A Case of VISA –
The Natural Progression of Antibiotic Resistance?

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Overview

- Background
- The Case
- History of *S. aureus* Resistance
- Definitions of VISA/VRSA
- Mechanisms of Resistance
- Laboratory Testing
- Epidemiology
- Management
- Infection Control
- Prevention?

Staphylococcus aureus

- What is it?
  - Common bacteria (gram-positive cocci)
  - Lives on skin and nasopharynx
  - Transmitted primarily by skin-to-skin contact
  - People can be colonized or infected with it
- MRSA = methicillin-resistant *S. aureus*
  - Traditionally causes infections in hospitalized patients or patients with multiple comorbidities
- VISA = vancomycin-intermediate *S. aureus*

Background

- Ongoing challenges controlling spread of healthcare-associated MRSA (HA-MRSA)
- Superimposed recent challenge of dealing with the rise of community-associated MRSA (CA-MRSA) causing serious infections in many young, otherwise healthy individuals

Superbugs more widespread than thought

Study: Drug-resistant staph infects up to 5 percent of hospital patients

Associated Press

updated 12:31 a.m. ET, Mon., June. 25, 2007

But then…

THE CITY OF NEW YORK

DEPARTMENT OF HEALTH AND MENTAL HYGIENE

Michael R. Bloomberg
Mayor

Thomas R. Frieden, M.D., M.P.H.
Commissioner

nyc.gov/health

2007 Alert # 31:
Surveillance for Vancomycin Resistance in *Staphylococcus aureus*

- **Six cases of vancomycin-intermediate *Staphylococcus aureus* infections have occurred in NYC since February 2007; the case fatality rate was 67%.**
- **Infections caused by vancomycin-intermediate (VISA) and -resistant (VRSA) *Staphylococcus aureus* infections are reportable in NYC**
- **Please submit all *S. aureus* isolates with a vancomycin MIC > 2.0 µg/ml to the Public Health Laboratory for confirmatory testing and molecular characterization**

Please Distribute to All Clinical Staff in Internal Medicine, Surgery, Pediatrics, Infectious Diseases, Emergency Medicine, Family Medicine, Laboratory Medicine and Infection Control Staff

October 3, 2007

And then…

The Case

- October 13, 2007
  - 70 y/o male with multiple medical problems presents to CUMC ED with VISA bacteremia

The Case

- July 2007, Hackensack NJ
  - Pt underwent CABG x4, biventricular PPM/ICD placement
- September-October 2007, Hackensack NJ
  - Readmitted 9/1 with septic shock, MRSA sternal osteomyelitis and MRSA bacteremia
  - Underwent partial sternectomy with omental flap
  - Treated with vancomycin for 2 weeks, then vancomycin + rifampin for 4 weeks
  - Was intubated in MICU, also *Pseudomonas* pneumonia, eventually underwent tracheostomy for failure to wean

- October 13, 2007
  - Family brought him to CUMC ED
  - Admitted to MICU on vent
  - Found to be bacteremic with what was initially thought to be MRSA, later confirmed to be VISA

- TTE negative
- TEE
  - Large filamentous structure on pacemaker wire in RA → RV
- 10/18 Pacemaker leads were removed for device-related endocarditis

date	*specimen*	*Organism*	*Vanco MIC*	*Other susceptibilities*
9/1	Blood	MRSA+	≤ 1	T/S, rifampin
9/1	Sternal wound	MRSA+	≤ 1	
9/15	Blood x 3	MRSA+	2	(now R rifampin)
9/18	Blood x2	MRSA+	2	
9/21	Blood	negative		
10/2	Blood	MRSA+	2	
10/8	Blood x2	MRSA+	≤ 1	
10/13	Blood x2	negative		
10/13	Nares	negative		
10/13	Rectal swab	VRE+		
10/14	Blood x4	**VISA+ (3/4)**	**3**	Linezolid 1.0 Dapto 1.0 Tige .19 Gent,Tetra,T/S
10/17	Blood x2	negative		

Treatment Course

- Vancomycin by level 10/14-10/26
- Gentamicin by level 10/13-10/22
- Linezolid 10/26-11/11
  - [discontinued for dropping platelets, down to 19K]
- Daptomycin (7.5 mg/kg) 11/11-12/6

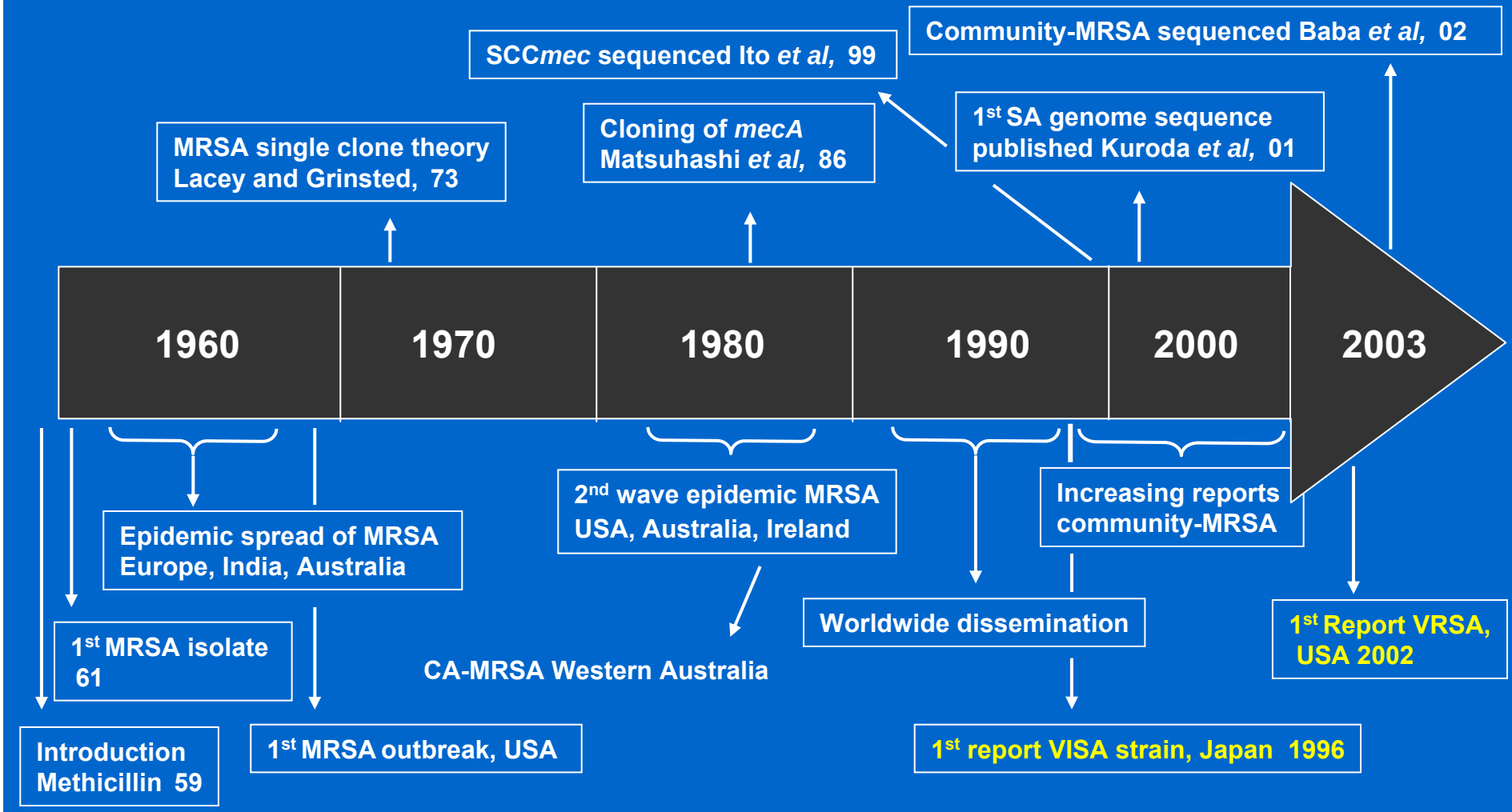
- Also received:
  - Imipenem
  - Piperacillin/tazobactam
  - Trimethoprim/sulfa
  - Tobramycin
  - Amikacin
  - Cefepime
  - Levofloxacin
  - Fluconazole
  - Caspofungin
  - valganciclovir

How did we get here?

