Vaccines to prevent antibiotic-resistant *Staphylococcus aureus* (MRSA) infections

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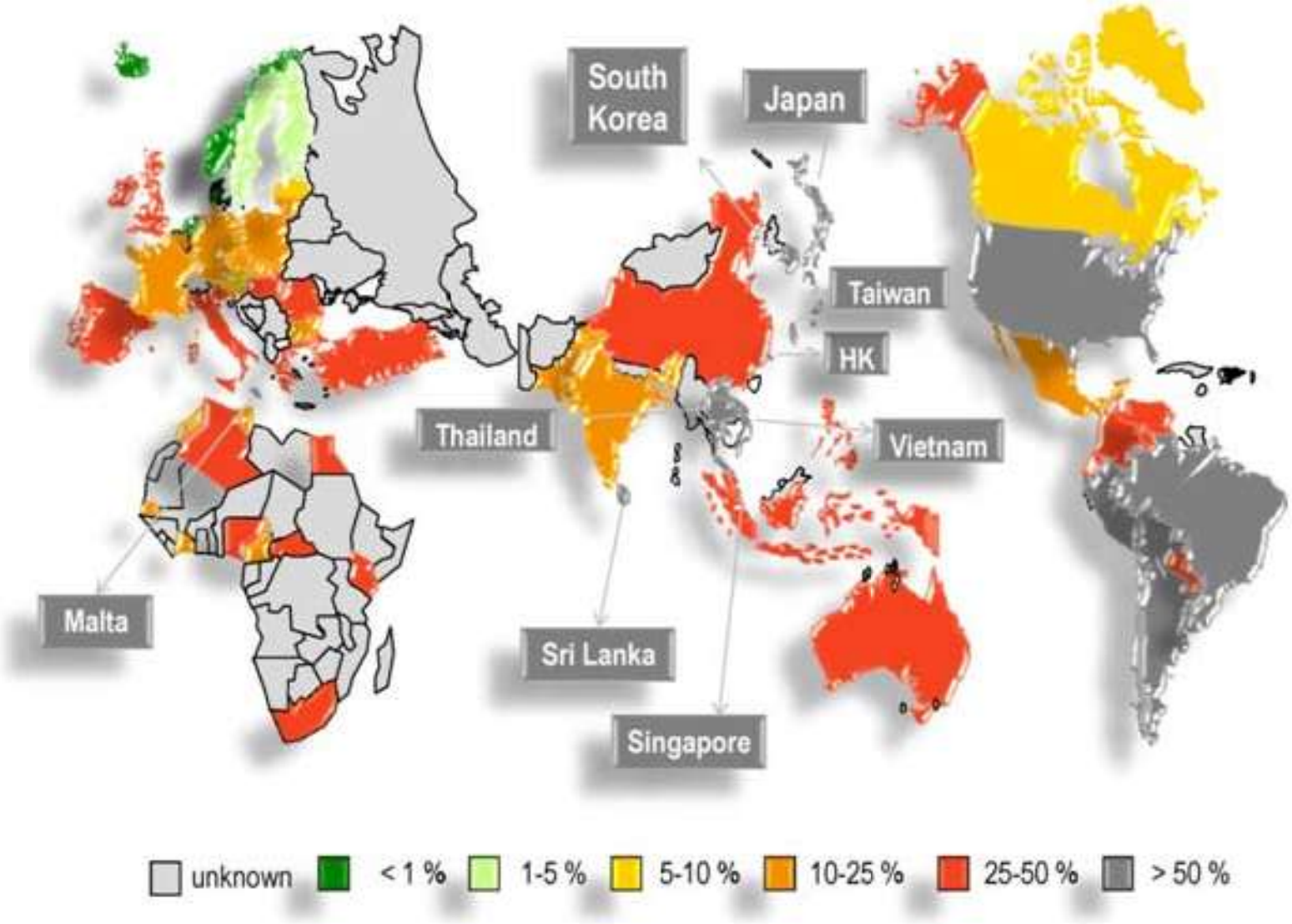
Global incidence of community-associated MRSA



J.R. Mediavilla *et al.* 2012, Curr. Opin. Microbiol. 15:588
S. Stefani *et al.* 2014, Int. J. Antimicrob. Agent. 39:273
H.W. Boucher and G.R. Corey 2008, CID 46: S344

