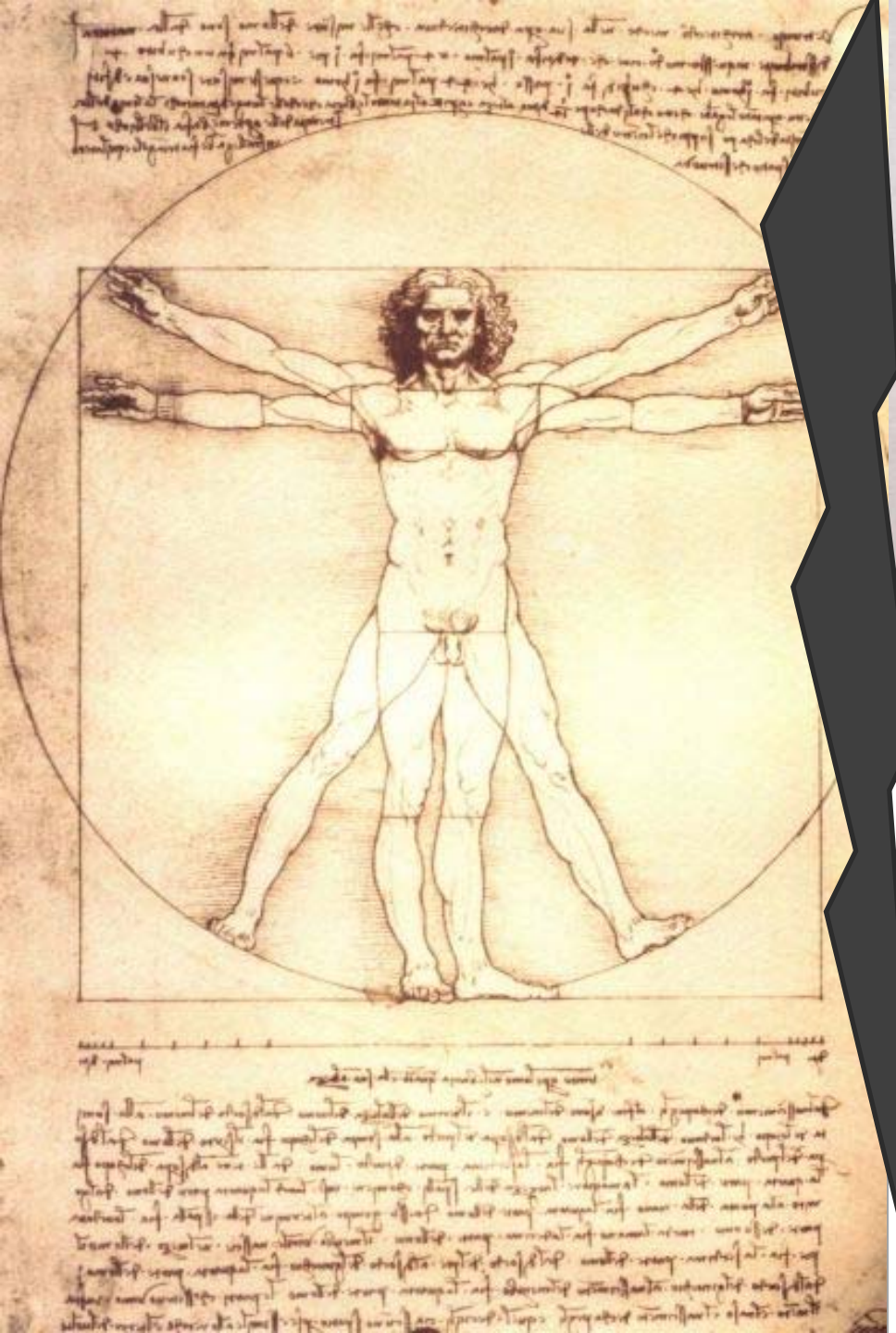
How to vanquish *S. aureus* in 2012 ?

az sint-jan
brugge - oostende av

Stefaan J. Vandecasteele
Nephrology and Infectious diseases
AZ Sint-Jan Brugge-Oostende AV

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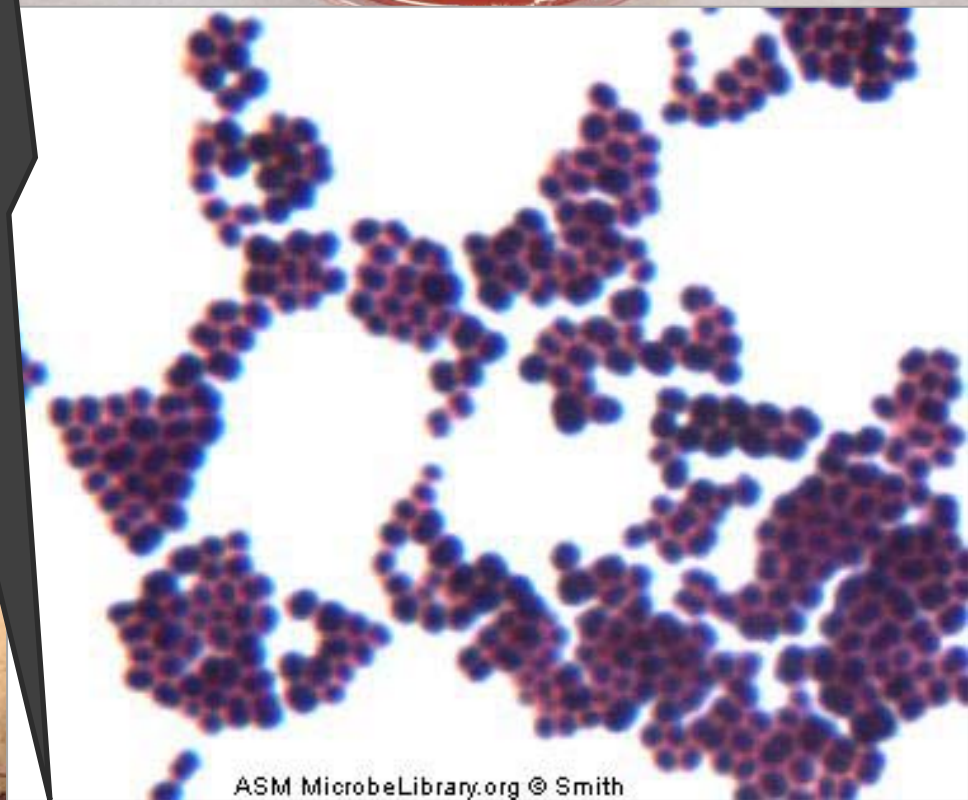
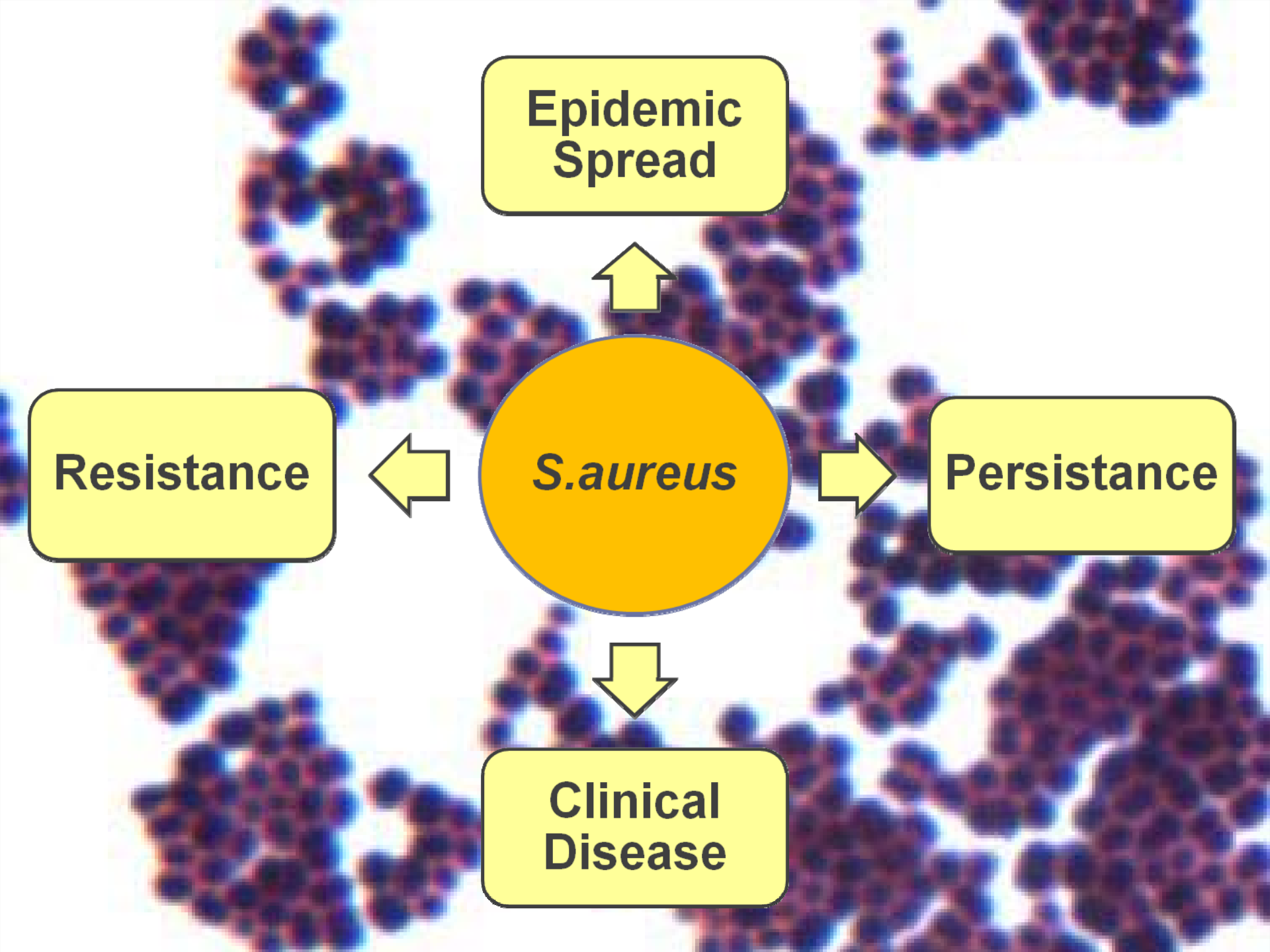
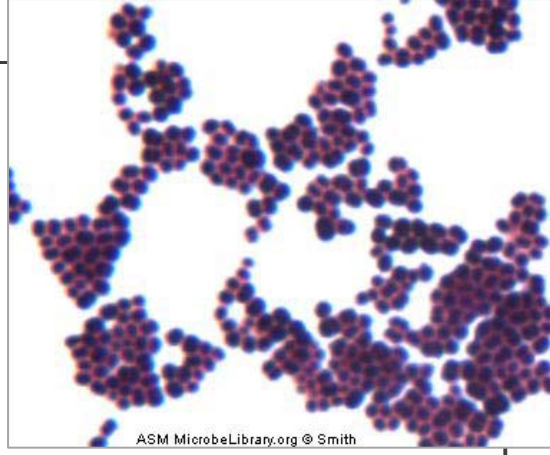

ASM MicrobeLibrary.org © Smith


Epidemic Spread
Resistance
S.aureus
Persistance
Clinical Disease



Epidemic Spread

Resistance

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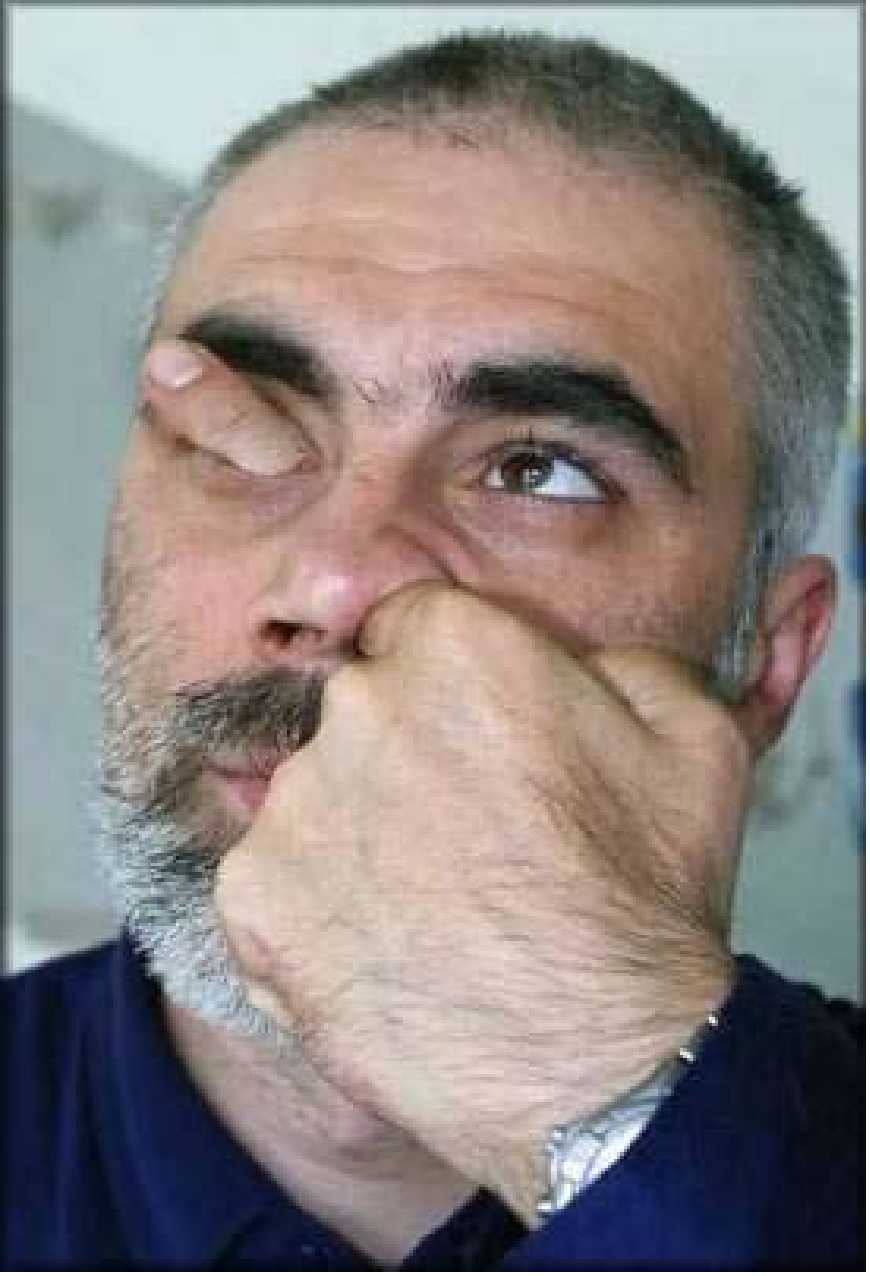


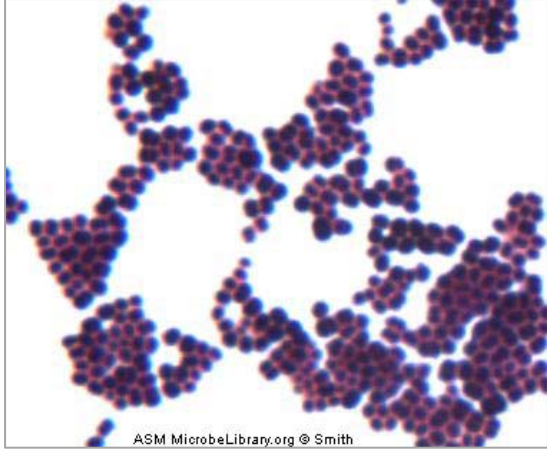
Persistent (epithial) carriers 20 %

Intermittent (mucinal) carriers 30 %

Persistent non-carrier 50 %

Vandenbergh, JCM, 1999, 3133-3140
Von Eiff, NEJM, 2001, 344, 11-16
Wertheim, Lancet Infect Dis, 2005, 5, 751-762
Dancer, Lancet Infect Dis, 2008, 8, 101-113

Epidemic Spread



Resistance

S.aureus

Persistance

Clinical Disease

1. Clinical Disease

- **“benign disease”:**

  Foliculitis, furunculosis

- **Invasive disease:**

  Cellulitis, osteomyelitis, artritis, pneumonia, SAB

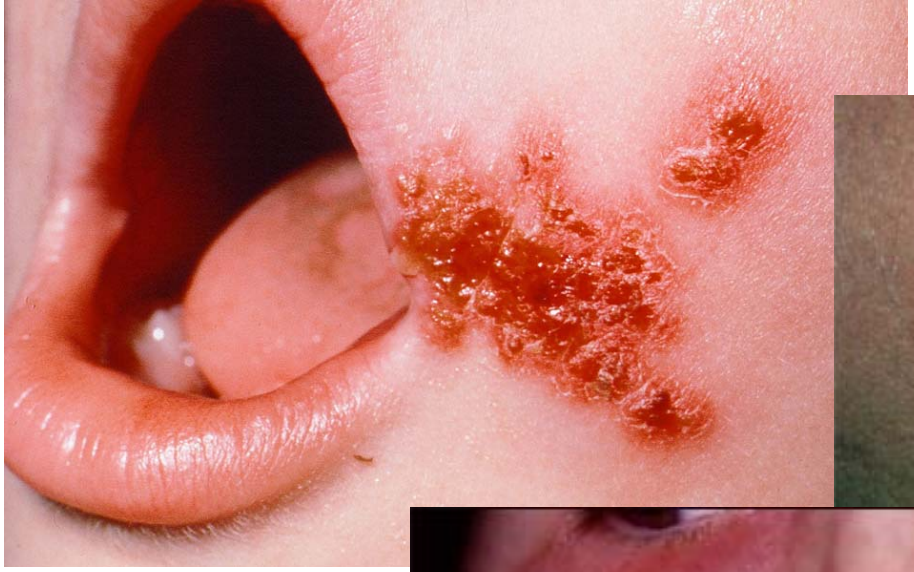
- **Foreign body associated disease:**

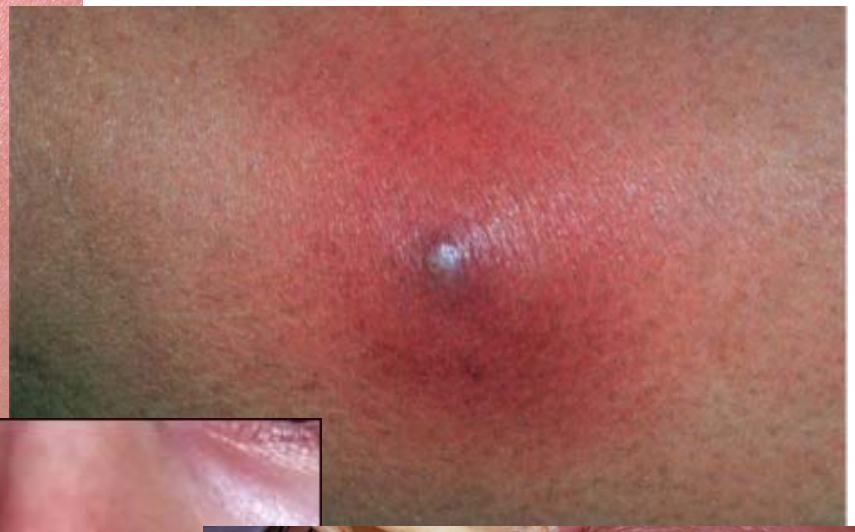
  Prosthetic joint infections, pacemaker infections, endocarditis, ...