History of *S. aureus* Resistance

Staphylococcus aureus

S. aureus Resistance Timeline



Modeled after Fitzgerald and Musser MRSA: Current Perspectives, '03

Courtesy of FL Lowy

Emergence of Antimicrobial Resistance in *S. aureus*

Drug	Year Drug Introduced	Years to Report of Resistance	Years until 25% Rate in Hospitals	Years until 25% Rate in Community
Penicillin	1941	1-2	6	15-20
Methicillin	1961	<1	25-30	40-50 (projected)
Vancomycin	1958	38 (VISA) 46 (VRSA)	??	??

Adapted from Chambers, EID 7:178-182, 2001

Microbiology

Definitions of VISA/VRSA

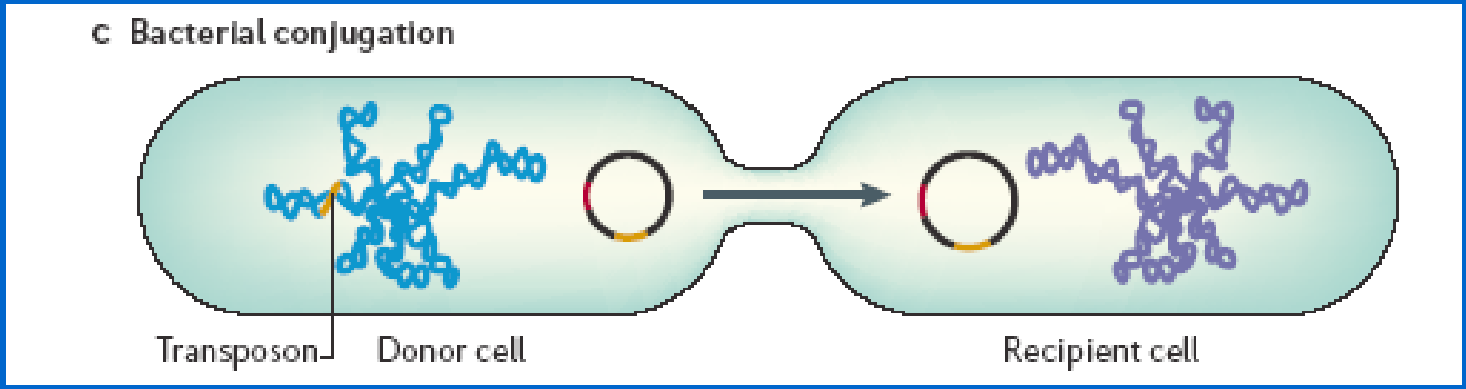
- There are national standards for defining what makes a *S. aureus* VISA or VRSA
- Set by Clinical and Laboratory Standards Institute (CLSI)
- Based on “cutoffs” or breakpoints of MICs (minimum inhibitory concentrations)
  - The minimum amount of an antibiotic which suppresses growth of the organism
- These breakpoints were lowered in 2006
  - The VISA category is now more inclusive (*i.e.*, more VISA will be identified)

Mechanisms of Resistance

- VISA
  - Abnormal cell wall synthesis
  - This leads to trapping of vancomycin in outer layers (prevents penetration to cell wall synthesis sites)

Mechanisms of Resistance

- VRSA
  - Acquires resistance mechanism (vanA gene) from VRE (vancomycin-resistant enterococcus) via transposon



Furuya and Lowy, Nat Rev Micro 2006

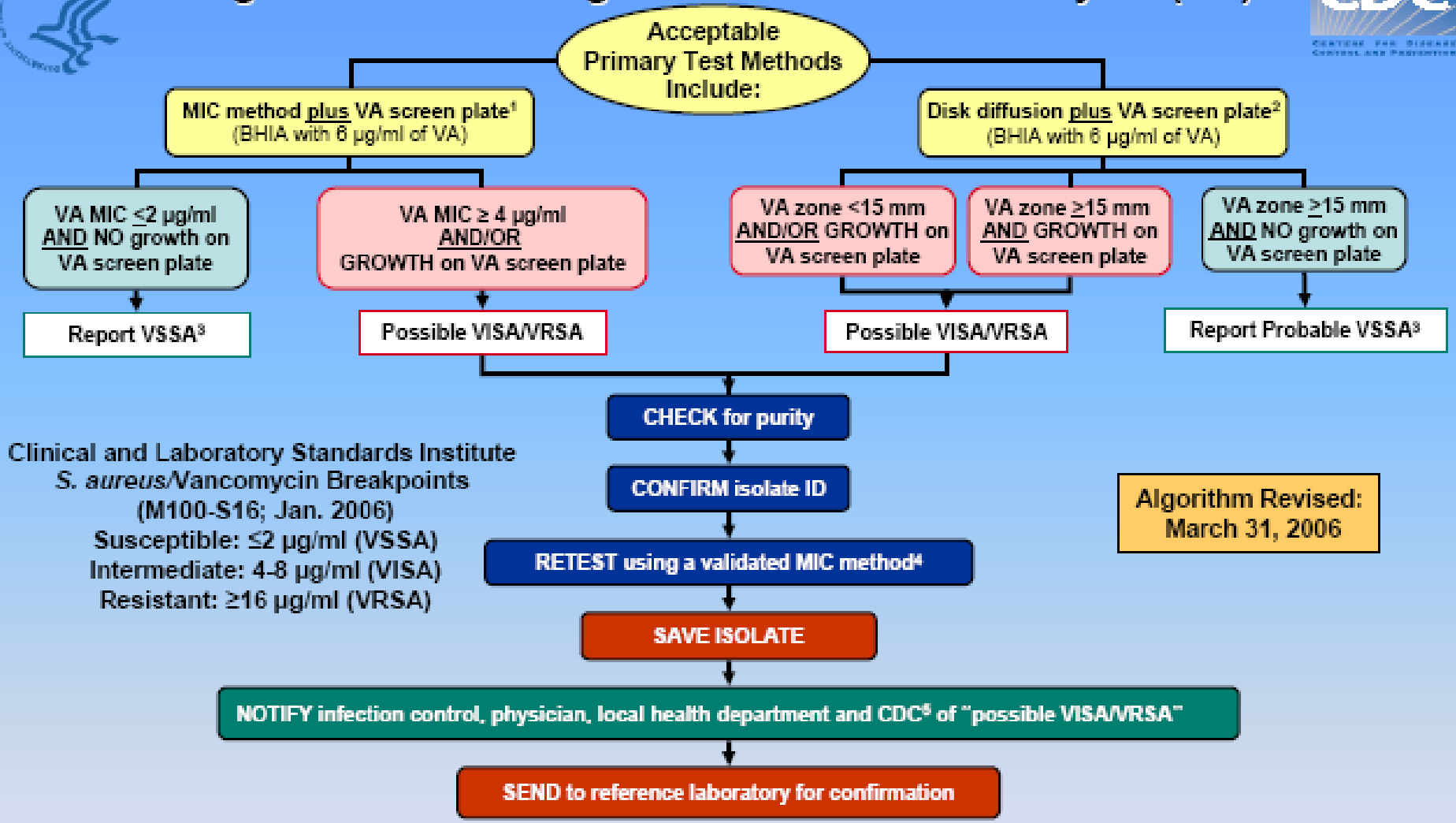
CLSI 2007
VANCO INTERPRETIVE CRITERIA

MICROBE	Susceptible	Intermediate VISA	Resistant VRSA
S. aureus	≤ 2 µg/mL*	4-8 µg/mL	≥ 16 µg/mL
CoNS	≤ 4 µg/mL	8-16 µg/mL	≥ 32 µg/mL

