

MRSA in Humans:
Epidemiology, Resistance, and Treatment

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Disclosures

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Grant or research support	Merck, Theravance, Cerexa, Pfizer, Novartis, MedImmune, Advanced Liquid Logics, National Institutes of Health
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Other relevant financial interests	NONE

Lessons Learned:

Epidemiology: *Dynamic & Dramatic*

Resistance: *Growing Problem*

Treatment: *Success, Setback, & Confusion*

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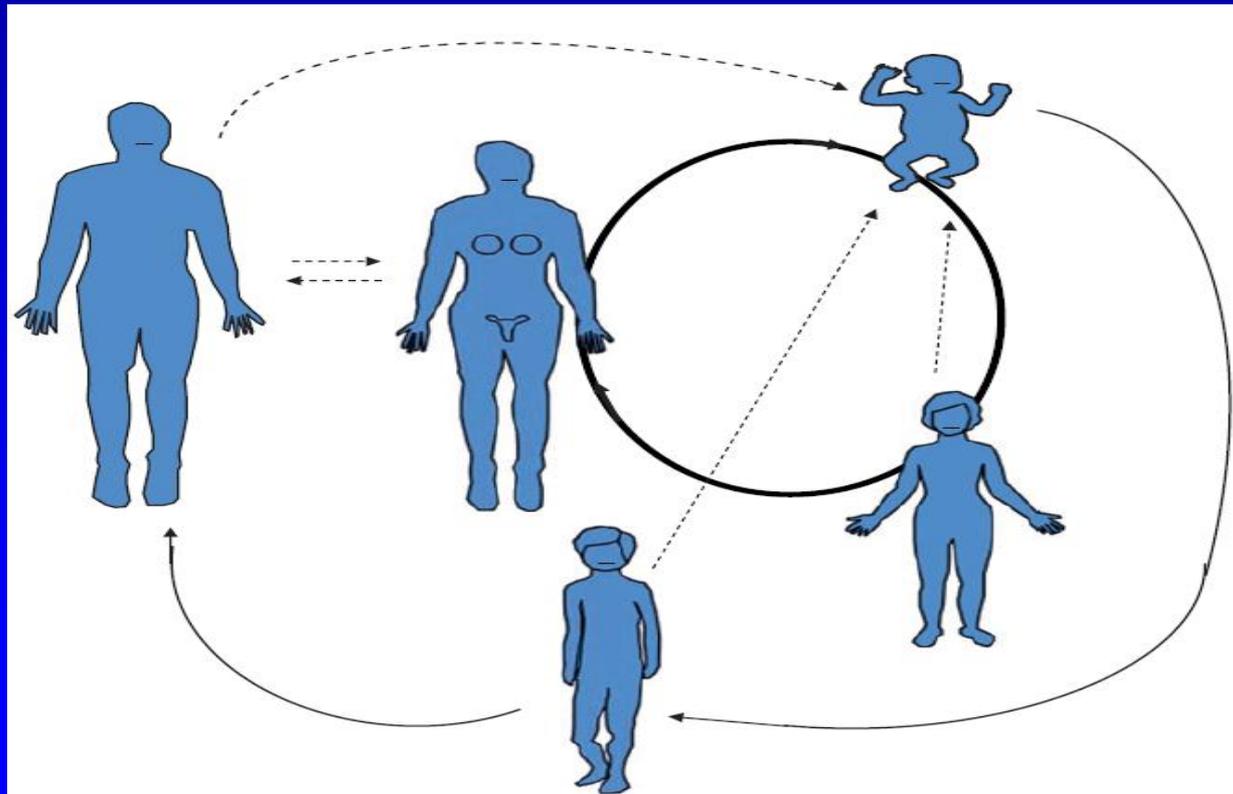
Intrafamilial Transmission of *S. aureus* is a Recent Phenomenon

United States: Crum *Am J Med* 2006;119: 943-51.

Netherlands: Mollema *J Clin Microbiol* 2010; 48: 202-7.

Spain: Perez-Roth *J Clin Microbiol*, 2010;48: 329-32.

Israel: Regev-Yochay *Pediatr Infect Dis J* 2009;28: 960-5.



Staphylococcus aureus Colonization Among Household Contacts of Patients With Skin Infections: Risk Factors, Strain Discordance, and Complex Ecology

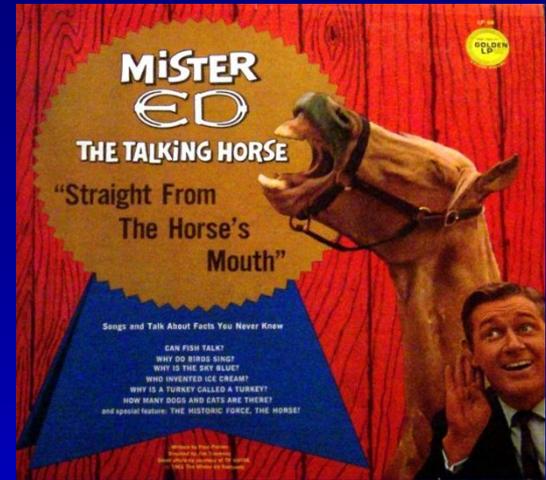
Clinical Infectious Diseases 2012;54(11):1523-35

- Patients with STI & their household contacts in LA, Chicago
- Nares, Oropharynx, Inguinal Region cultured
- Colonization: Index patients: 40% (137/350)
 Household contacts: 53% (405/812)
- Nares only culture would have missed 48% of *S. aureus*
- Most common infecting and colonizing strain USA300
- 65% households had >1 *S. aureus* genotype

CONCLUSIONS

USA300 MRSA associated with household transmission
Decolonization may need to address extra-nasal sites

Human-Animal MRSA Transmission

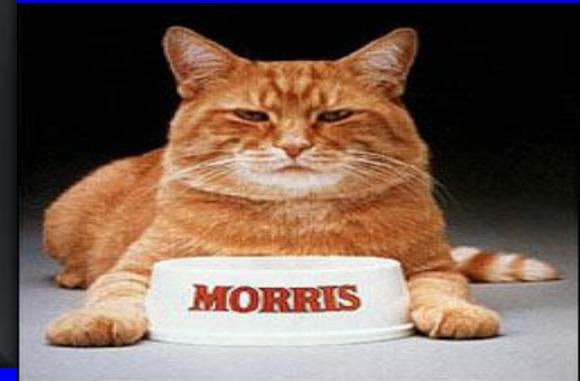
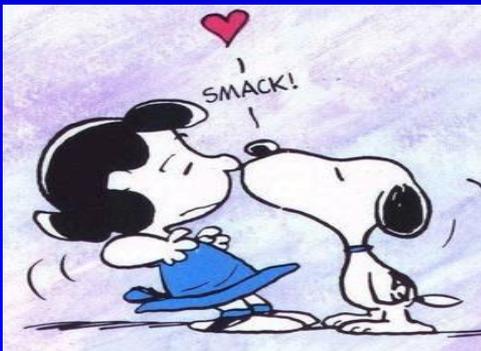


MRSA Transmission between Cows and Humans

Methicillin-resistant *phylococcus aureus* in Horses and Horse Personnel, 2000–2002

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 13, No. 4

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 11, No. 3, March 2005



Transmission of a Panton-Valentine Leucocidin-Positive, Methicillin-Resistant *Staphylococcus aureus* Strain between Humans and a Dog

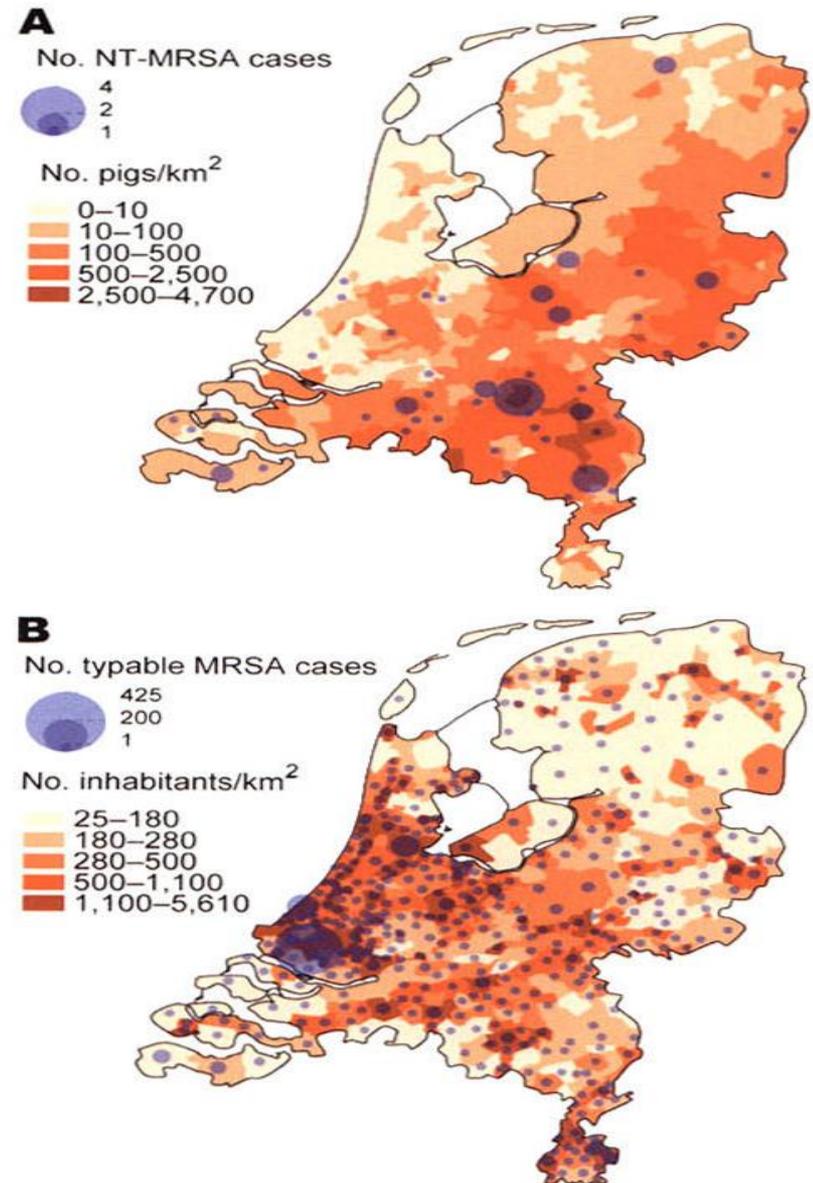
Methicillin-Resistant *Staphylococcus aureus* in a Family and Its Pet Cat

JOURNAL OF CLINICAL MICROBIOLOGY, Dec. 2005, p. 6209–6211

N ENGL J MED 358:11 WWW.NEJM.ORG MARCH 13, 2008

Emergence of Methicillin-Resistant *Staphylococcus aureus* of Animal Origin in Humans

- NT-MRSA - distinct clone (ST398) in Dutch Pigs
- Unknown Prior to 2002
- Now > 20% human MRSA in Netherlands



MRSA ST398 in Midwestern US Swine & Swine Workers

Smith TC et al *PLOS ONE* 2009; 4:e4258.