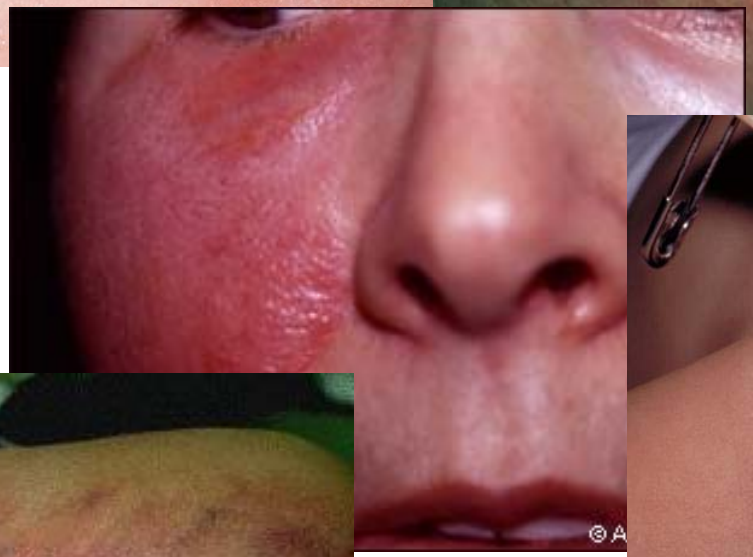
- **Toxin mediated disease:**

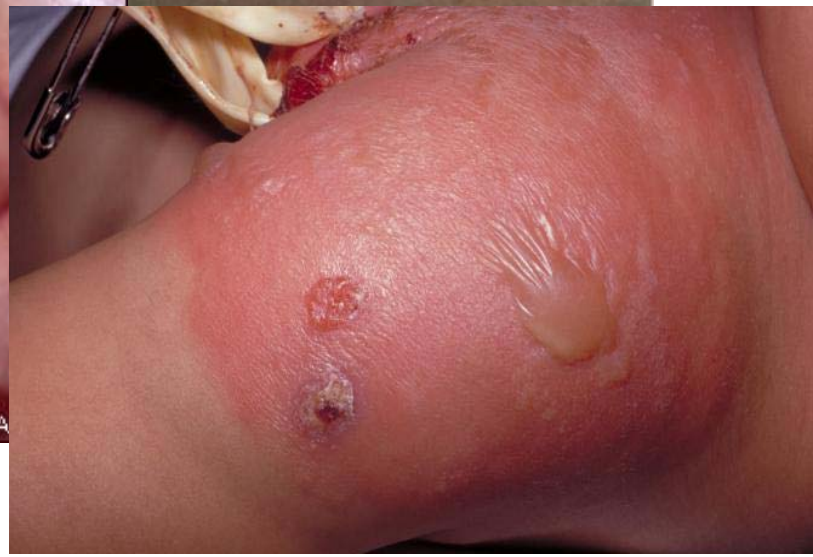
  TSS, SSSS, food poisining

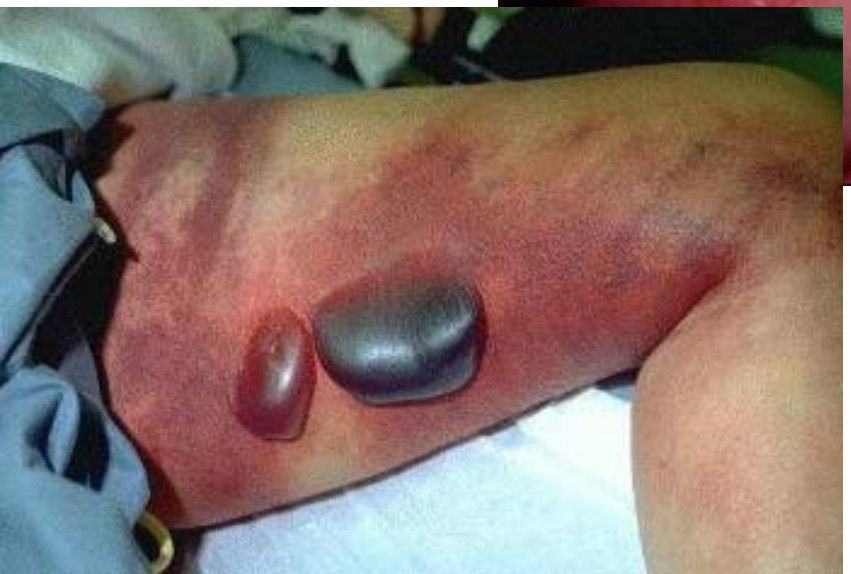
Wertheim, Lancet Infect Dis, 2005, 5, 751-762











S. aureus bacteremia:

- **3 types:**
  - Community acquired, no predisposing factors
  - Community acquired, predisposing factors
  - Healthcare asscociated or nosocomial
- 17-39/100.000/year
- **N° 1** in nosocomial and community acquired bacteremia

Fowler, Arch Int Med, 2003, 163, 2066-2072
Van Hal, Clin Microb Rev, 2012, 362)386.

Table 2. Outcomes of 724 Patients With *Staphylococcus aureus* Bacteremia

Outcome	No. (%)
Complicated *S aureus* bacteremia*	310 (43)
Complicated infection present at the time of the initial hospitalization	228 (74)†
Infective endocarditis	89 (39)
Septic arthritis	54 (24)
Deep tissue abscess	41 (18)
Vertebral osteomyelitis	22 (10)
Epidural abscess	18 (8)
Septic thrombophlebitis	17 (8)
Psoas abscess	13 (6)
Meningitis	12 (5)
Other complications‡	16 (7)
Attributable mortality	86 (28)
Recurrent *S aureus* infection§	70 (23)
Recurrent *S aureus* bacteremia	49 (16)
S aureus isolated only from sterile body site other than blood‖	21 (7)
Embolic stroke	18 (6)
No complications due to *S aureus* bacteremia	412 (57)
Uncomplicated *S aureus* bacteremia	341 (47)
Death due to causes other than *S aureus* bacteremia¶	71 (10)
Outcomes missing	2 (<1)

43 % complicated

28 % mortality

23 % recurrence

Fowler, Arch Int Med, 2003, 163, 2066-2072

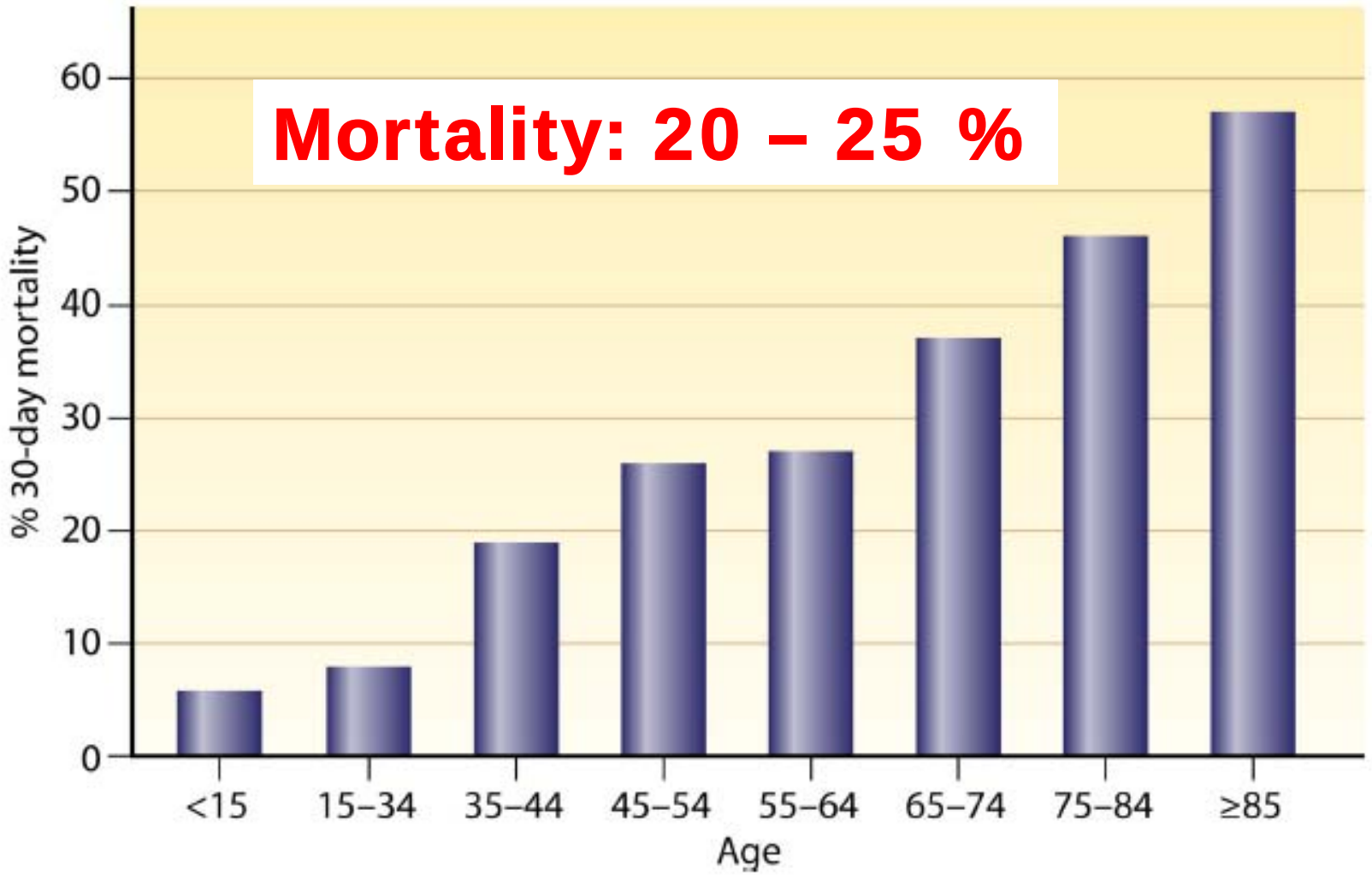
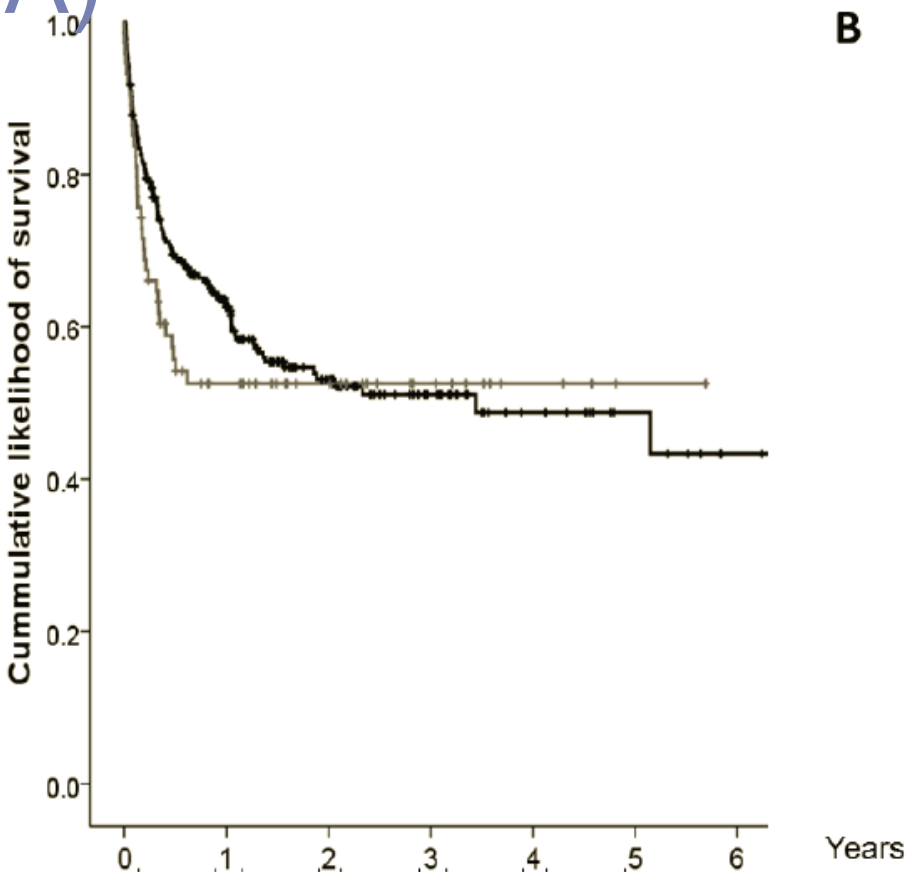


FIG 1 Impact of age on overall 30-day mortality from *Staphylococcus aureus* bacteremia. Percentages of patients who succumbed at 30 days following an episode of *Staphylococcus aureus* bacteremia are stratified by 10-year age

Van Hal, Clin Microb Rev, 2012, 362-386.

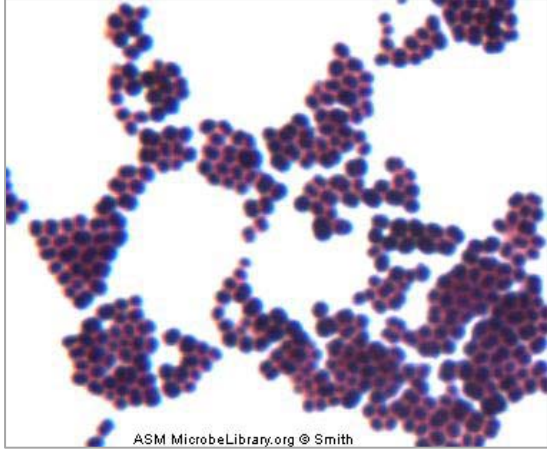
S.aureus prothetic joint infection

- 345 episodes *S. aureus* prosthetic joint infections (82 MRSA)
- **Treatment failure in 45 % patients**
  - 7 % death
  - 15 % persistance/relapse
  - 78 % salvage with removal
- 98 patients: 78 % cure if no retention



Lora-Tamayo, CID, 2012, ePublished 31 aug,
Senneville, CID, 2011;53(4):334–340

Epidemic Spread



Resistance

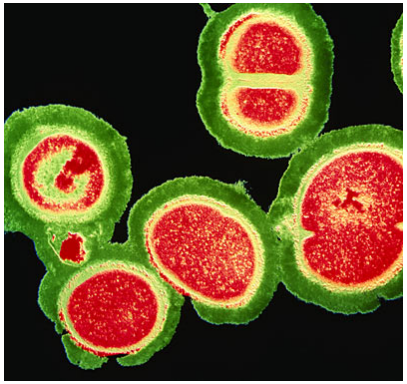
S.aureus

Persistance

Clinical Disease

Vancomycin Susceptibility

EUCAST richtlijnen



Susceptible	Intermediate	Resistant
≤4 µg/mL	8 – 16 µg/mL	≥ 32 µg/mL
↓	↓	↓
≤2 µg/mL	4 – 8 µg/mL	≥ 16 µg/mL