*MIC breakpoint was lowered from ≤ 4 µg/mL to 2 in 2006

Retest Vancomycin ≥ 2 with alternate AST
Send any isolates with Vanco MIC > 2 to NYCDOH OR CDC Lab for confirmation

Algorithm for Testing *S. aureus* with Vancomycin (VA)



Clinical and Laboratory Standards Institute
S. aureus/Vancomycin Breakpoints
(M100-S16; Jan. 2006)
Susceptible: ≤2 µg/ml (VSSA)
Intermediate: 4-8 µg/ml (VISA)
Resistant: ≥16 µg/ml (VRSA)

Algorithm Revised: March 31, 2006

Important Footnotes

[1] Laboratories using automated MIC methods that have not been validated for VRSA detection should add a commercial VA agar screen plate (6 µg/ml).

[2] Disk diffusion will not differentiate VISA (MICs 4-8) from susceptible strains (MICs 0.5-2). VA screen plate will not reliably detect strains for which MIC=4.

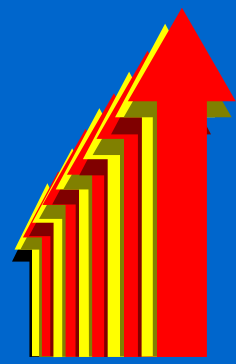
[3] If concerned about a result based on a patient's history, send to a reference lab for MIC testing.

[4] Validated methods: reference broth microdilution, agar dilution, Etest® (0.5 McFarland inoculum, Mueller-Hinton agar), MicroScan® overnight and Synergies plus™; BD Phoenix™ system. For other automated methods, check with the manufacturer about FDA-clearance to detect MICs ≥4 (i.e., VISA/VRSA).

[5] Report to CDC by email: SEARCH@cdc.gov

More VISA/VRSA info: http://www.cdc.gov/ncidod/dhqp/ar_visavrsa.html

Rising MICs ("MIC Creep")



- UCLA (2000-2004)
  - 1 MRSA was VISA (MIC = 8 µg/mL)
  - TREND: Vanco MICs from ≤ 0.5 → 1 µg/mL over 5 yrs
  - Vanco MIC of 1 µg/mL
    - 2000 = 20%
    - 2004 = 70%
- North Carolina (2001-2005)
  - Mean MIC increased from 0.62 (2001) to 0.94 (2005)

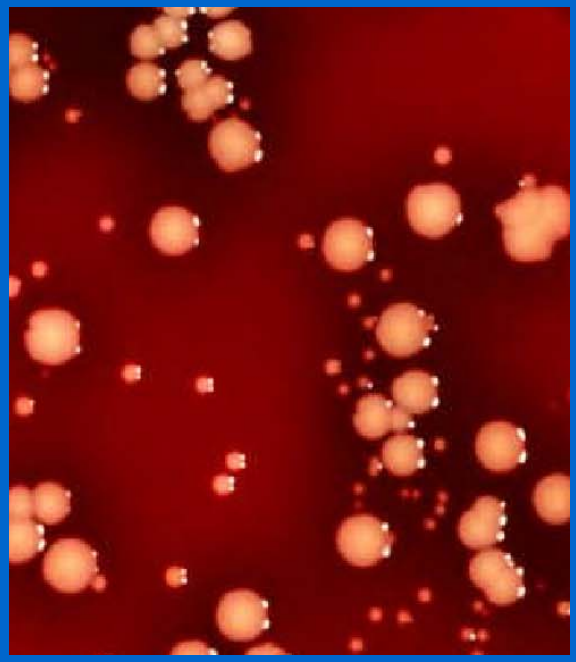
JCM 2006 44:3883-3886
JAC 2007 60: 788-94

hVISA

- Heteroresistant VISA (hVISA)
  - MICs to vanco are in susceptible range
  - However, sub-populations of daughter cells that are vancomycin intermediate or resistant
  - Controversial topic at ICAAC
  - No standard method of testing
  - E-strip – GRD – 2.0 McFarland

