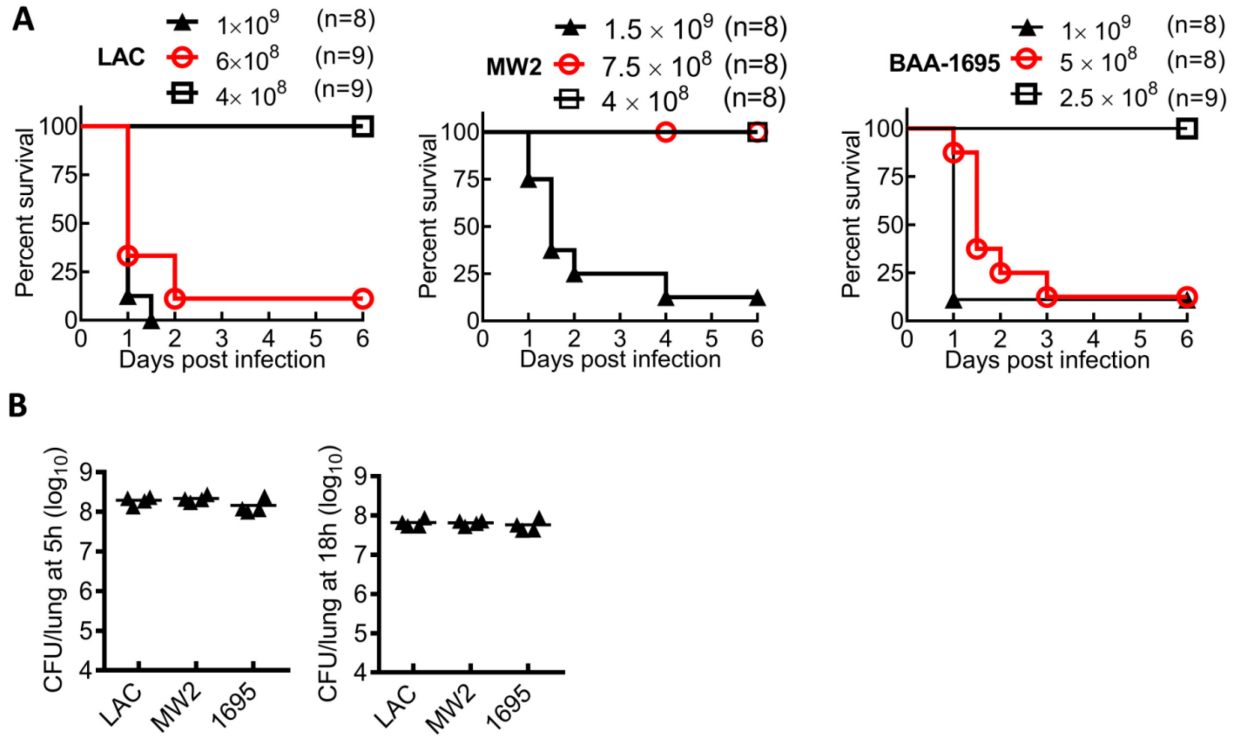
Supplemental Table S1: *Staphylococcus aureus* strains

Strain	Genotypes or characteristics	Colony color	Resource or reference
LAC13C	USA300, SCC*mec*IV , pvl^+	Yellow	(9)
LACJE2	USA300, SCC*mec*IV , pvl^+	Yellow	(9)
BAA 1695	(Non USA100 – 1100) MRSA, pvl^-	White	ATCC
MW2	USA400, MRSA	Yellow	ATCC
NEWMAN	MSSA	Yellow	ATCC
BAA 1692	USA100 SCC*mec*II , Agr type II, pvl^-	White	ATCC
BAA 1750	USA200, pvl^-	White	ATCC
BAA 1760	USA200, pvl^-	White	ATCC
BAA 15565	MSSA	Cream	ATCC
BAA 29213	MSSA	White	ATCC
BAA 1556	USA300, SCC*mec*IV , pvl^+	Cream	ATCC
BAA 1696	USA400, SCC*mec*IV , pvl^+	Yellow	ATCC
HFH-30522	USA500, SCC*mec*IV , pvl^-	Cream	BEI
NRS70/N315	USA100, SCC*mec*II, pvl^-	Yellow	BEI
NRS668	USA800, SCC*mec*IV , pvl^-	Cream	BEI
NRS689	USA700, SCC*mec*IV , pvl^-	Gray	BEI
NRS715	USA600, SCC*mec*IV , pvl^-	Gray	BEI
NRS 484	USA1100, SCC*mec*IV , pvl^+	Cream	BEI
NRS 155 (502AΔ*agr*)	MSSA	Gray	BEI
502A	MSSA	Gray	(20)
NRS 385	USA500, SCC*mec*IV , pvl^-	Yellow	BEI
NRS 686	USA500, SCC*mec*IV , pvl^-	Yellow	BEI
NRS 483	USA1000, SCC*mec*IV , pvl^+, enterotoxin B^+	Yellow	BEI

