Increasing antibiotic susceptibility in *Staphylococcus aureus* in Boston, Massachusetts, 2000 - 2014: an observational study

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Background

Staphylococcus aureus is a major pathogen but rates of nosocomial infection due to methicillin-resistant *S. aureus* (MRSA) have been declining over the past 10 years across the United States and Europe[1,2].

It is not known whether this decline represents an absolute decrease in *S. aureus* infections or a shift towards infection from more drug-susceptible strains. Though scarce, there is evidence for the latter hypothesis in several recent observational studies[3].

In this study, we determine whether the decline in rates of infection by MRSA has been accompanied by changes in rates of infection by methicillin susceptible, penicillin resistant *S. aureus* (MSSA) and penicillin susceptible *S. aureus* (PSSA). We test if these dynamics are associated with specific genetic lineages and evaluate gains and losses of resistance at the strain level.

Methods

Part 1

Study design

Retrospective analysis of electronic medical records of 31,753 adults hospitalized at the Massachusetts General Hospital and the Brigham & Women's Hospital (BWH) between Jan 1 2000 and Dec 31 2014 with isolates growing *S. aureus* from any body site.

Nasal surveillance swabs and duplicate specimens were excluded.

Antibiotics

Penicillin	Gentamicin
Methicillin	Tetracycline
Erythromycin	TMP-SMX
Clindamycin	Rifampin
Levofloxacin	Vancomycin

***S. aureus* subtypes**

Subtype	Penicillin	Oxacillin
PSSA	S	S
MSSA	R	S
MRSA	R	R

Clinical covariates

- Age
- Gender
- Charlson comorbidity index (CCI)
- Site of infection*

*Includes blood, lung, skin / soft tissue and other

Outcomes

Rates of infection by *S. aureus* subtypes and antibiogram-types per 1,000 inpatients over time**

Rates of resistance to other major antibiotics by *S. aureus* subtypes over time**

Mean resistance by *S. aureus* subtypes over time**

**Adjusted for clinical covariates

Part 2

Study design

Whole genome sequencing of 180 isolates from adults presenting to the BWH between January and July 2016 using a newly developed microfluidics platform[4].

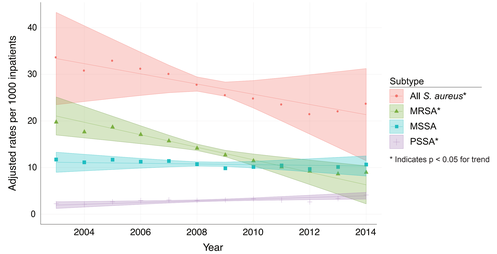
Analysis

Reads were mapped to USA300 and a maximum likelihood phylogeny was built from the reference-based core genome SNPs with sequence type (ST) 152 as the outgroup. We inferred by parsimony the number of acquisitions and losses of beta-lactam resistance within ST5 and ST8 using N315 as the reference genome for ST5 and USA300 as the reference genome for ST8.

Patients with infection by MRSA are older and more sick than those with other subtypes.

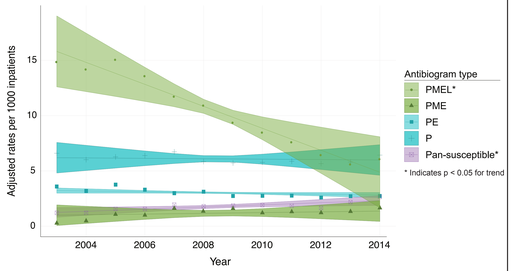
	All	MRSA	MSSA	PSSA
n	45 707	22 779	18 154	4754
Mean age (SD)	58.8 (18.3)	61.5 (18.1)	55.6 (18.2)	57.8 (18.1)
Mean CCI (median)	2.8 (2)	3.0 (2)	2.4 (2)	2.6 (2)

***S. aureus* is declining, mostly due to a decline in MRSA; PSSA has been increasing.**



There has been an annual decline in the incidence of *S. aureus* infections by 4.2% per year, which is largely driven by a decline in MRSA by 10.9% per year. PSSA has been increasing at a rate of 6.1% per year while there was no change in MSSA.

There are two subpopulations within MRSA with differing trajectories; PSSA is pan-susceptible.