HETERORESISTANT VISA

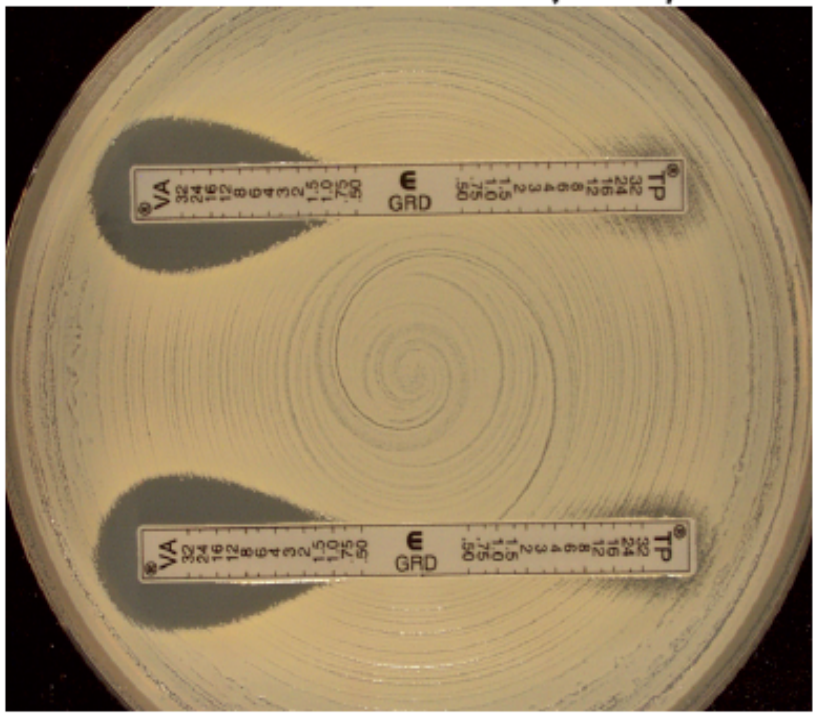
48 hr Incubation



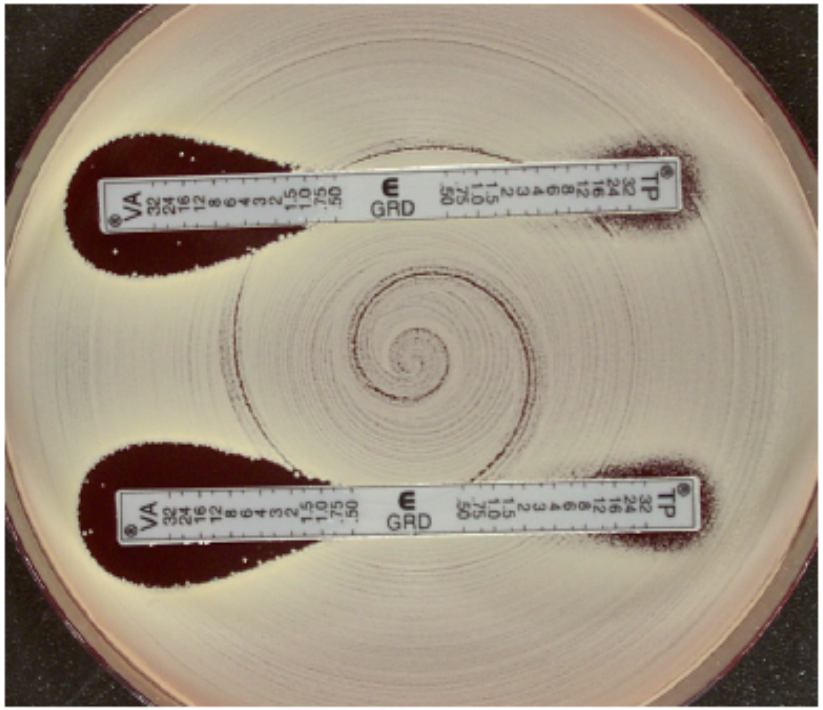
Large colonies are MRSA
Subpopulation of small, slow growing are VISA

GRD E-test
(Glycopeptide Resistance Detection)

S. aureus ATCC 700698 (Mu3/hGISA)



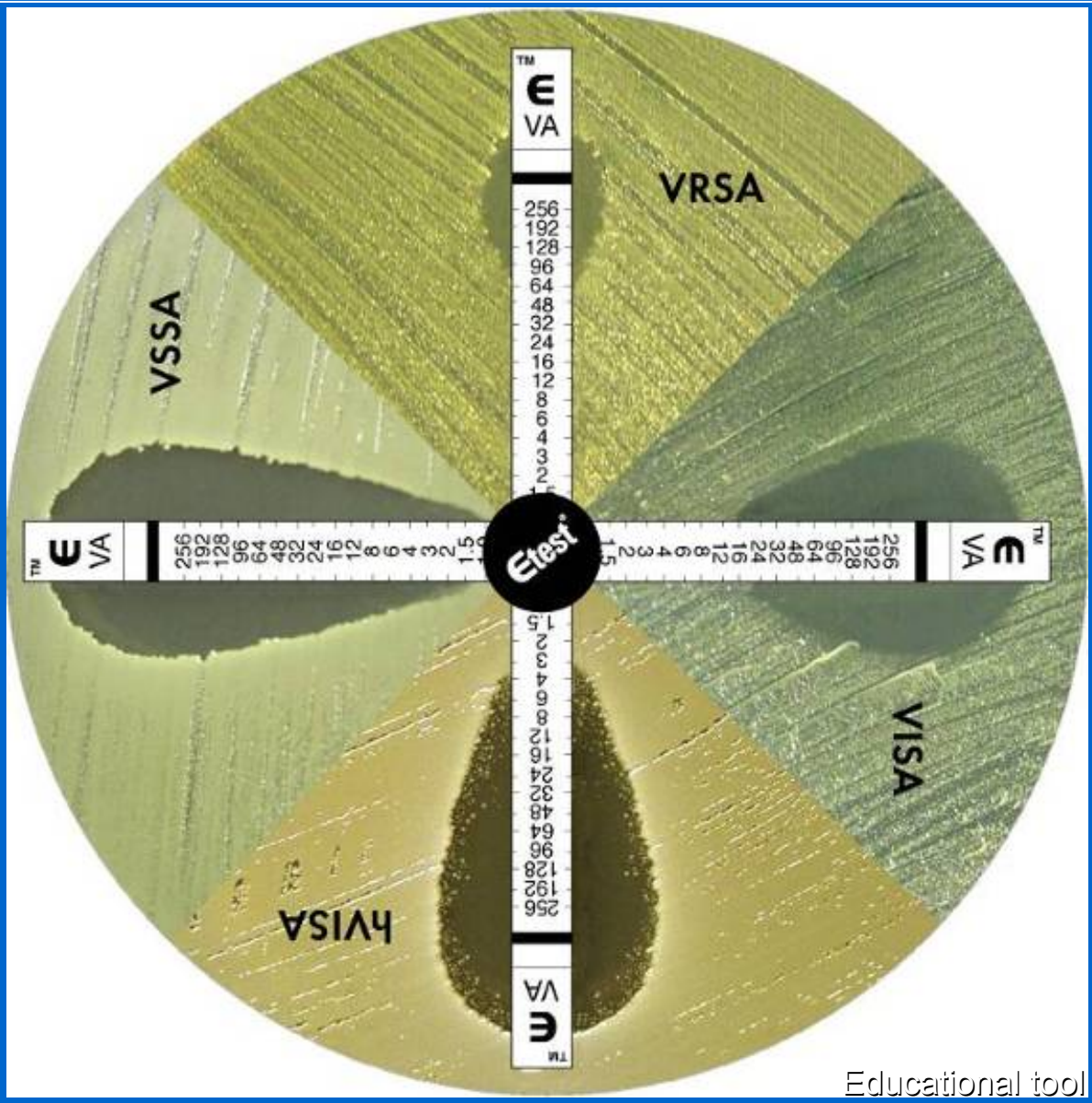
MHA



MHB

IUO; Recommend 2 McFarland and 24 - 48hr incubation

Etest - Vancomycin vs Staphylococci



Educational tool - Cubist, 2005

NYC PHL EXPERIENCE

- 2006 0 VISA
- 2007 18 VISA
  - MICs 3ug/mL – 6ug/mL
  - 15 tested against Dapto
    - 7 = Susceptible (MICs 0.75ug/mL – 1ug/mL)
    - 8 = Non-Susceptible (MICs 1.5ug/mL – 3ug/mL)
  - 11 tested against Linezolid
    - All susceptible (MICs 1ug/mL – 3ug/mL)
- 2008 1 VISA MIC = 3ug/mL
  - Dapto and Linezolid = Susceptible

NYC PHL TESTING ALGORITHM

- Confirm purity and ID of isolate.
- Determine Vanco, Dapto and Linezolid MIC using E-test.
- Send to Molecular Typing Lab for molecular characterization if VISA or VRSA.
- Send to NYS Wadsworth for testing if Vanco intermediate (>2ug/mL) or resistant (>8ug/mL).

NYS Wadsworth Center

- Confirms Vanco MIC using E-test
- **Reports any MICs of 3 as 4ug/mL**
- Performs PCR to detect vanA gene on all confirmed VISA/VRSA isolates

Notes from Discussion with Jan

- **Presented a poster at ICAAC on VISA.**
- **Described experiences in detecting VISA in blood cultures from 2 patients at UCLA**
  - **Pt A – 8 isolates over a 47 day period**
  - **Pt B – 17 isolates over a 39 day period**
- **MRSA had typical *S. aureus* morphology**
- **VISA colonies were heteromorphic**
  - **length of time to detection in BacTAlert was 9.6 h to 3.7 days for MRSA and 2.3 d to 4.8 days for VISA**
  - **MICs for daptomycin were up to 4 dilutions higher for VISA than for MRSA**
  - **Some VISA isolates looked like CoNS & gave negative results when tested with Staph latex reagent !**

Epidemiology of VISA/VRSA

First VISA Case

- Japan 1996
  - 4 month-old infant s/p cardiac surgery
  - Postop MRSA sternal wound infection
  - Treated with total 41 days of vancomycin
  - Multiple recurrences → finally found to have MRSA with vancomycin MIC of 8 μg/mL (Mu50)

Hiramatsu, JAC 1997; 40: 135-6.

