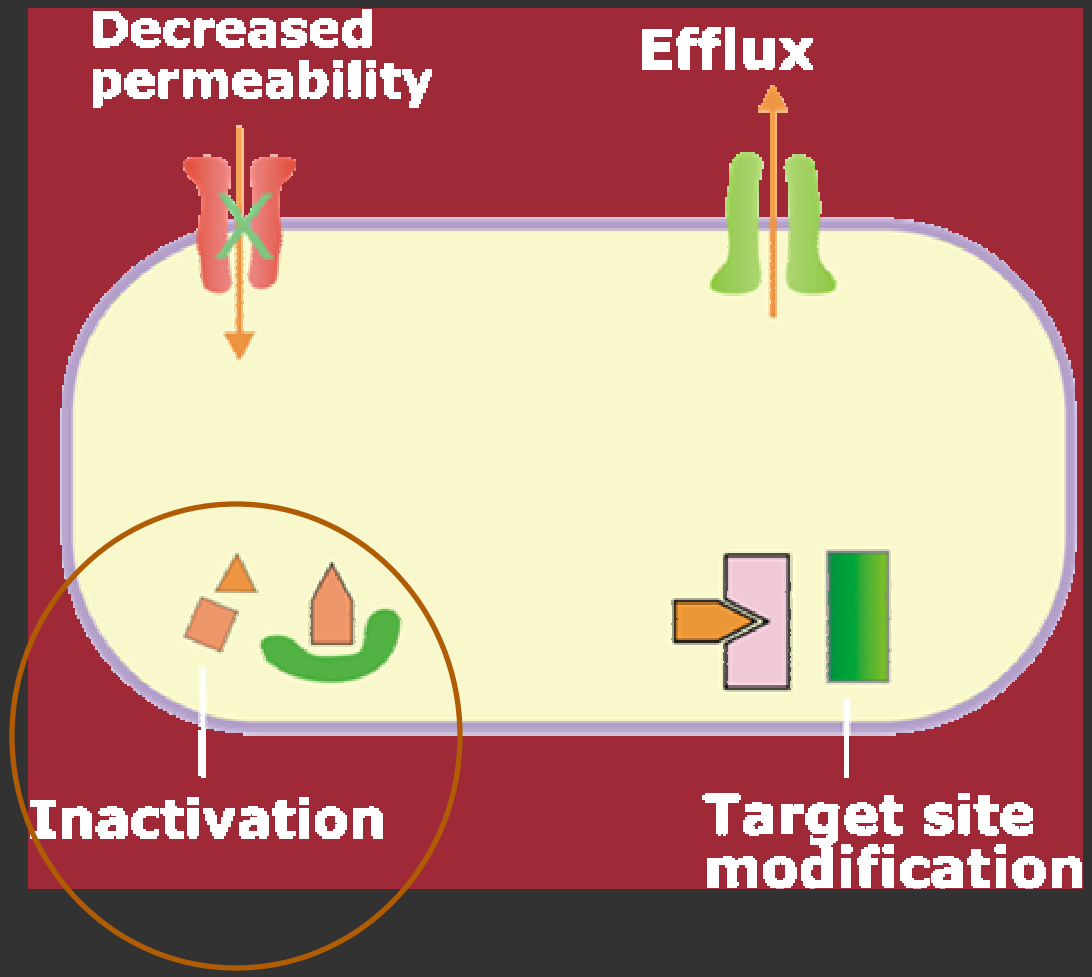
Boyce & Pittet, MMWR Recomm Rep 2002 (HICPAC); Muto et al, Infec Control Hosp Epidemiol 2003 (SHEA Guidelines)

PREVENTION OF MRSA IN THE COMMUNITY

- keep nails short and clean
- change underwear, sleep wear
- wash clothes and towels daily
- use of antimicrobial soaps
- application of mupirocin to the anterior nares.
- wounds should be covered with clean, dry bandages; if the wound cannot be kept covered, patients should be excluded from daycare, athletic practice, or other activities with close contact until the wound is healed

Gorwitz et al, Summary of an experts' meeting convened by the CDC,2006, www.cdc.gov/ncidod/dhqp/pdf/ar/CAMRSA_ExpMtgStrategies.pdf