- Cultured nares of 299 swine and 20 workers from 2 hog farms
- Overall MRSA Prevalence:
 - Swine 49% (147/299)
 - Workers 45% (9/20)
- ST398 was only strain present

CC398 MRSA is Present in Hog Workers from Industrial, but not Antibiotic-Free Facilities in North Carolina

- Similar *S. aureus* carriage in both groups
 - Industrial: 41%
 - Antibiotic-Free: 40%
- CC398 Carriage
 - Industrial Workers: 41% (17/41)
 - Antibiotic Free Workers 7% (3/42)

Livestock-Associated MRSA in US Patients: Where's the Beef?

NEWSFOCUS

INFECTIOUS DISEASE

From Pigs to People: The Emergence of a New Superbug

The discovery of a novel strain of MRSA able to jump from livestock to humans has sparked a multicountry effort to see how dangerous it might be

The first infection was puzzling, almost inexplicable. In July 2004, Andreas Voss of Radboud University Nijmegen Medical Center in the Netherlands admitted a 6-month-old girl for surgery to repair a congenital heart defect.

Because an infection with the common bacterium *Staphylococcus aureus* would pose a grave risk following heart surgery, Voss and his colleagues screened the baby girl for the microbe. They found not just *S. aureus* but also a menacing drug-resistant form known as methicillin-resistant *S. aureus* (MRSA). The physicians were flummoxed. Although MRSA has reached epidemic proportions in much of the developed world, MRSA infections are rare in the Netherlands, thanks to an aggressive "search and destroy" policy the country launched in the mid-1990s to combat

or other livestock harbored MRSA, and no MRSA strain had ever been known to jump from livestock to humans. If the Dutch doctors' fears were correct, a novel strain had just gained that ability, opening up a new route for a potentially dangerous superbug to spread among humans. "Initially, we were very much afraid that this would be a major problem that could spread to the entire population," says Jan Kluytmans, a microbiologist at VU University Medical Center in Amsterdam whom Voss recruited early on to help investigate.

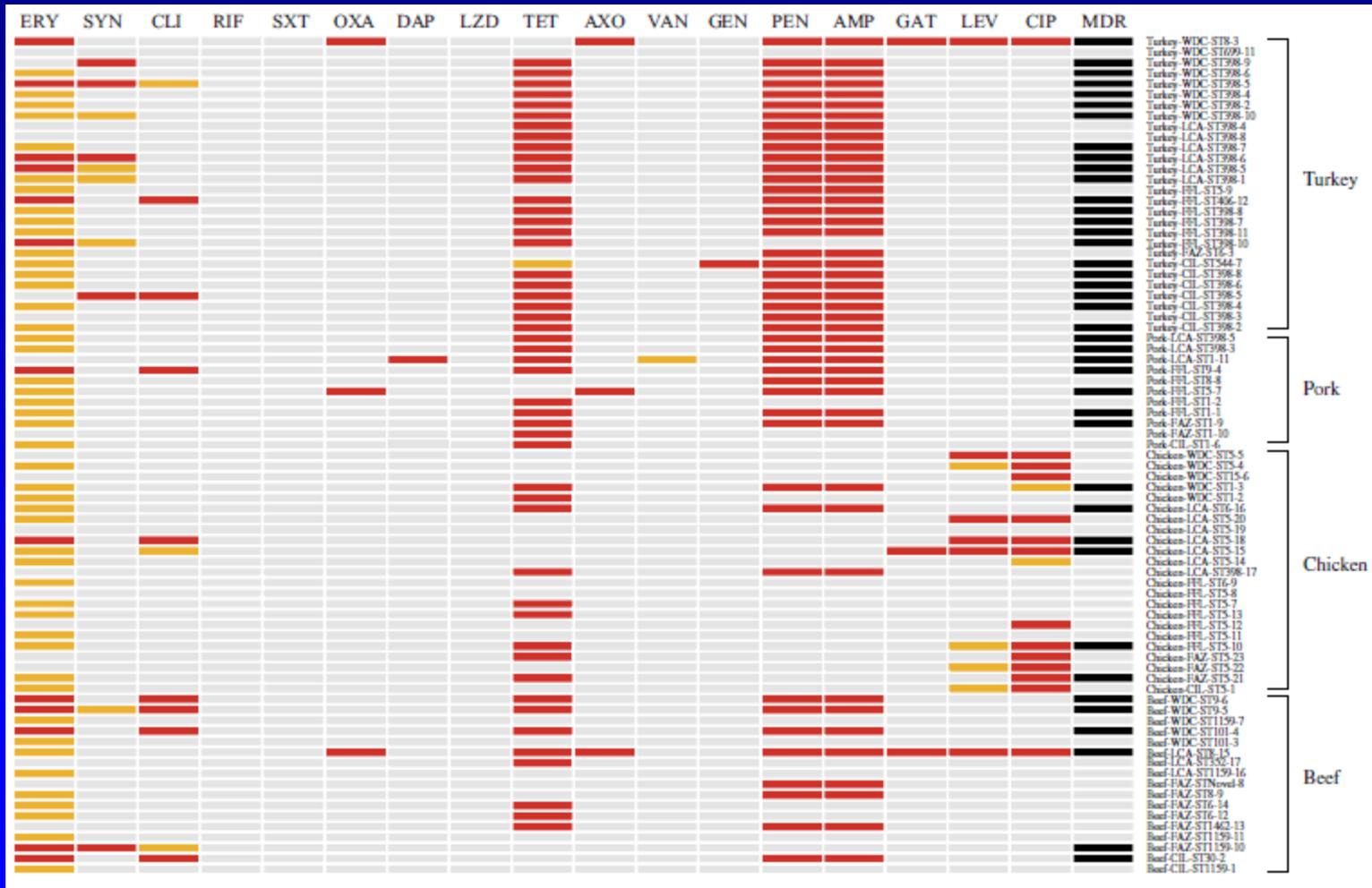
In recent months, the dangers of livestock-associated MRSA



Index case. MRSA from pigs on Eric and Ine van den Heuvel's farm was detected in their daughter, Eveline, when she was an infant.

nag.org on Voss et al.

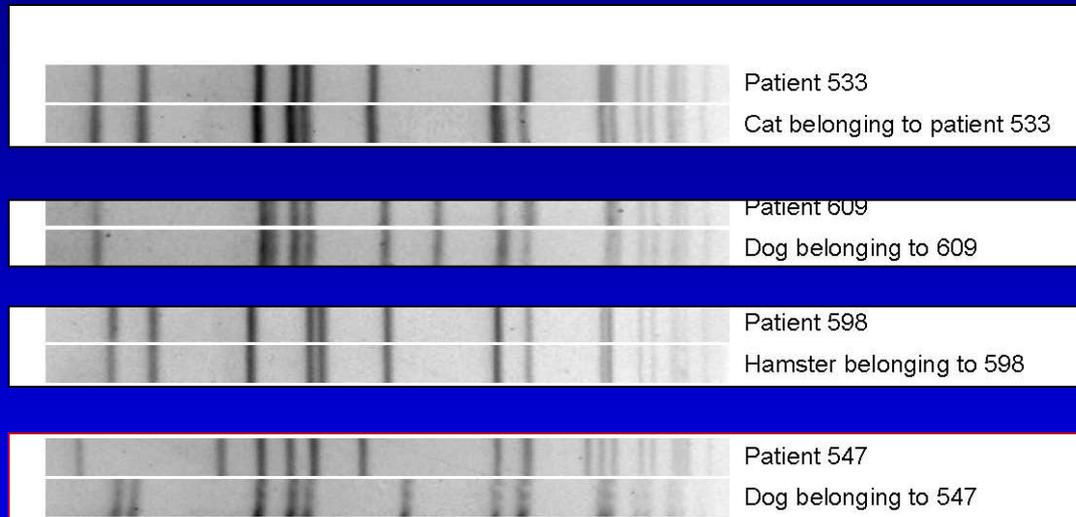
Multi-Drug Resistant *S. aureus*, but Not MRSA, is Common in Meat Products





Transmission of MRSA between Companion Animals and Infected Human Patients Presenting to Outpatient Medical Care Facilities

Jorge Pinto Ferreira^{1,2*}, Kevin L. Anderson¹, Maria T. Correa¹, Roberta Lyman¹, Felicia Ruffin², L. Barth Reller², Vance G. Fowler Jr.²



- 6% of MRSA-infected outpatients lived with an animal colonized with identical MRSA strain
- no MRSA found in the control population (human and animal)

Drug-Resistant Human *Staphylococcus Aureus* in Sanctuary Apes Pose a Threat to Endangered Wild Ape Populations

FRIEDER SCHAUMBURG¹, LAWRENCE MUGISHA^{2,3}, BRUCE PECK⁴, KARSTEN BECKER¹,
THOMAS R. GILLESPIE^{5,6}, GEORG PETERS¹, AND FABIAN H. LEENDERTZ^{7*}

American Journal of Primatology 00:1–5 (2012)

- Nares/oropharyngeal cultures of Chimpanzees and sanctuary workers in Uganda and Zambia
- *Carriage: 58% chimpanzees
33% humans*
- *45% of all Chimp isolates were human-associated lineages*
- *Higher antibiotic resistance than wild chimps*
- *Concern: release of sanctuary-raised chimps risks transmission to wild chimps*

CONCLUSION: Plans to reintroduce sanctuary apes should be reevaluated in light of the high risk of introducing human-adapted S. aureus into wild ape populations where treatment is impossible.