MIC

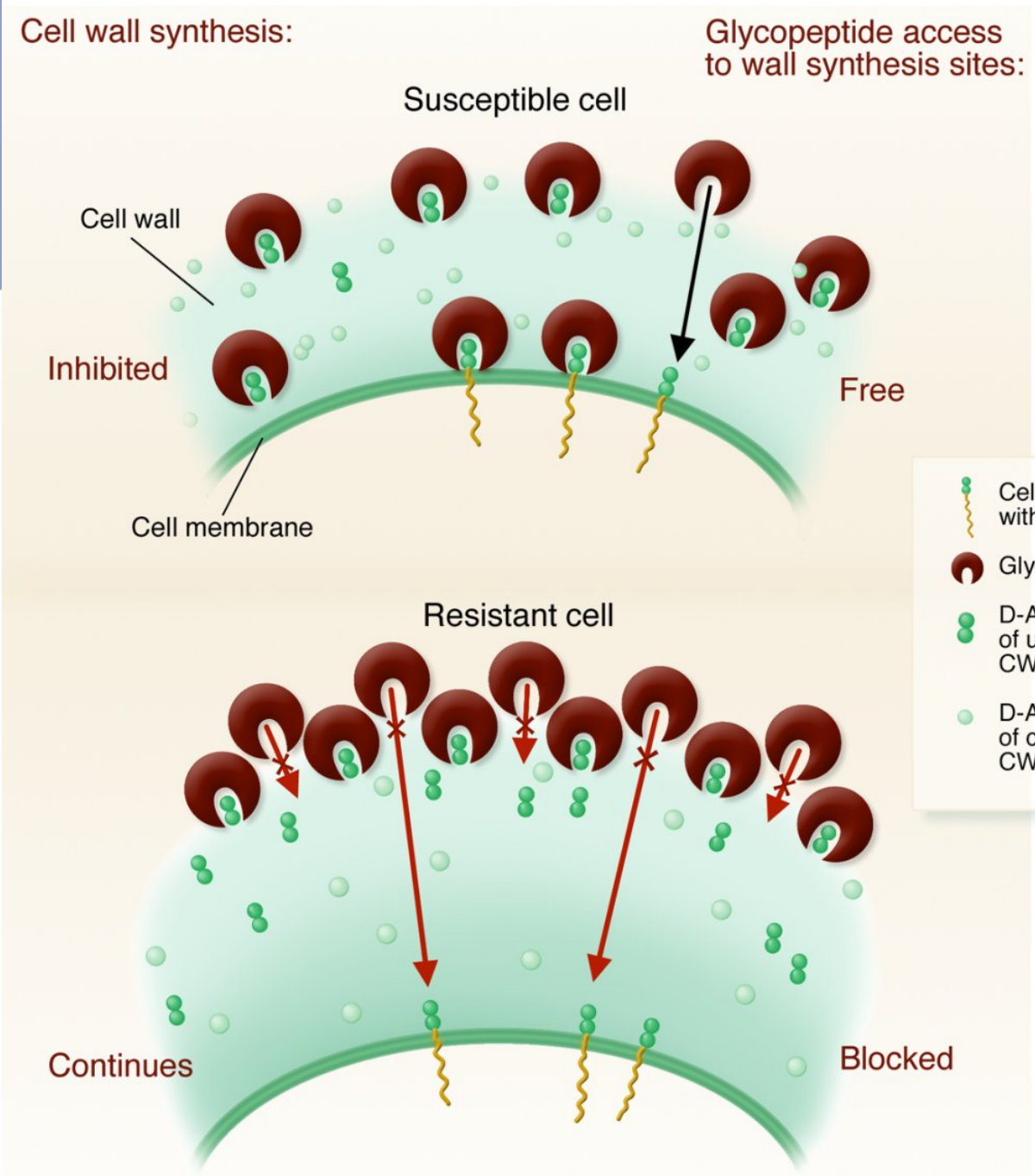
VRSA

VISA

hVISA

MRSA

Creep in MIC



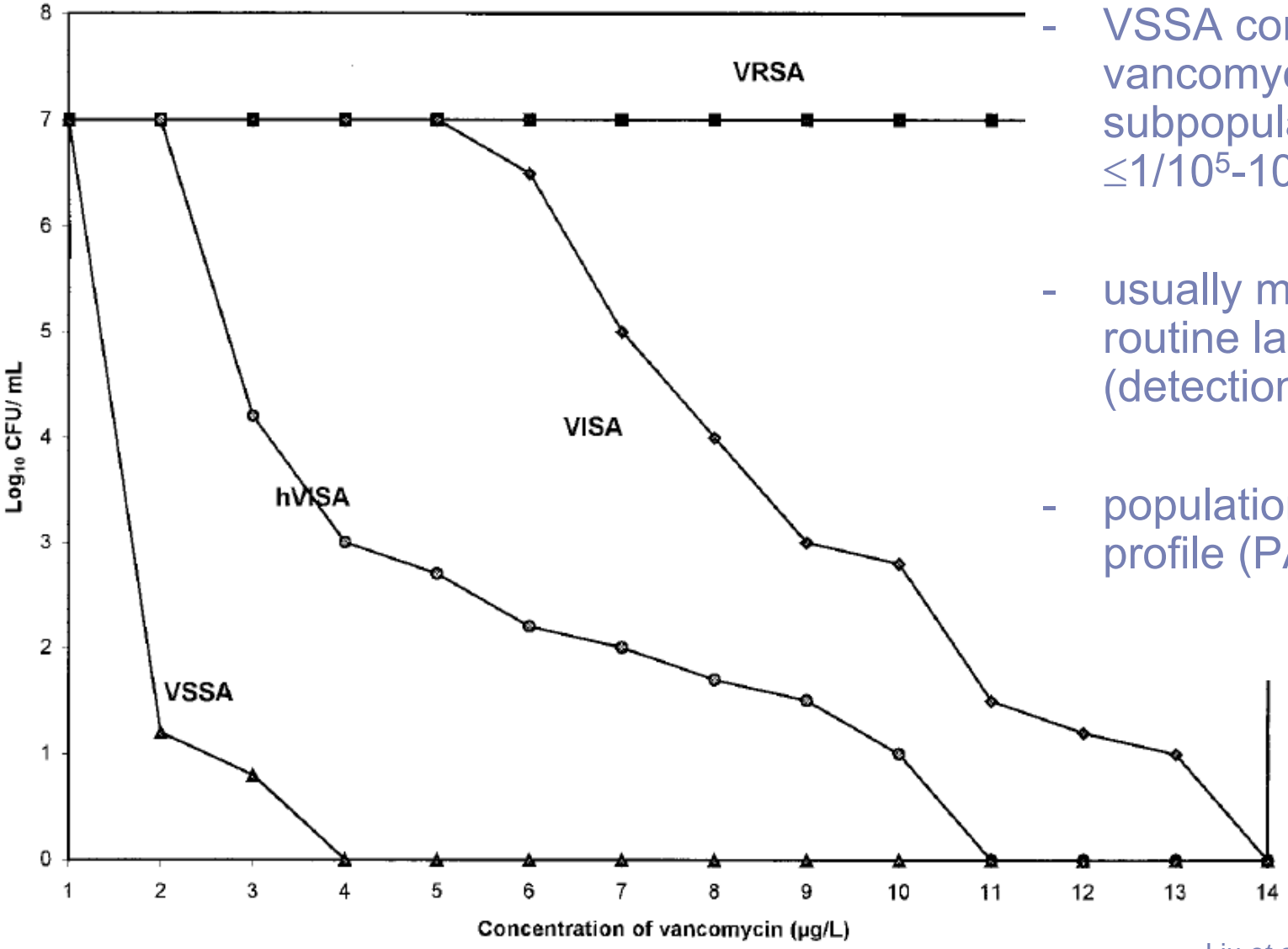
VISA

- Thickened cell wall with more peptidoglycan layers.
- Vancomycin must bind more peptidoglycan to induce osmetic cytolysis

VRSA

- *Van*A gene=high-level vancomycin resistance
- D-ala-D-ala ➔ D-ala-D-lac

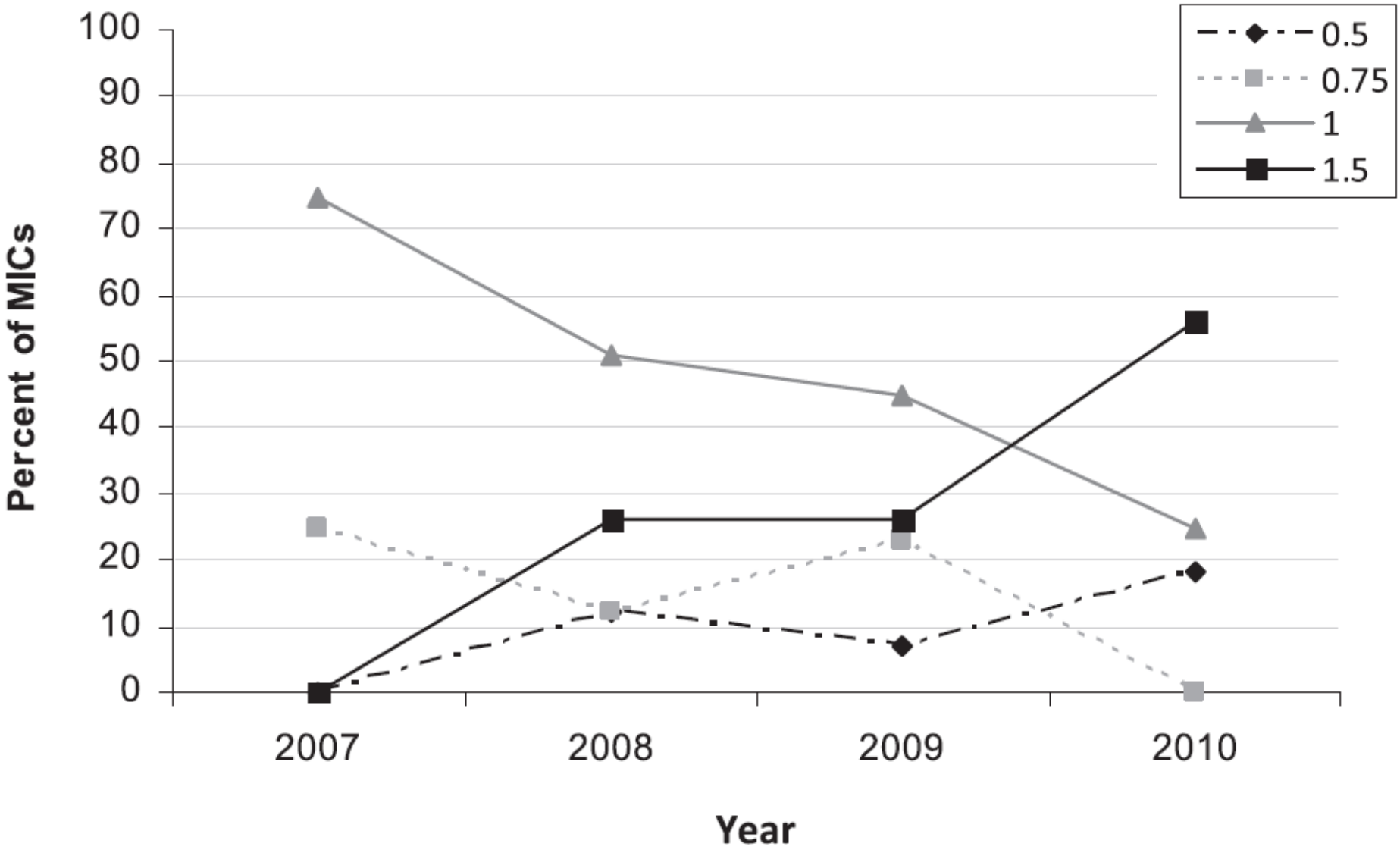
hVISA =heterogenous vancomycin intermediary susceptible *S. aureus*



- VSSA containing vancomycin resistant subpopulations (usually $\leq 1/10^5$-10^6)
- usually missed by routine lab techniques (detection limit 10^4)
- population analysis profile (PAP)

Liu *et al*, *AAC*, 2003,47:3040-5.

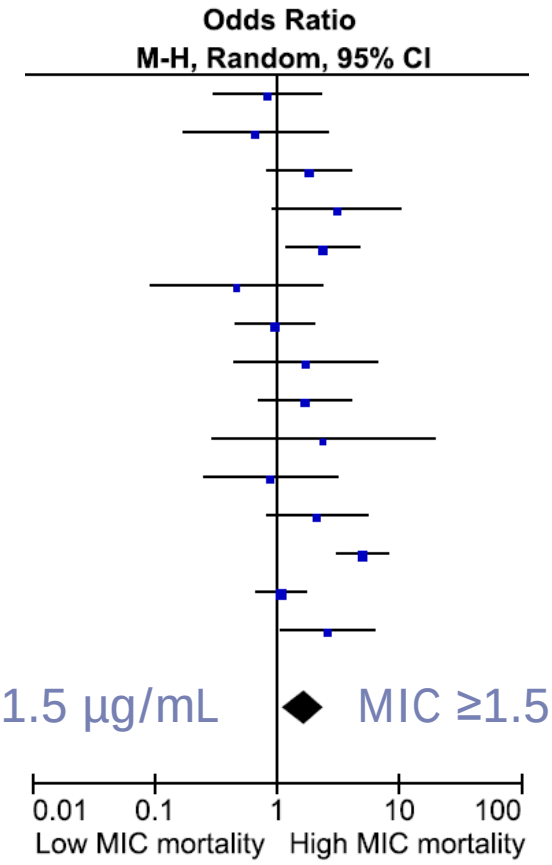
The creep in Vancomycin MIC



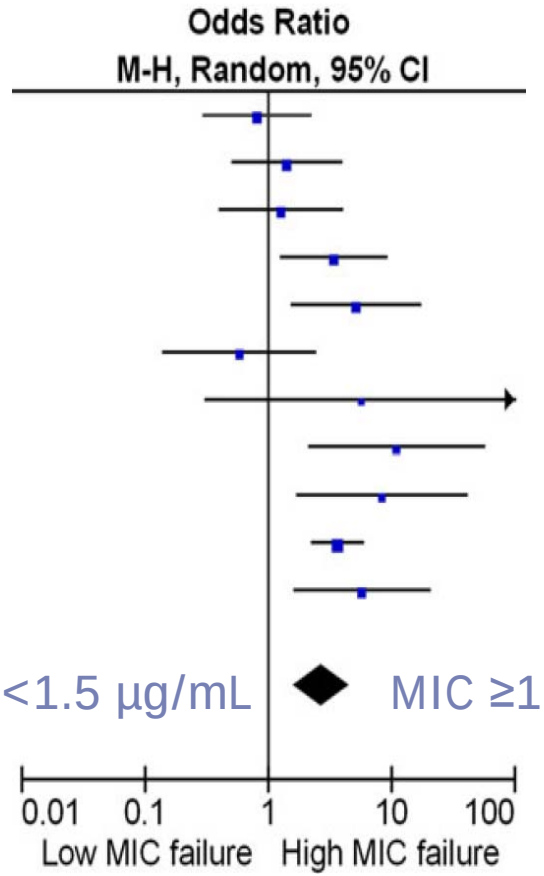
Edwards B *et al*. J Clin Microbiol 2012;50:318-325

Clinical Significance of Vancomycin MIC

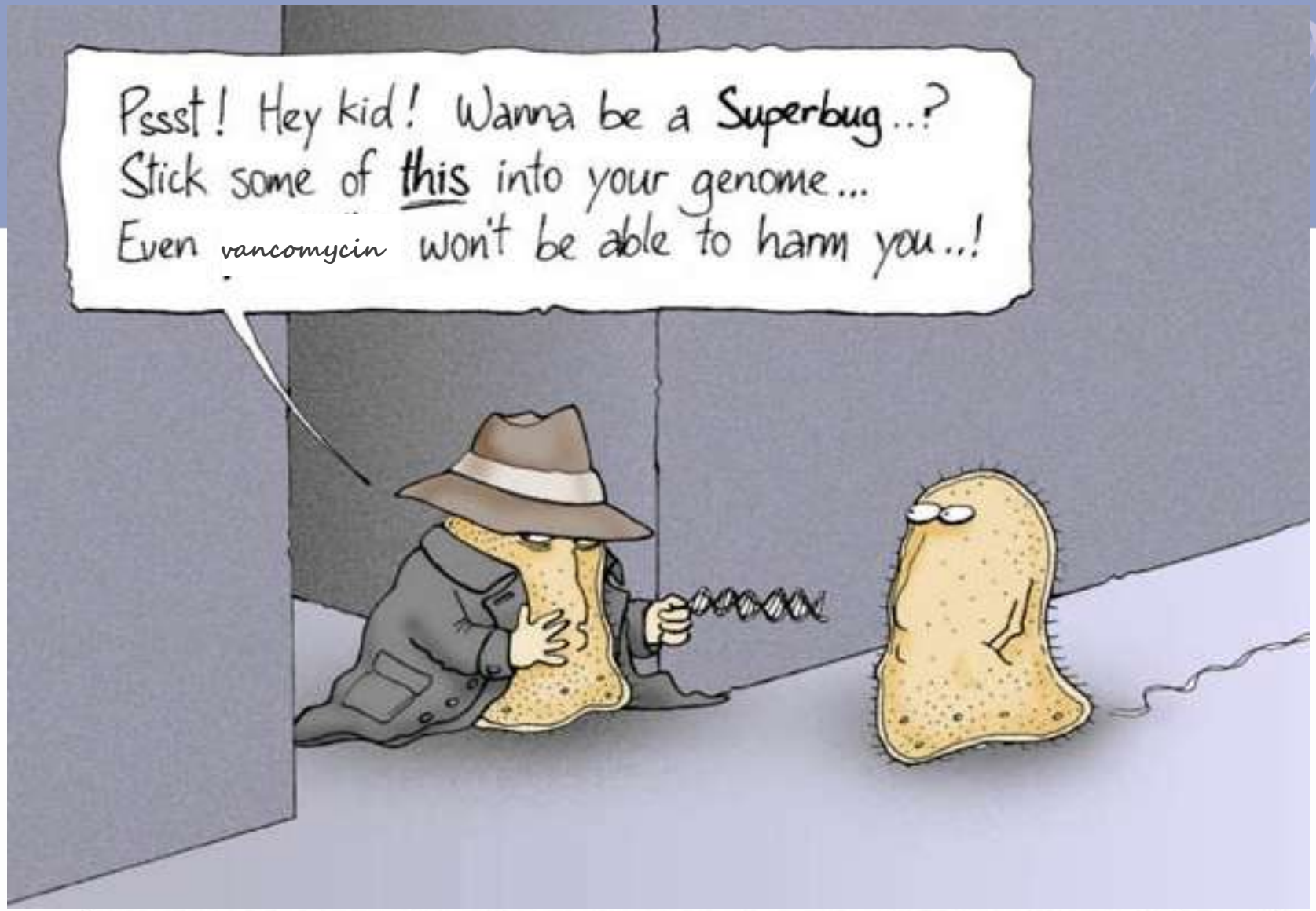
Mortality



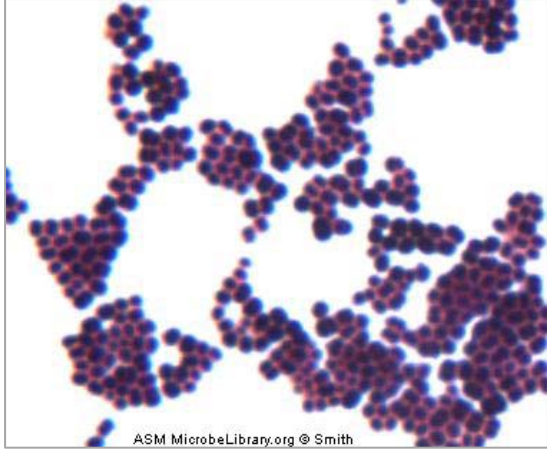
Treatment Failure



Van Hal *et al*. Clin Infect Dis 2012;54:755-71.