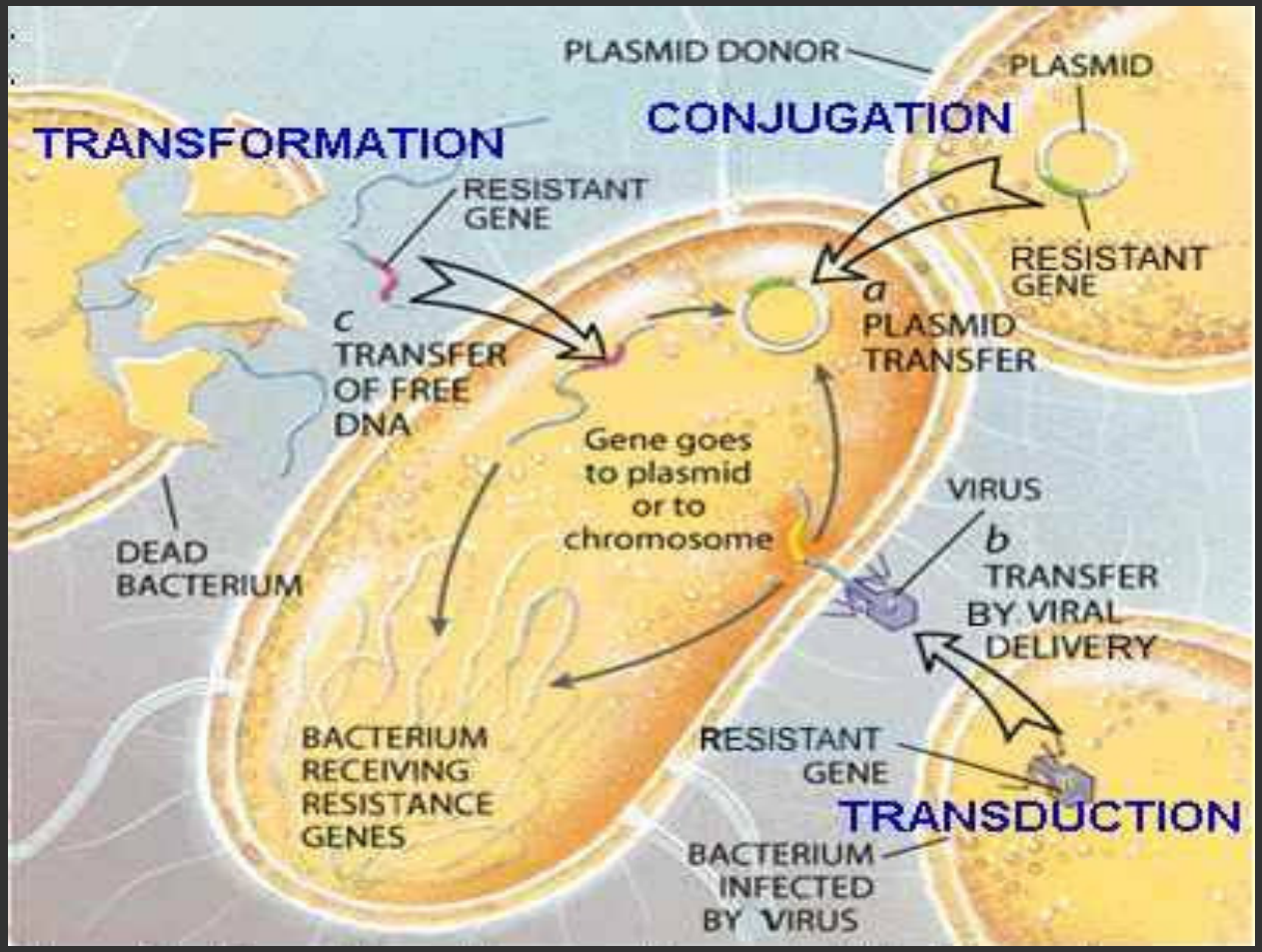
MECHANISMS OF RESISTANCE

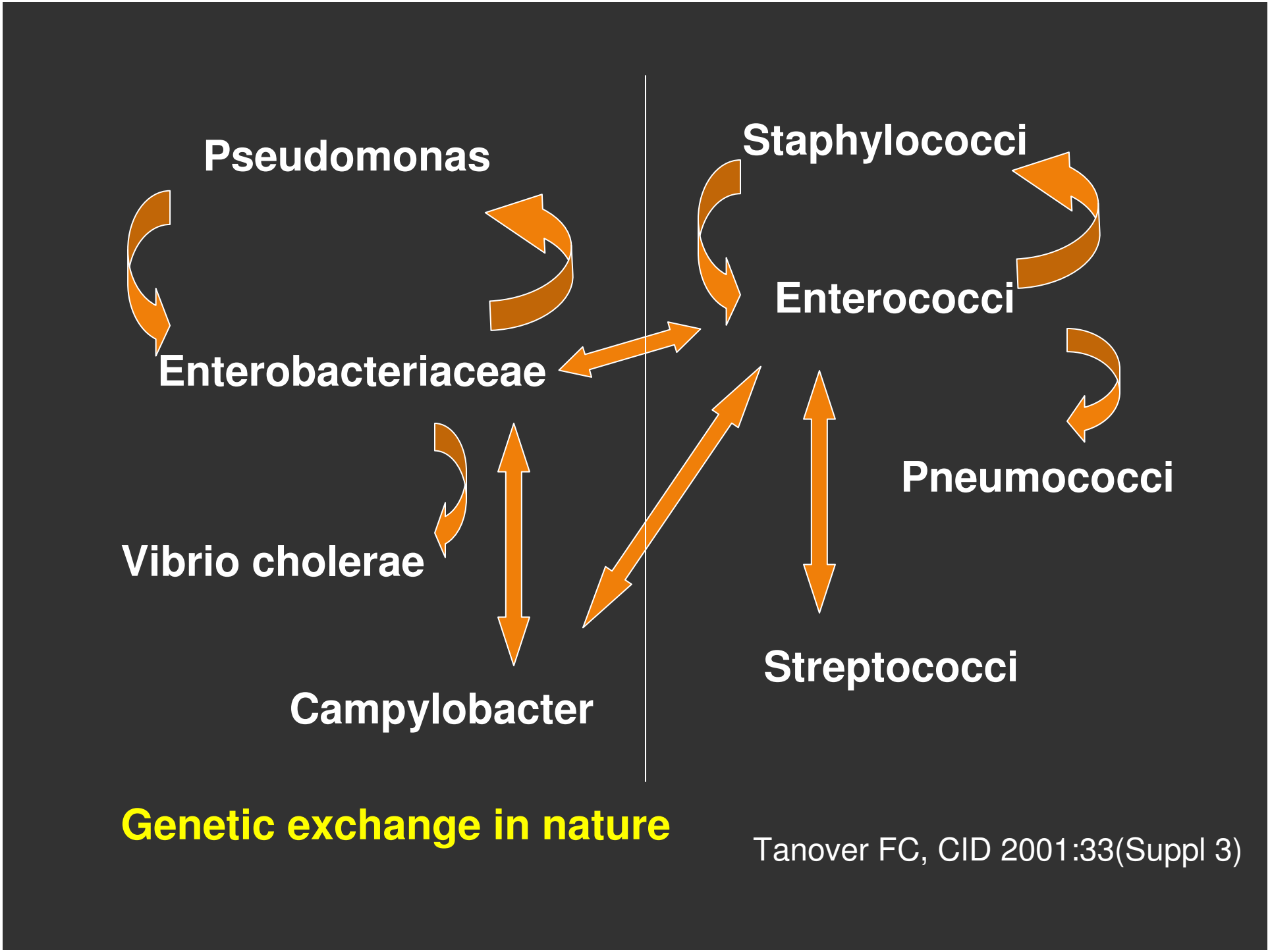


RESISTANCE TO β-LACTAMS

- Gram-negative β-lactamases
  - Major resistance mechanism in nosocomial GNB pathogens
  - >470 β-lactamases
  - Spread by integration within mobile genetic elements