Soft Tissue Infection



Epidemiology of *Staphylococcus aureus* Blood and Skin and Soft Tissue Infections in the US Military Health System, 2005-2010

JAMA. 2012;308(1):50-59

- DOD TRICARE recipients (56 million person-years)
- Unadjusted: Bacteremia: 4.7/ 100 000 person-years
STI: 142.8 per 100 000 person-years
- Bacteremia: All forms Decreased Significantly
 - Community* ↓ *MRSA* to 1.2/100,000 $p=0.005$
↓ *MSSA* to 1.7/100,000; $p=0.005$
 - Hospital* ↓ *MRSA* to 0.4/100,000 $p=0.005$
↓ *MSSA* to 0.3/100,000; $p=0.05$
- SSTI: No significant overall trend in frequency
Prevalence of Community MRSA ↓ to 52% ($p < 0.001$)

CONCLUSIONS: All forms of *S. aureus* bacteremia and proportion of Community SSTI due to MRSA declined

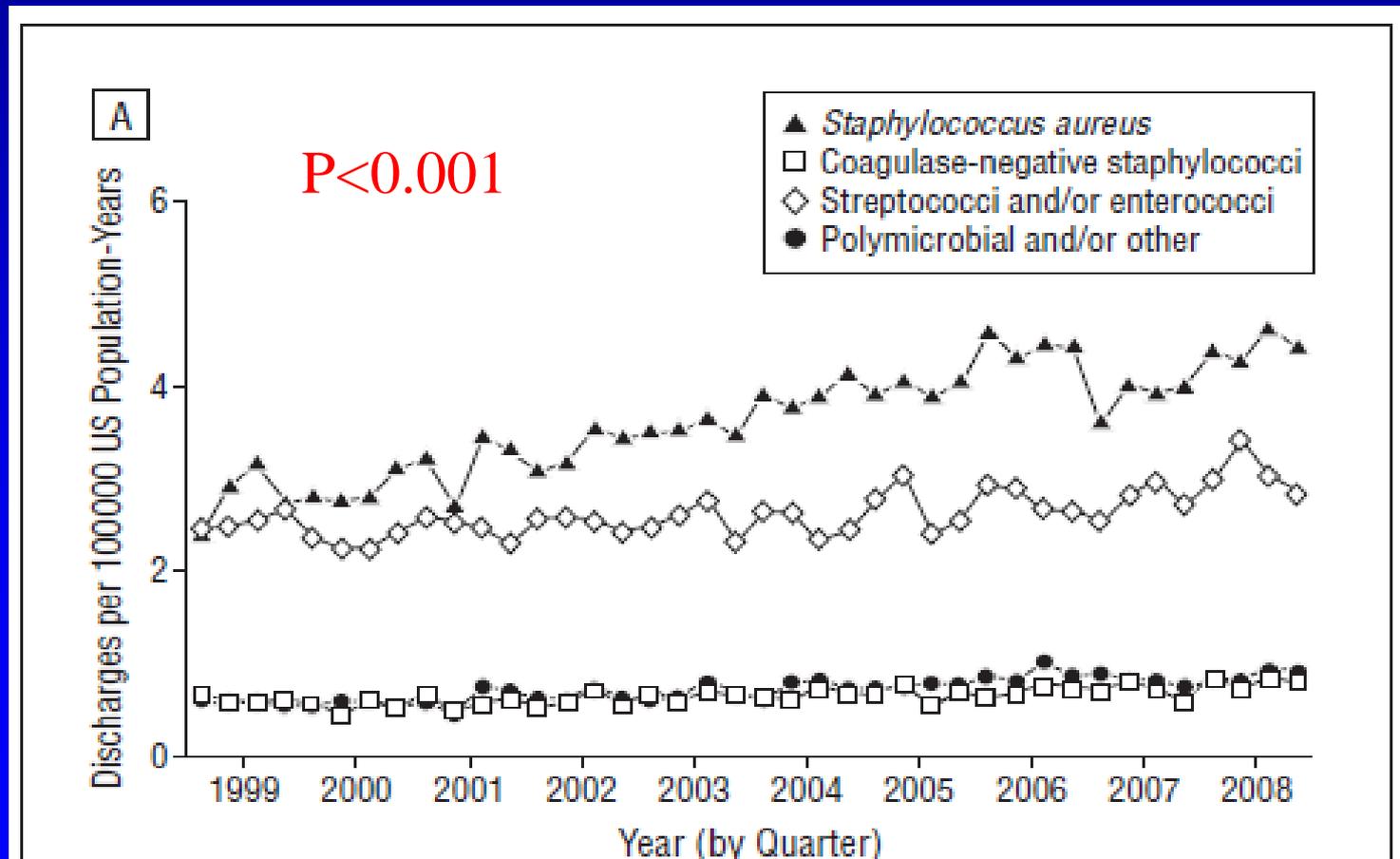
Endocarditis



Increasing US Rates of Endocarditis With *Staphylococcus aureus*: 1999-2008

ARCH INTERN MED/VOL 172 (NO. 4), FEB 27, 2012

Nationwide Inpatient Sample (NIS) Dataset
78.2 Million Patients from 1999-2008



Preeminence of *Staphylococcus aureus* in Infective Endocarditis: A 1-Year Population-Based Survey

Christine Selton-Suty,¹ Marie Célard,² Vincent Le Moing,^{3,4} Thanh Doco-Lecompte,⁵ Catherine Chirouze,⁶ Bernard Jung,^{7,8} Christophe Strady,⁹ Matthieu Revest,¹⁰ François Vandenesch,² Anne Bouvet,¹¹ François Delahaye,^{12,13} François Alla,¹⁴ Xavier Duval,^{8,15,16} Bruno Hoen,^{6,17} and on behalf of the AEPEI Study Group^a

Clinical Infectious Diseases 2012;54(9):1230-9

- Compared to 1999¹

S. aureus ↑

Streptococci ↓

- Primary risk factor: Healthcare contact

¹ Hoen B, *JAMA* 2002; 288:75–81.

Associations of Bacterial Genotype & Endocarditis

Methicillin-Susceptible *Staphylococcus aureus* Endocarditis Isolates Are Associated With Clonal Complex 30 Genotype and a Distinct Repertoire of Enterotoxins and Adhesins

Juhsien J.C. Nienaber,¹ Batu K. Sharma Kuinkel,¹ Michael Clarke-Pearson,¹ Supaporn Lamlerththong,¹ Lawrence Park,^{1,2} Thomas H. Rude,¹ Steve Barriere,³ Christopher W. Woods,^{1,4} Vivian H. Chu,^{1,2} Mercedes Marín,⁵ Suzana Bukovski,⁶ Patricia Garcia,⁷ G.Ralph Corey,^{1,2} Tony Korman,⁸ Thanh Doco-Leconte,⁹ David R. Murdoch,¹⁰ L. Barth Reller,¹ and Vance G. Fowler Jr,^{1,2} for the International Collaboration on Endocarditis-Microbiology Investigators^a

The Journal of Infectious Diseases 2011;204:704–13

An Association Between Bacterial Genotype Combined With a High-Vancomycin Minimum Inhibitory Concentration and Risk of Endocarditis in Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infection

Clare E. Miller,¹ Rahul Batra,^{1,2} Ben S. Cooper,^{3,4} Amita K. Patel,² John Klein,² Jonathan A. Otter,¹ Theodore Kypraios,⁵ Gary L. French,¹ Olga Tosas,² and Jonathan D. Edgeworth^{1,2}

Clinical Infectious Diseases 2012;54(5):591–600

“Team Science” Approach to *S. aureus*: A Case Study

Polymorphisms in fibronectin binding protein A of *Staphylococcus aureus* are associated with infection of cardiovascular devices

Steven K. Lower^{a,1,2}, Supaporn Lamlertthon^{b,c,2,3,4}, Nadia N. Casillas-Ituarte^{a,1,2}, Roberto D. Lins^{d,1}, Ruchirej Yongsunthon^{a,5}, Eric S. Taylor^a, Alex C. DiBartola^a, Catherine Edmonson^e, Lauren M. McIntyre^e, L. Barth Reller^b, Yok-Ai Que^f, Robert Ros^g, Brian H. Lower^a, and Vance G. Fowler, Jr.^{b,2,3}