S. aureus and MRSA infections in the United States of America

- *S. aureus* is a commensal of the human nares, skin and GI tract as well as an invasive pathogen
- US Department of Defense 2005-2010: *S. aureus* **skin and soft tissue infection (SSTI)** 122-168/100,000; **bacteremia** 3.6-6/100,000/year
- US DoD 2005-2010 annual incidence: community onset **MRSA** bacteremia 1.2-1.7/100,000; hospital onset 0.4-0.7/100,000
- 2010-2012 prospective study of 30,209 military trainees: 4.15% SSTI; 1.1 % MRSA SSTI
- **Very-low-birth-weight infants** (VLBW) in the US 60,000/yr: 3.6% late onset (>72 h post delivery) **bacteremia/meningitis** (26% mortality)
- **End-stage renal disease patients** undergoing **hemodialysis** annual incidence: invasive MRSA infection 4.2/100 patients
- MRSA infection in **surgical patients** occurs in spite of antibiotic prophylaxis (0.8-1%); **recurrence** is frequent (8-21% for bacteremia patients)
- Are there non-antibiotic means of preventing *Staphylococcus aureus* infection in high risk patients? Immunotherapy or vaccination?

M. Landrum *et al.* 2012, JAMA 308:50
M.W. Ellis *et al.* 2014, CID 58:1540

A. Shane *et al.* 2012, Pediatrics 129:914
D.B. Nguyen *et al.* 2013, CID 57:1393

At risk populations for *S. aureus* and MRSA infection in any country

- Healthy humans of all ages with attack rates of 1% - 3% per year (elevated for <10 yoa or >65 yoa)
- Individuals colonized with *S. aureus*/MRSA in the nares
- Hospital admissions: surgical patients, low-birth weight neonates, indwelling catheters, endotracheal intubation
- Immunosuppressive or cancer therapy
- Diabetics and endstage-renal disease patients
- Nursing home residents
- Patients with implantation of foreign bodies such as prosthetic joints, implants and heart valves
- ICU patients at risk for ventilator associated pneumonia

B. Spellberg and R.S. Daum 2012, Sem. Immunopathol. 34:355
A. DeDent *et al.* 2012, Sem. Immunopathol. 34:317
A. van Belkum *et al.* 2009, Infect. Genet. Evol. 9:32

Why are people not vaccinated against MRSA?

Past & current clinical trials towards for staphylococcal vaccines

Drug	Company	Mechanism	Target	Status
StaphVAX	**NABI**	**Vaccine**	**CP5/CP8**	**failed phase 3**
Altastaph	NABI	Antibody	CP5/CP8	ended
Pentastaph	NABI/GSK	Vaccine	CP5/CP8	failed phase 3
Aurograb	NOVARTIS	Antibody	lipoprotein	failed phase 3
Veronate	INHIBITEX	Antibody	ClfA	failed phase 3
Tefibazumab	INHIBITEX	Antibody	ClfA	ended
Pagibaximab	BIOSYNEXUS	Antibody	LTA	failed phase 3
V710	**MERCK**	**Vaccine**	**IsdB**	**failed phase 3**
SAR279356	SANOFI	Antibody	PNAG	ended
NVD3	NOVADIGM	Vaccine	Als3	phase 1/2
STEBVax	IBT	Vaccine	Seb	phase 1
SA3Ag	PFIZER	Vaccine	CP5+8/ClfA	phase 2b
PF-06290510	**PFIZER**	**Vaccine**	**CP5+8/ClfA/MntC**	**phase 2b**
MEDI4893	MEDIMMUNE	Antibody	Hla	phase 2b

StaphVAX phase III clinical trial (NABI)

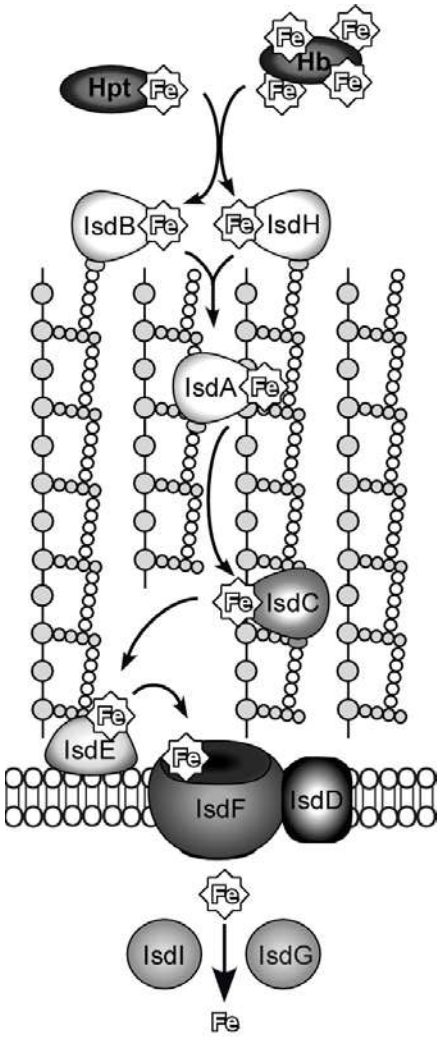
Is the capsular polysaccharide a protective antigen for MRSA?