MECHANISMS OF GENE TRANSFER





Genetic exchange in nature

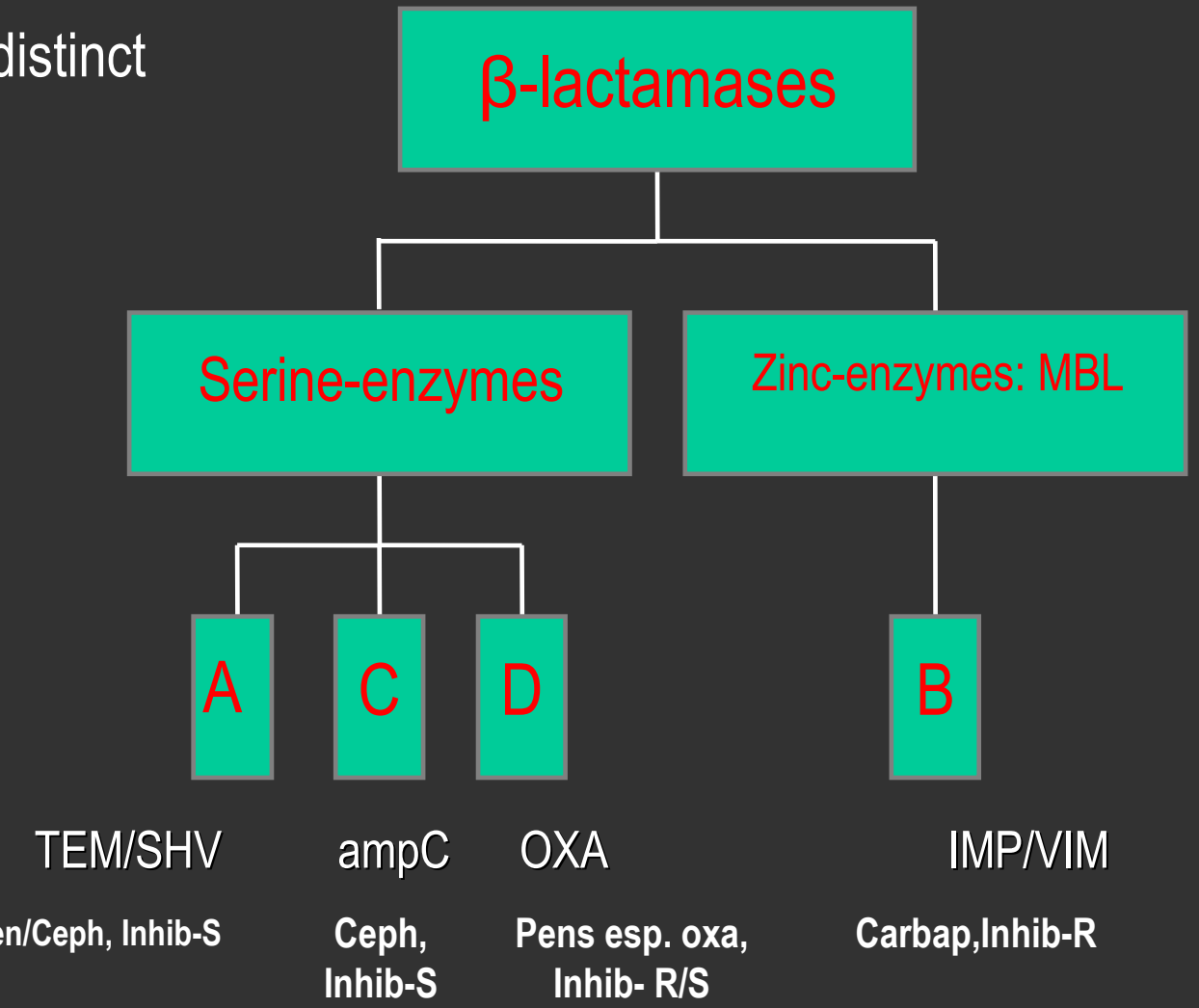
Tanover FC, CID 2001:33(Suppl 3)

MODIFIED BUSH–JACOBY–MEDEIROS CLASSIFICATION OF B–LACTAMASES

Functional Group	Substrate profile	Molecular Class	Inhibitor	Example
1	Cephalosporinase	C	Oxa	AmpC, MIR-1
2a	Penicillinase	A	Clav.	*S.aureus*
2b	Broad spectrum	A	Clav.	TEM-1/2, SHV-1
2be	Extended spectrum	A	Clav.	TEM 3-29, TEM46-104 SHV2-28, CTX-M types
2br	Inhibition resistant	A	-	TEM 30-41 (IRT1-12)
2c	Carbenicillinase	A	Clav.	PSE-1
2d	Oxacillinase	D	(Clav.)	OXA-1 (OXA-2 &-10 derived ESBL)
2e	Cephalosporinase	A	Clav.	FPM-1 *P. vulgaris*, CepA *B. fragilis*.
2f	Carbapenemase	A	Clav.	IMI-1, NmcA, Sme 1-3
3	Metallo-enzyme	B	-	*S.maltophilia*
4	Penicillinase	-	-	*B.cepacia*