VISA

- Now reported in US, Asia, Europe
- Most are methicillin-resistant (some are MSSA)
- Still rare, but starting to increase
- >20 cases in US

hVISA Rising Prevalence

- Turkey
  - 256 MRSA isolates, 1998-2001
  - Overall hVISA prevalence 18%
    - 1.6% in 1998 → 36% in 2001
- Detroit
  - 2.3% in 1986 → 8.2% 2003-6

Sancak, J Antimicrob Chemother 2005; 56: 519-23

Rybak et al, ECCMID 2007 [abstract]

Patient Characteristics

- Early reports
  - Bacteremias
  - Associated with central venous catheters or other prosthetic material
  - Dialysis

Fridkin et al, CID 2003

- Prospective surveillance of *S. aureus* isolates with reduced vancomycin susceptibility (SA-RVS) = MIC $\geq$ 4 µg/mL
- 19 case patients with SA-RVS infection compared to 42 control patients with MRSA infection

Fridkin, CID 2003; 36: 429-39

Fridkin study

- SA-RVS (VISA)
  - More likely to be bloodstream infections
  - More likely to die in hospital (63% vs 12%)
    - Not necessarily attributable mortality
- Risk factors
  - *Recent MRSA from clinical culture (preceding 3 months)
  - *Recent vancomycin exposure (preceding 6 months)

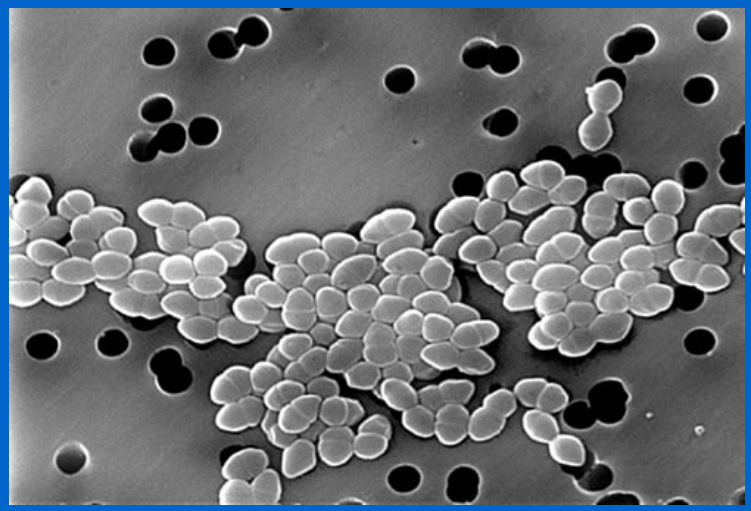
Table 3. Clinical and demographic characteristics of case patients (those infected with *Staphylococcus aureus* with an MIC of vancomycin of ≥4 μg/mL) and control patients (those infected with oxacillin-resistant *S. aureus* [MRSA] with an MIC of vancomycin of ≤2 mg/mL), United States, 1999–2001.

Characteristic	Case patients (n = 19)	Control patients (n = 42)	OR (95% CI)[a]
MRSA isolated from clinical culture			
In prior month	11 (58)	9 (21)	5.0 (1.6–16.3)
In prior 2–3 months	16 (84)	10 (24)	17.1 (4.1–70.8)
Vancomycin use			
In prior 6 months, median duration in weeks (range)[c]	8 (1–20)	0 (0–5)	
In prior month	18 (95)	10 (24)	58.0 (6.8–487)
In prior 2 months	13 (68)	8 (19)	9.2 (2.7–31.7)
In prior 3–6 months	9 (47)	7 (19)	4.5 (1.3–15.1)

VRSA

- First VRSA reported in 2002, Michigan
- Seven cases reported in US
- Michigan, Pennsylvania, New York
- Many patients have had chronic ulcers/wounds or prosthetic material and both MRSA and VRE
- Theory that the co-existence of MRSA and VRE leads to exchange of *vanA* gene from VRE to MRSA (sometimes on biofilms on prosthetic material)
- Unclear pathogenicity of VRSA

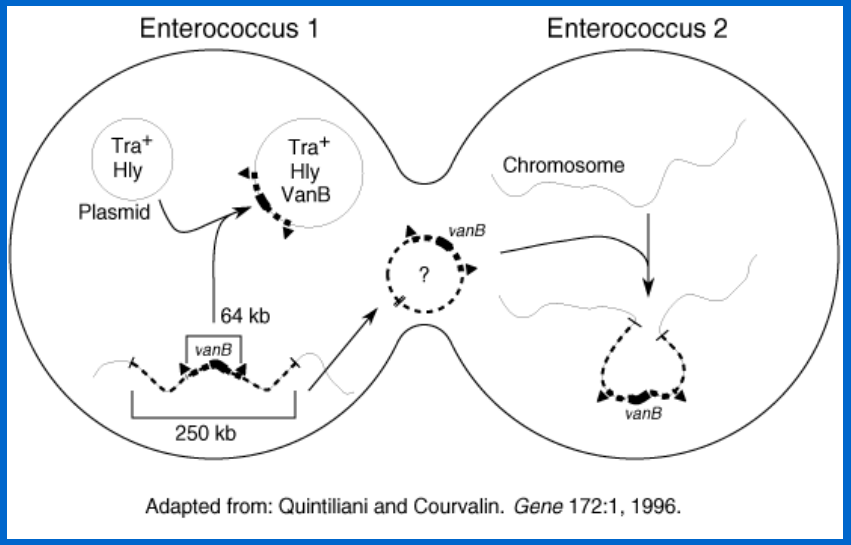
Vancomycin-resistant enterococci



VRE

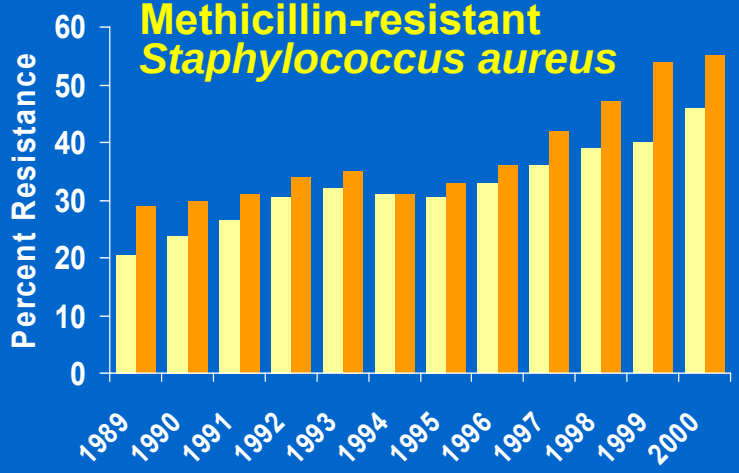
- Mediated by van gene (vanA and vanB)
- Alter target for vancomycin from D-alanine-D-alanine to D-alanine-D-lactate