- *Pseudomonas* exotoxin A conjugates to type 5 [→**4**)-3-O-Ac-β-D-ManNAc-(1→**4**)-α-D-FucNAc-(1→3)-β-D-FucNAc-(1→]$_n$ and type 8 [→**3**)-4-O-Ac-β-D-ManNAc-(1→**3**)-α-D-FucNAc-(1→3)-β-D-FucNAc-(1→]$_n$
- Double-blinded, placebo-controlled, randomized U.S. trial with 3,600 ESRD hemodialysis patients to prevent bloodstream infection
- Efficacy evaluated as reduction of *S. aureus* bloodstream infection from week 3-35. Patients were boosted with StaphVAX and followed for 6 more months.
- **No reduction in *S. aureus* bacteremia in the StaphVAX vs. placebo groups**
- **Clinical *S. aureus* isolates elaborate one of two capsular polysaccharides (type 5 and type 8); non-capsulating variants occur in approximately 20% and constitute the pandemic USA300 clone**
- ***S. aureus* CPS is neither required for colonization nor essential for the pathogenesis of SSTI and bloodstream infections**

H. Shinefield *et al.* 2002, NEJM 346:491; Matalon *et al.* 2012, ISSSI

V710 phase IIb/III trial (Merck)

Is the IsdB surface protein a protective antigen for MRSA?

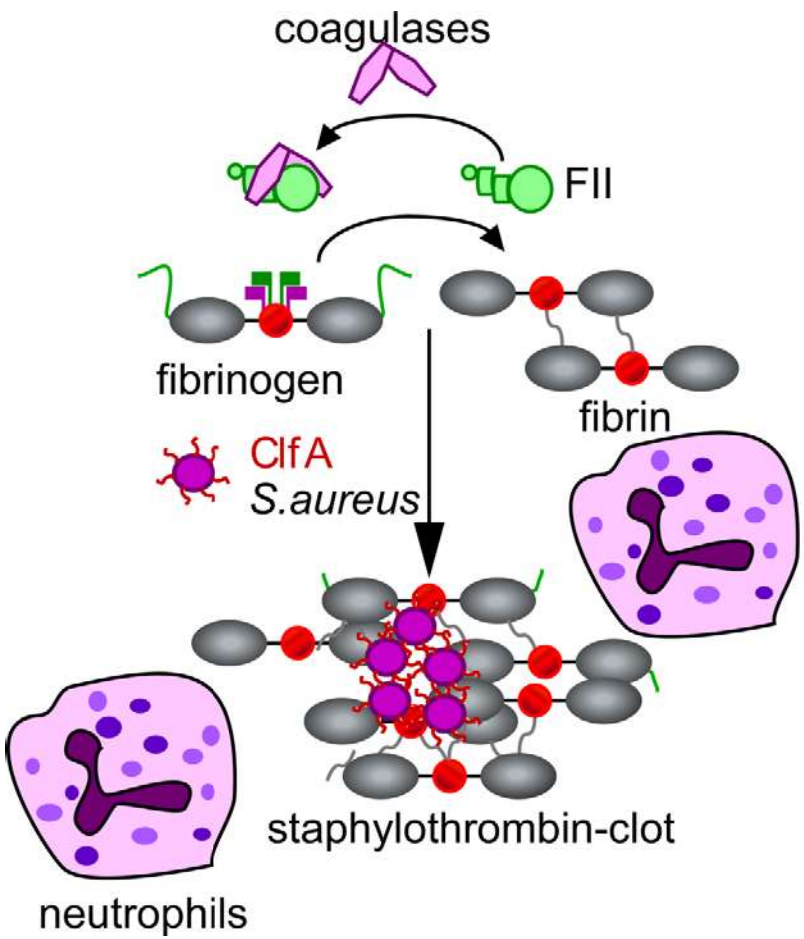


- IsdB, a surface protein and hemophore of *S. aureus*, was expressed in *Pichia pastoris* and purified in its heme-bound form (V710)
- Single, preoperative 60 µg V710 vaccine dose (no adjuvant); V710 vs. placebo in 7,045 thoracic surgery patients
- Endpoints: post-operative deep surgical wound infections and bacteremia over 90 days
- **V710 immunization did not protect against surgical wound infections or bacteremia**
- **Among patients who developed *S. aureus* infection, those in the vaccine group were about 5 times more likely to die, and to die of multi-organ system failure, than those in the placebo group**