AMBLER CLASSIFICATION OF B-LACTAMASES

Four evolutionarily distinct molecular classes

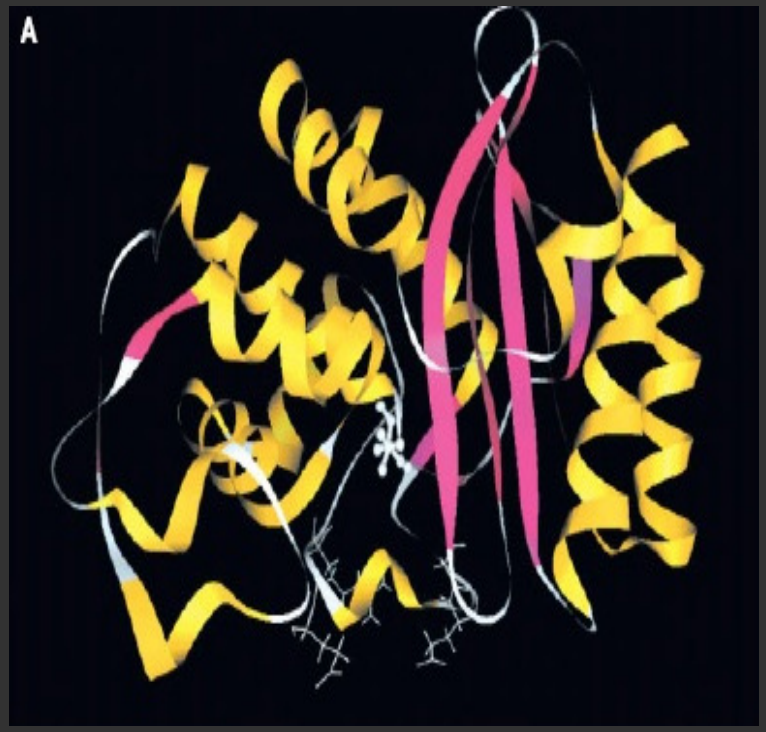


β-LACTAM RESISTANCE: ESBL PRODUCTION

- global problem
- Found in *Klebsiella* and *E. coli* and in a small, expanding group of Gram-negative bacilli (*Enterobacter, Salmonella, Proteus,* and *Citrobacter* , *Acinetobacter*, *Morganella morganii*, *Serratia marcescens*, *Shigella dysenteriae*, *Pseudomonas aeruginosa*, *Burkholderia cepacia*, and *Capnocytophaga ochracea*)

Jones et al. Int J Antimicrob Agents 2002;20:426–431
Sader et al. Diagn Microbiol Infect Dis 2002;44:273–280

ESBL'S: DERIVED FROM TEM AND SHV



TEM

160 TEM type ESBLs

SHV

>100 SHV type ESBLs

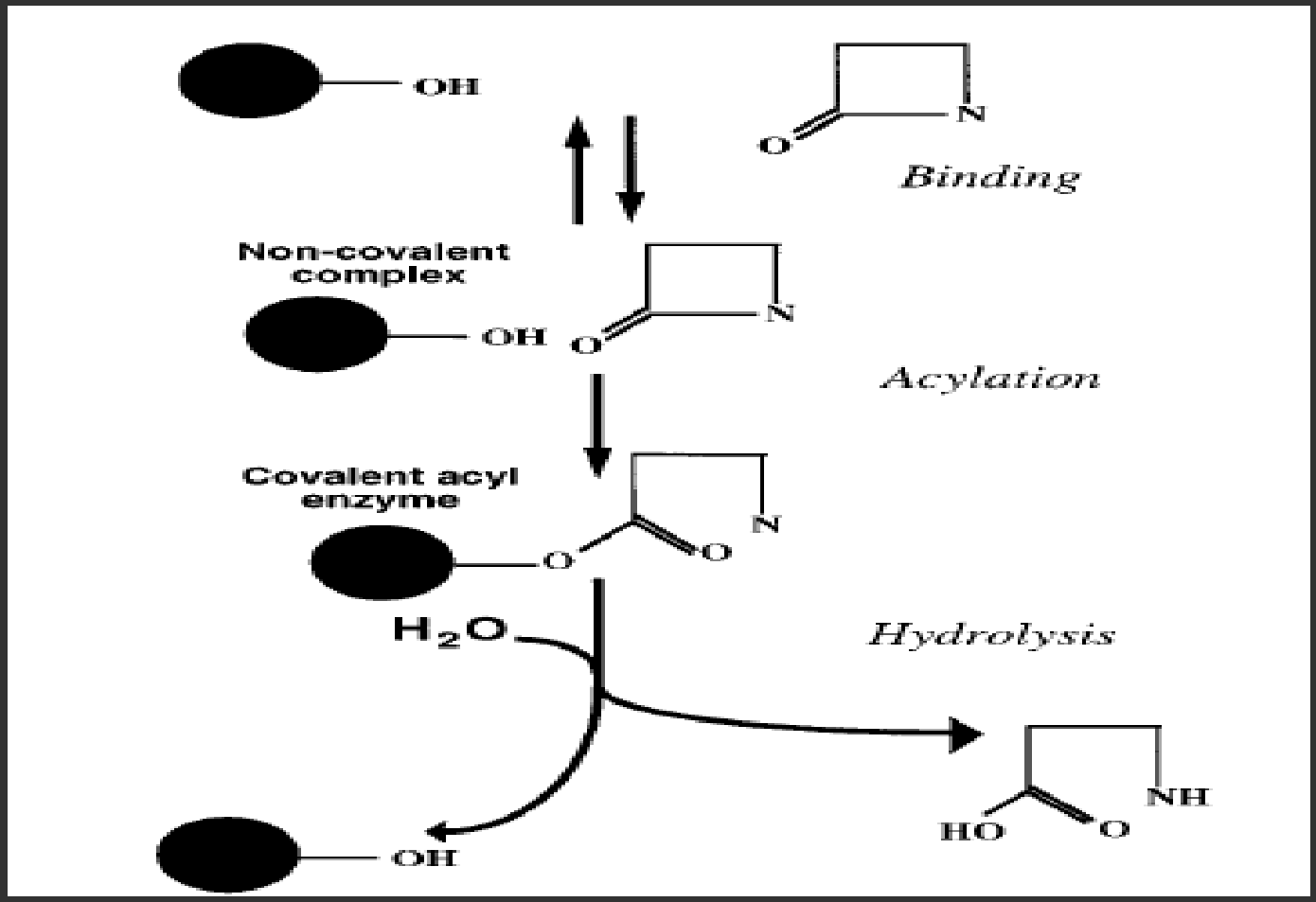
Figures from Jacoby G, N Engl J Med 2005;252(4):383

