The Evolution of MRSA: Does it Matter for Infection Control?

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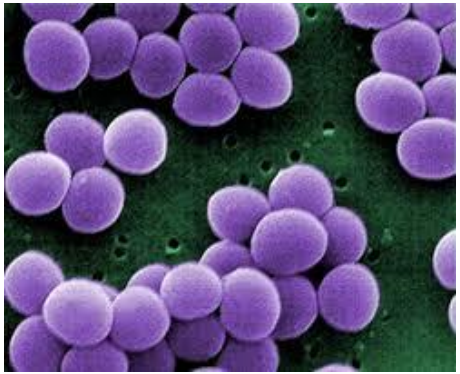
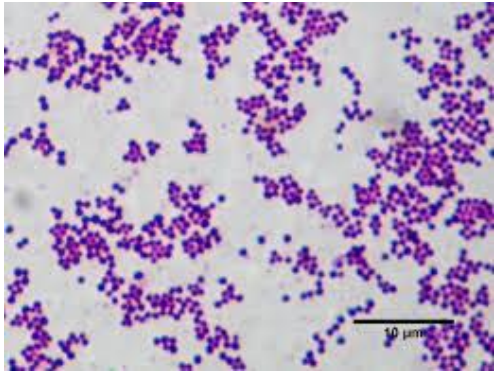
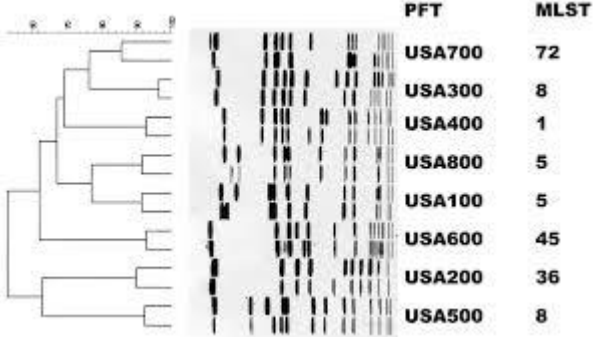
Disclosures

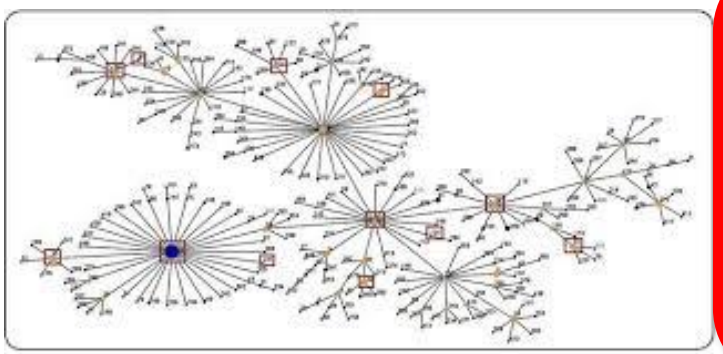
- Salary and benefits from Cepheid a molecular diagnostics company

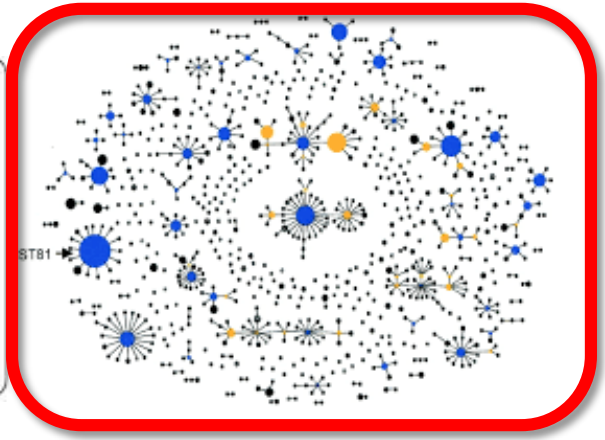
Staphylococcus aureus – What comes to mind?







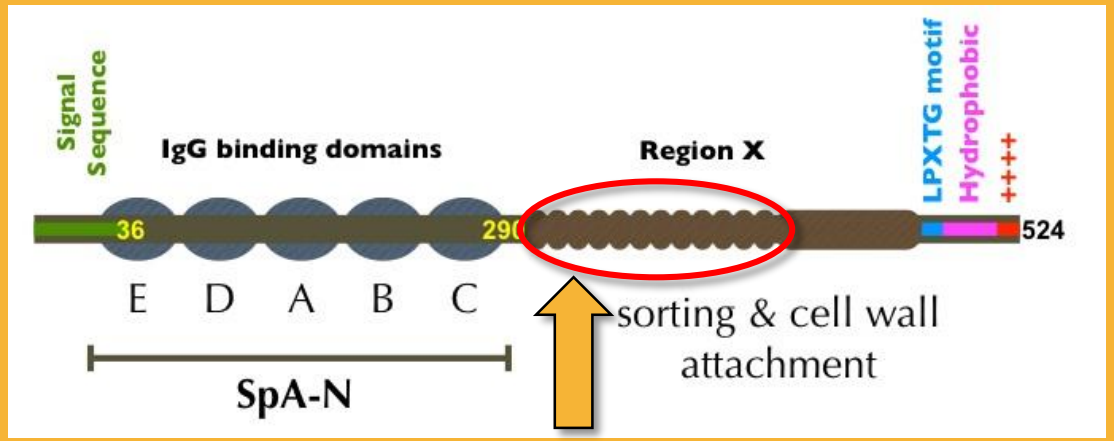




The Continuing Diversification of MRSA Leads to Several Challenges

- Strains not detected by molecular methods
- Phenotypically susceptible MRSA (stealth MRSA)
- Emergence of virulent clones
- All of which are challenges for infection prevention

spa Typing Indicates Increasing *S. aureus* Diversity



Repeated sequences yield spa types

Spa-types: 18,613

Gives you a sense of the constant evolution that this organism undergoes, including acquisition of virulence factors and antimicrobial resistance genes