V. G. Fowler *et al.* 2013, JAMA 309:1368

SA4Ag Phase IIb trial (Pfizer)

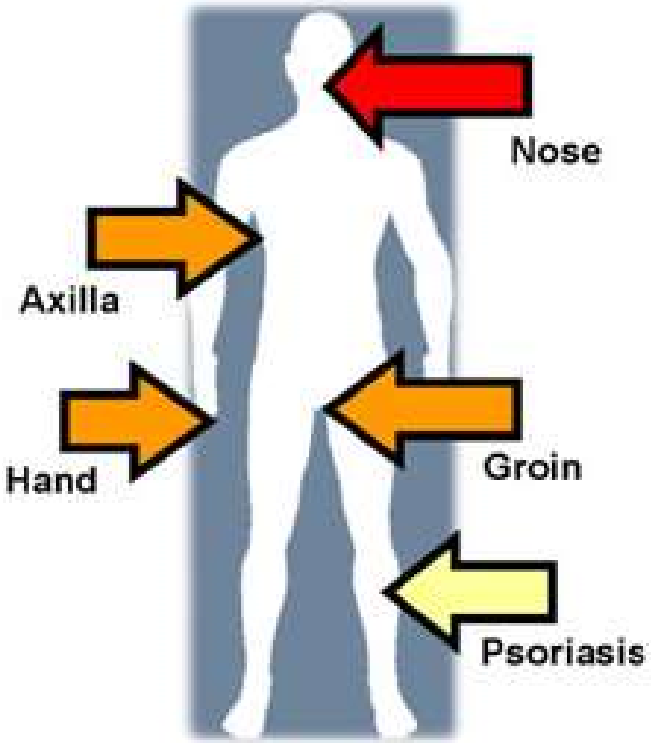
Is ClfA surface protein – together with CPS5/8 & MntC- a protective antigen for MRSA?



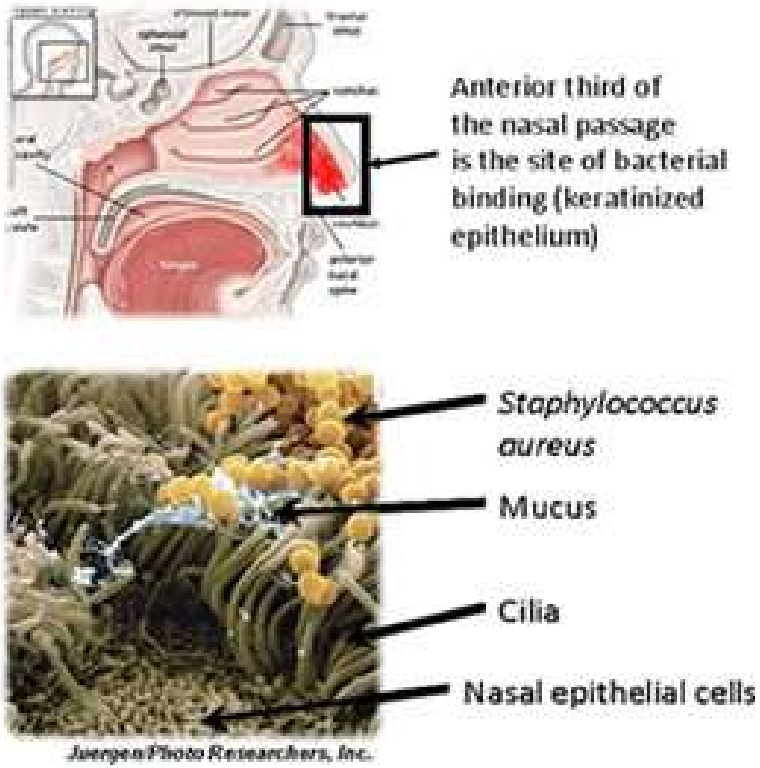
I.L. Scully *et al.* 2014, Front. Immunol. 5:109

- r*m*ClfA, the recombinant mature form of ClfA surface protein, a fibrinogen/fibrin binding protein of *S. aureus*, was purified
- CPS5 & CPS8 were purified and conjugated to CRM197
- Recombinant manganese transporter protein C (rP035A) was purified
- Phase IIb trial: Single, preoperative (10-60 days) 0.5 ml SA4Ag vaccine dose (no adjuvant); SA4Ag vs. placebo in 2,600 patients receiving posterior instrumented lumbar spinal fusion procedures
- **Endpoints: post-operative deep surgical wound infections or bacteremia over 180 days**
- Start date July 2015
- Estimated completion March 2017

Why do we need to get humans vaccinated against *S. aureus*/MRSA?