It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.



Epidemic Spread

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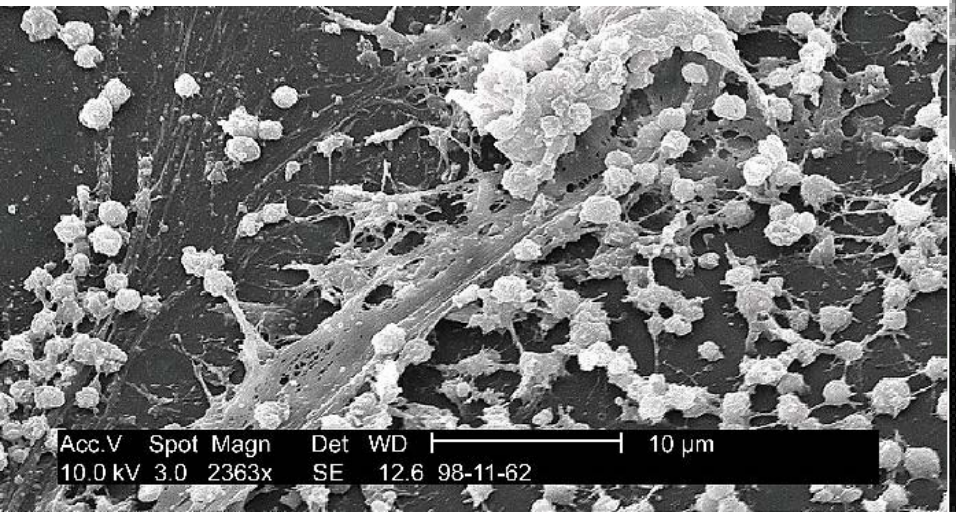
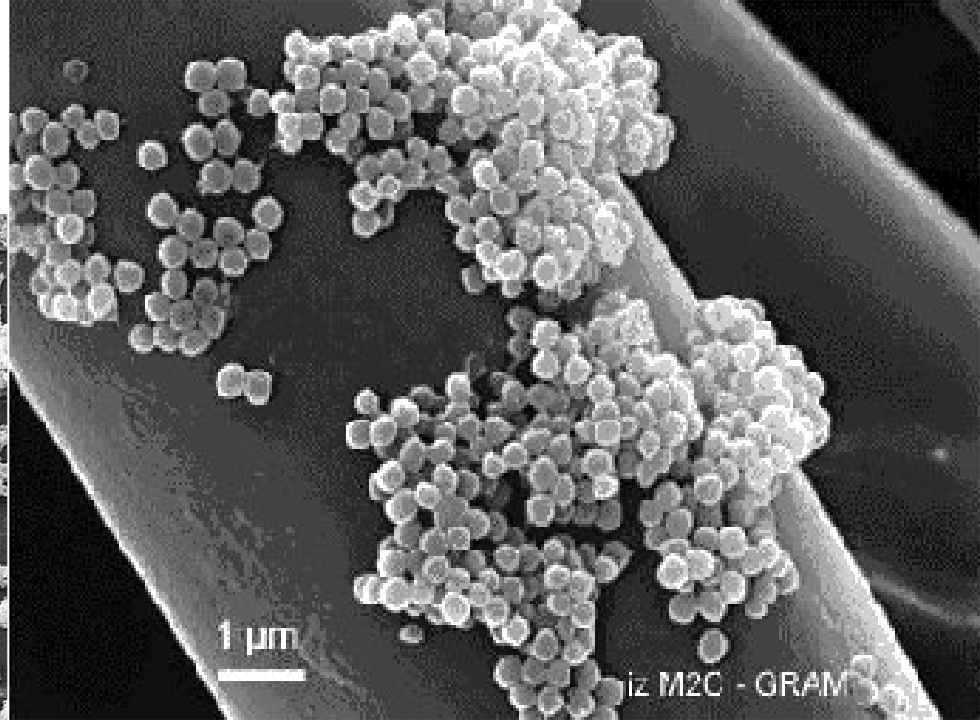
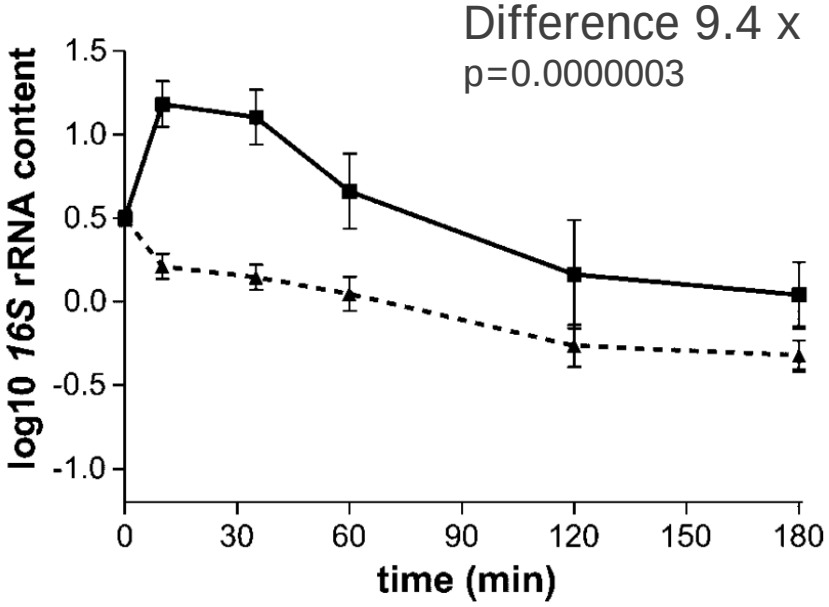
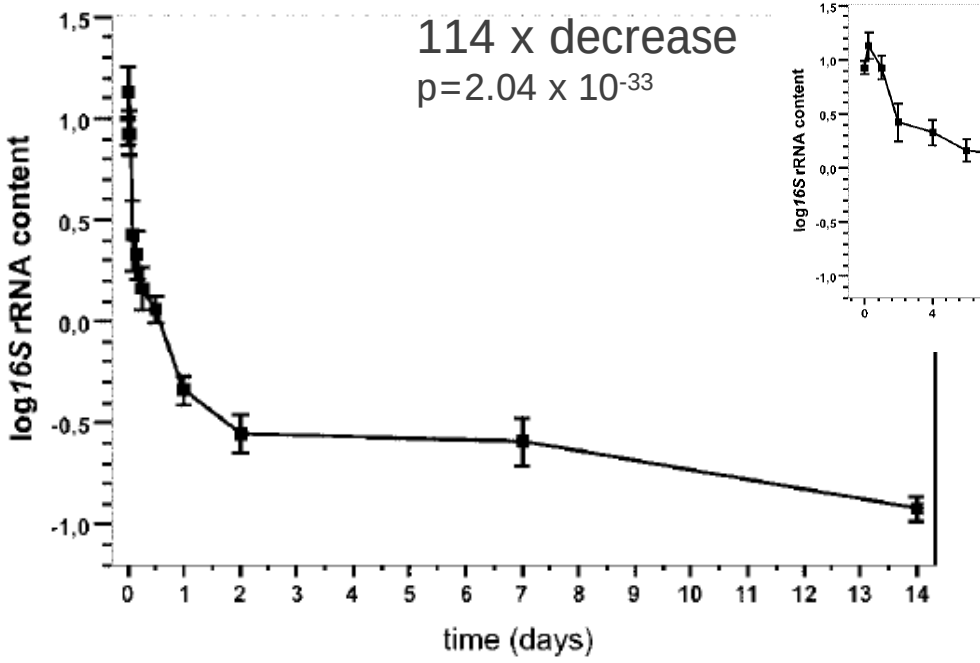
Biofilm formation









Vandecasteele, J. Bacteriol, 2004, 2236-9

Biofilm-associated bacteria persist the killing effect of antibiotics

- *S. aureus* MBC for oxacillin, vancomycin, gentamycin, rifampin and fleroxacin increases > 256 ×

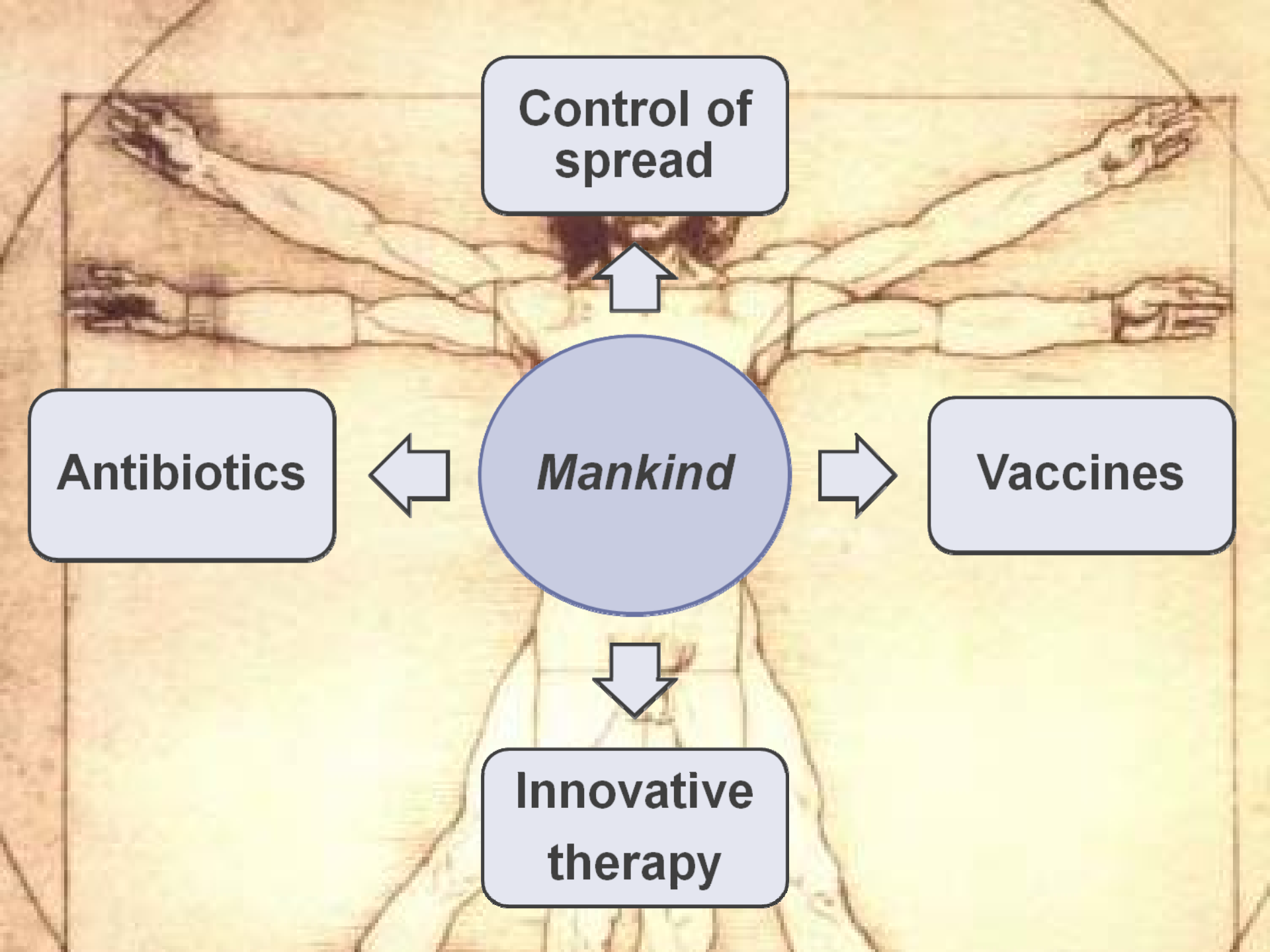
Chuard, 1991, J Infect Dis, 1991, 1369-73

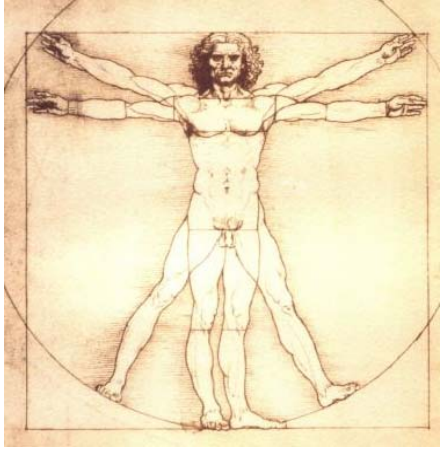
- Surface attached *S. aureus* resists killing of high doses of vancomycin, fluoroquinolones and aminoglycosides

Chuard, Antimicrob Agents Chem, 1993, 625-32

- Tobramycin is bacteriostatic on sessile CoNS but bacteriocidal on planktonic CoNS

Duguid, 1992, J Antimicrobiol Chem, 803-10


Control of spread
Antibiotics
Mankind
Vaccines
Innovative therapy



Control of spread

Antibiotics

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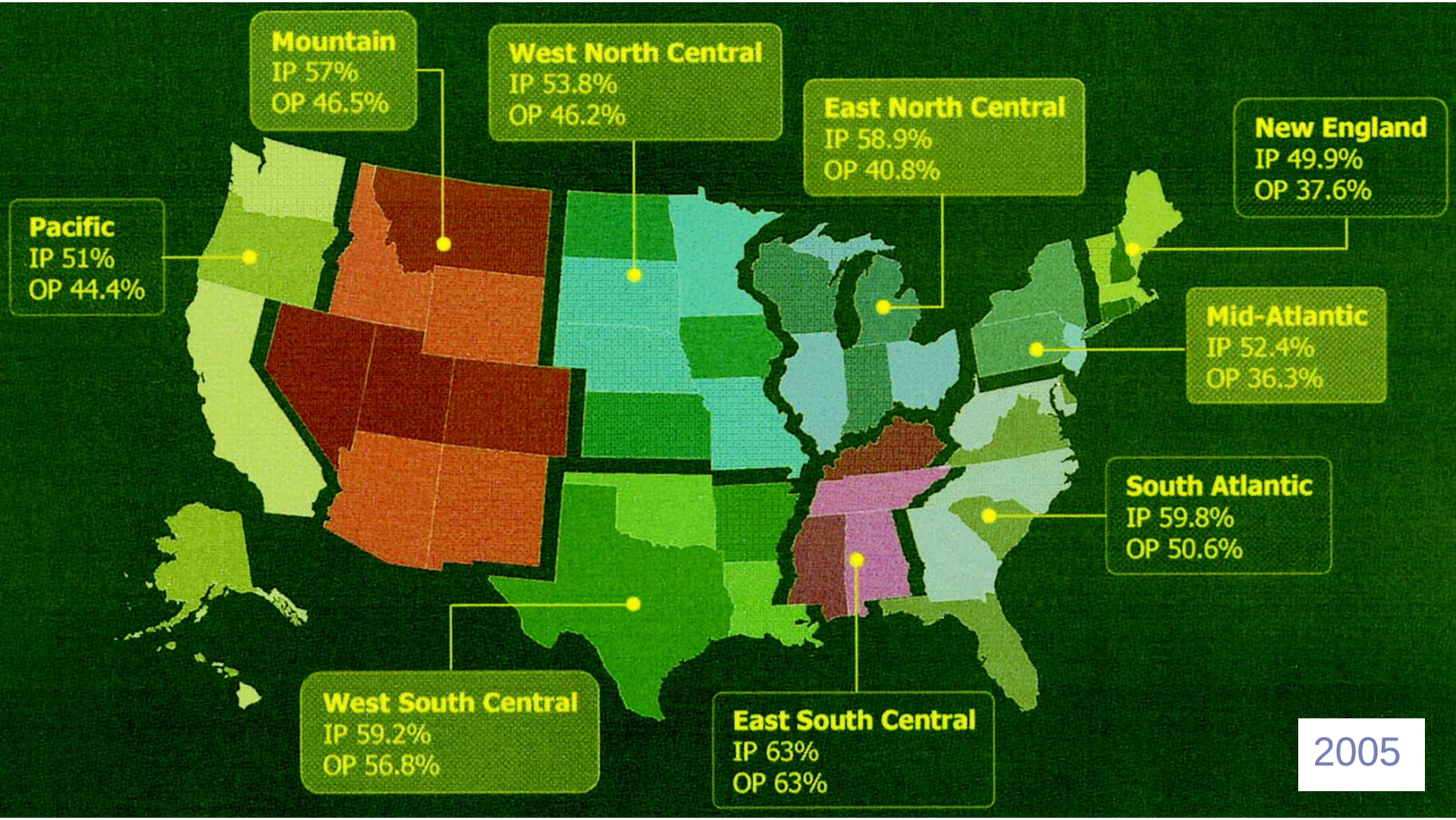
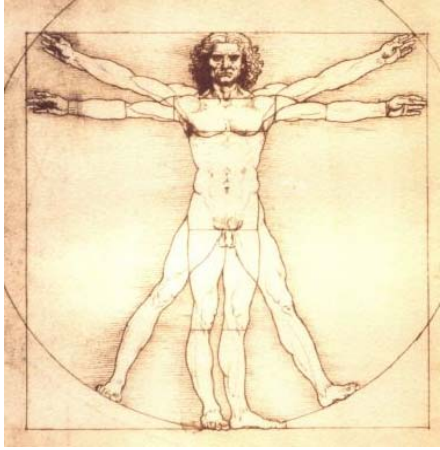