Sequence data curated by SeqNet.org

https://www.spaserver.ridom.de/
Accessed on 3/8/2019

Diversity and Molecular Diagnostics

- *Staphylococcus aureus* is a genetically dynamic organism that can harbor a wide variety of mobile genetic elements including resistance genes
- *S. aureus* isolates are continually under selective pressure from antibiotic use, immune responses, and environmental factors that often lead to genetic changes in the organism in order to survive. Not every strain responds in the same way.
- The sequence changes that the organism undergoes may occur in regions targeted by molecular diagnostics and may impact the accuracy of those tests.
- Antimicrobial resistance genes are among the genetic elements often acquired by *S. aureus*

Characterization of the staphylococcal cassette chromosome *mec* insertion site in 108 isolates lacking the *mecA* gene and identified as methicillin-resistant *Staphylococcus aureus* by the Xpert MRSA assay

M. Stojanov · D. S. Blanc

MSSA called MRSA

Eur J Clin Microbiol Infect Dis. 2014 Nov;33(11):1967-71

Analysis of Staphylococcal Cassette Chromosome *mec* in BD GeneOhm MRSA Assay-Negative Strains

MRSA called MSSA

Meng Zhang,[a] Teruyo Ito,[a,b] Shanshuang Li,[a] Shigeki Misawa,[c] Shigemi Kondo,[d] Takashi Miida,[d] Akimichi Ohsaka,[e] Keiichi Hiramatsu[a,b]

Antimicrobial Agents and Chemotherapy p. 2890–2891 June 2013 Volume 57 Number 6

Failure of the BD GeneOhm StaphSR Assay for Direct Detection of Methicillin-Resistant and Methicillin-Susceptible *Staphylococcus aureus* Isolates in Positive Blood Cultures Collected in the United States[▽]

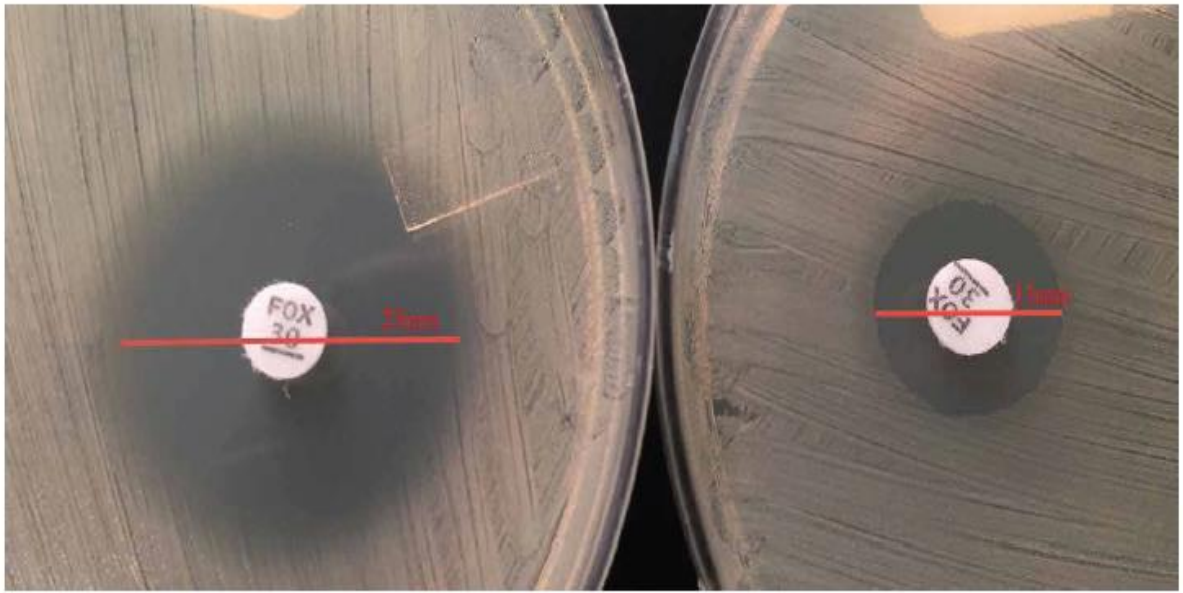
James W. Snyder,[1]* Gina K. Munier,[2] Stacy A. Heckman,[2] Pamela Camp,[3] and Timothy L. Overman[3,4]

A few in both directions

JOURNAL OF CLINICAL MICROBIOLOGY, Nov. 2009, p. 3747–3748

Wound infections caused by inducible meticillin-resistant *Staphylococcus aureus* strains

Christopher Penn [a], Carol Moddrell [a], Isabella A. Tickler [b], Mary Ann Henthorne [a], Megan Kehrli [a], Richard V. Goering [c], Fred C. Tenover [b,*]