Supplemental Table S2: Mutant strains

Strain Number	Gene Symbol	Gene Disrupted	Resource or reference
NE1354	*hla*	Alpha-hemolysin precursor (41, 42)	(9)
NE1532	*agrA*	Accessory gene regulator protein A (43, 44)	(9)
NE1787	*srtA*	Sortase (45, 46)	(9)
NE1366	*katA*	Catalase (47)	(9)
NE1444	*crtM*	Squalene desaturase (12, 13)	(9)
NE1929	*dps*	General stress protein 20U (48)	(9)
NE1848	*pvl*	Panton-Valentine leukocidin, LukS-PV (49, 50)	(9)
NE518	*crtQ*	4,4'-diaponeurosporenoate glycosyl transferase	(9)
NE1224	*sod*	Fe/Mn family superoxide dismutase (51)	(9)
NE1622	*saeR*	Response regulator SaeR (52, 53)	(9)
NE1684	*arlR*	Response regulator arlR (54)	(9)
NE1193	*sarA*	Staphylococcal accessory regulator A (55)	(9)
NE543	*clfA*	Clumping Factor A (56, 57)	(9)
NE302	*cap5a*	Capsular polysaccharide biosynthesis protein Cap5A (58, 59)	(9)
NE295	*adsA*	Adenosine synthase A (60)	(9)
NE911	*ahpC*	Alkyl hydroperoxide reductase subunit C (47)	(9)
NE1373	*oatA*	O-acetyltransferase (61)	(9)
LAC13CΔ*psm*	*psm*	Phenol soluble modulins (55)	(16)
LAC13C *spa:kan*	*spa*	Surface protein A	(62)



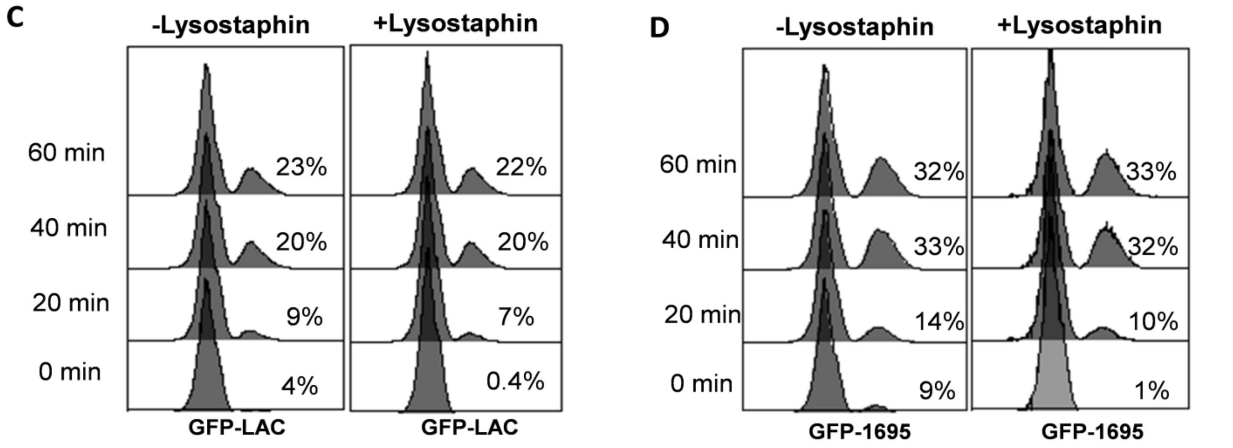
Supplemental Figure S1. The pathogenic success of prevalent CA-MRSA strains is not associated with their lethality in mice. (**A**) Survival of C57BL/6 mice after intranasal (i.n.) infection with high doses of LAC-JE2 (LAC), MW2 or BAA-1695. Data shown were combined from two independent experiments. (**B**) Numbers of bacteria remaining in the lungs 5 and 18 h after i.n. infection with 5×10^8 CFU/mouse *S. aureus*. Data shown are representative of two independent experiments.

A

Time (min)	-lysostaphin (cfu/100 MHS)	+lysostaphin (cfu/100 MHS)
0	510	0
60	770	860

B

Time (min)	-lysostaphin (cfu/100 MHS)	+lysostaphin (cfu/100 MHS)
0	530	3
60	520	540



Supplemental Figure S2. Alveolar macrophages are efficient in *S. aureus* uptake. Numbers of (**A**) GFP-LAC-JE2 and (**B**) GFP-1695 associated with MH-S cells, and (**C-D**) kinetics of GFP-LAC-JE2 (GFP-LAC) (**C**) and GFP-1695 (**D**) internalization by MH-S cells at 37^0C. MH-S cells were inoculated with *S. aureus* at MOI 10 and co-incubated for 60 min on ice, allowing bacteria binding onto the cells, before further incubation at 37^0C. At various time points, i.e., 0, 20, 40, and 60 min, extracellular bacteria were lysed by adding 20ug/ml of lysostaphin and incubating the cell cultures for 10 min at 37 °C. Data shown are representative of two independent experiments.