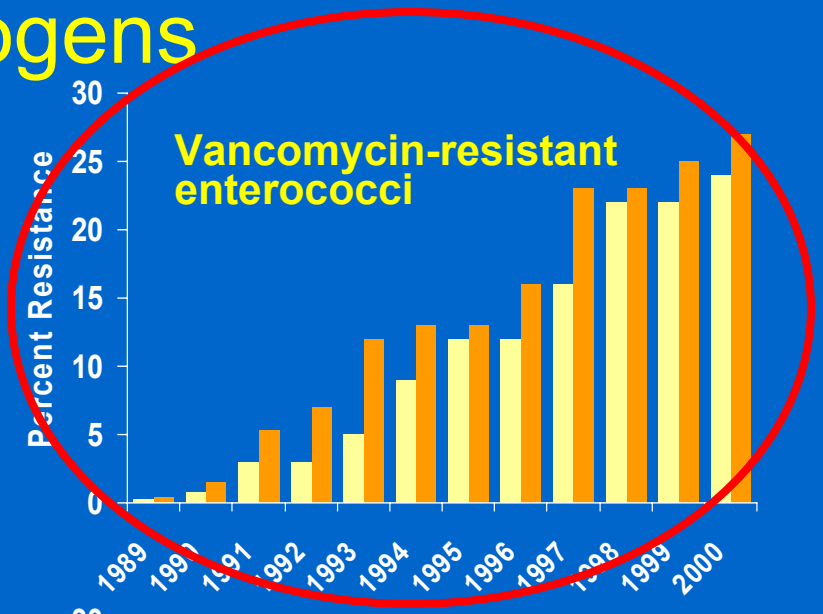
- VRE was very rare around the world until 1990's
- Became more common in US hospitals

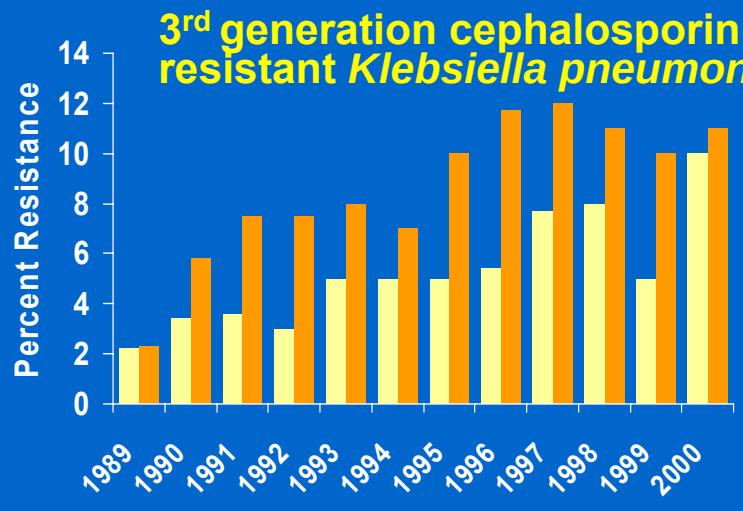


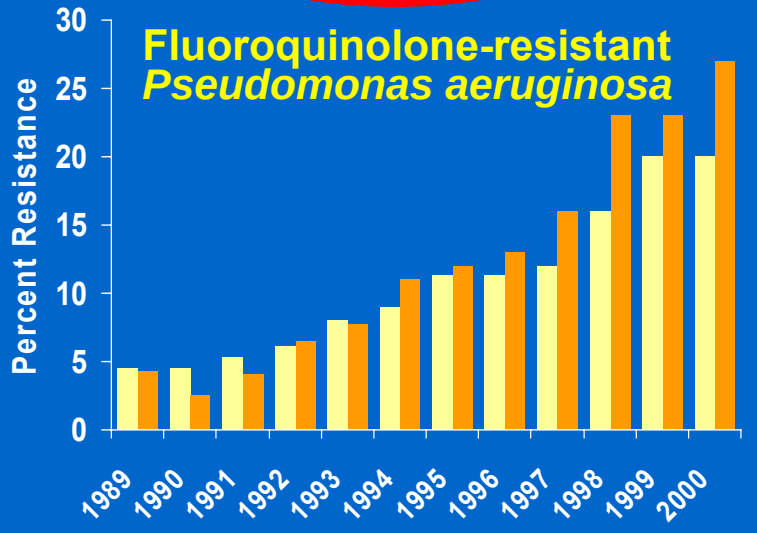
Adapted from: Quintiliani and Courvalin. *Gene* 172:1, 1996.

Increasing Resistance in ICU/non-ICU Pathogens







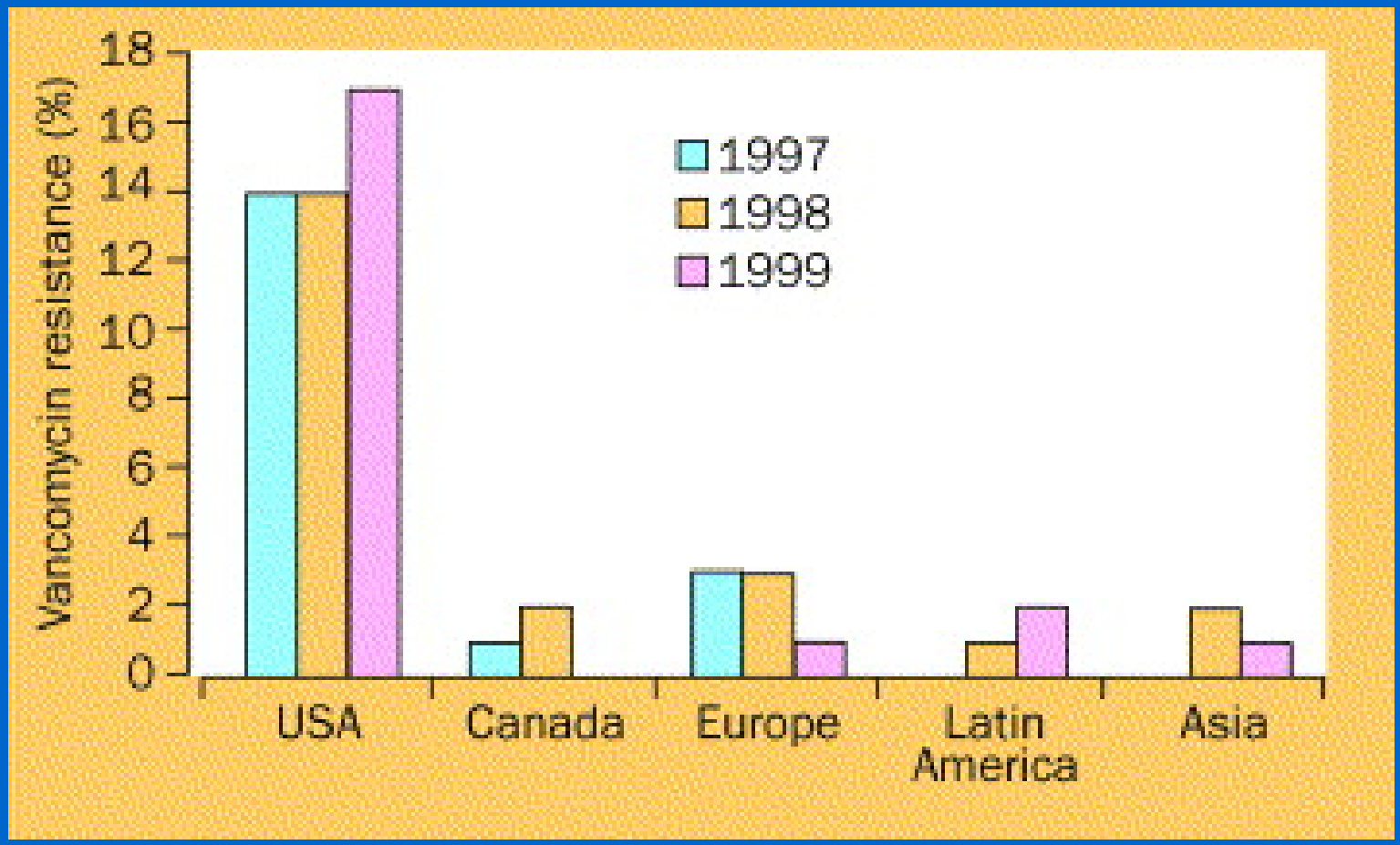


Non-Intensive Care Unit Patients

Intensive Care Unit Patients

Source: National Nosocomial Infections Surveillance (NNIS) System (www.cdc.gov)