Oxacillin-susceptible Pre-induction

Resistance emerges after induction

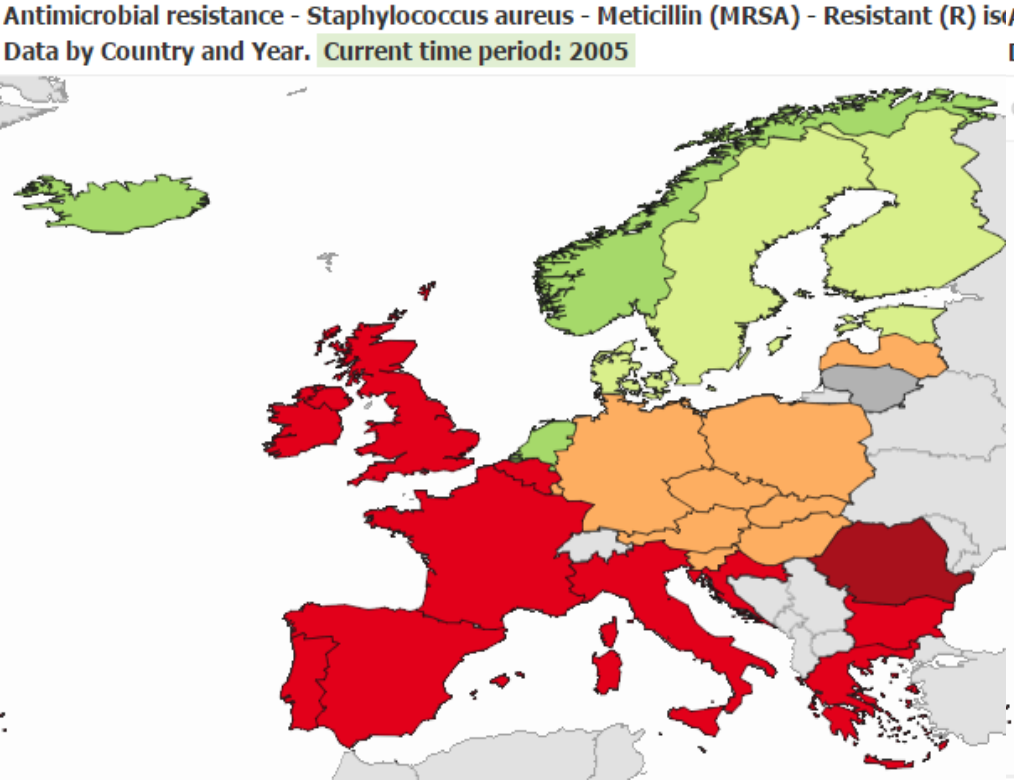
Molecular methods called these strains MRSA, but colonies were phenotypically oxacillin-susceptible.

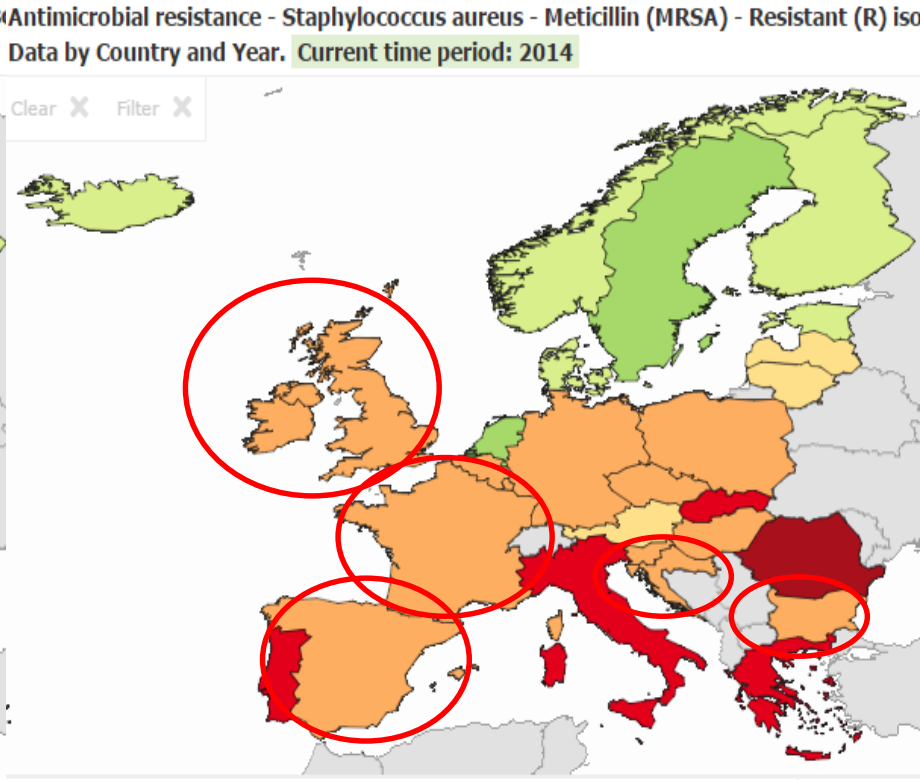
However, when exposed to cefoxitin, colonies became oxacillin resistant.

Resistance may emerge on therapy.