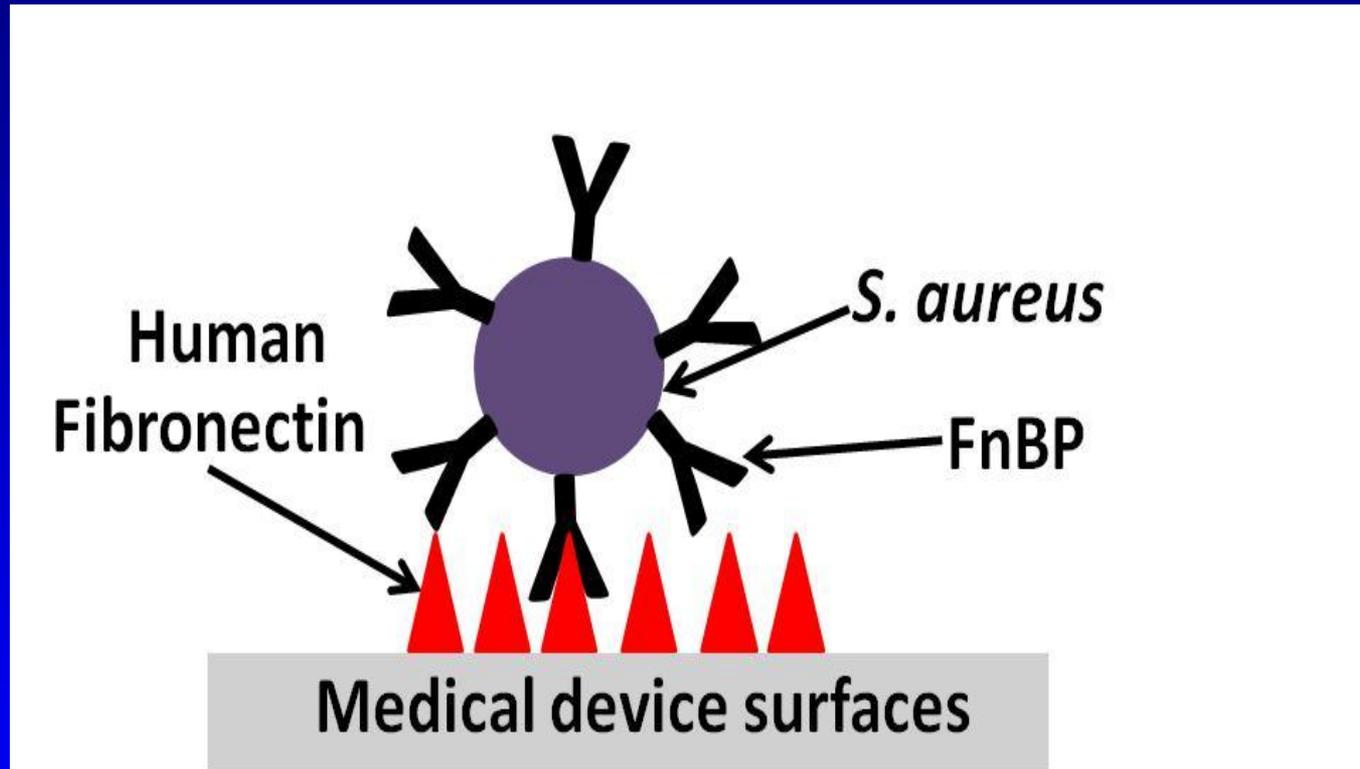
^aOhio State University, Columbus, OH 43210; ^bDuke University Medical Center, Durham, NC 27705; ^cNaresuan University, Phitsanulok, Thailand 65000; ^dUniversidade Federal de Pernambuco, Recife, PE 50670-901, Brazil; ^eUniversity of Florida, Gainesville, FL 32611; ^fUniversity of Lausanne, Lausanne, 1011 Switzerland; and ^gArizona State University, Tempe, AZ 85287

Edited by Richard P. Novick, New York University School of Medicine, New York, NY, and approved October 5, 2011 (received for review June 8, 2011)

18372–18377 | PNAS | November 8, 2011 | vol. 108 | no. 45

“Bedside to bond”

Fibronectin-FnBP binding



- **FnBP is a bacterial surface protein**
- **FnBP binds to human fibronectin**

CLINICAL RESEARCH AND BACTERIOLOGY

Clinical Groups:

- **Cardiac Device Infection (CDI):**

Pacemaker + SAB + Device Infection

- **Cardiac Device Uninfected (CDU):**

Pacemaker + SAB + Device Uninfected

FnBPA-binding region



FnBPA-1	~~GPIIQNNKFEYKEDTIKETLTGQYDKNLVTTVEEEYDSS
FnBPA-2	~~~~~TLDIDYHTAIDGGGGYVD~~GYIETIEETDSS
FnBPA-3	~~~~~AIDIDYHTAVDSEAGHVG~~GYTESSEESNP
FnBPA-4	~~~~~IDF~EESTHENS KHHA~~~DVVEYEEDTNP
FnBPA-5	GGQVTTE SNLVEFDE E STKGIVTGAV~~~SDHTTVEDTK
	D
FnBPA-6	~~EYTTE SNLIELVDELPEEHGQ~~~~~AQQPVEEITK
FnBPA-7	NNHHISHS~~~~~GLGTENGH~~~GNYDVIEEIEENS
FnBPA-8	~~~~~HVDTKSFL~GYEGGQNS~~~GNQSFEEDTEEDKP
FnBPA-9	KYEQQGN~~IVDIDFDSVPQI H GQN K ~~~GNQSFEEDTEEDKP
	Q N
FnBPA-10	KYEHGGN~~IIDIDFDSVPH H IHGFNK~~~H T E I I E E D T N K D K P
	Q N
FnBPA-11	S YQFGGH~NSVDFEEDTLPKVSGQNE~~~GQQTIEEDTTP
	N

3 SNPs are More Common in CDI

non-synonymous SNP	binding region	amino acid change*	occurrence of non-synonymous SNP		P-value	relative risk (RR)
			CDI	CDU		
GAG to GAT	FnBPA-5	E652D	12 (46)	1 (5)	0.003	9.2
CAT to CAA	FnBPA-9	H782Q	14 (54)	1 (5)	0.0004	10.8
AAA to AAT	FnBPA-9	K786N	14 (54)	3 (15)	0.01	3.4

* E = Glutamic acid, D = Aspartic acid, H = Histidine, K = Lysine, N = Asparagine, Q = Glutamine, S = Serine and T = Threonine

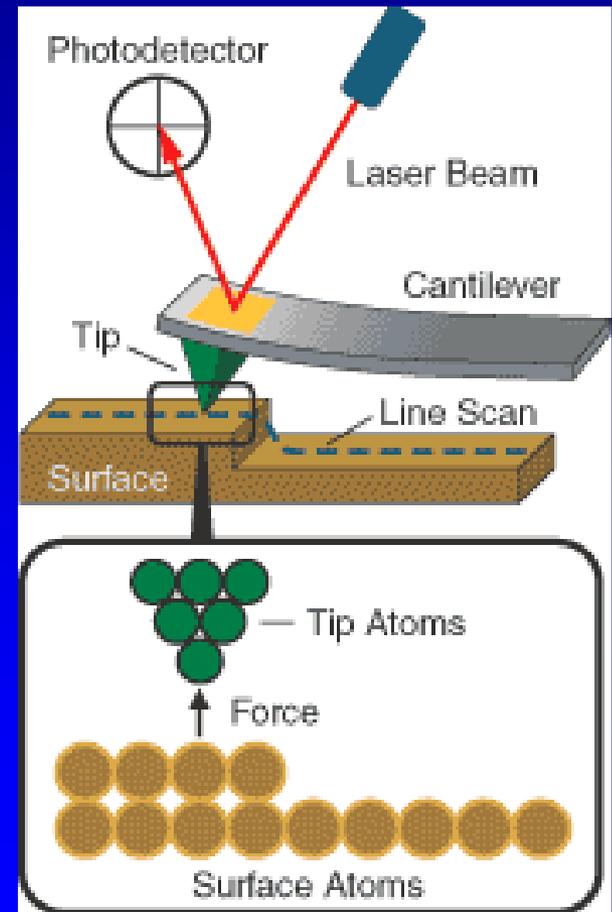
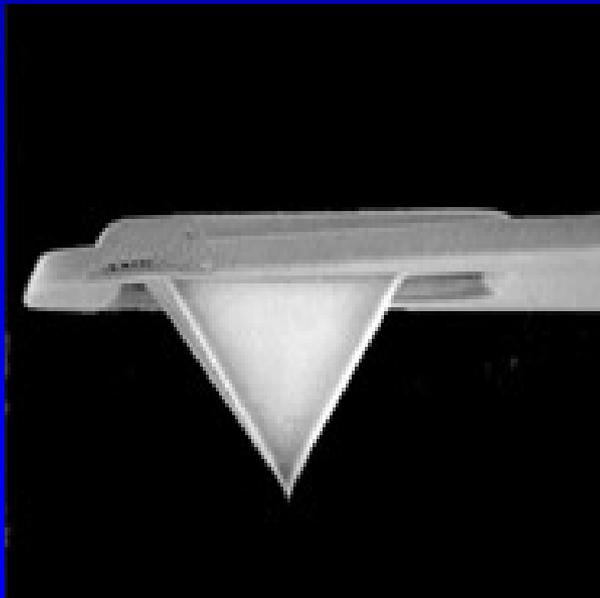
Having > 1 of these SNPs increased the risk of CDI 11.5 times