Trends in vancomycin resistance in enterococcal isolates from SENTRY data, 1997-1999



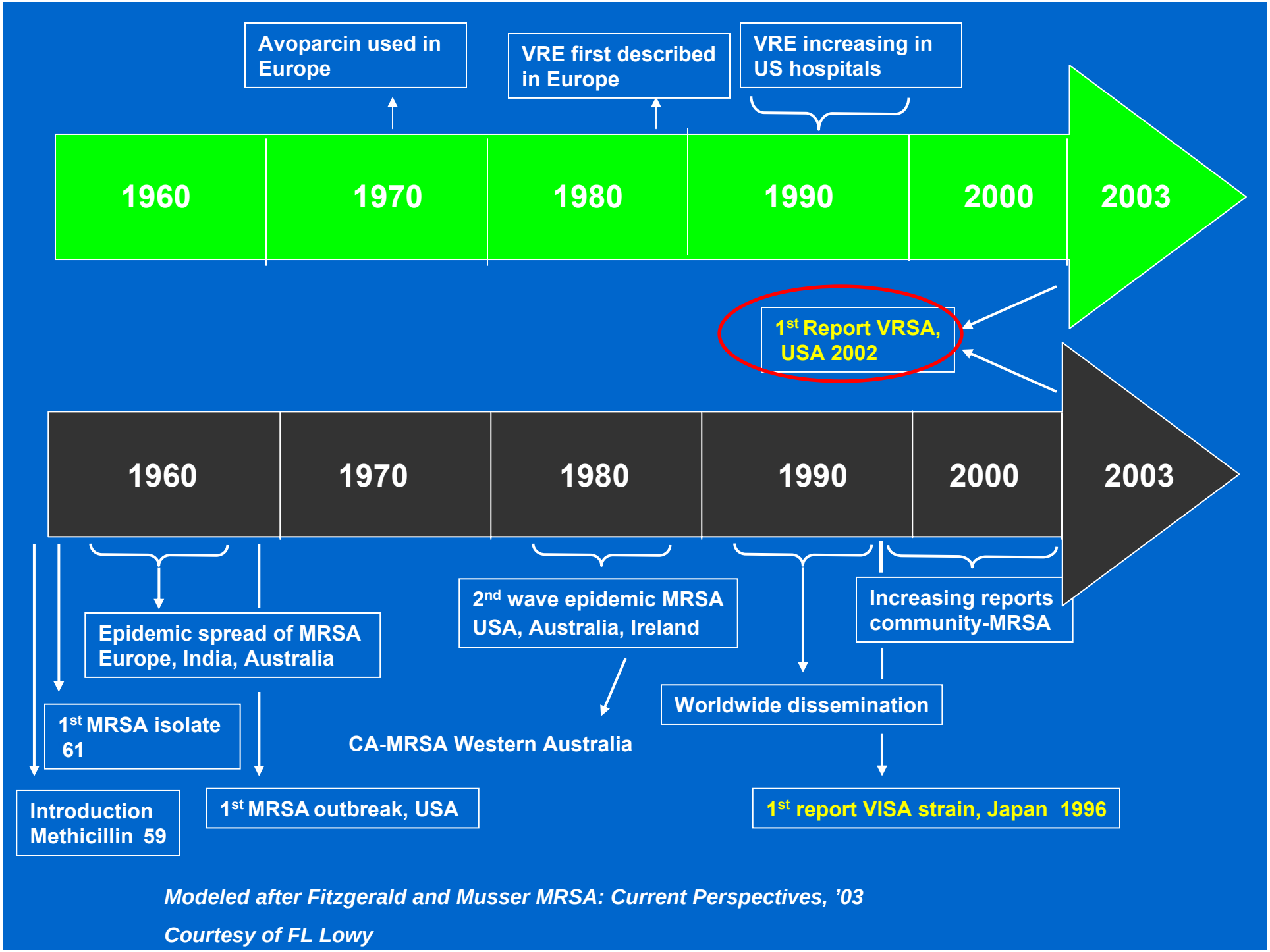
Harbarth et al, Lancet Infect Dis 2001; 1: 251-61.

US vs Europe: Difference in Reservoirs

- Europe
  - Avoparcin (a glycopeptide) was used for growth promotion in food animals in Europe since the 1970's
  - VRE first described there in 1988
  - VRE has been isolated from food animals, humans on farms, other healthy individuals
  - Avoparcin subsequently banned in 1997
  - Very few nosocomial VRE infections despite higher community colonization with VRE than in US
- US
  - Avoparcin never used in food animals
  - Yet skyrocketing rates of nosocomial VRE infection

Why the difference?

- VRE strains appear to be different between US and Europe
- Strains from animals thought to be less pathogenic to humans



Modeled after Fitzgerald and Musser MRSA: Current Perspectives, '03

Courtesy of FL Lowy

Treatment Options for VISA

Treatment Options

Table 2. MIC_{50} data, MIC_{90} data, and percentage of isolates susceptible by MIC value for select antimicrobial agents for all patient isolates of *Staphylococcus aureus* with reduced susceptibility to vancomycin (MIC of vancomycin, ⩾4 μg/mL).

Antimicrobial agent	All isolates (n = 21)				Isolates with MIC of vancomycin of ⩾4 μg/mL, percentage susceptible (n = 15)	Isolates with MIC of vancomycin of ⩾8 μg/mL, percentage susceptible (n = 6)
	MIC_{50}, μg/mL	MIC_{90}, μg/mL	MIC range, μg/mL	Susceptible, %		
Chloramphenicol	8	16	8–16	81	87	67
Clindamycin	>8	>8	⩽0.12 to >8	14	13	17
Erythromycin	>8	>8	0.5 to >8	10	13	0
Gentamicin	16	>16	⩽1 to >16	48	67	33
Linezolid[a]	2	2	1–4	100	100	100
Oxacillin	>16	>16	0.25 to >16	10	0	33
Penicillin	>2	>2	0.25 to >2	0	0	0
Quinupristin-dalfopristin	1	2	0.5–2	78	79	75
Rifampin	8	>8	⩽0.12 to >8	48	60	33
Teicoplanin	8	8	2–16	95	100	83
Tetracycline	<0.5	1	⩽0.5–16	90	87	100
TMP-SMZ	0.25	>8	⩽0.25 to >8	71	60	100
Vancomycin[b]	4	8	4–8	71	100	0

Fridkin 2003

Vancomycin

- There are data to show that higher vanco MICs (even within “S” range) lead to lower treatment success

- Hidayat et al, 2006
  - Prospective cohort study comparing pts receiving vanco for MRSA infections: 51 pts with high vanco MICs (≥2 µg/mL) vs 44 with low vanco MICs
  - High-MIC group had lower end-of-treatment responses (62% vs 85%) and higher infection-related mortality (24% vs 10%) than low-MIC group

Hidayat, Arch Intern Med 2006; 166: 2138-44

Vancomycin

- Sakoulas, 2004
  - 30 patients with MRSA bacteremia treated with vancomycin (≥ 5 days of vanco troughs 10-15 µg/mL)
  - Relationship between Outcome & MIC:
    - MIC ≤ 0.5 = 55.6 % success
    - MIC 1-2 = 9.5 % success (90.5 % FAILURE!)
- Of note, these patients are a subset from studies looking at patients who had failed vancomycin therapy
- Clinical failure, yet MIC value within CLSI ”S” range
- Reference method unable to detect clinical resistance?
- hVISA? suboptimal PK/PD?
- *For serious MRSA infections, vancomycin probably should NOT be used if MIC >1 µg/mL*

Sakoulas *et al*, JCM 2004; 42: 2398-2402

Combination β-lactam/vancomycin

- Sieradzki and Tomasz, 1997
  - Highly vancomycin-resistant *S. aureus* isolate became very sensitive to β-lactams
- Climo et al, 1999
  - In vivo rabbit model of VISA endocarditis
  - The higher the vancomycin MICs, the greater the synergy between vancomycin and β-lactams
- Controversial as to whether synergy is really seen; conflicting data have appeared since then

Sieradzki and Tomasz, J Bacteriol 1997; 179: 2557-66.