Journal of Global Antimicrobial Resistance 1 (2013) 79–83

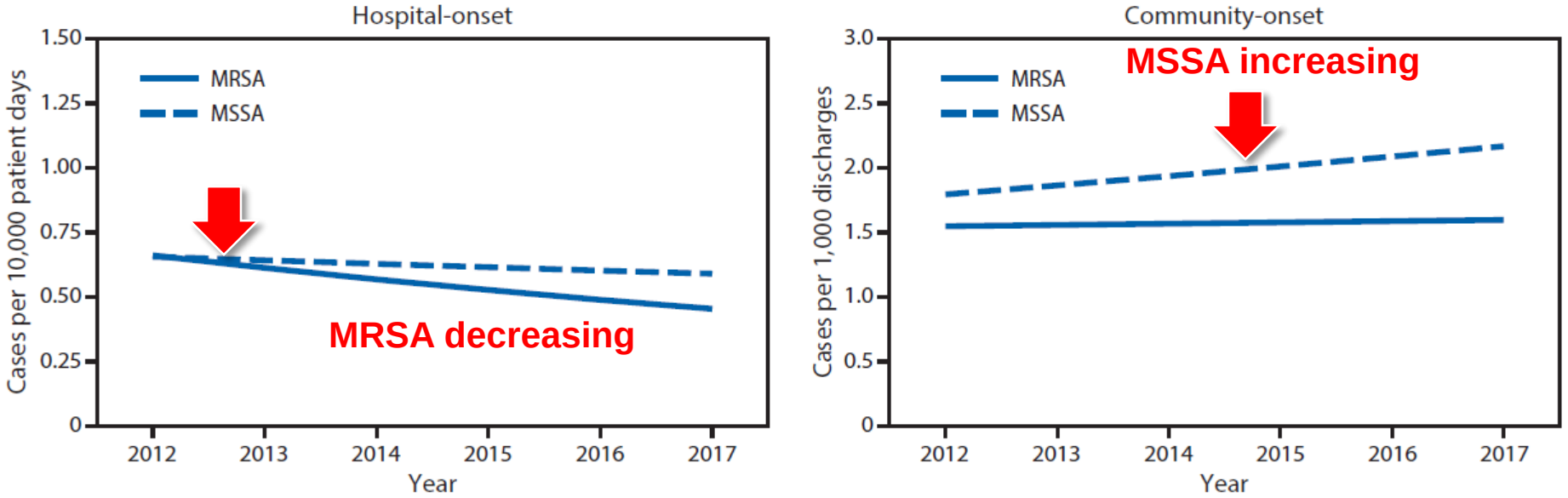
Decreasing Prevalence of MRSA in Europe 2005-2014: Infection Prevention Works





Vital Signs: Epidemiology and Recent Trends in Methicillin-Resistant and in Methicillin-Susceptible *Staphylococcus aureus* Bloodstream Infections — United States

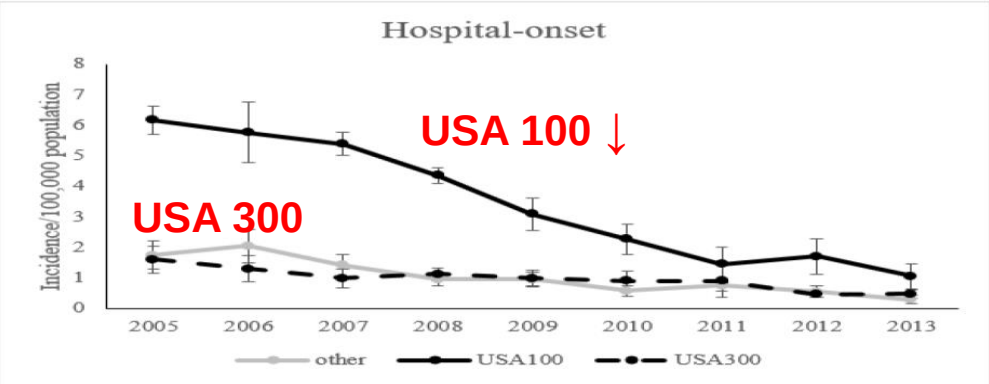
FIGURE 2. Adjusted* hospital-onset and community-onset rates of *Staphylococcus aureus* bloodstream infections — Premier and Cerner Hospitals, United States, 2012–2017



Trends in incidence of methicillin-resistant *Staphylococcus aureus* bloodstream infections differ by strain type and healthcare exposure, United States, 2005–2013. ***Clin Infect Dis (in press) 2019***

Isaac See, Yi M, Valerie Albrecht, Maria Karlsson, Ghinwa Dumyati

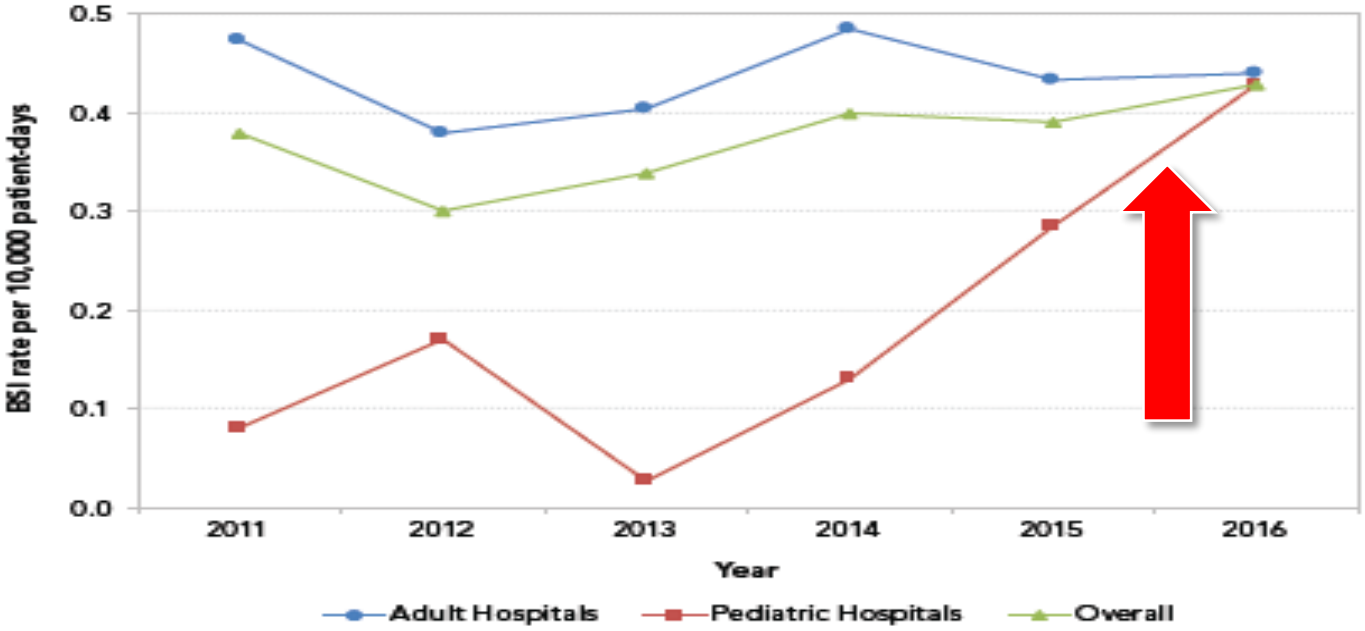
New strains have increased virulence factors and ability to spread, that makes them an infection issue. Most of the decline in MRSA BSIs was from decreases in USA100 BSI incidence. **Prevention of USA300 MRSA BSIs in the community will be needed to further reduce burden from MRSA BSIs.**