S. aureus/MRSA
Colonization Hotspots

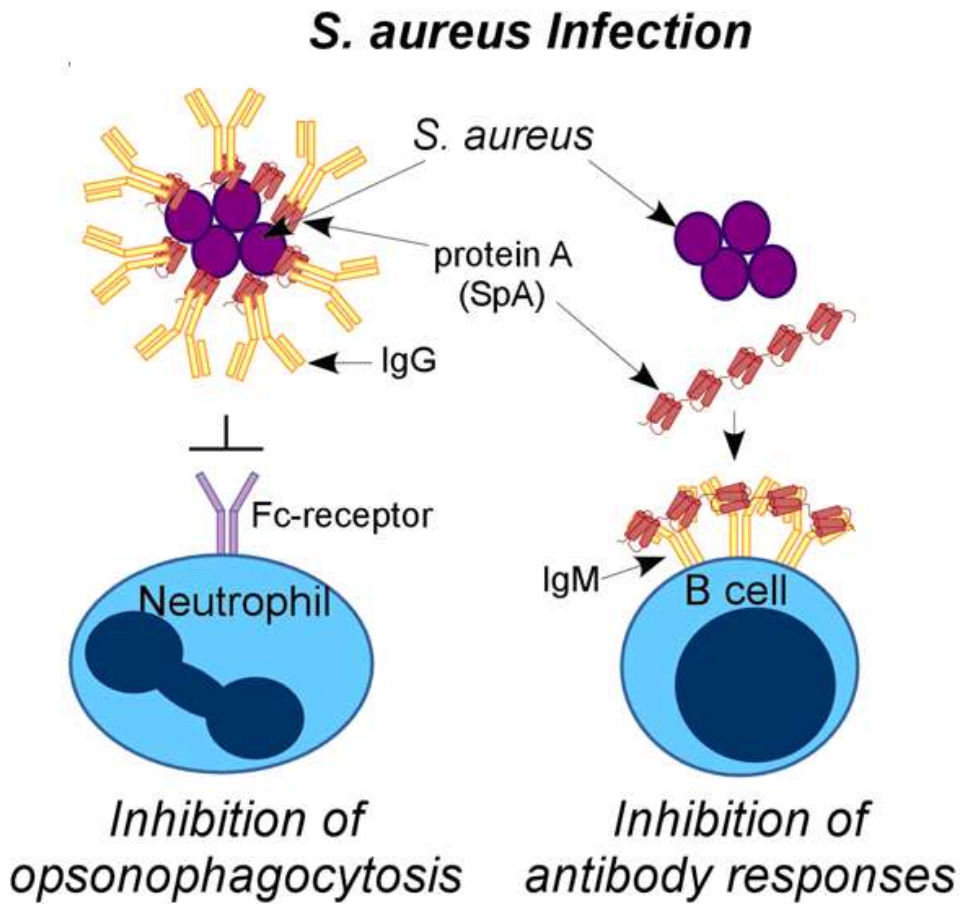


Characteristics of *S. aureus*
Nasal Colonization

- **Colonization promotes *S. aureus* SSTI, surgical wound infection and bacteremia**
- **Can vaccination reduce colonization with MRSA/*S. aureus*?**

A. van Belkum *et al.* 2009, Infect. Genet. Evol. 9:32

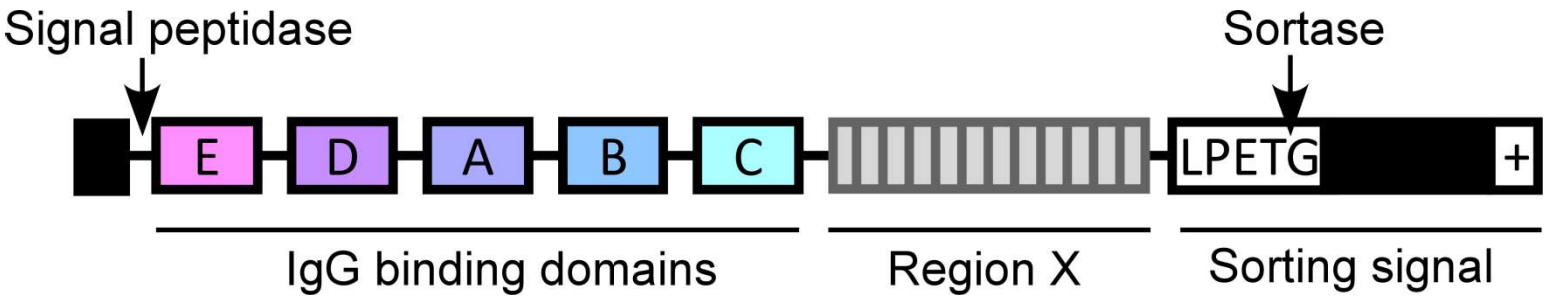
Staphylococcal protein A (SpA)