CTX-M: GLOBAL PROBLEM

- named for their greater activity against cefotaxime
- arose not by mutation, but by plasmid acquisition of beta-lactamase genes normally found on the chromosome of *Kluyvera* species
- >60 CTX-M enzymes*
- most common ESBL type worldwide**
- Enterobacteriaceae
- Role of food chain?***

*www.lahey.org/studies/webt.htm
** Canton R; Coque TM, Curr Opin Microbiol. 2006
***Bertrand et al, J Clin Microbiol,44(8), 2006

ESBL ACTIVITY EXAMPLE: ACTION OF A SERINE BETA-LACTAMASE

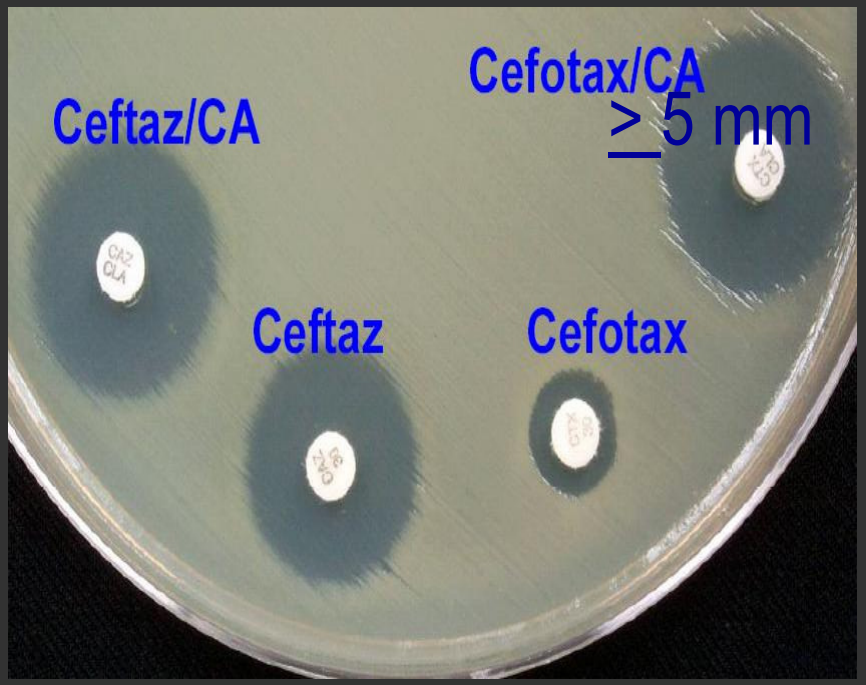


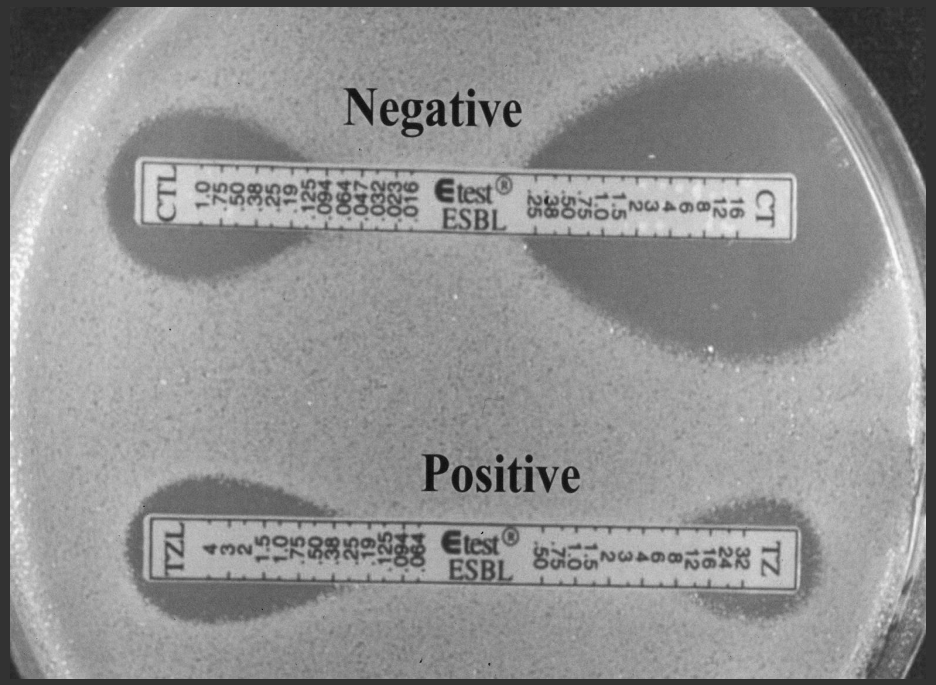
Livermore, CMR,8(4):557-584

IDENTIFICATION

- Clinical and Laboratory Standards Institute (CLSI) recommends screening isolates of *E. coli, K. pneumoniae*, *K. oxytoca* or *Proteus* spp. by disk diffusion or broth dilution for resistance, followed by a confirmatory test for increased susceptibility in the presence of clavulanate
- no currently CLSI recommended tests for ESBLs in enteric organisms other than E. coli, Klebsiella and Proteus
- Others: etest strip with clavulanate added to one side of a dual oxyimino-beta-lactam gradient