CANADIAN ANTIMICROBIAL RESISTANCE SURVEILLANCE SYSTEM

2017 REPORT

FIGURE 2: Rate of healthcare-associated MRSA blood stream infection (BSI), 2011-2016



MRSA Healthcare-associated bloodstream infections 2011-2016 in Canada

https://ipac-canada.org/photos/custom/Members/pdf/CARSS-2017-Report-EN-corrected_CPO.pdf

Publication date: March 2018

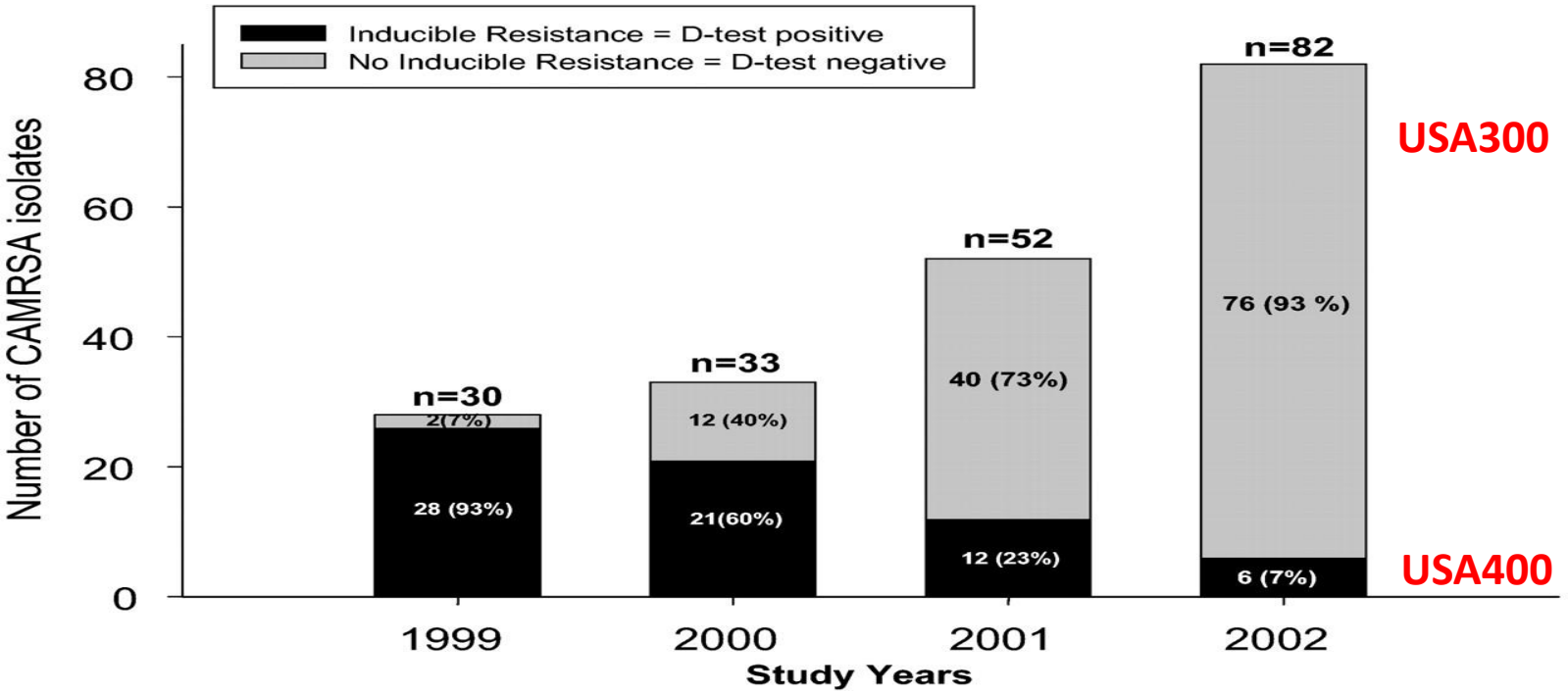
Historical View of Strain Evolution

Community MRSA: the Story of USA300

Four Pediatric Deaths from Community-acquired Methicillin-Resistant *S. aureus* -- Minnesota and North Dakota, 1997-1999 (MMWR 48:707; 1999)