A. Forsgren & J. Sjöquist 1966, J. Immunol. 97:822
J. Sjöquist & G. Stahlenheim 1969, J. Immunol. 103:467
A. Forsgren & P. Quie 1974, J. Immunol. 112:1177

A. Forsgren *et al.* 1976 , Eur. J. Immunol. 6:207
C. Goodyear & G. Silverman 2003, JEM 197:1125

Staphylococcal protein A (SpA)

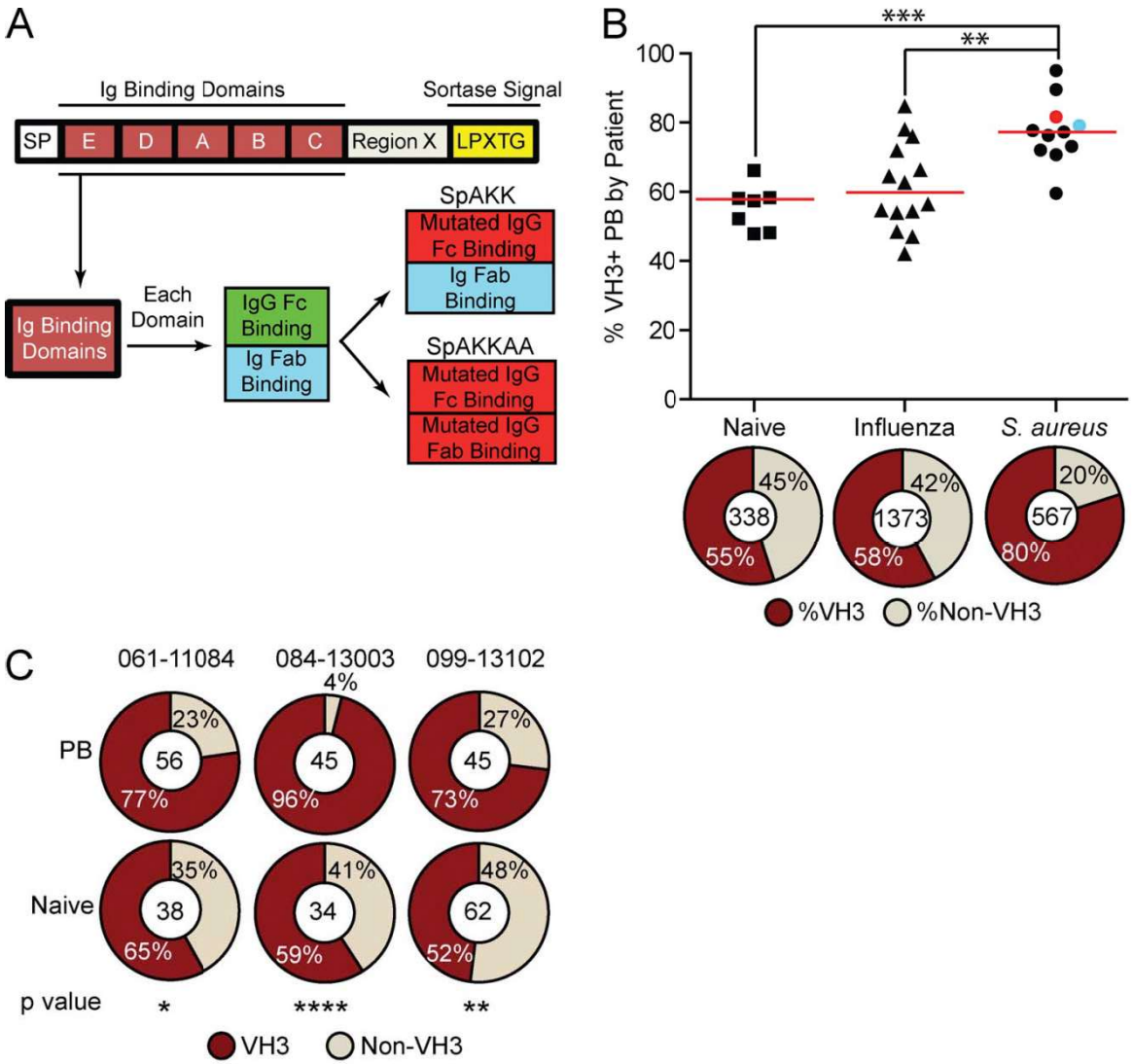


- Staphylococcal protein A, a surface protein, binds vertebrate immunoglobulin on the bacterial surface
- Protein A is comprised of five immunoglobulin binding domains with high sequence conservation
- Region X spans the cell wall; the sorting signal promotes SpA anchoring to peptidoglycan
- **Protein A blocks antibody-induced opsonophagocytosis of staphylococci and B cell development**