ATOMIC FORCE MICROSCOPY

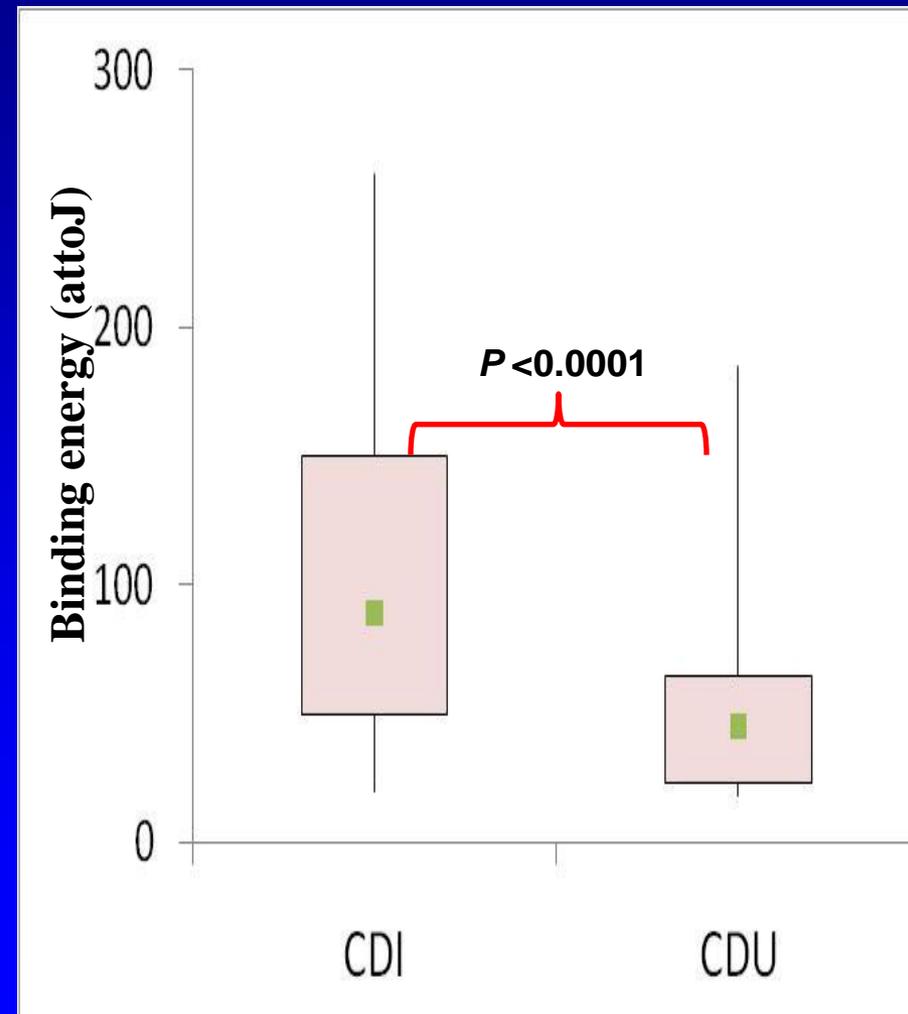
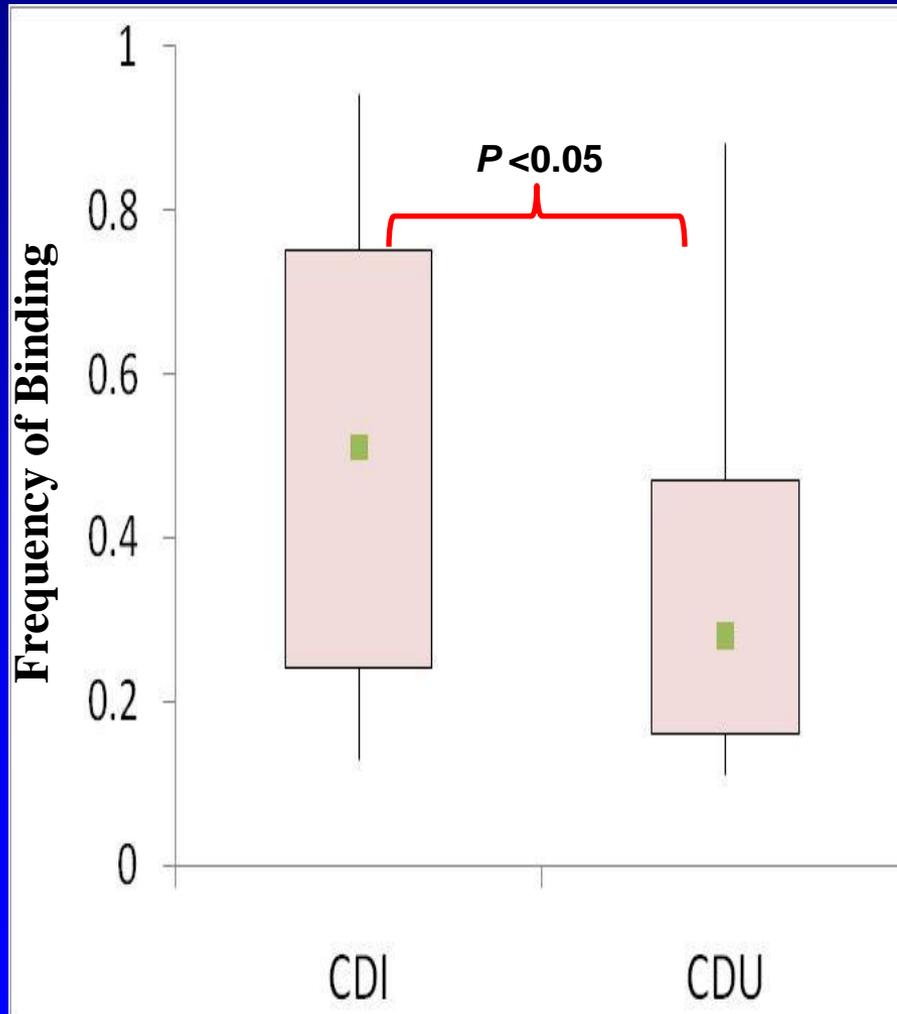


Atomic Force Microscope (AFM)

- measuring binding forces between fibronectin and a single cell of *S. aureus*



CDI Isolates Associated With Increased Strength & Binding Frequency



SNP Number and Binding Energy Are Directly Associated

Occurrence of SNPs in FnBPA	Binding energy		
	Low (<74 aJ)	High (>74 aJ)	<i>P</i> value
CDI and CDU			
≤1 SNP at 652, 782, 786	20	10	<0.01
>1 SNP at 652, 782, 786	3	13	

MOLECULAR DYNAMIC SIMULATIONS OF FN-FNBPA BOND

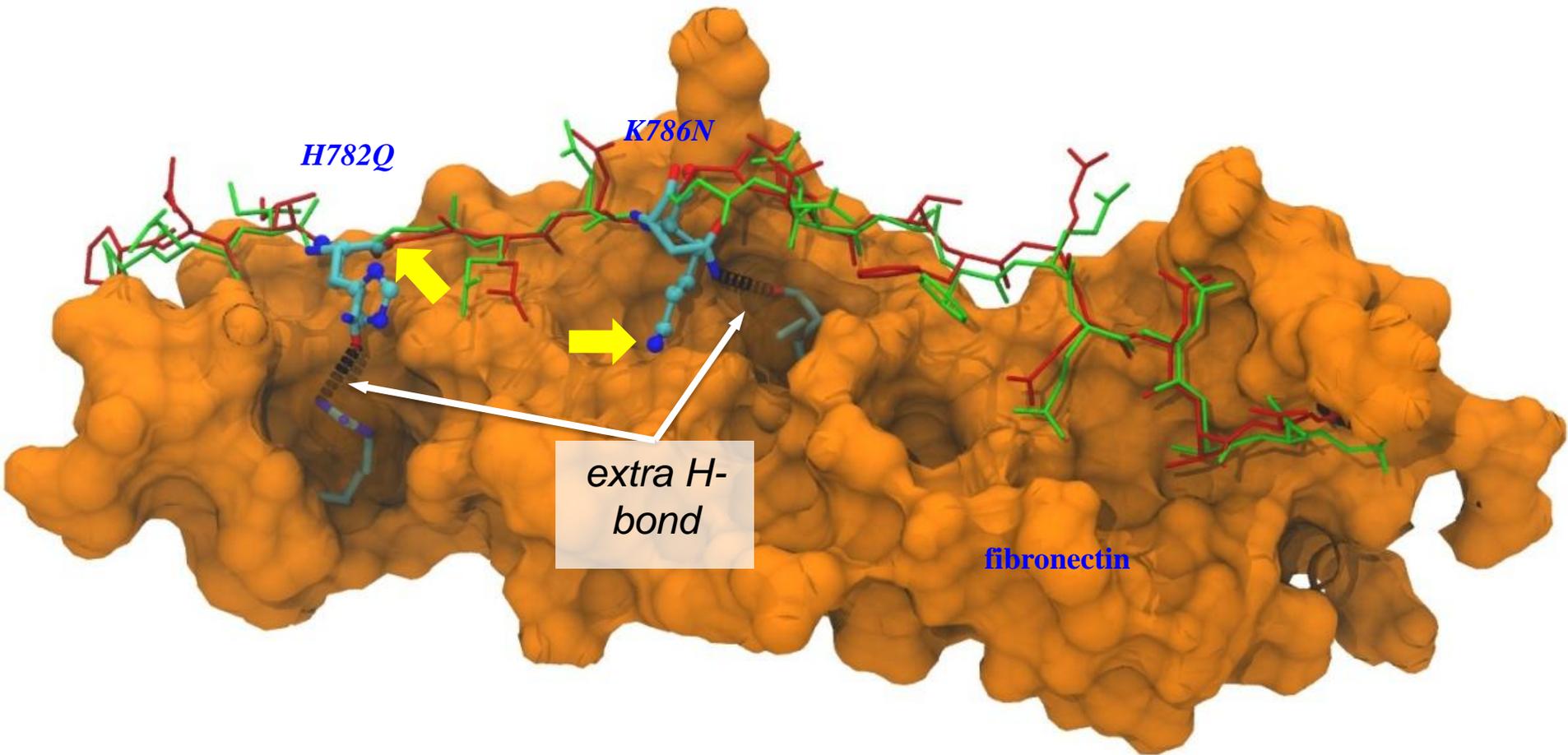


MD Simulation



- Chinook Supercomputer (Dept. of Energy, Richland, Washington)
 - 160 trillion calculations/second
 - \$21 million to build in 2009
- Calculations: 4 d (24h/d) (=2.8 core years on desktop)
- > 72, 000 atoms in each Fn-FnBPA simulation
- 10^9 atomic interactions calculated 10 million times for each simulation