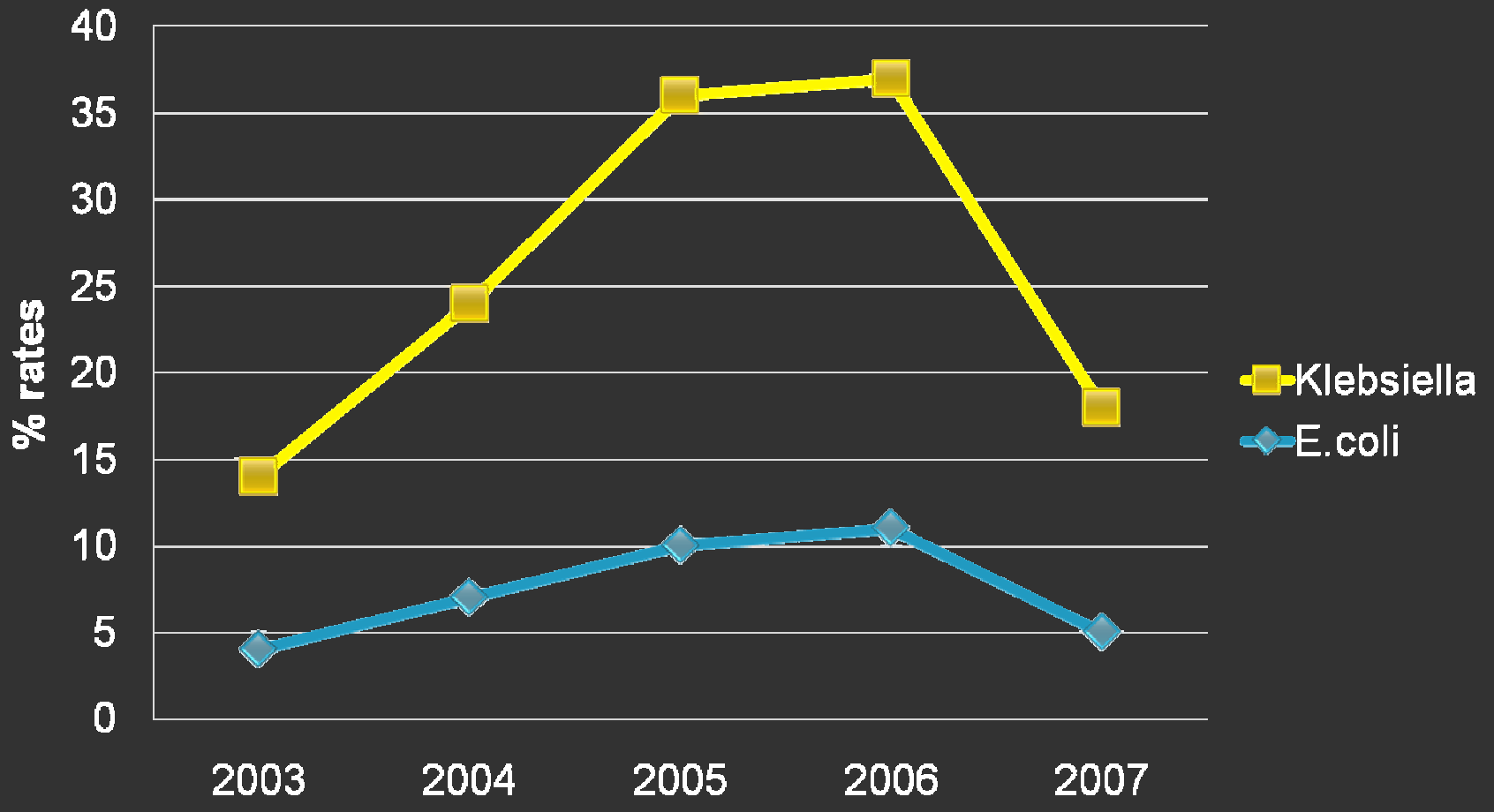
ESBL DETECTION IN THE LAB





- ≥3 fold decrease in MIC or 5mm increase in Disc Diffusion Method

EXTENDED-SPECTRUM BETA LACTAMASES (ESBLS) SURVEILLANCE RATES 2003-2007



Carlos C, ARSP

RISK FACTORS

- length of hospital/ICU stay
- CVP/arterial caths
- emergency abdominal surgery
- gastrostomy or jejunostomy tube
- LBW
- prior antibiotic
- prior residence in a long-term care facility
- severity of illness
- urinary catheter
- ventilatory assistance
- hemodialysis

Paterson et al, International prospective study of Klebsiella pneumoniae bacteremia: implications of extended-spectrum beta-lactamase production in nosocomial Infections, Ann Intern Med 2004
Jacoby G, Munoz-Price L, The new beta-lactamases, N Engl J Med 2005

Risk factors of infections caused by ESBL- producing *Escherichia coli* and *Klebsiella pneumoniae* (N=105) at PCMC, 2006=08

Predictor	P	Odds Ratio	95% CI	
Constant	0.742		Lower	Upper
Age	**0.017**	**1.01**	**1.01**	**1.03**
Unit	0.143	1.51	0.87	2.64
Co morbid	**0.002**	**1.32**	**1.11**	**1.56**
Previous hospitalization	0.139	1.70	0.84	3.44
Previous antibiotic use	**0.000**	**1.33**	**1.18**	**1.59**
Mechanical ventilation	0.474	1.43	0.54	3.76
Invasive procedure	**0.023**	**1.78**	**1.62**	**1.97**

Caguioa L, Santos J, CLINICAL IMPACT AND RISK FACTORS OF INFECTIONS CAUSED BY EXTENDED-SPECTRUM-ß-LACTAMASE- PRODUCING *ESCHERICHIA COLI* AND *KLEBSIELLA PNEUMONIAE (ESβL-EK)* AMONG PATIENTS AT PCMC

THERAPY OF ESBL INFECTIONS

Antibiotic	Activity
Third-generation cephalosporins	–
Cefepime	–
Quinolones	+/–
Piperacillin/tazobactam	+/–