- **All nasal and clinical disease isolates express protein A**
- **Modulates mucosal immune response to *S. aureus* colonization of human nares**

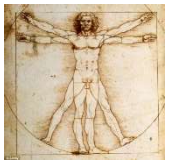
J. Sjöquist *et al.* 1972, Eur. J. Biochem. 29:572
J. Sjödahl 1977 , Eur. J. Biochem. 73:343
M. Uhlén *et al.* 1984, JBC 259:1695
B. Guss *et al*. 1984, Eur. J. Biochem. 138:413

O. Schneewind *et al.* 1992, Cell 70:267
O. Schneewind *et al.* 1995, Science 268:103
A. Cole *et al.* 2012, J. Immunol. 188:4925
A. Votintseva *et al*. 2014, BMC Microbiol. 14:63

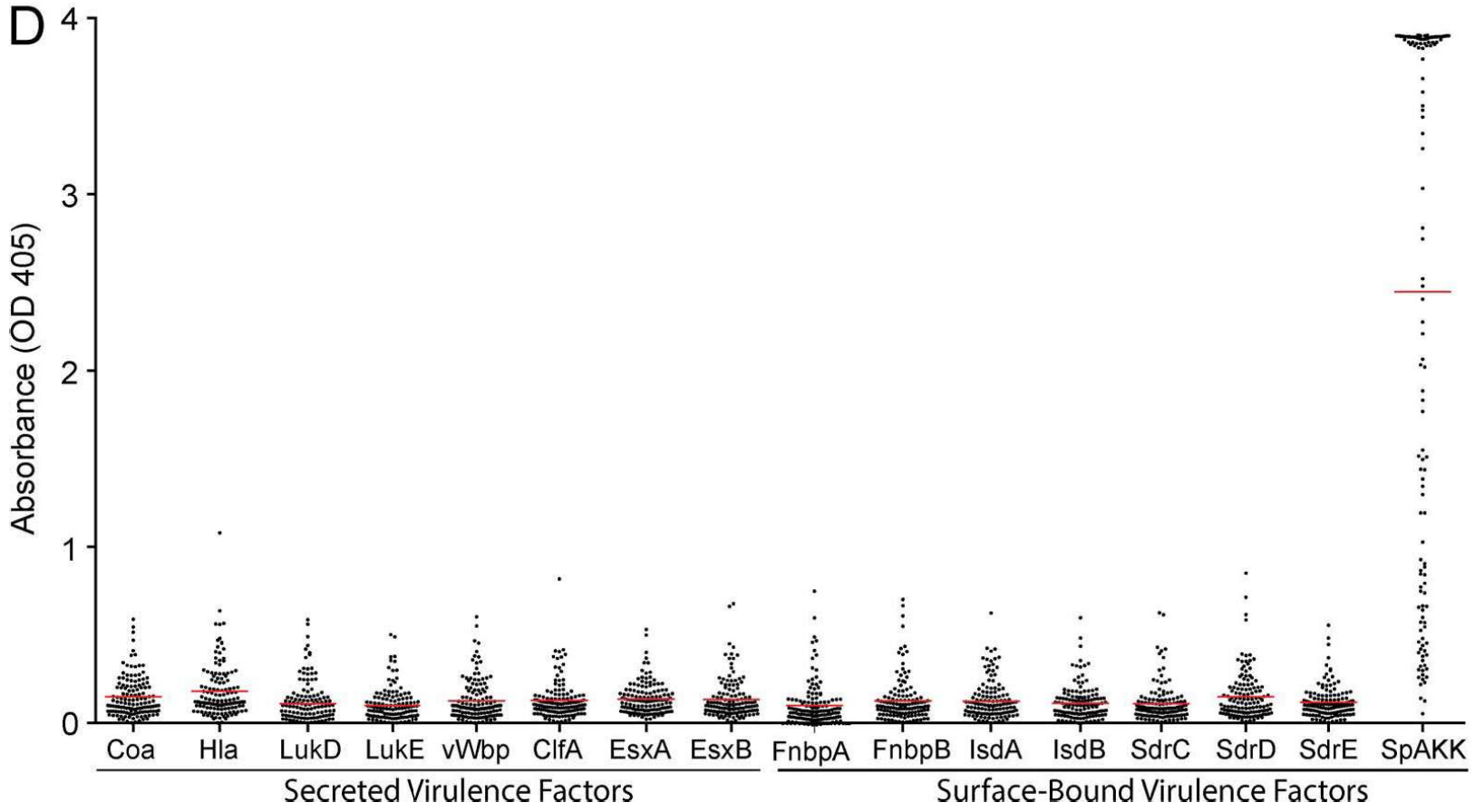
Staphylococcus aureus infection expands VH3 plasmablasts (PB) in human blood