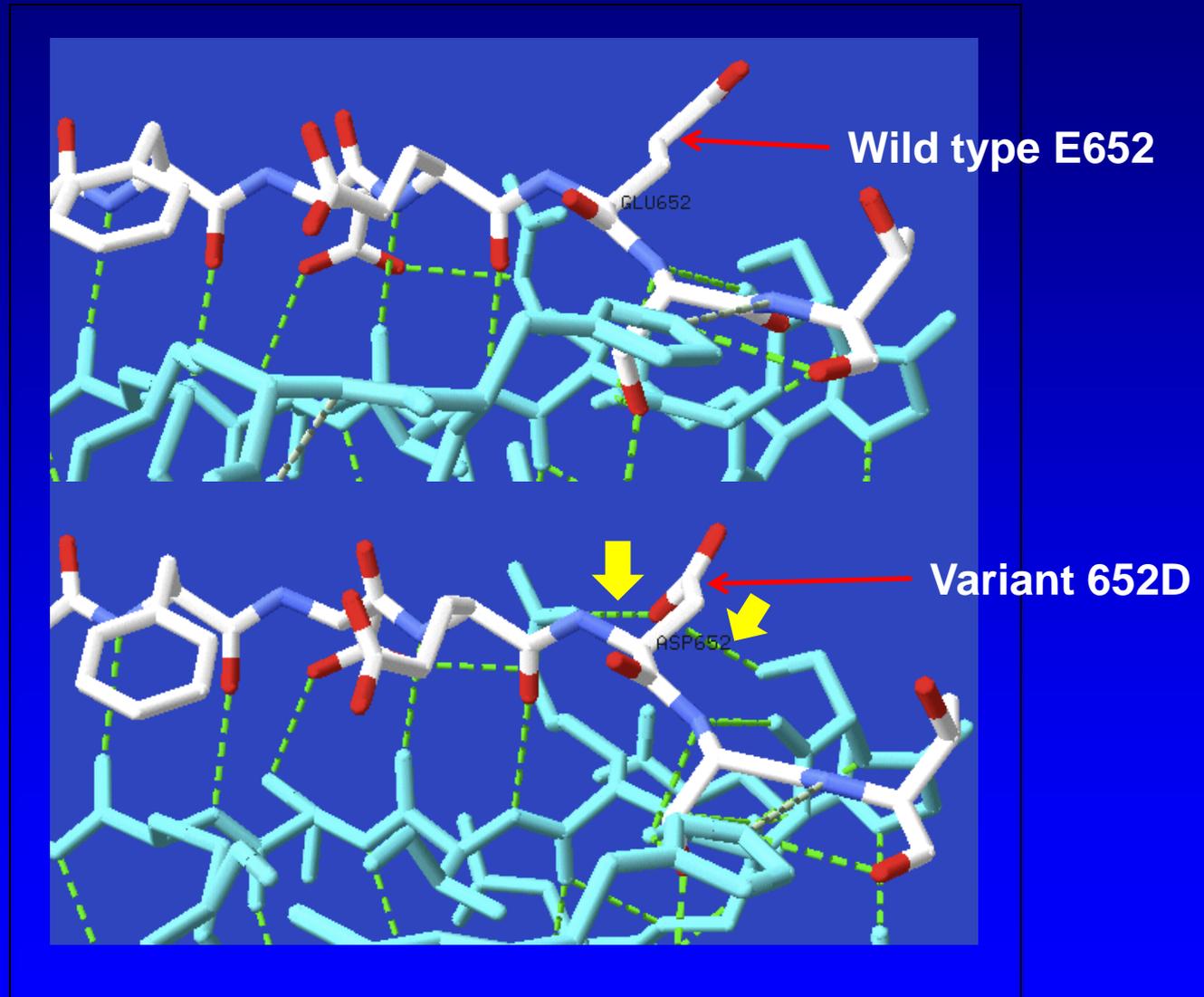
FnBPA-9: H782Q & K786N



782Q and 786N form extra hydrogen bonds with fibronectin

FnBPA-5: E652D

X-ray crystal structure model



Fibronectin Binding Protein A & Cardiac Device Infection

- Three SNPS (E652D, H782Q and K786N) were significantly more common in CDI
- Fibronectin adherence:
 - higher in CDI
 - in isolates multiple SNPs
- Potential Mechanism: Increased hydrogen bonds between human fibronectin and *S. aureus* fibronectin binding protein A

Community Acquired Pneumonia



Prevalence of Methicillin-Resistant *Staphylococcus aureus* as an Etiology of Community-Acquired Pneumonia

Clinical Infectious Diseases 2012;54(8):1126-33

- 627 Prospectively enrolled patients from 12 University ED in Winter-Spring 2006-7
- 2.4% Culture confirmed MRSA
- MRSA USA300 in all genotyped isolates
- Risk factors for MRSA CAP:
 - *Presentation*: Shock, Pressors, Comatose, Intubation
 - *History*: Prior MRSA, Contact with STI Patient, Nursing Home
 - *Radiograph*: Cavitation, Multiple Infiltrates
- **CONCLUSIONS:**
 - MRSA CAP: uncommon, severe, often USA300

Impact of USA300 Methicillin-Resistant *Staphylococcus aureus* on Clinical Outcomes of Patients With Pneumonia or Central Line-Associated Bloodstream Infections

Fernanda C. Lessa,¹ Yi Mu,¹ Susan M. Ray,² Ghinwa Dumyati,³ Sandra Bulens,^{1,4} Rachel J. Gorwitz,¹ Gregory Fosheim,¹ Aaron S. DeVries,⁵ William Schaffner,⁶ Joelle Nadle,⁷ Kenneth Gershman,⁸ Scott K. Fridkin,¹ for the Active Bacterial Core surveillance (ABCs) MRSA Investigators of the Emerging Infections Program

Clinical Infectious Diseases 2012;55(2):232-41

- 100 Community Onset Pneumonia & 236 CLA-BSI MRSA Isolates from unique patients from 6 Metropolitan centers
- USA100 vs. USA300
- USA300 was Associated with Early Complications in Pneumonia (admission - 48h)
- USA300 not associated with mortality in either Pneumonia or BSI

Negative Studies for PVL

Panton-Valentine Leukocidin Is Not the Primary Determinant of Outcome for *Staphylococcus aureus* Skin Infections: Evaluation from the CANVAS Studies

Amy Tong¹, Steven Y. C. Tong^{1,4}, Yurong Zhang¹, Supaporn Lamlerththon^{1,3}, Batu K. Sharma-Kuinkel¹, Thomas Rude¹, Sun Hee Ahn¹, Felicia Ruffin¹, Lily Llorens⁵, Ganesh Tamarana⁵, Donald Biek⁵, Ian Critchley⁵, Vance G. Fowler Jr.^{1,2*}

Kevin R. Braughton,^c Frank R. DeLeo,^c Steven L. Barriere,^c PLoS ONE May 2012 | Volume 7 | Issue 5 | e37212
Journal of Clinical Microbiology March 2012 | Volume 50 | Number 3

Presence of Genes Encoding the Panton-Valentine Leukocidin Exotoxin Is Not the Primary Determinant of Outcome in Patients with Complicated Skin and Skin Structure Infections Due to Methicillin-Resistant *Staphylococcus aureus*: Results of a Multinational Trial[∇]

In-Gyu Bae,^{1,2,3} Giang T. Tonthat,² Martin E. Stryjewski,^{1,4} Thomas H. Rude,² Lindsay F. Reilly,² Steven L. Barriere,⁵ Fredric C. Genter,⁵ G. Ralph Corey,^{1,2} and Vance G. Fowler, Jr.^{1,2*}

Clinical Infectious Diseases 2011;53(8):766-771
JOURNAL OF CLINICAL MICROBIOLOGY, Dec. 2009, p. 3952-3957

Genotypic Characteristics of *Staphylococcus aureus* Isolates from a Multinational Trial of Complicated Skin and Skin Structure Infections^{∇†}

Steven J. Campbell,¹ Hitesh S. Deshmukh,¹ Charlotte L. Nelson,² In-Gyu Bae,^{1,4} Martin E. Stryjewski,² Jerome J. Federspiel,¹ Giang T. Tonthat,¹ Thomas H. Rude,¹ Steven L. Barriere,³ Ralph Corey,^{1,2} and Vance G. Fowler, Jr.^{1,2*}

Medicine: 2011 - Volume 90 - Issue 3 - pp 317-318
JOURNAL OF CLINICAL MICROBIOLOGY, Feb. 2008, p. 678-684

Lessons Learned:

The Epidemiology of *S. aureus* is Dynamic

- Interfamilial transmission: Often USA300
Often beyond the nose
- Prevalence of *S. aureus* in infections is syndrome specific
- Zoonotic Transmission of MRSA happens
- New clones of *S. aureus* will continue to emerge
- Genetic techniques will increasingly help us understand the Epidemiology and Pathogenesis of *S. aureus*

Lessons Learned:

Epidemiology: *Dynamic & Dramatic*

Resistance: *Growing Problem*

Treatment: *Success, Setback, & Confusion*

“False Negative” MRSA by PCR-based Diagnostics

- *S. aureus* LG251: methicillin resistant but tested neg for *mecA* by PCR
- *mecA* homologue (*mecA*_{LG251}) in novel type XI SCCmec
- 3 diff MLST in cows
- Identified in human isolates in Scotland, England, Denmark
- *spa* type 843 predominant in cows & humans

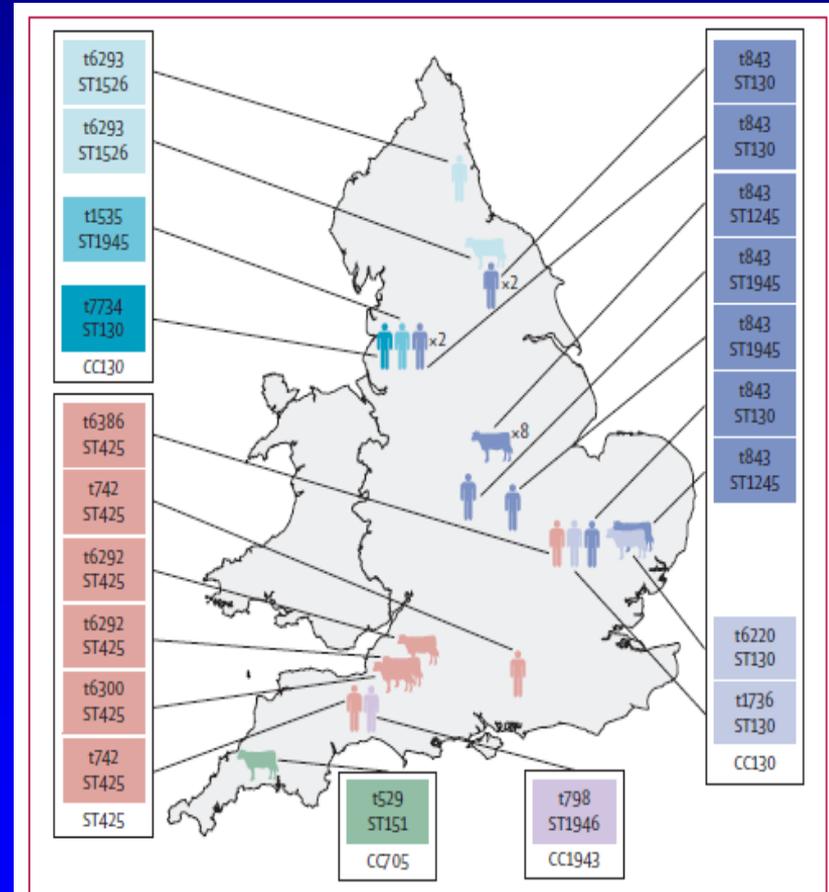


Figure 2: Geographical distribution of the bovine and human methicillin-resistant *Staphylococcus aureus* strains carrying the *mecA*_{LG251} gene in England