Carbapenems	+++

CONSEQUENCES

- higher mortality
- longer hospital stay
- greater hospital expenses
- reduced rates of clinical and microbiologic response

Lautenbach E et al, Extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae: risk factors for infection and impact of resistance on outcomes Clin Infect Dis 2001

Paterson D et al, Antibiotic therapy for Klebsiella pneumoniae bacteremia: implications of production of extended-spectrum beta-lactamases Clin Infect Dis 2004

LOGISTIC REGRESSION ANALYSIS OF OUTCOMES AMONG INFECTIONS CAUSED BY ESBL-EK (PCMC)

Predictor	p value	Odds Ratio	95% CI Lower	95% CI Upper
Length of Hospital Stay	0.0008	2.10	1.45	4.28
Mortality				
with ESβL infection	0.0000	2.52	1.44	4.30
with inappropriate initial antibiotic	0.0040	2.11	1.39	4.10

Caguioa L, Santos J, CLINICAL IMPACT AND RISK FACTORS OF INFECTIONS CAUSED BY EXTENDED-SPECTRUM-ß-LACTAMASE- PRODUCING *ESCHERICHIA COLI* AND *KLEBSIELLA PNEUMONIAE (ESβL-EK)* AMONG PATIENTS AT PCMC

CONTROL OF ESBL OUTBREAKS

- Barrier control: isolation, gowns, gloves*
- Restriction of oxyiminocephalosporins
- Combination of both**
- Gut decontamination ? ***

*Lucet et al, Clin Infect Dis 1999 Dec;29(6):1411-8
**Pena et al, Antimicrob Agents Chemother 1998 Jan;42(1):53-8
*** Paterson et al, Clin Infect Dis 2001 Jul 1;33(1):126-8

PREVENTION OF RESISTANCE (CDC)

- Prevent infections
- Effective infection control to prevent transmission
- Judicious antibiotic prescribing
- Diagnose and treat effectively:
  - Early recognition
  - Selection of appropriate antibiotic
  - Optimization of antibiotic therapy

Thank you!