IP = inpatients; OP = outpatients

Shorr, CID, 2007, 45:S171–S176



Control of spread

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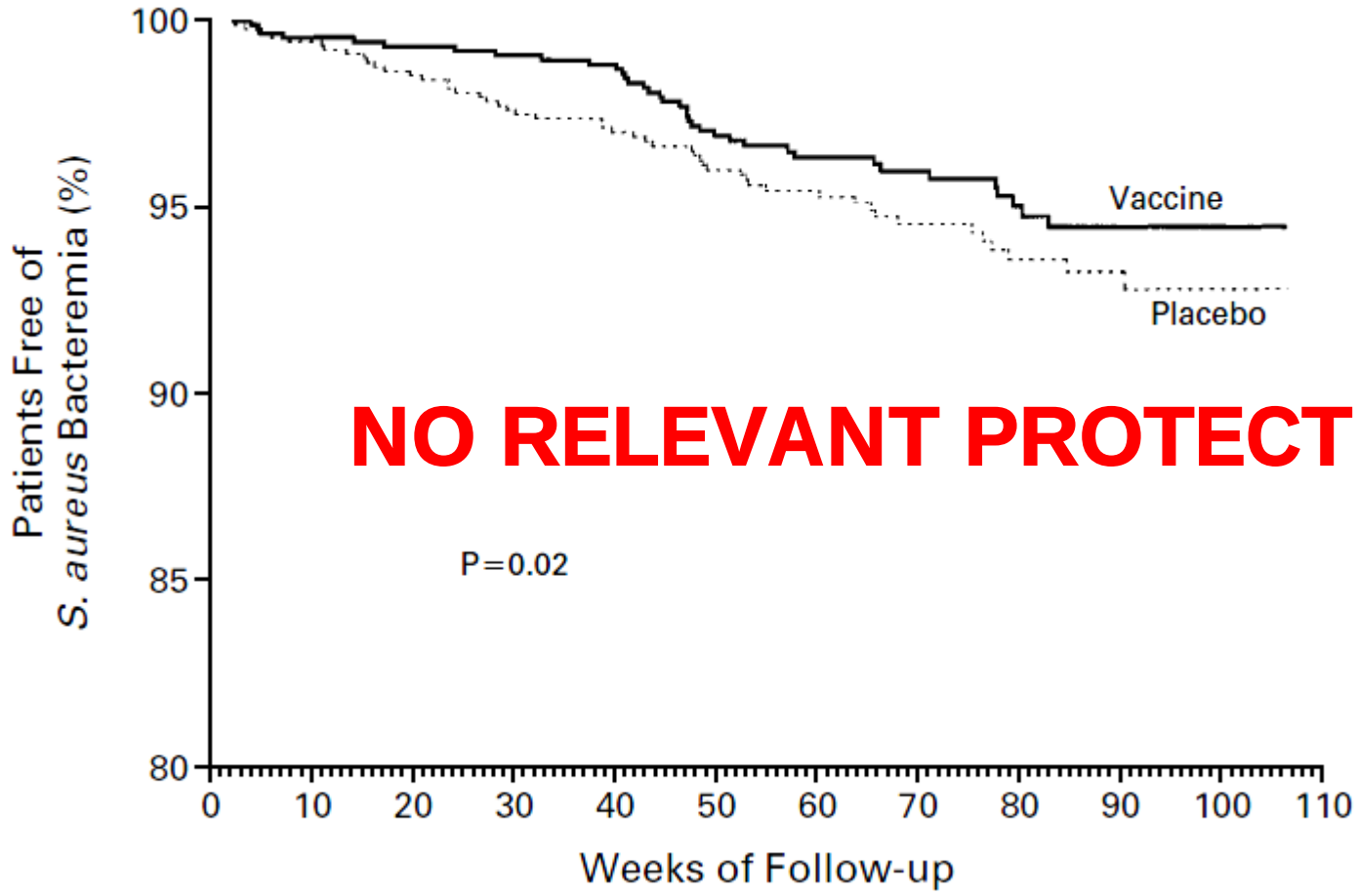
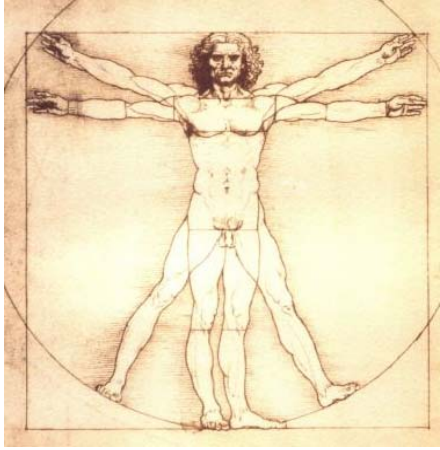
Innovative therapy

***All vaccine trials failed*:**



1804 dialysis patients

Shinefield, NEJM, 2002, 346, 491-496.



Control of spread

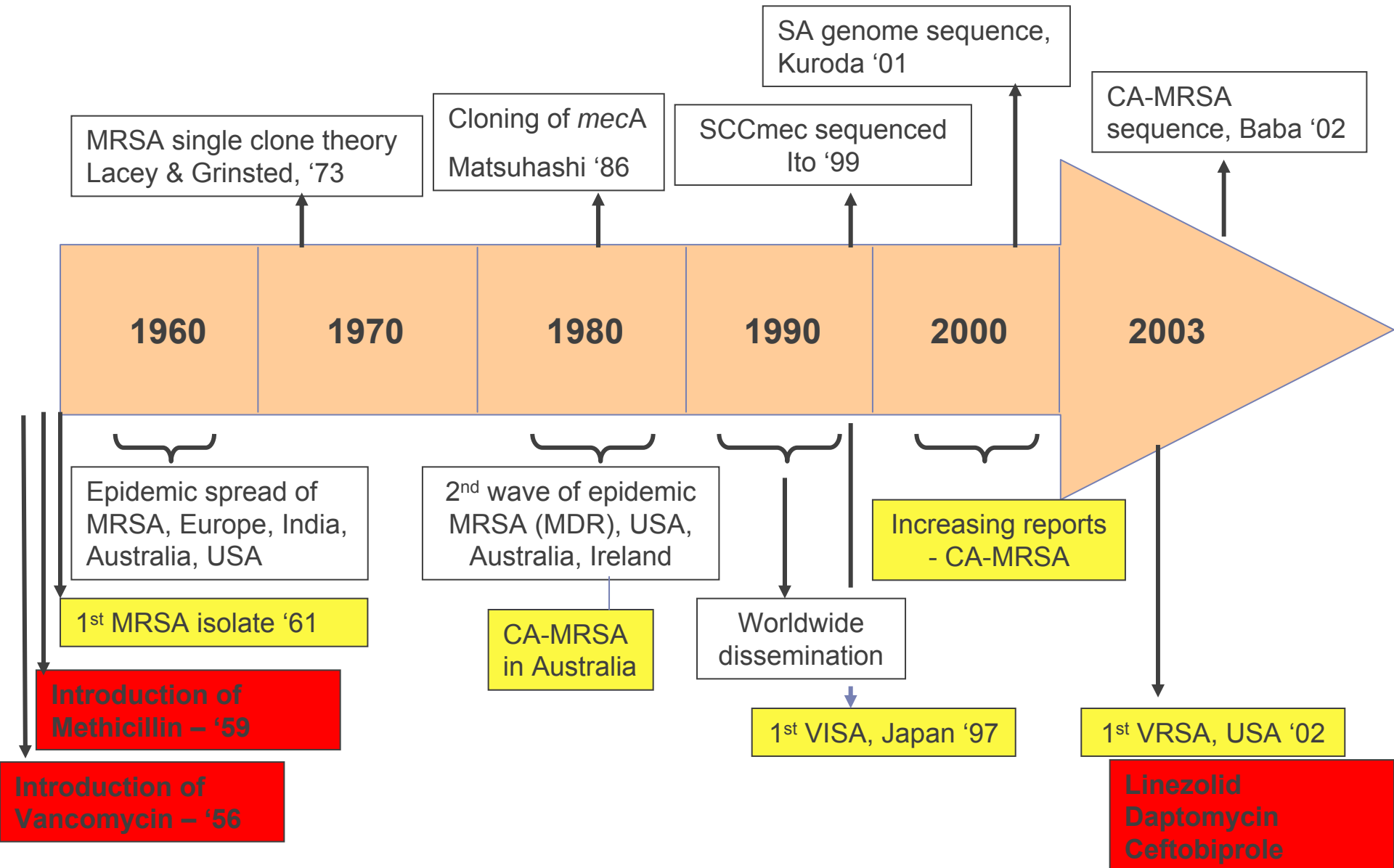
Antibiotics

Mankind

Vaccines

Innovative therapy

S. aureus and resistance



4 rules of thumbs:

1. Vanco inferior to β-lactam
2. Vanco = standard for MRSA/E
3. Use of rifampicin in FBI
4. Duration of treatment

1. Vanco inferior to β-lactam:

- Experimental (killing time & endocarditis)

LaPlante, AAC, 2004, 48, 4665-72
Apellaniz, J Chemother, 1991, 3, 91-97

- Pneumonia & endocarditis

Chang, Medicine, 2003, 82, 333-339
Gonzalez, CID, 1999, 29, 1171-1177
Gentry, Pharmacotherapy, 1997, 17, 990-997

- Lower morbidity/mortality in bacteremia

Siegman-Igra, Scan J Infect Dis, 2005, 37,:572-578
Kim, AAC, 2008 52(1):192-7.
Schweizer, BMC Infect Dis, 2011,19;11:279

- Better outcome in dialysis patients

Stryjewski et al, CID, 2007, 44, 190-196
Chan, JASN, 2012, 23(9):1551-9..

30-50 % ???

Inoculum effect cephazolin:

- 19 % MSSA isolates ~ treatment failure

TABLE 2. Correlation between cefazolin MIC and inoculum size for 98 strains

	Inoculum size	% of strains inhibited at cefazolin concn (μg/ml)							
		≤1	2	4	8	16[a]	32	64	≥128
$5x10^4$	Low	100	0	0	0	0	0	0	0
$5x10^5$	Standard	89	5	6	0	0	0	0	0
$5x10^6$	Intermediate	33	50	8	2	2	1	3	0
$5x10^7$	High	23	12	20	24	5	9	3	2

[a] CLSI breakpoint for nonsusceptibility.

Nannini, AAC, 2009, 53(8):3437-41

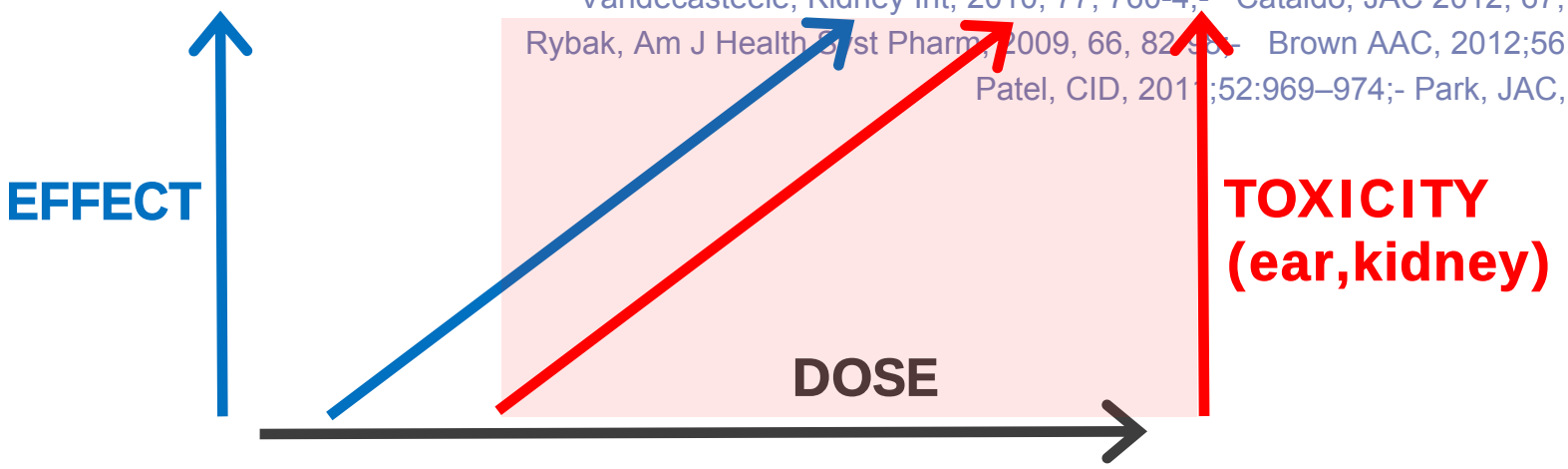
2. Vanco = standard for MRSA/E:

- **No clear superiority for comparaters** (linezolid, daptomycin, tigecyclin, ceftobiprole)

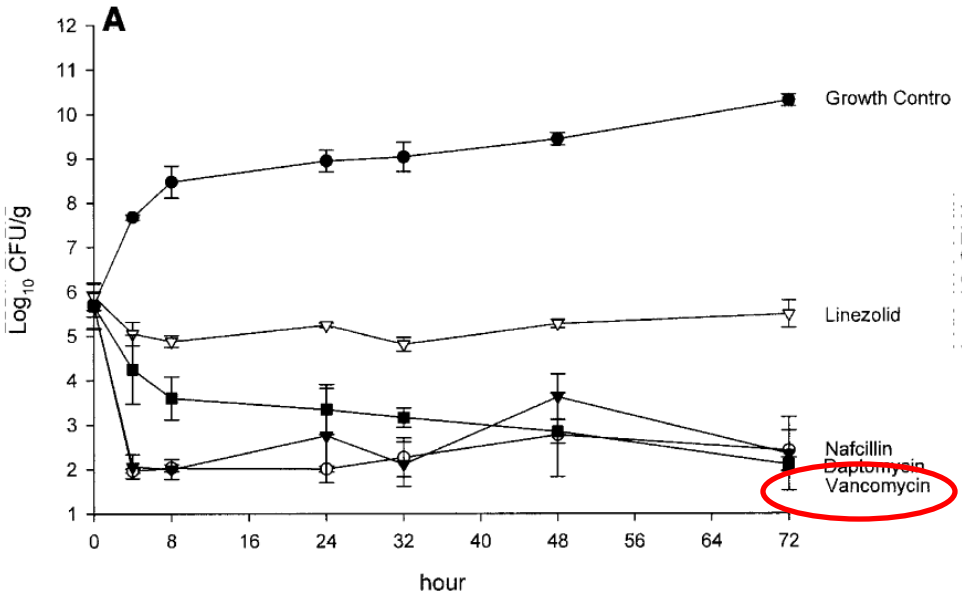
Liu, CID, 2011, 52, e18-e55;- Cataldo, JAC, 2012, 67, 17-24
Shorr, JAC, 2005, 56, 923-9;- Vardakas, Mayo Clin Proc, 2012, 87, 349-63
Beibei, Int J Antimicrob Ant, 2010, 35, 3-12;- Kalil, Crit Car Med, 2010, 38, 1802-8
Logman, Curr Med Res Opin, 2010, 26, 1565-78;- Walkey, Chest, 2011, 139, 1148-55
McCaine, 2010, 50, 1120-6

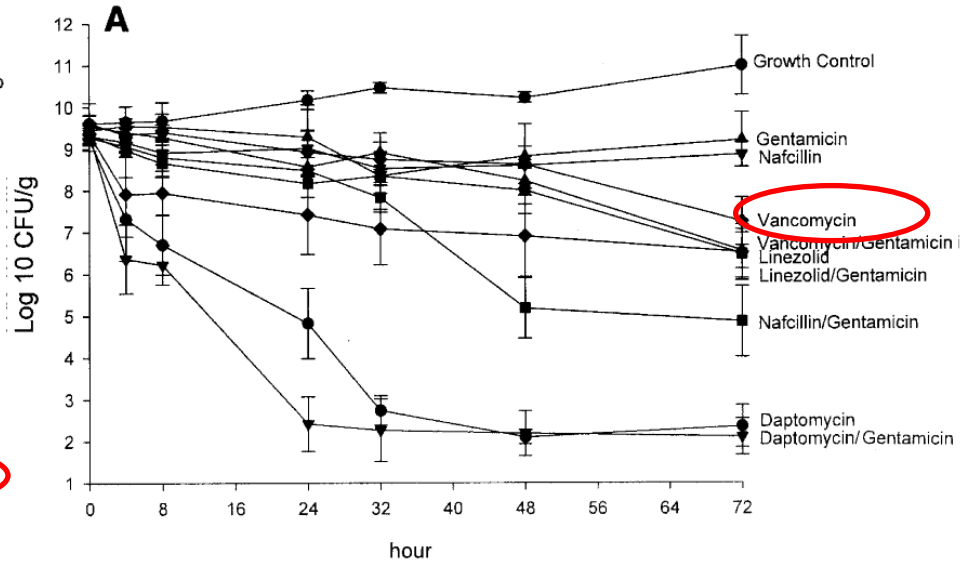
- **Dose/toxicity *versus* dose/effect** relation

Vandecasteele, Kidney Int, 2010, 77, 760-4;- Cataldo, JAC 2012, 67, 17-24
Rybak, Am J Health Syst Pharm, 2009, 66, 82 s&- Brown AAC, 2012;56:634-8
Patel, CID, 2011;52:969–974;- Park, JAC, 2012,



The inoculum effect of vancomycin:





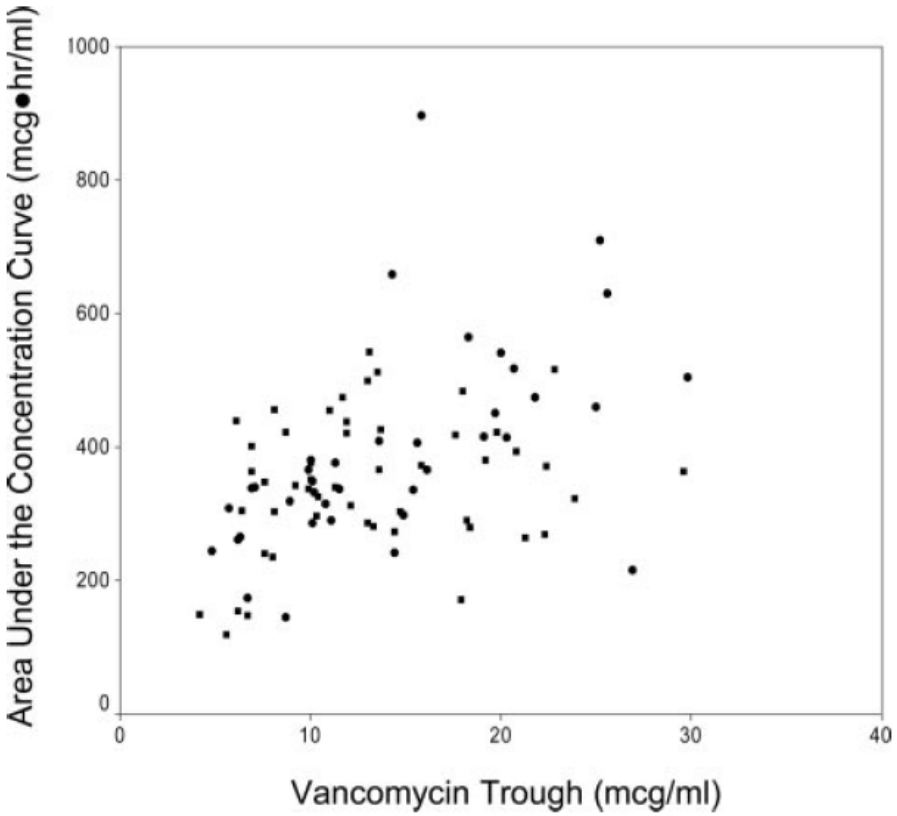
$5x10^5$

↓ 3 log / 48 hour

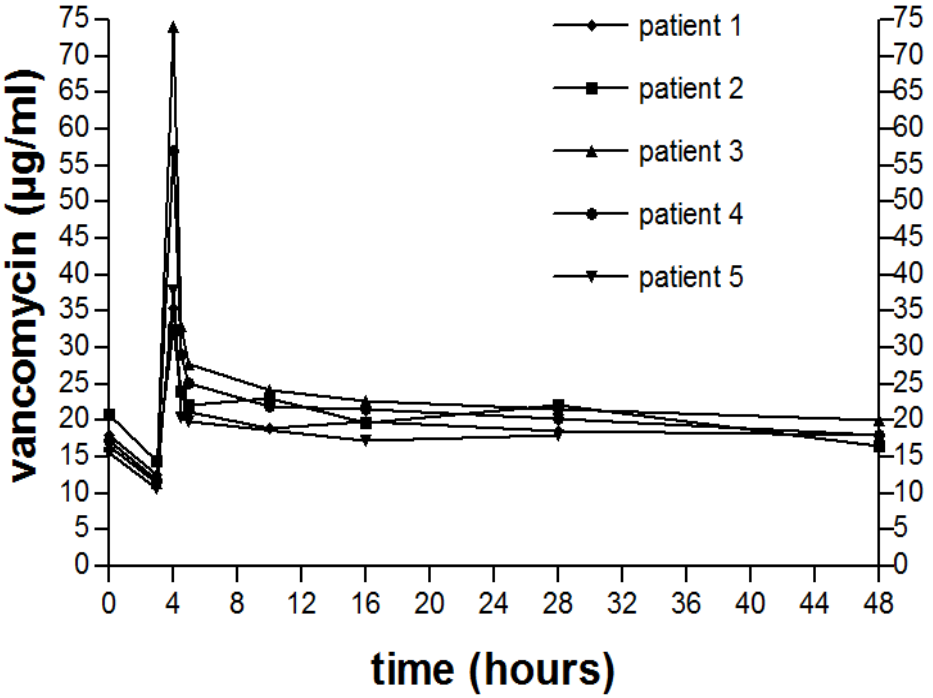
$5x10^9$

↓ < 1 log / 48 hour

Excellent corelation trough and AUC



$r^2 = 0.44$; P<0.01



$r^2 = 0.97$, p=0.016

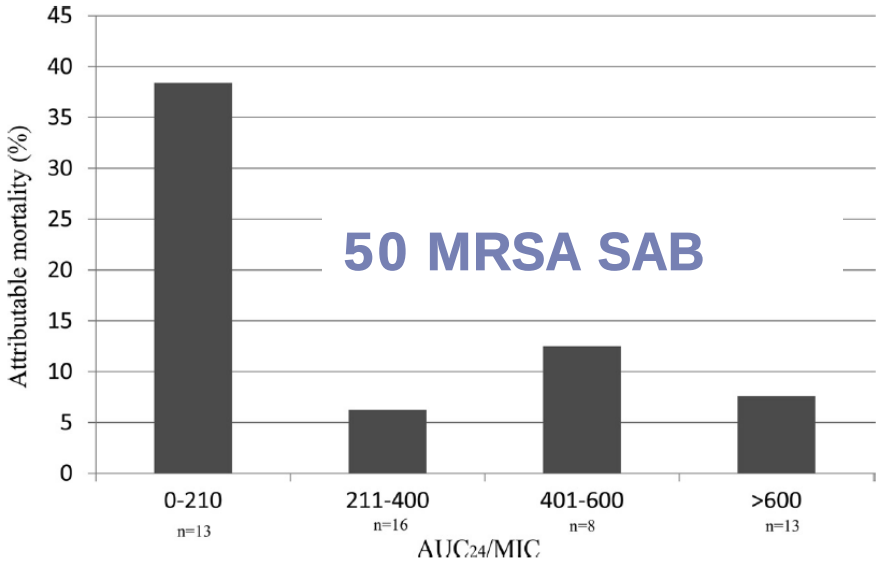
Trough 16,6 - 20,9 µg/mL

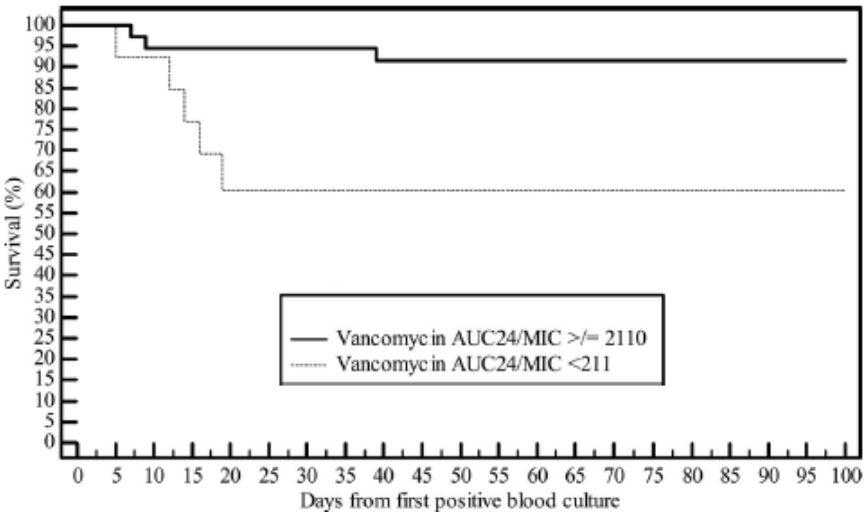
24h AUC/MIC 455 – 541

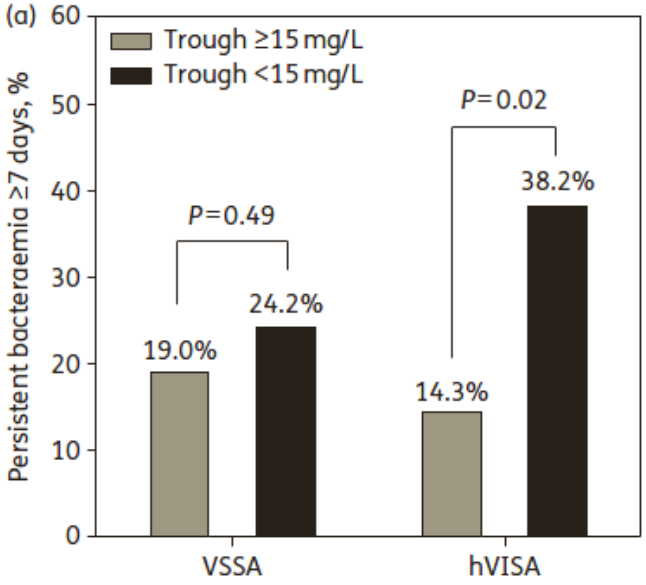
Jeffres, Chest, 2006;130: 947-55

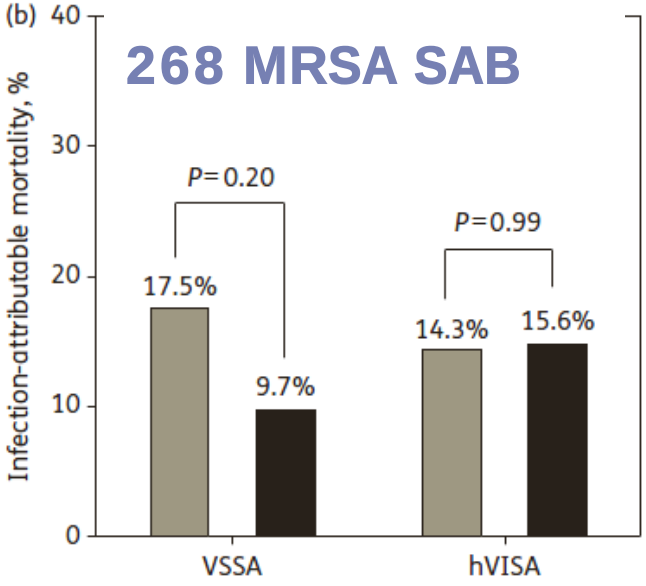
Vandecasteele, CID, 2011;53:124-9

Dose/effect corelation vancomycin









Brown, AAC, 2012;56:634-8.

Park, JAC, 2012, 67, 1843-1849.

Continuous or intermittent infusion?

Cataldo, JAC 2012, 67, 17-24
Vandecasteele, Kidney Int, 2010, 77, 760-4;
Rybak, Am J Health Syst Pharm, 2009, 66, 82-98

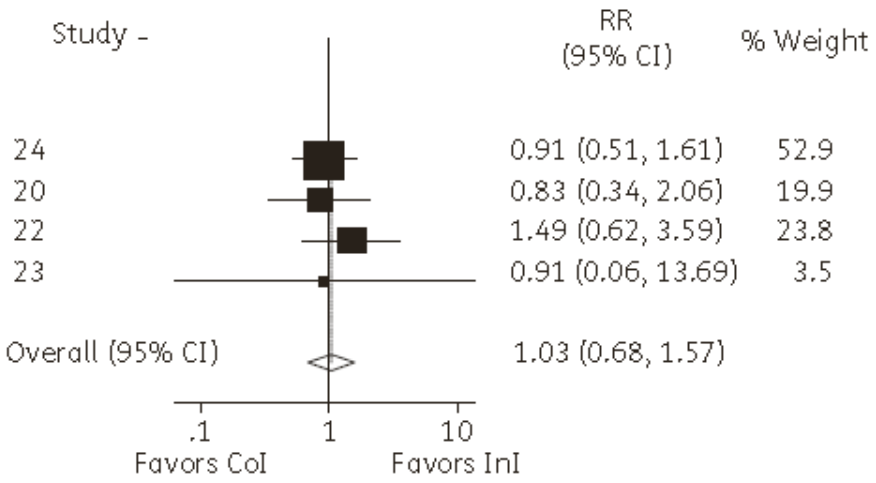


Figure 3. Forest plot summary (fixed effect) of the unadjusted RR of the studies included in the meta-analysis comparing overall mortality rates in patients treated with CoI versus InI of vancomycin.

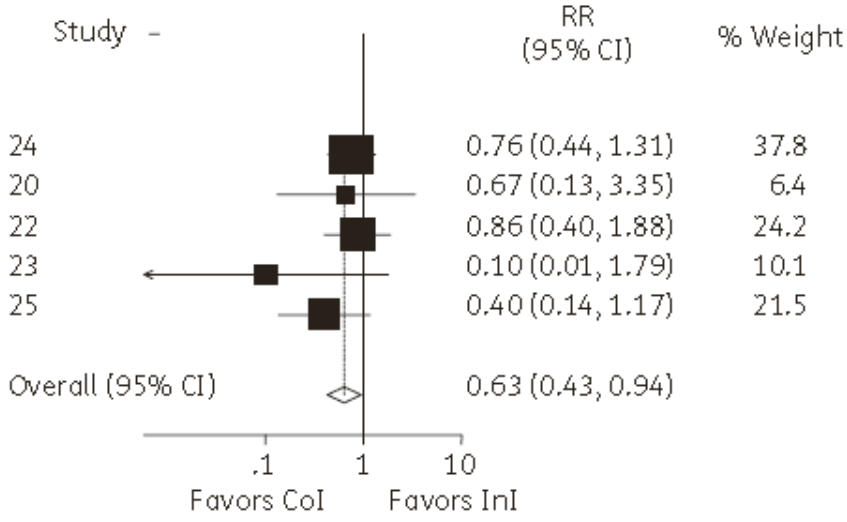


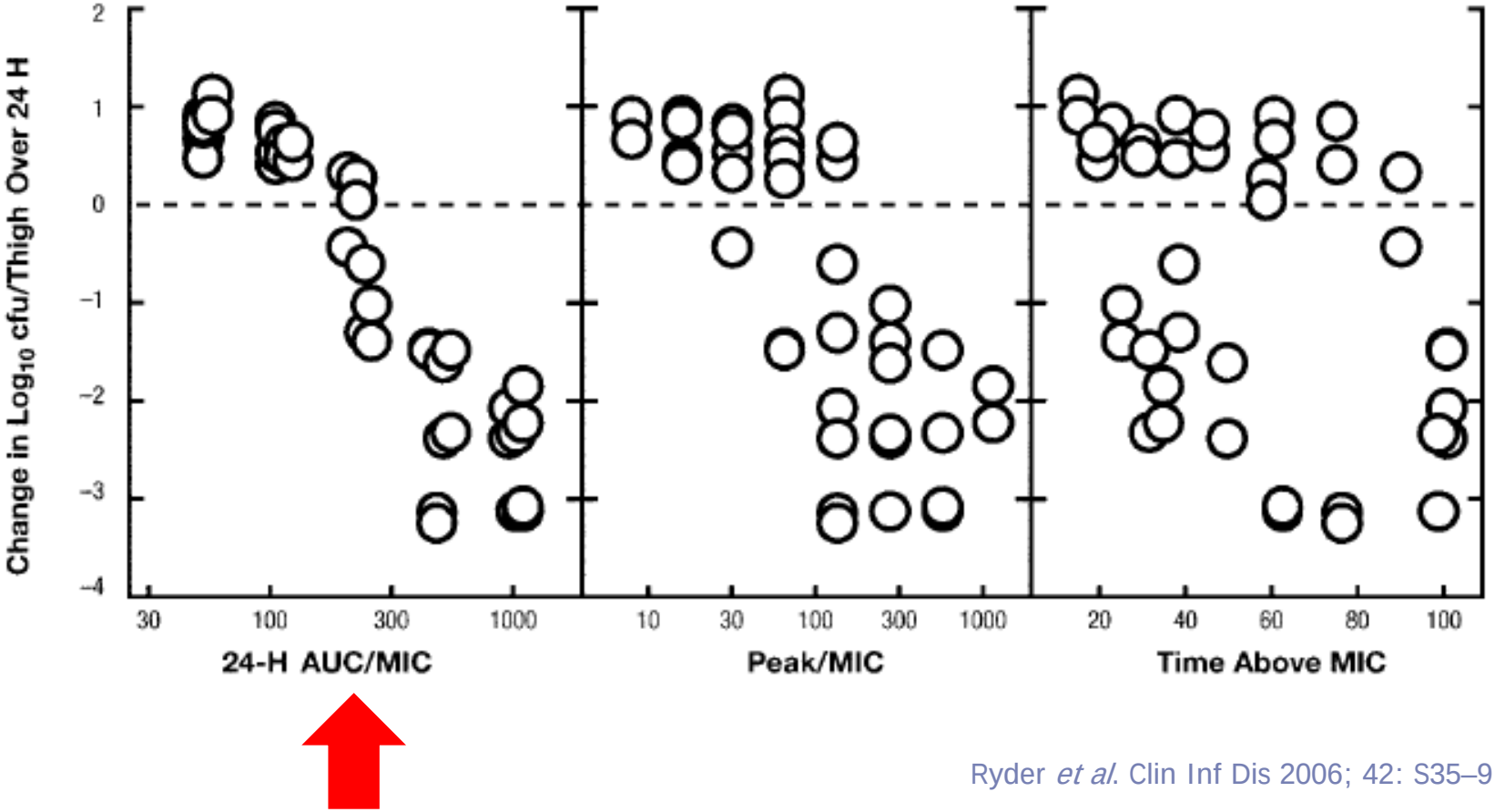
Figure 2. Forest plot summary (fixed effect) of the unadjusted RR of the studies included in the meta-analysis comparing nephrotoxicity rates in patients treated with CoI versus InI of vancomycin.