Linezolid

Mechanisms of Linezolid Resistance: Methylation of 23S rRNA

Horizontal Acquisition of Mobile Element: *cfr*

JAMA 2010; 301: 2260

- 1st Description in Man from Colombia: (Toh *Mol Microbiol* 2007, 64:1506-14)
- Product hypermethylates A2503 in 23S rRNA & affects Binding
- *cfr* associated with mobile genetic elements, suggests transferable
- 12 ICU patients from April-June 2008 with LRSA - 4 clones

Point Mutation of Chromosomal Gene: *rlmN*

Gao, *PLoS Pathogens* 2010; 6 (6): e1000944

- RlmN: Conserved RNA Methyltransferase
- Mutation leads to increased methylation of 23S rRNA at A2503
- Linezolid Resistance acquired in patient with Persistent MRSA

Summary: Linezolid Resistance

Two Paths, Single Destination

- **Treatment emergent:** Several mutations, uncommon
- **Plasmid-mediated:** *cfr* is the problem
Horizontal acquisition
- **Affects Binding**
 - Mutation of 23S rRNA subunit
 - Methylation of A2503 in 23S rRNA
- **Concern:** Increased use = increased resistance
 - *ZEPHYR trial*
 - *Patent Expiry in 2015*

Lessons Learned:

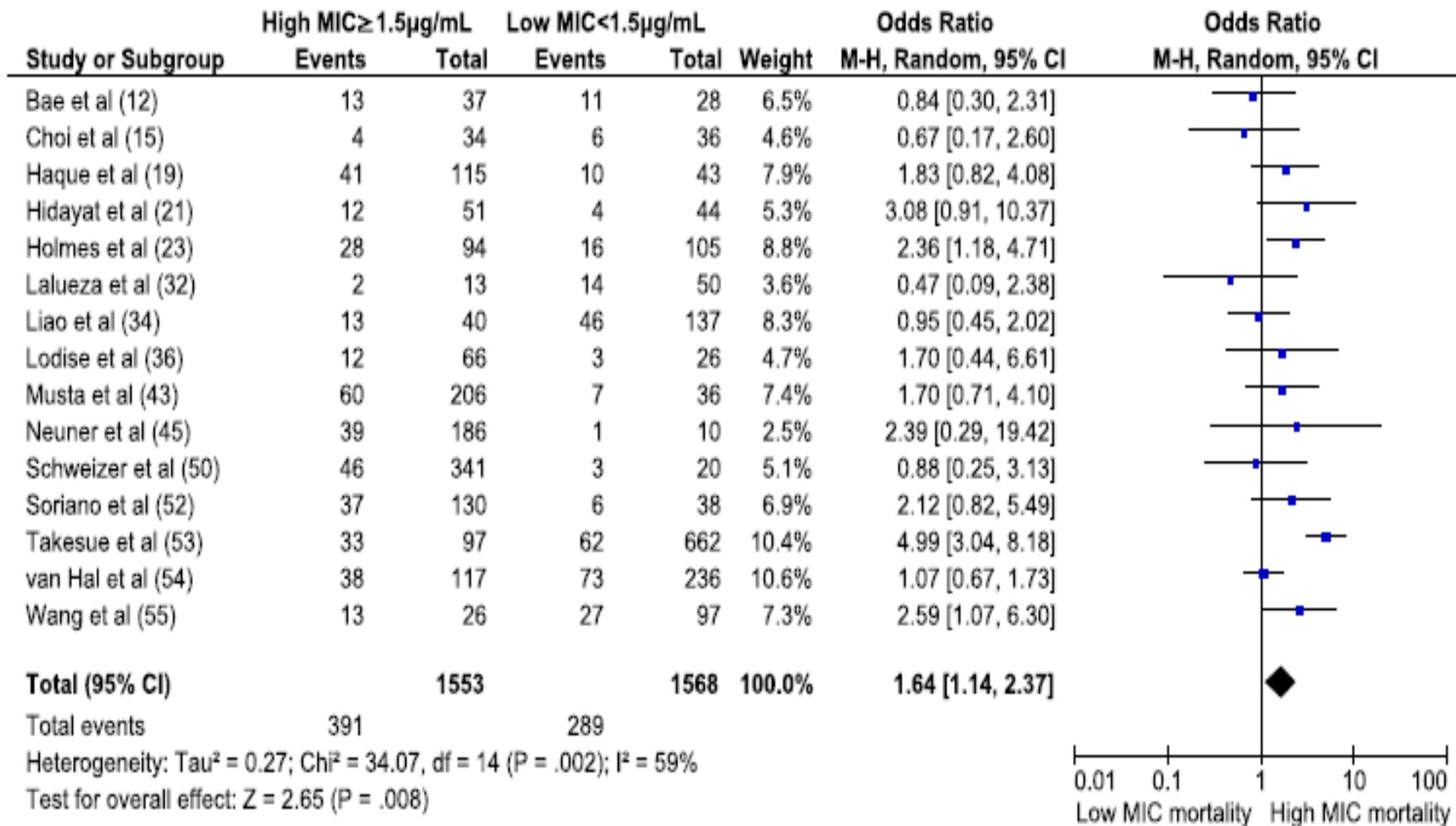
Epidemiology: *Dynamic & Dramatic*

Resistance: *Growing Problem*

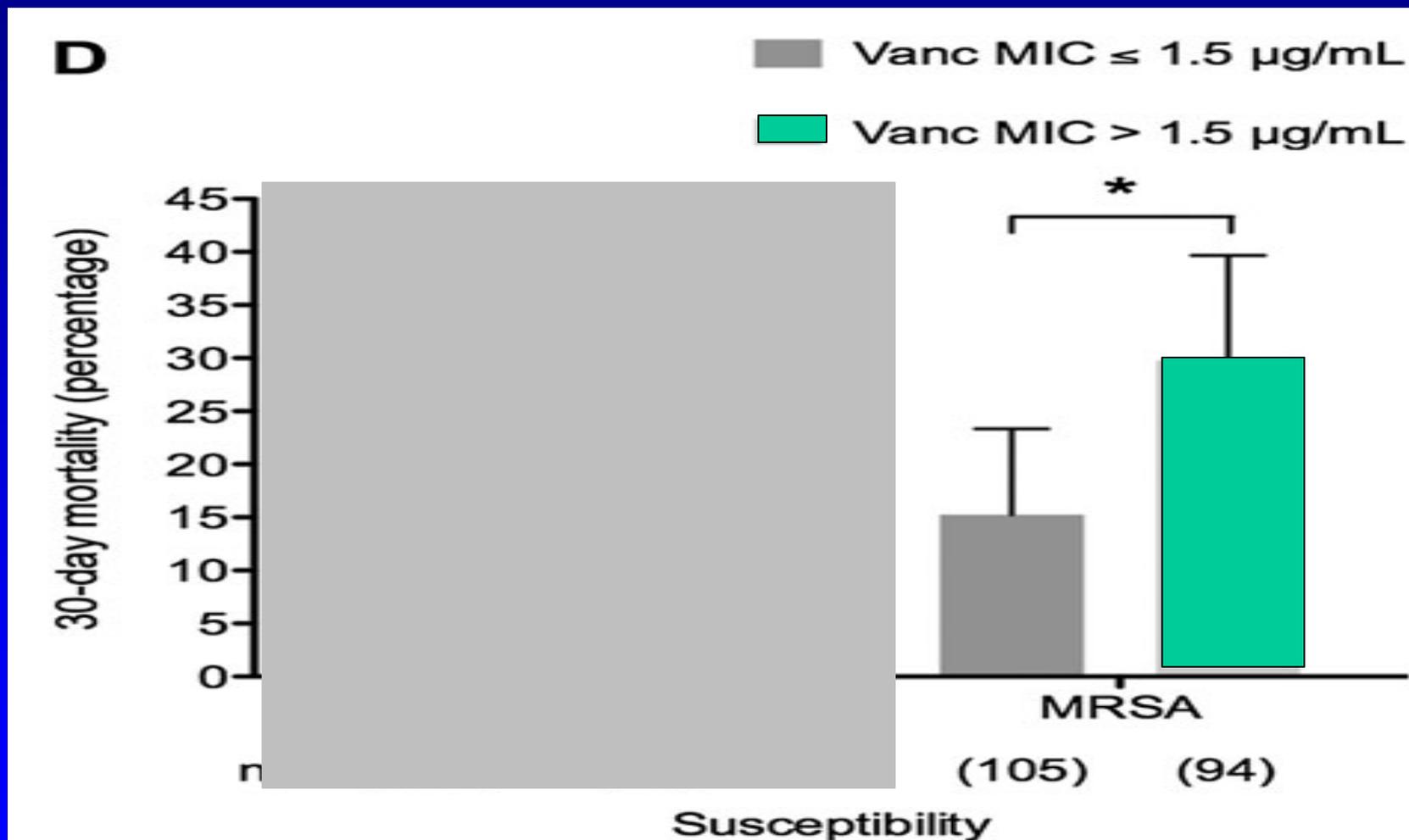
Treatment: *Success, Setback, & Confusion*

Confusion

MRSA Infection with Vanco MIC $\geq 1.5\mu\text{g/mL}$ Associated with Mortality



Vancomycin MIC Associated with 30 Day Mortality in MSSA Bacteremia



Is all Vancomycin Created Equal?

No

Generic Vancomycin Products Fail *In Vivo* despite Being Pharmaceutical Equivalents of the Innovator[∇]

Omar Vesga,^{1,2*} Maria Agudelo,^{1,3} Beatriz E. Salazar,^{1,4}
Carlos A. Rodriguez,^{1,5} and Andres F. Zuluaga^{1,5}

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 2010, p. 3271–3279

Generic Vancomycin Enriches Resistant Subpopulations of *Staphylococcus aureus* after Exposure in a Neutropenic Mouse Thigh Infection Model

Carlos A. Rodriguez,^{a,b} Maria Agudelo,^{a,b} Andres F. Zuluaga,^{a,b} and Omar Vesga

Antimicrob. Agents Chemother. 2012, 56(1):243.