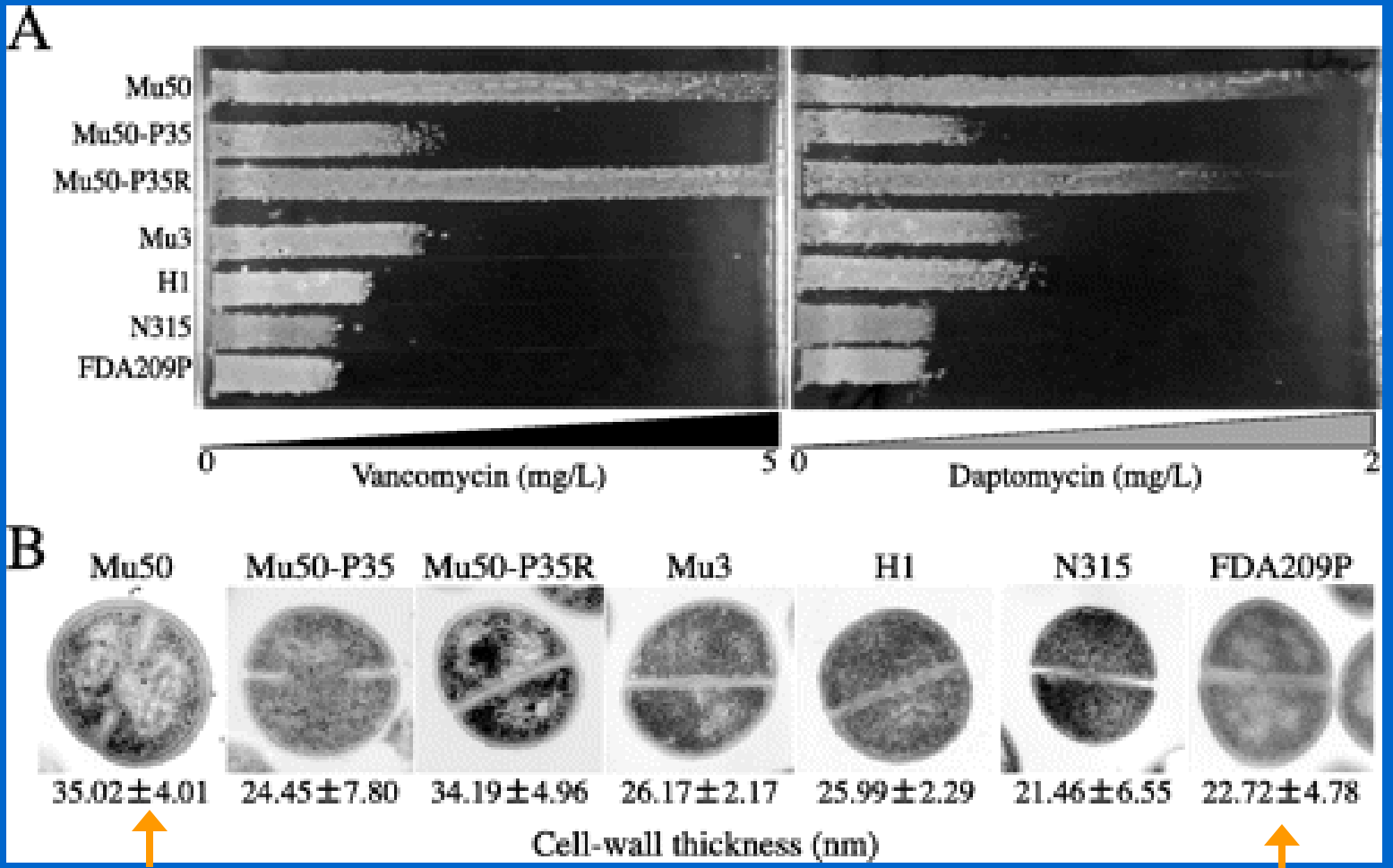
Climo, AAC 1999; 43: 1747-53.

Daptomycin

- Cyclic lipopeptide (new class of antibiotic)
- FDA approved in 2003
- Penetrates cell wall to bind cytoplasmic membranes
- Bactericidal in vitro

Cross-Resistance: Daptomycin and Vancomycin?

Abx gradient gel assay



Vanco MIC 8

Vanco MIC 0.5

Cui et al, AAC 2006; 50: 1079-82.

Cross-Resistance: Daptomycin and Vancomycin?

- Thickened cell wall of VISA may make it difficult for daptomycin (a large molecule) to penetrate and get to site of action (cytoplasmic membrane)
- Of note, 3/6 VISA cases in NYC were tested for daptomycin susceptibility → all 3 were resistant
- *Daptomycin may not necessarily be effective in treating VISA or hVISA infections

Newer Options

- New glycopeptides
  - Dalbavancin (lipoglycopeptide)
  - Oritavancin (semisynthetic glycopeptide)
- New broad-spectrum cephalosporin
  - Ceftobiprole

Infection Control

Infection Control

- There is no reason to believe VISA cannot be transmitted from patient to patient just as is MRSA
- VISA outbreak, France, 1999-2000
  - 21 patients with same clone in 14-bed ICU
  - Control measures:
    - Twice weekly screening of all pts
    - All HCW screened
    - Sampling of environment → if ≥ 1 sample positive, room closed until cx negative
    - Geographical cohorting, nurse cohorting
    - Restricted visitors
    - Doubling of nursing assistants
    - Twice daily environmental cleaning
    - Restricted admissions
  - Of note, baseline patient-nurse ratio was 14:3 (>4:1) during day, 14:1 at night
  - Took 10 months to get outbreak under control

de Lassence, CID 2006; 42: 170-8

CDC Guidelines for Investigation/Control of VISA/VRSA (2006)

	MRSA	VISA/VRSA
Private room	X	X
Gown/gloves	X	X
Hand hygiene	X	X
Dedicated staff		X
Dedicated non-disposable items (e.g. BP cuffs, adhesive tape)		X
Staff education/communication		X
Consult with DOH, CDC before transferring/discharging pt		X

Our patient

- Transferred to and kept in MICU-B
  - For expected better staff adherence to isolation precautions
  - ICPs reviewed case with staff
  - Education of family
- No known transmission
  - Although all pts in MICU-B are screened for MRSA on admission, they are not re-screened thereafter

Prevention??

- Is this natural progression? How do we halt it?
  - Infection Control practices
  - Antimicrobial Stewardship
    - More judicious use of antibiotics
    - Vancomycin is over-utilized
    - At NYPH, clinicians must obtain approval from ID before prescribing vancomycin
    - However, as of March 2007, adult patients in Milstein can receive 96 hours of vancomycin without prior approval
    - The impact of this is being closely followed