Equi-efficient

less toxic

The basis of the AUC/MIC model:

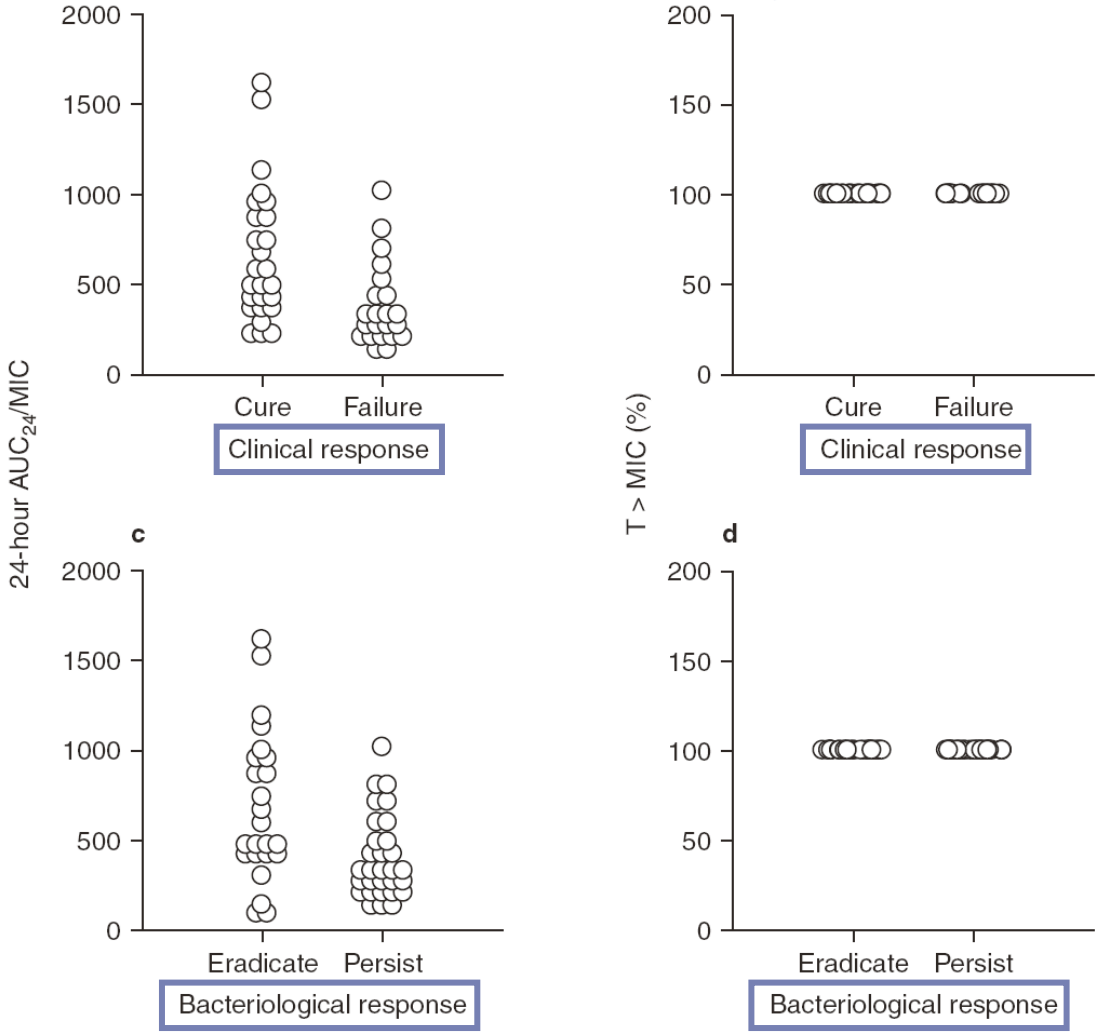
Experimental mouse model
Never published; 1987 ICAAC.



Ryder *et al*. Clin Inf Dis 2006; 42: S35–9

The basis of the AUC/MIC model:

107 patients with pneumonia
AUC mostly based on models



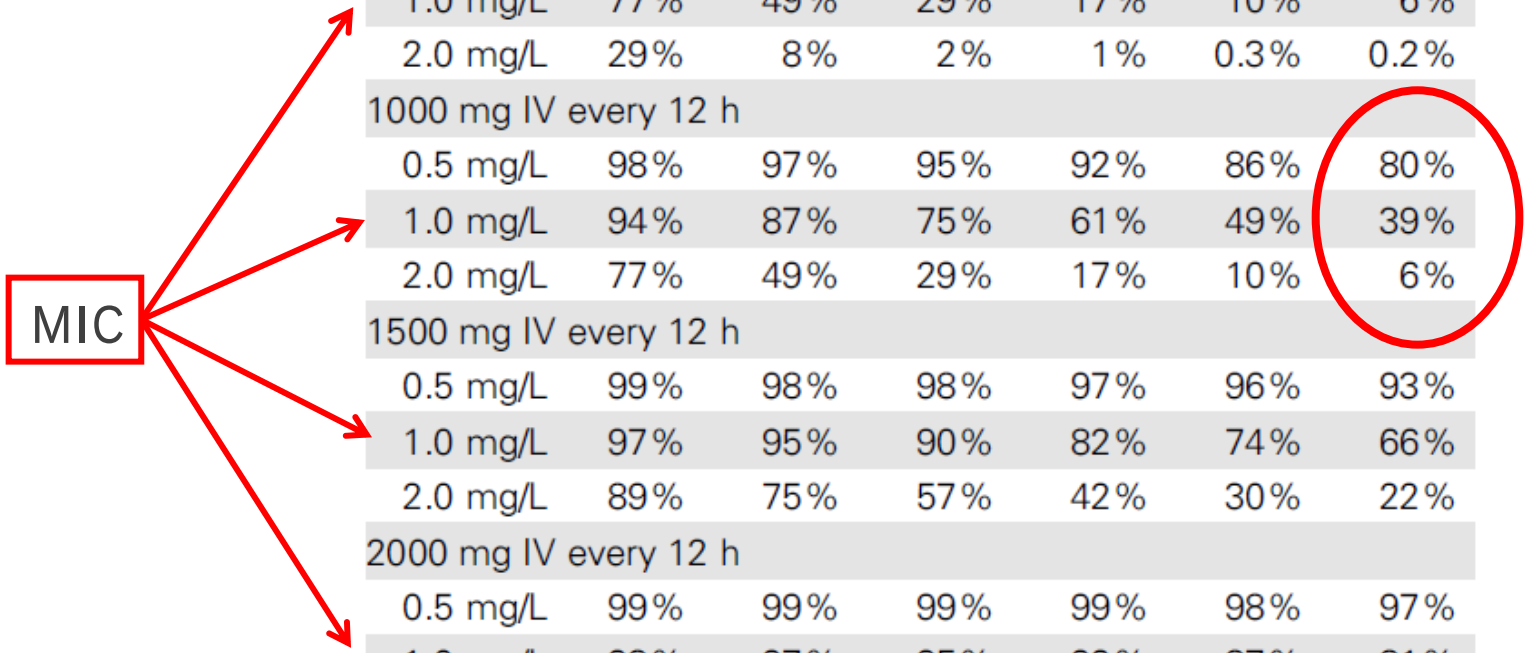
Moise-Broder, Clin Pharmacokinet 2004;43: 925-942

The basis of the AUC/MIC model:

Monte Carlo analysis on 37 patients

Probability of target achiement

CLCR	20	40	60	80	100	120 ml/min
500 mg IV every 12 h						
0.5 mg/L	94%	87%	75%	61%	49%	39%
1.0 mg/L	77%	49%	29%	17%	10%	6%
2.0 mg/L	29%	8%	2%	1%	0.3%	0.2%
1000 mg IV every 12 h						
0.5 mg/L	98%	97%	95%	92%	86%	80%
1.0 mg/L	94%	87%	75%	61%	49%	39%
2.0 mg/L	77%	49%	29%	17%	10%	6%
1500 mg IV every 12 h						
0.5 mg/L	99%	98%	98%	97%	96%	93%
1.0 mg/L	97%	95%	90%	82%	74%	66%
2.0 mg/L	89%	75%	57%	42%	30%	22%
2000 mg IV every 12 h						
0.5 mg/L	99%	99%	99%	99%	98%	97%
1.0 mg/L	98%	97%	95%	92%	87%	81%
2.0 mg/L	94%	87%	75%	61%	49%	39%



Patel *et al*. Clin Infect Dis 2011;52:969–974

- Slow acting antibiotic: $T_{1/2}$ 32 hours
- Dose *versus* effect: AUC > 450; trough 15-20 µg/ml ?
- Dose *versus* nephro/ototoxicity: 12-45 % ?
- Continious *versus* intermittent infusion ?
- Inoculum effect
- Biofilm and intracellular activity ?

Vanco remains the standard for MRSA

Table 2 | Proposed vancomycin dosing in patients with normal renal function and in CKD

Vancomycin intermittent dosing schedule

Loading dose: 25–30 mg/kg in all patients, with maximum infusion rate of 15 mg/min

Maintaining dose

CKD stage	CrCl (ml/min per 1.73 m^2)	Vancomycin dose
0	>90	15–20 mg/kg per 12 h
2	60–89	20–30 mg/kg per 24 h
3A	45–59	15–20 mg/kg per 24 h
3B	30–44	10–15 mg/kg per 24 h
4	15–29	7–10 mg/kg per 24 h
5	<15	10 mg/kg per 48 h

Vancomycin continuous infusion

Loading dose: 15 mg/kg in all patients, with maximum infusion rate of 15 mg/min

Maintaining dose

30 mg/kg/24 hour

Infusion rate (g per 24 h)=(0.029 × CrCl (ml/min)+0.94) × target trough level × 24/1000

Vandecasteele, Kidney Int, 2010, 77, 760-417-24
Rybak, Am J Health Syst Pharm, 2009, 66, 82-98

VDC - Vancomycine Dose Calculator (release 1.2)

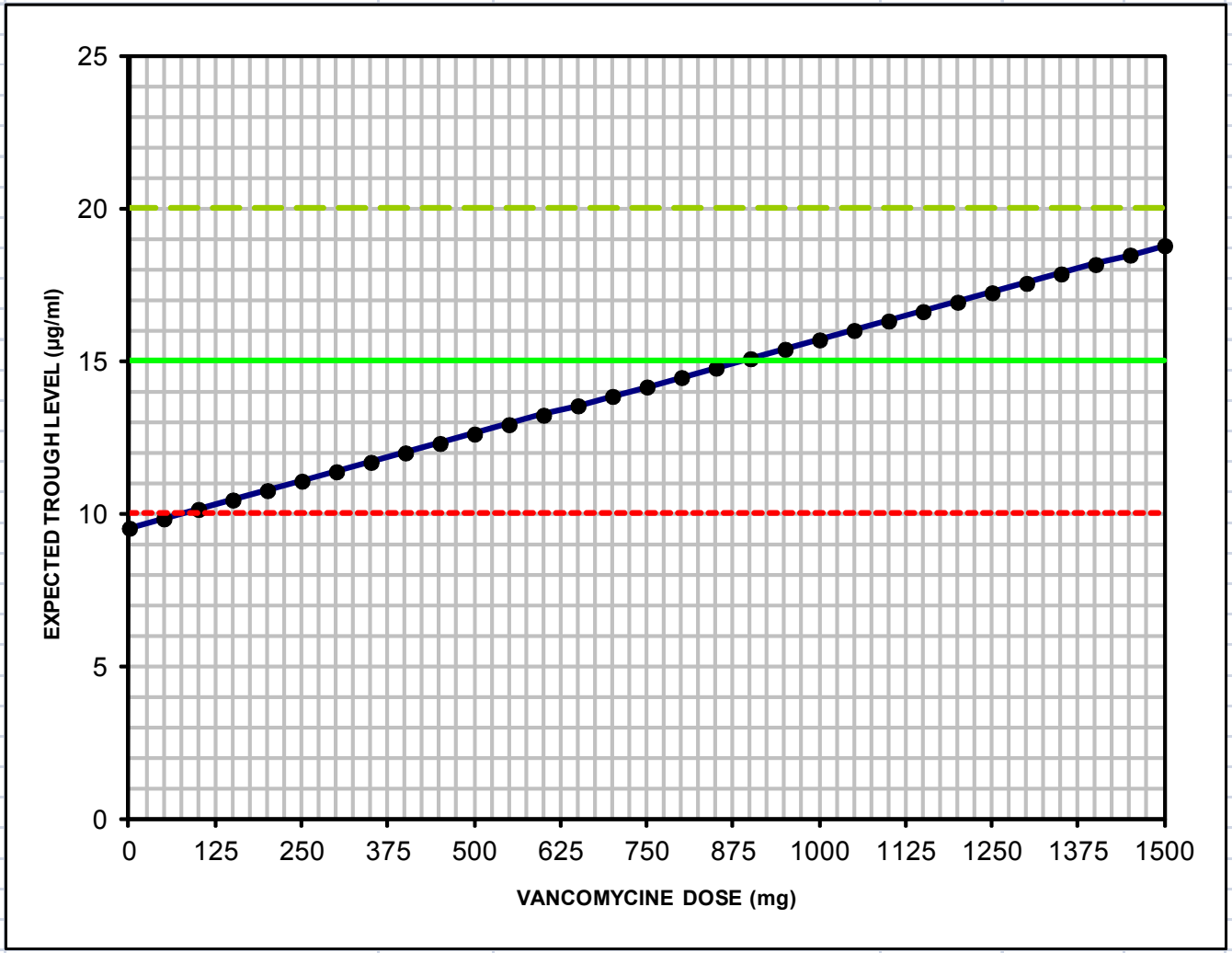
© 2011 Dr. Vandecasteele SJ & Dr. De Vriese AS, Department of Nefrology, AZ St-Jan Brugge-Oostende AV, Brugge, Belgium

Trough level before (µg/ml)	12
Weight (kg)	89
Days to next dialysis	2

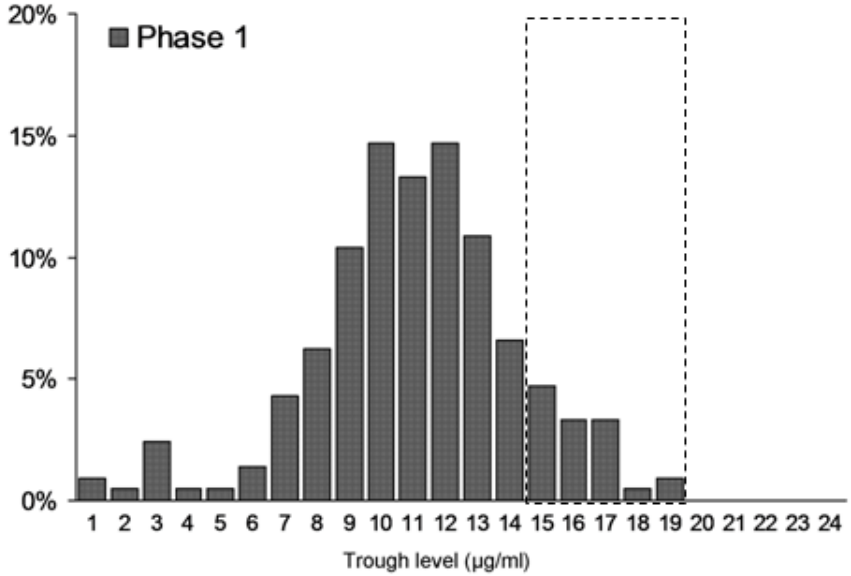
Recommended **Loading** Dose (mg) = **2225**

Recommended Maintenance Dose (mg) = **1300**

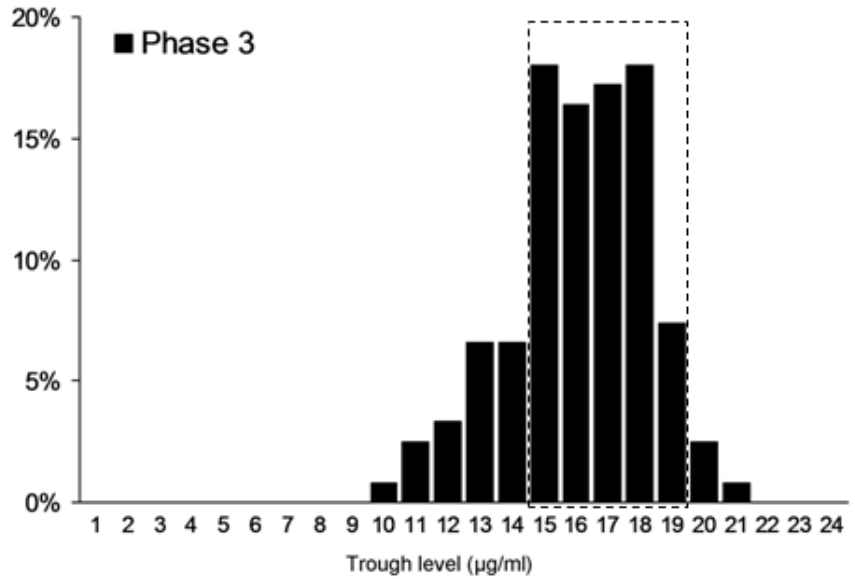
DOSE	Expected TL
0	9,5
50	9,8
100	10,1
150	10,4
200	10,8
250	11,1
300	11,4
350	11,7
400	12,0
450	12,3
500	12,6
550	12,9
600	13,2
650	13,5
700	13,8
750	14,1
800	14,5
850	14,8
900	15,1
950	15,4
1000	15,7
1050	16,0
1100	16,3
1150	16,6
1200	16,9
1250	17,2
1300	17,5
1350	17,9
1400	18,2
1450	18,5
1500	18,8



http://www.azbrugge.be/VancomycinDoseCalculator/



Before intervention



With VDC calculator

Table 1. Percentage of Trough Levels in Defined Ranges Before the Use of the Vancomycin Dose Calculator (Phase 1) and During the Validation of the β-Version (Phase 3)

	Phase 1			Phase 3		
Trough level	No.	(%)	Mean μg/mL ± SD	No.	(%)	Mean μg/mL ± SD
<5 μg/mL	9	4.3	3.02 (1.01)	0	0	–
5–9.9 μg/mL	48	22.7	8.56 (1.12)	0	0	–
10–14.9 μg/mL	127	60.2	12.14 (1.31)	24	19.7	13.20 (1.24)
15–19.9 μg/mL	27	12.8	16.56 (1.27)	95	77.9	17.21 (1.37)
≥20 μg/mL	0	0	–	3	2.4	21.03 (0.32)

NOTE. SD, standard deviation.