Yes

Product Quality of Parenteral Vancomycin Products in the United States

S. Nambiar,^a R. D. Madurawe,^b S. M. Zuk,^c S. R. Khan,^d C. D. Ellison,^d P. J. Faustino,^d D. J. Mans,^e M. L. Trehy,^e M. E. Hadwiger,^e
M. T. Boyne II^e K. Biswas,^e and E. M. Cox^a

Antimicrob. Agents Chemother. 2012, 56(6):2819

Quality Assessment of U.S. Marketplace Vancomycin for Injection Products Using High-Resolution Liquid Chromatography-Mass Spectrometry and Potency Assays

Michael E. Hadwiger,^a Cynthia D. Sommers,^a Daniel J. Mans,^a Vikram Patel,^b and Michael T. Boyne II^a

Antimicrob. Agents Chemother. 2012, 56(6):2824.

- Similar in Rabbit Endocarditis Model

(Tattevin #B-645 ICAAC 2012)

The Recommendation

Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists

MICHAEL RYBAK, BEN LOMAESTRO, JOHN C. ROTSCHAFFER, ROBERT MOELLER JR., WILLIAM CRAIG, MARIANNE BILLETER, JOSEPH R. DALOVISIO, AND DONALD P. LEVINE

Am J Health-Syst Pharm. 2009; 66:82-98

Based on these study results, an AUC/MIC ratio of ≥ 400 has been advocated as a target to achieve clinical effectiveness with vancomycin.

Data for AUC/MIC and Clinical Outcome

Summary of Studies comparing AUC/MIC to Clinical Outcome in Patients with *S. aureus* Infection

	Design	Infection type	MIC	Outcome	Finding
Association between Outcome and AUC/MIC					
Moise-Broder ¹	Retrospective n=50 (Van Rx)	HAP/VAP MR/MSSA	BMD	Clinical & Microbiological Success	AUC/MIC \geq 350 Asstd with "Clinical Success": OR 7.19; 95% CI: 1.9-27.3
Kullar ²	Retrospective n=320	MRSA Bacteremia	BMD	Composite: - 30-d death, - SAB>7d - Symptoms	AUC/MIC<421 Asstd with failure (61.2% v. 48.6%; p=0.038) No Difference: - Median AUC/MIC - % MIC>1)
Brown ³	Retrospective n=50	MRSA IE/ Bacteremia	Etest	Attributable Mortality (n=8)	AUC ₂₄ /MIC <211 Associated with Attributable Mortality OR: 10.4 (3.89-16.77)

No Association between Outcome and AUC/MIC

Neuner ⁴	Retrospective n=222	MRSA Bacteremia	Etest	Persistent MRSAB (n=19)	No significant association between AUC/MIC and Persistent MRSAB
Holmes ⁵	Prospective N=182	<i>S. aureus</i> Bacteremia	BMD	30d Mortality (n=38)	No assn of AUC/MIC>400 and better outcome

¹Clin Pharmacokin 2004; 43:925; ²CID 2011; 52:975; ³ AAC 2012; 56: 634; ⁴DMID 2010; 67:228; ⁵ICAAC 2011 #A1681

NEGATIVE *IN VIVO* DATA

Vancomycin Dosed to Achieve $AUC/MIC \geq 400$ Did Not Improve Outcome of MRSA Endocarditis Caused by Strains With Different VAN MICs

- 3 MRSA isolates with MIC 0.5, 1, and 2ug/mL each used to infect rabbits at control, regular dose, and high dose vanco (n=45 rabbits/isolate)
- After 2 days of VAN neither sterilization rate nor reduction in bacterial density in vegetations improved with Cmin levels of 15-20 mg/L or with AUC/MIC index ≥ 400 .

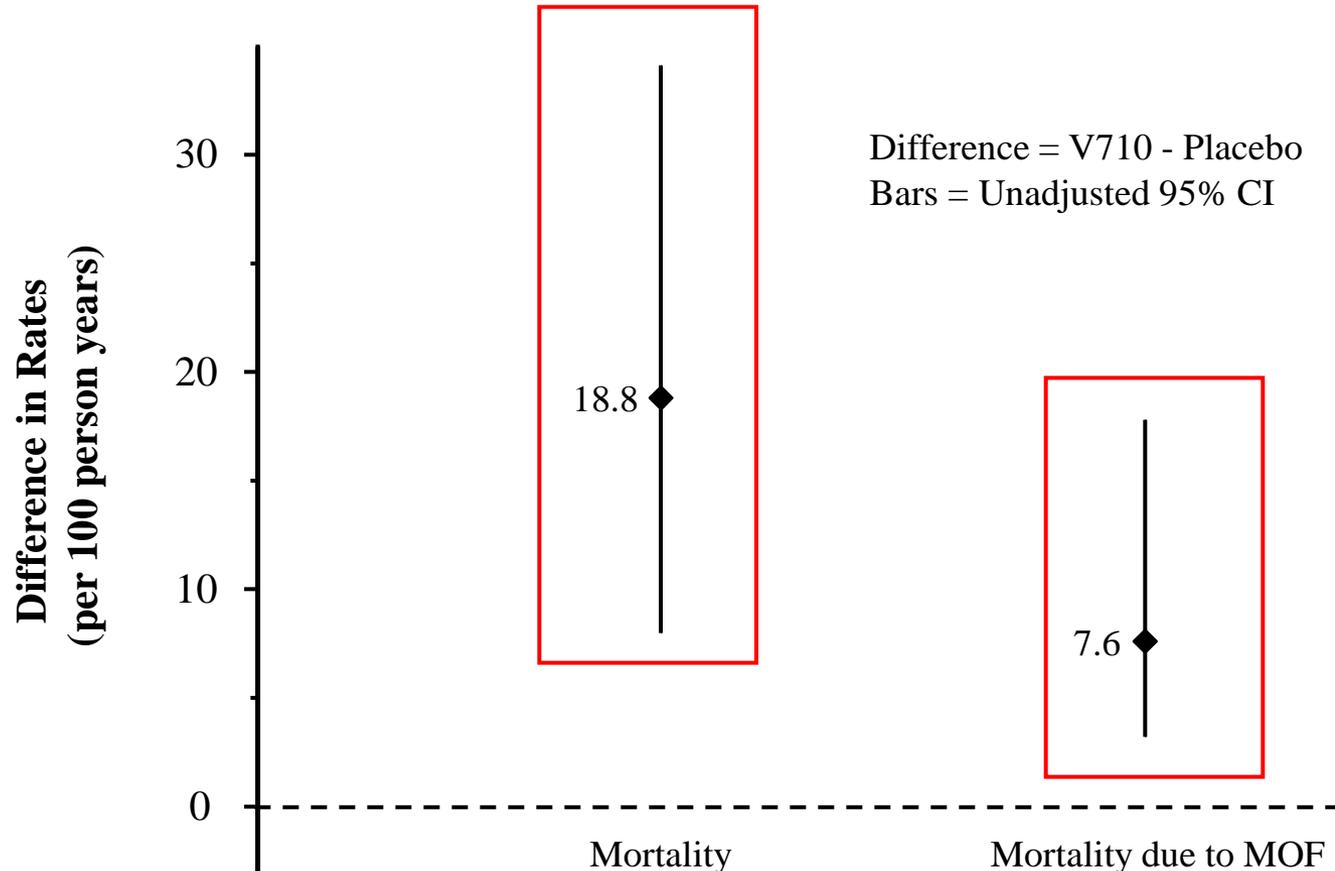
Setback

**Efficacy and Safety
of an Investigational *S. aureus* Vaccine in
Preventing Bacteremia and Deep Sternal
Wound Infections After Cardiothoracic
Surgery**

**VG Fowler Jr, KB Allen, ED Moreira, M Moustafa,
F Isgro, HW Boucher, GR Corey, Y Carmeli, R Betts,
JS Hartzel, NA Kartsonis, D Guris, S Smugar,
B Turnbull, MJ DiNubile, MT Onorato,
and A Sobanjo-ter Meulen**

ECCMID, London, March 31, 2012

Analysis of Mortality and Multi-Organ Failure (MOF) in Subjects with Any *S. aureus* Infections



Any <i>S. aureus</i> Infection	
V710	73
Placebo	96

Deaths	Follow-Up Time (yrs)	Rate (per 100 person-yrs)
15	65.2	23.0
4	94.4	4.2

MOFs	Follow-Up Time (yrs)	Rate (per 100 person-yrs)
5	65.9	7.6
0	94.5	0.0

Success

Linezolid in Methicillin-Resistant *Staphylococcus aureus* Nosocomial Pneumonia: A Randomized, Controlled Study

Richard G. Wunderink,¹ Michael S. Niederman,² Marin H. Kollef,³ Andrew F. Shorr,⁴ Mark J. Kunkel,⁵ Alice Baruch,^{5,a} William T. McGee,⁶ Arlene Reisman,⁵ and Jean Chastre⁷

Clinical Infectious Diseases 2012;54(5):621–9

- Randomized, Double-Blind Controlled Multicenter trial of Linezolid IV or Vanco for MRSA HCAP/HAP/VAP
- Design: Hierarchical Non-inferiority-superiority¹
- 1° Endpoint: Clinical Cure at End of Study in evaluable Per Protocol patients
- Cure rates in PP and mITT patients with MRSA HAP were higher in LNZ vs. VAN (58% v. 47%; p=0.042)
- Significance lost in HCAP, HAP, & VAP subgroups²
- Nephrotox higher in VAN (18.2%) vs. LNZ (8.4%)
- No difference in mortality
- Conclusion: LNZ Superior to VAN in MRSA HAP/VAP
- Lots of letters to editor

¹Spellberg *Clin Infect Dis.* (2012) doi: 10.1093/cid/cis688 ; ²Torres *Clin Infect Dis* 2012;54(5):630.

Treatment Summary

- **Confusion:** We need a definitive trial to characterize clinical role of Vanco AUC/MIC
- **Setback:** Vaccine studies should proceed with caution (but proceed nonetheless)
- **Success: ZEPHYR:**
 - *showed LNZ superior to VAN in clinical cures*
 - *Hierarchical non-inferiority superiority design*

Lessons Learned:

Epidemiology: *Dynamic & Dramatic*

Resistance: *Growing Problem*

Treatment: *Success, Setback, & Confusion*