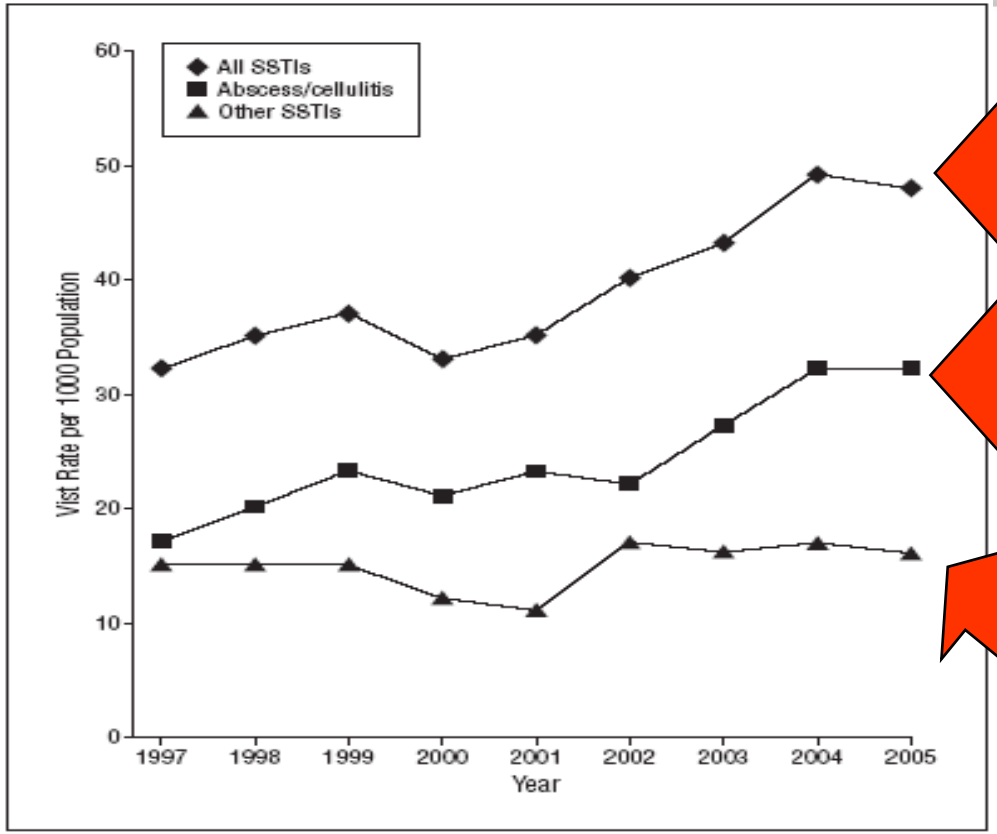
- **Background:** Children with severe staphylococcal disease treated seemingly appropriately with cephalosporins, failed therapy due to resistance and died.
- **Key finding:** MRSA infections were emerging in community settings among patients without established risk factors (e.g., recent hospitalization, recent surgery, residence in a long-term-care facility, or injecting-drug use) and antimicrobial therapy needed to be modified.
- **Strain type: USA400 (MW2) ST1: SCC*mec*IV, PVL+**
- **Beginning of a major change in MRSA epidemiology**

Change from USA400 to USA300 in Pediatric CA-MRSA Isolates, Dallas Texas, 1999-2002



Chavez-Bueno et al. Antimicrob Agents Chemo 2005;49:2283

Annual rates of visits for skin and soft-tissue infections (SSTIs) in the United States (1997-2005)



Increase in SSTIs from 32.1 to 48.1/1000 population a 50% increase (p=0.003)

Increase in visits for abscess/cellulitis increased from 4.6 to 9.6 million; a 109% increase (p=0.001)

Other SSTI visits (like impetigo) remained steady

ARCH INTERN MED/VOL 168 (NO. 14), JULY 28, 2008

Identification and Characterization of the Multidrug Resistance Gene *cfr* in a Panton-Valentine Leukocidin-Positive Sequence Type 8 Methicillin-Resistant *Staphylococcus aureus* IVa (USA300) Isolate[▽]

Anna C. Shore,[1]† Orla M. Brennan,[1]† Ralf Ehricht,[2]† Stefan Monecke,[3]† Stefan Schwarz,[4]† Peter Slickers,[2] and David C. Coleman[1]*

TABLE 3. Antimicrobial resistance profiles of M05/0060 harboring the *cfr*-encoding conjugative plasmid pSCFS7, its cured derivative M05/0060-C1 lacking pSCFS7, *S. aureus* recipient strain XU21, and its transconjugant derivative XU21-T1 harboring pSCFS7

Isolate or derivative	*cfr* and *fexA* carriage	MIC (μg/ml)[a]									
		TIA	VIR M_1	Q-D	LZD	CLI	CHL	FFC	ERY	OXA	VAN
MRSA M05/0060	*cfr*, *fexA*	≥128	32	2	8	≥128	256	256	≥64	≥32	1
MRSA M05/0060-C1		1	1	0.5	1	0.25	8	4	≥64	≥32	1
S. aureus XU21		1	1	0.25	1	0.25	8	4	0.5	0.12	1
S. aureus XU21-T1	*cfr*, *fexA*	≥128	32	2	4	≥128	128	256	0.5	0.12	1

Since ST8-MRSA-IVa/USA300 has proved to be a successful clone capable of epidemic spread, the emergence of a *cfr*-positive variant of this strain is cause for significant concern and warrants close surveillance.

USA300 with Reduced Susceptibility to Critical Antimicrobial Agents

Intermediate Vancomycin Susceptibility in a Community-associated MRSA Clone

Christopher J. Graber,* Margaret K. Wong,*
Heather A. Carleton,*
Françoise Perdreau-Remington,*
Barbara L. Haller,* and Henry F. Chambers*

We describe a case of treatment failure caused by a strain of **USA300 CA-MRSA** with intermediate susceptibility to vancomycin and reduced susceptibility to daptomycin. 56-year-old man with lumbar osteomyelitis after a 6-weeks of vancomycin for catheter-associated septic thrombophlebitis.