Vandecasteele, CID, 2011;53:124-9

We need

1. a universal and simple dose calculator and shedule for all degrees of kidney failure
2. Clear experimental guidance to support this shedule with hard end points (mortality/morbidity)
3. New antibiotics

3. Rifampicin in FBI:

Zimmerli, JAMA, 1998,20;279(19):1537-41

- 98 episodes of FBI; failure OR, **0,40** [0.17–0.97], p=0,01

Senneville, CID, 2011;53(4):334–340

- 345 episodes of FBI: adjusted risk for late failure **0,49** [0,26-0,91]; p=0,024

Lora-Tamayo, CID, 2012, ePublished 31 aug,

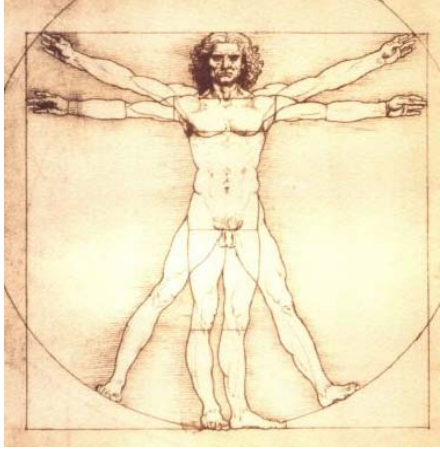
Do not use rifampicin as sole AB

4. Duration of treatment:

Guideline, not evidence-based !!

- SSTIs — 5-14 days
- Pneumonia — 7-21 days
- Uncomplicated bacteremia — ≥ 14 days
  (no IE, T°<72 h; no prosthetic joint; BC < 48 h)
- Complicated bacteremia — 4-6 weeks
- Osteomyelitis — > 8 weeks
- Septic arthritis — 21-28 days
- Prosthetic joint related — 3-6 months

Liu, CID, 2011;52(3):e18–e55



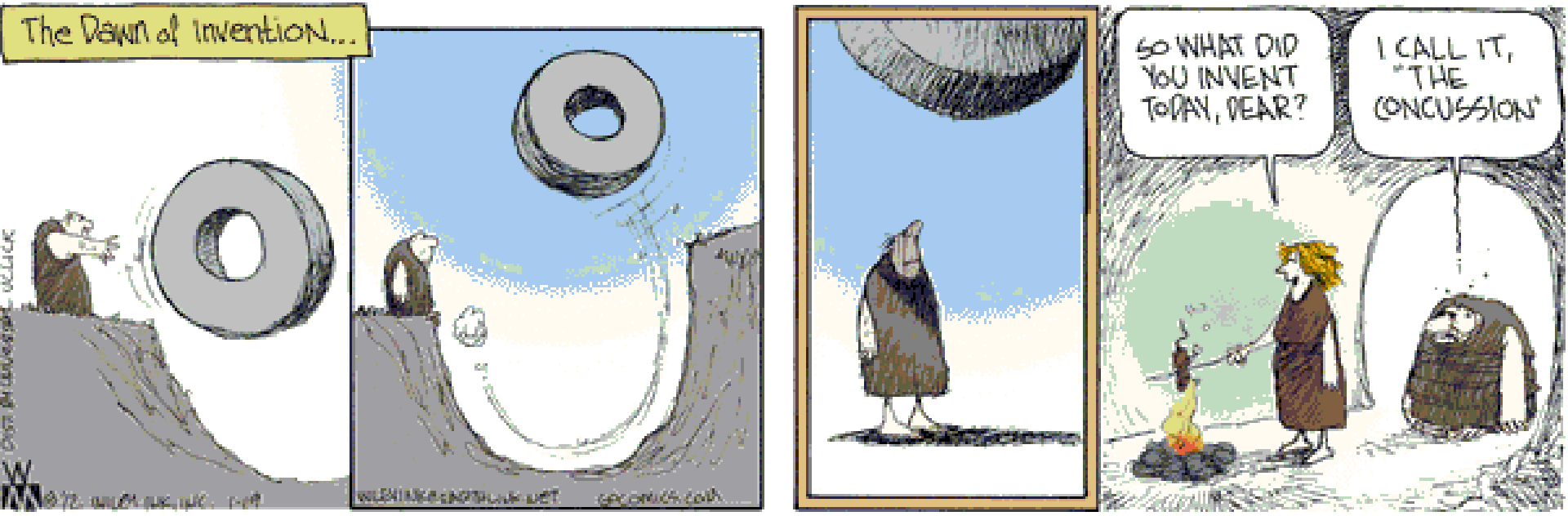
Control of spread

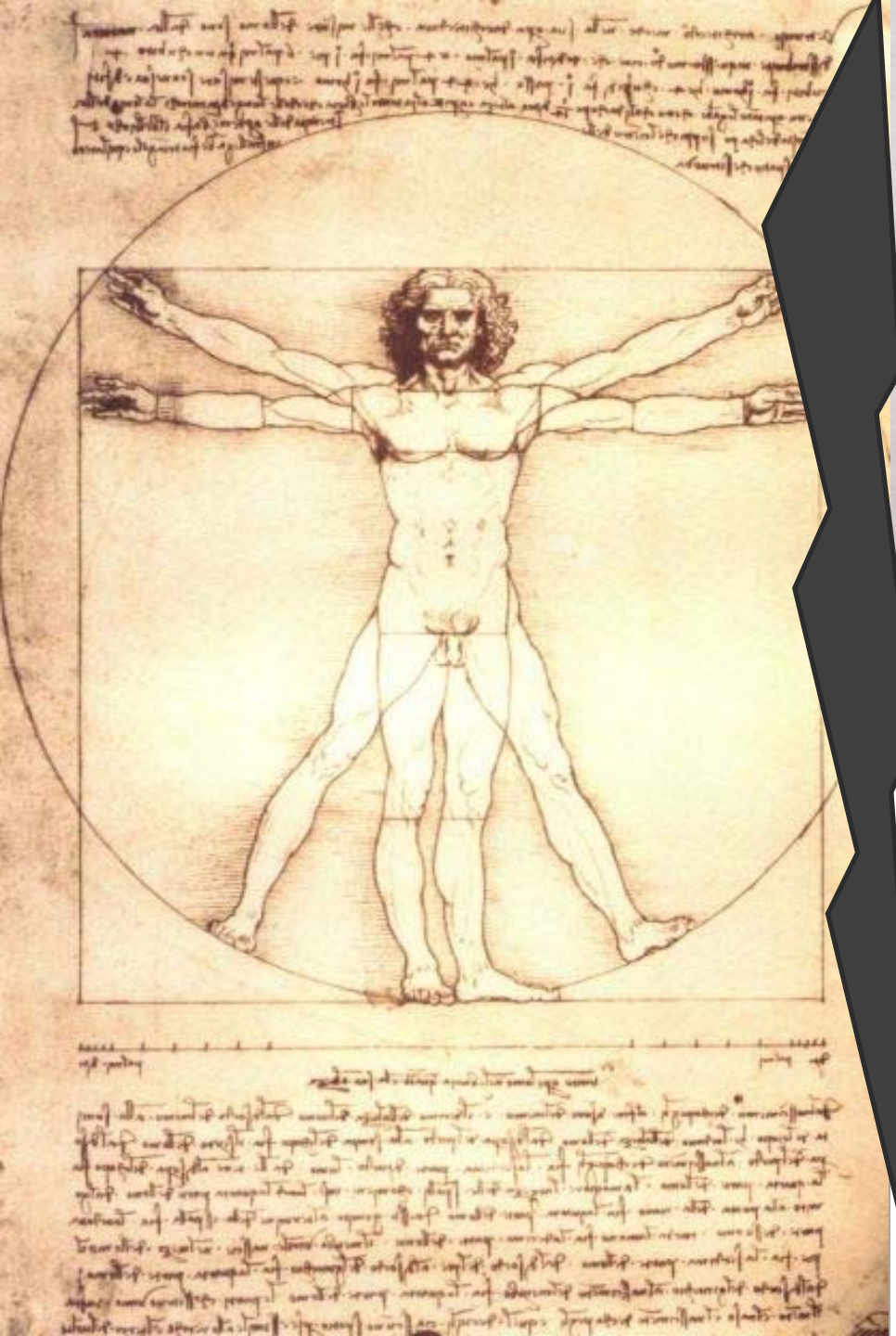
Antibiotics

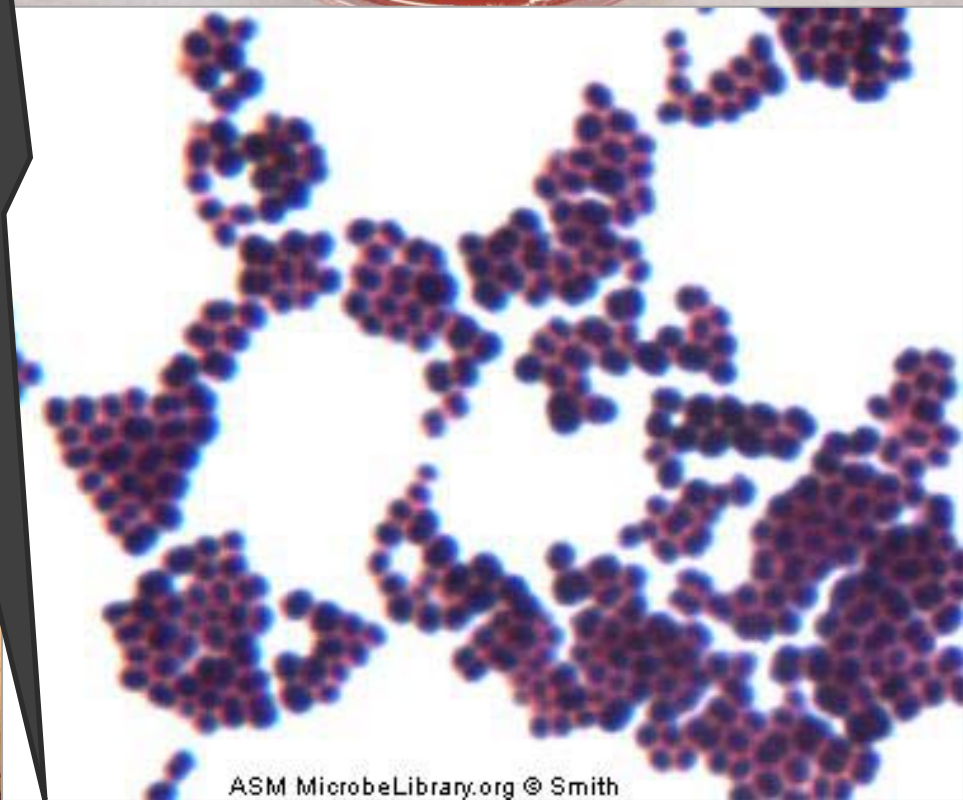
Mankind

Vaccines

Innovative therapy


The Dawn of Invention...
SO WHAT DID YOU INVENT TODAY, DEAR?
I CALL IT, "THE CONCUSSION"

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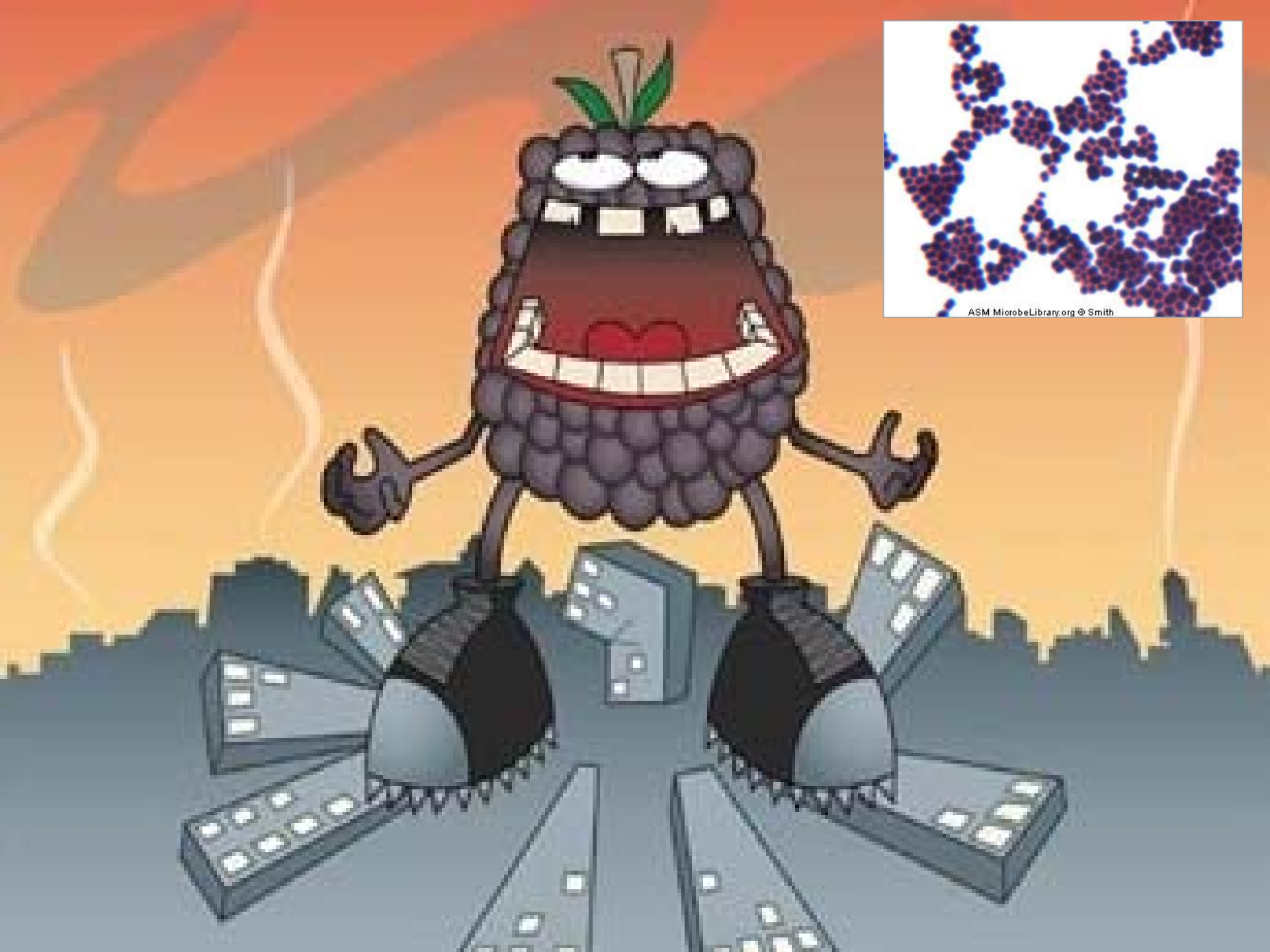
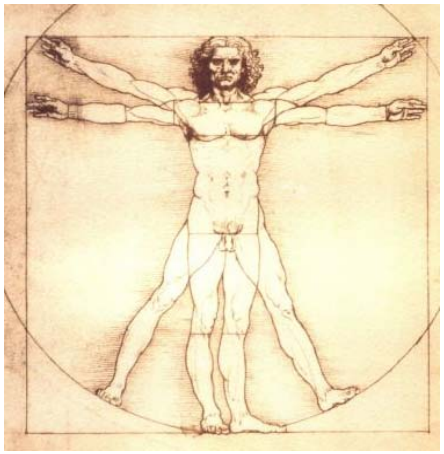
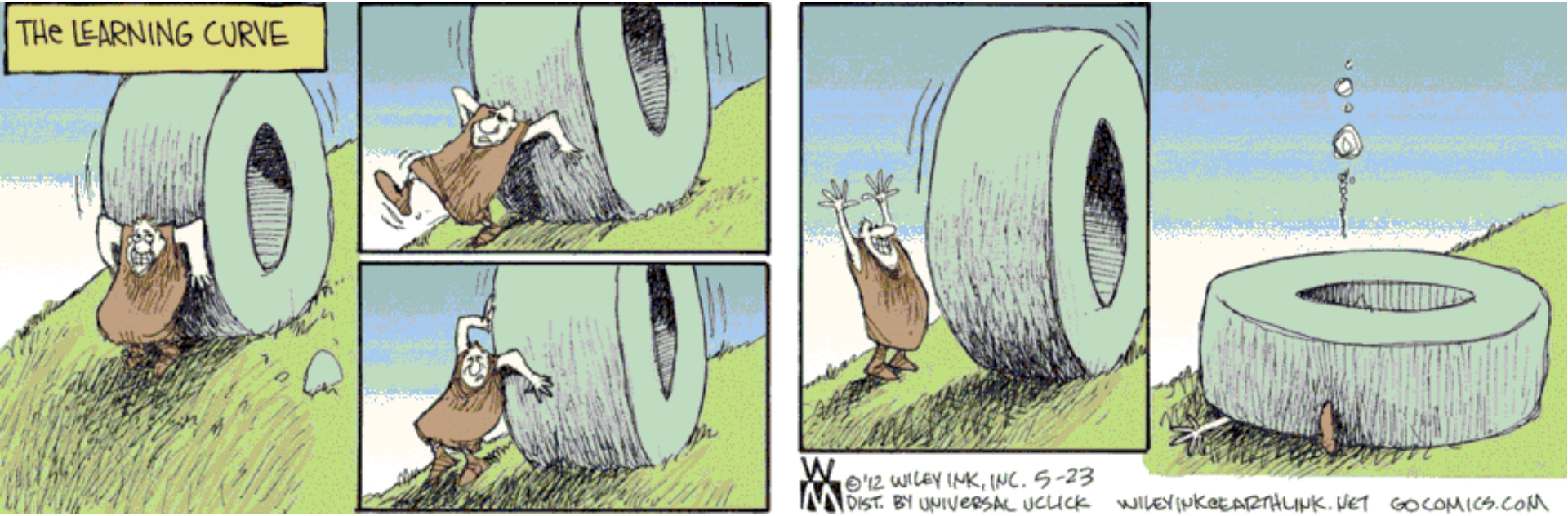

ASM MicrobeLibrary.org © Smith

“Man is a god when he dreams and a beggar when he thinks”






PHILOSOPHICAL SEMI-RETIREMENT
RHETORICAL QUESTIONS ONLY