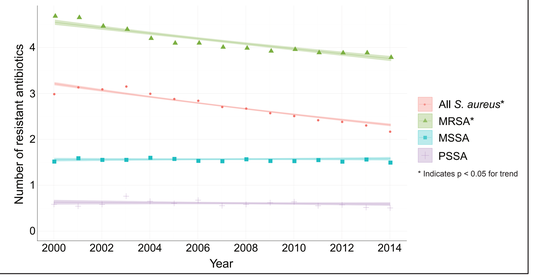


The MRSA 'antibiogram-type' resistant to penicillin, methicillin, erythromycin and levofloxacin (PMEL) has been declining at 12.1% per year. The PSSA 'antibiogram-type' is pan-susceptible and increasing at 5.3% per year. A different MRSA 'antibiogram-type' resistant to penicillin, methicillin and erythromycin (PME) had a non-significant increase of 3.0% per year.

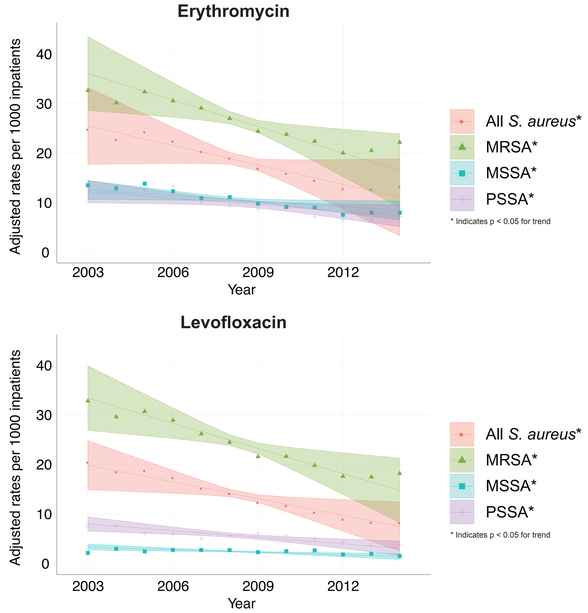
***S. aureus* has become overall more susceptible to antibiotics.**

The average *S. aureus* isolate is resistant to 0.8 *less* antibiotics in 2014 than in 2000.

This is entirely explained by a decline in resistance in the MRSA subtype. Levels of resistance have not changed in MSSA or PSSA.



Resistance is declining in *S. aureus* to erythromycin and levofloxacin.

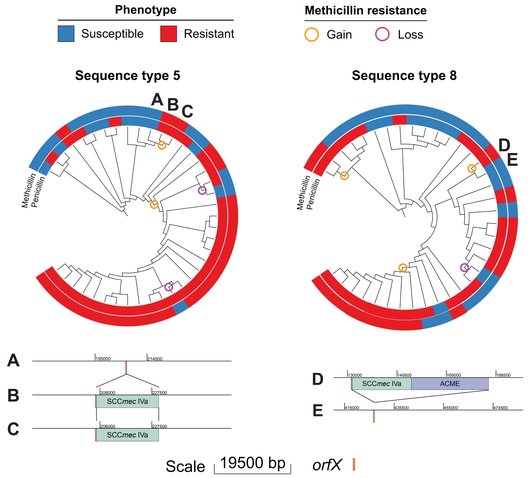


Resistance to erythromycin is declining in MRSA as well as in the more drug susceptible MSSA and PSSA subtypes. Resistance to levofloxacin is declining among all subtypes of *S. aureus*.

Subtype	Antibiogram-type	Clonal complex 5	8	Other
MRSA	PMEL	**97%**	3%	0%
	PME	20%	**80%**	0%
MSSA	PE	6%	24%	**70%**
	P	15%	19%	**66%**
PSSA	Pan-susceptible	18%	14%	**68%**

MRSA 'antibiogram-types' correspond to major circulating lineages; PSSA and MSSA are polyclonal.

Methicillin resistance is dynamic at the strain level.



Resistance to beta lactams is gained and lost multiple times among sequence type 5 (USA100) and sequence type 8 (USA300) MRSA lineages.

Conclusions

At two large tertiary care centers in Boston, MA, *S. aureus* infections overall have decreased in rate largely due to a decline in hospital-associated MRSA lineages.

With the concomitant increase in PSSA and in community-associated drug-susceptible MRSA lineages, *S. aureus* has become more susceptible to antibiotics over the past decade.

We observed gain and loss of beta-lactam resistance occurring at the strain level, suggesting an alternative determinant of population level antibiotic resistance in *S. aureus* separate from clonal transmission.

Further work is needed to define the factors driving the dynamics of antibiotic resistance in this highly adaptable pathogen.