Emerging Infectious Diseases • Vol. 13, No. 3, March 2007

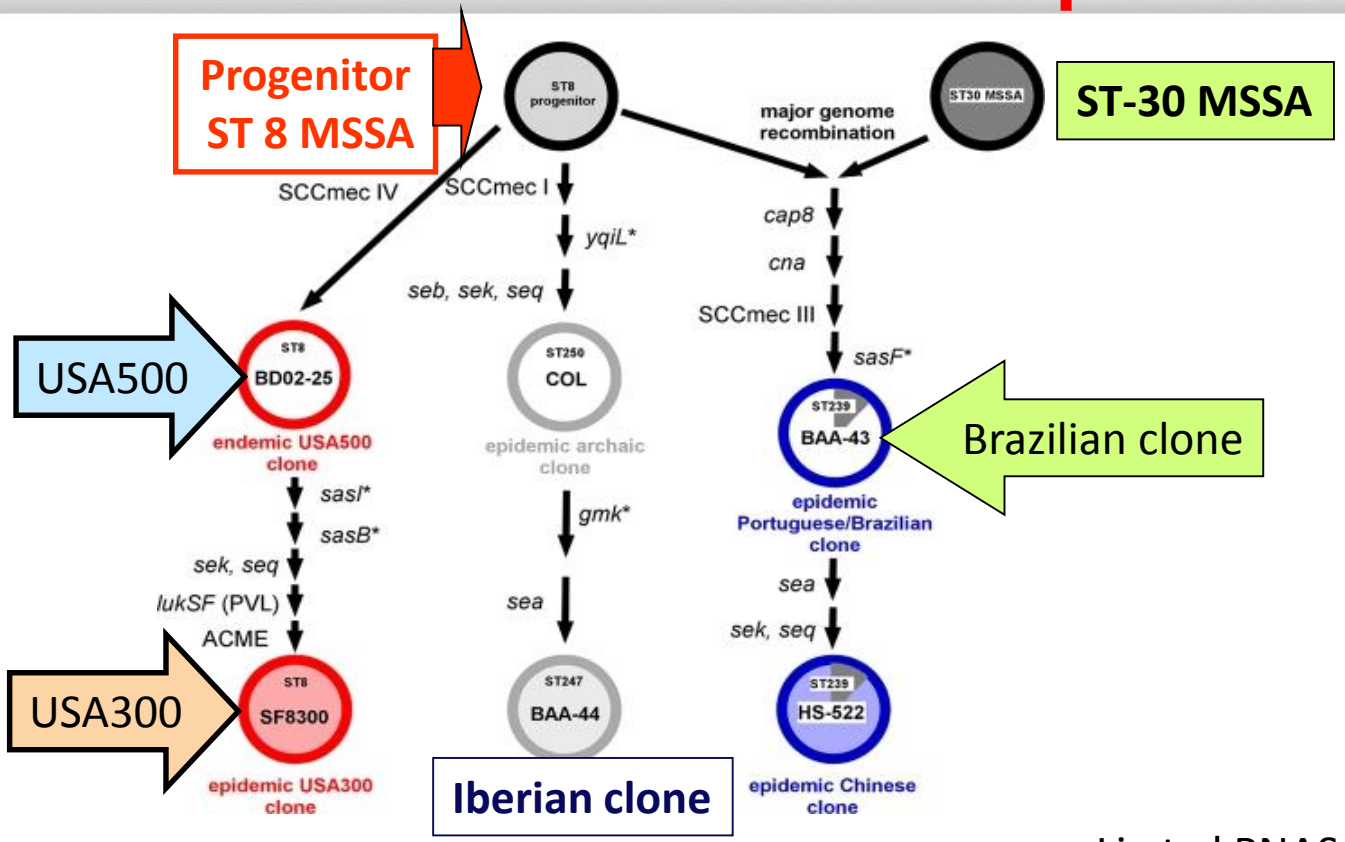
Comparing PFGE to spa types for Blood and Nasal MRSA Isolates

TABLE 1 *spa*, SCC*mec*, and pulsed-field gel electrophoresis types of study isolates[a]

	Blood		Nares	
PFGE type	*spa* type-SCC*mec* (*n*)[b]	Total no. of isolates (194)	*spa* type-SCC*mec* (*n*)	Total no. of isolates (299)
USA100	t002-II (43), t002-NT (1), t045-II (4), t062-II (1), t062-IV (1), t067-II (1), t088-II (1), t214-II (1), t242-II (9), t242-NT (1), t688-II (1), t985-II (1), t1062-II (1), t2358-II (1), t2666-II (1), t6778-II (1)	69	t002-II (110), t002-NT (5), t010-II (1), t045-II (5), t062-II (1), t067-II (4), t071-II (1), t088-II (3), t105-II (3), t105-NT (4), t242-II (15), t242-NT (5), t509-II (2), t535-II (1), t539-II (2), t548-II (1), t548-NT (1), t570-II (1), t586-II (1), t837-II (1), t895-II (1), t1220-II (1), t1567-II (1), t2666-II (1), t3557-II (1), t3558-II (1), t4371-II (1), t4916-II (1), t4963-II (1), t5081-II (1), t-6778-II (1)	178
USA200	None observed	0	t021-IV (1)	1
USA300	t008-IV (76), t008-NT (2), t024-IV (1), t051-IV (1), t304-IV (2), t334-IV (1), t622-IV (1), t648-IV (1), t1617-IV (1), t2743-IV (2), t3908-IV (1), t4069-IV (2), t4229-IV (1), t6774-IV (1)	93	t008-IV (60), t008-NT (3), t024-IV (3), t190-IV (1), t211-IV (1), t334-II (1), t622-IV (1), t681-IV (1), t951-IV (1), t1779-IV (1), t6127-IV (1), t6774-IV (1)	75
USA400	t127-IV (1)	1	t1178-IV (1)	1
USA500	t064-IV (8)	8	t064-IV (8); t451-IV (1)	9
USA700	None observed	0	t148-IV (1), t148-NT (1)	2
USA800	t002-IV (3), t062-IV (1), t1265-IV (1)	5	t002-IV (12), t088-IV (3), t111-IV (1), t306-IV (1), t1265-IV (2), t5213-IV (1)	20
USA1000	t216-IV (1)	1	t216-IV (1), t316-IV (1), t437-IV (1), t976-NT (1)	4
CMRSA9	t008-VIII (1), t197-VIII (1)	2	t008-VIII (1)	1
EMRSA15	t020-IV (1)	1	t032-IV (1)	1
ST239-associated pattern	t037-III (2)	2	t037-III (2)	2
Unnamed[c]	Unnamed-II (1), unnamed-IV (1), t189-IV (1), t668-II (5), t6770-II (2), t6771-IV (1), t6775-II (1)	12	Unnamed-II (1), unnamed-IV (2), t450-II (1), t579-II (1)	5

USA300 contains at least 13 spa types which can harbor several different SCC*mec* types

Origins of USA300- One of the Many Descendents of Clonal Complex 8

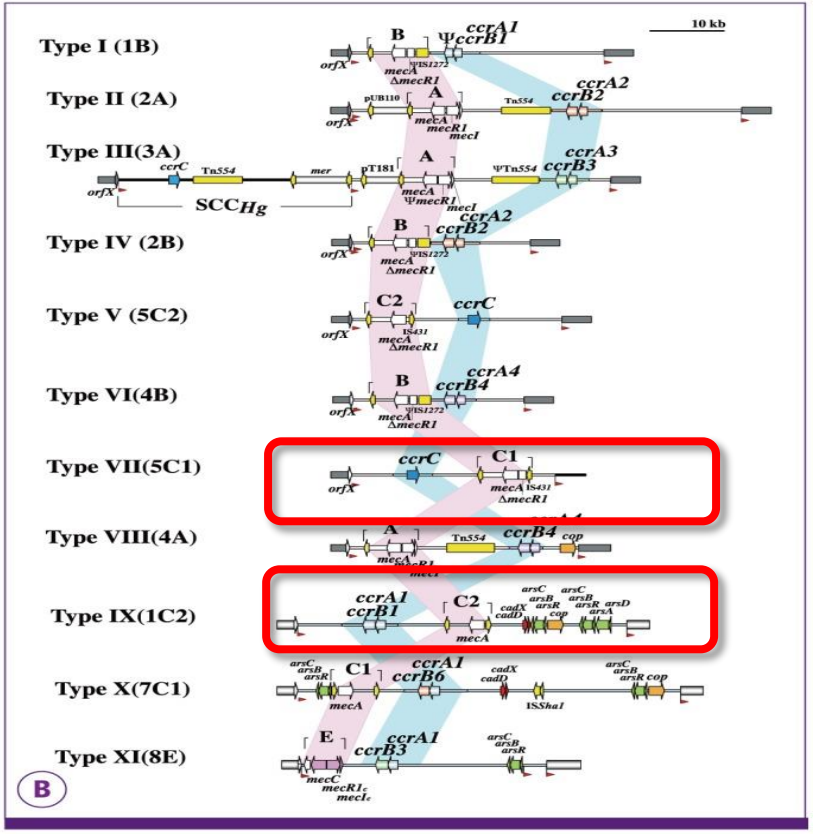


Li et al PNAS 2009

Strain diversity is also about the methicillin-Resistance elements

Genomic Basis for Methicillin Resistance in *Staphylococcus aureus*

Keiichi Hiramatsu[1,2], Teruyo Ito[1], Sae Tsubakishita[3], Takashi Sasaki[4], Fumihiko Takeuchi[4], Yuh Morimoto[1,2], Yuki Katayama[1], Miki Matsuo[1], Kyoko Kuwahara-Arai[1], Tomomi Hishinuma[1,2], and Tadashi Baba[1,2]



Staphylococcal Cassette Chromosome *mec* (SCC*mec*) elements, which contain the methicillin resistance gene, can be divided into several major types.

These have both stable regions (*mec* and *ccr*) and variable regions. Some include additional antimicrobial resistance genes. Note the inversion of *mec* and *ccr* in types VII and IX

Infect Chemother 2013;45(2):117-136

Novel Types of Staphylococcal Cassette Chromosome *mec* Elements Identified in Clonal Complex 398 Methicillin-Resistant *Staphylococcus aureus* Strains[▽‡]

Shanshuang Li,[1,2†] Robert Leo Skov,[3] Xiao Han,[2] Anders Rhod Larsen,[3] Jesper Larsen,[3] Marit Sørum,[3] Mireille Wulf,[4] Andreas Voss,[5] Keiichi Hiramatsu,[1,2] and Teruyo Ito[1,2*]

Antimicrobial Agents and Chemotherapy, June 2011, p. 3046–3050

What does this mean for Infection Prevention?

- Be aware of the fact that epidemic clones continue to emerge and disseminate.
- USA300 is a remarkably successful clone, but others, like ST398, the livestock clone, are emerging in humans and causing outbreaks in the Netherlands and elsewhere
- Be aware that some oxacillin-susceptible *S. aureus* especially from multidrug-resistant strains from blood cultures, may be MRSA

Conclusions

- *Staphylococcus aureus* is a genetically dynamic organism that continually acquires new virulence mechanisms and antimicrobial resistance genes
- Some of these virulence genes can lead to increased chance for outbreaks
- Some mutations mask methicillin resistance, which is readily recovered when the strain is exposed to antibiotics
- Infection preventionists need to be vigilant for potential outbreaks as new strain types are introduced into hospitals
- Nonetheless, remember that infection control works and rates are dropping globally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