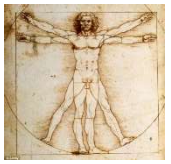


N. Pauli *et al.* 2014, JEM 211:2331



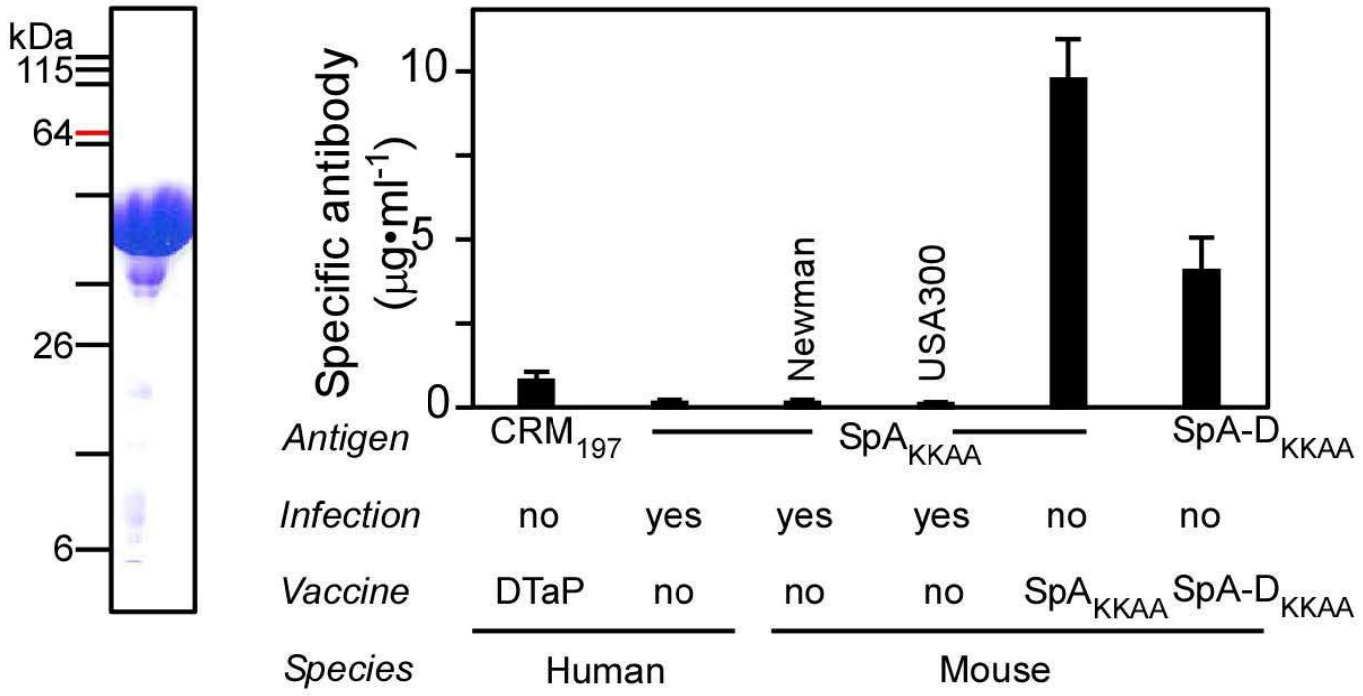
Antigen-specificity of PB BCRs (antibodies) in human blood with or without *S. aureus* infection





N. Pauli *et al.* 2014, JEM 211:2331

Non-toxigenic protein A vaccine (SpA_{KKAA})



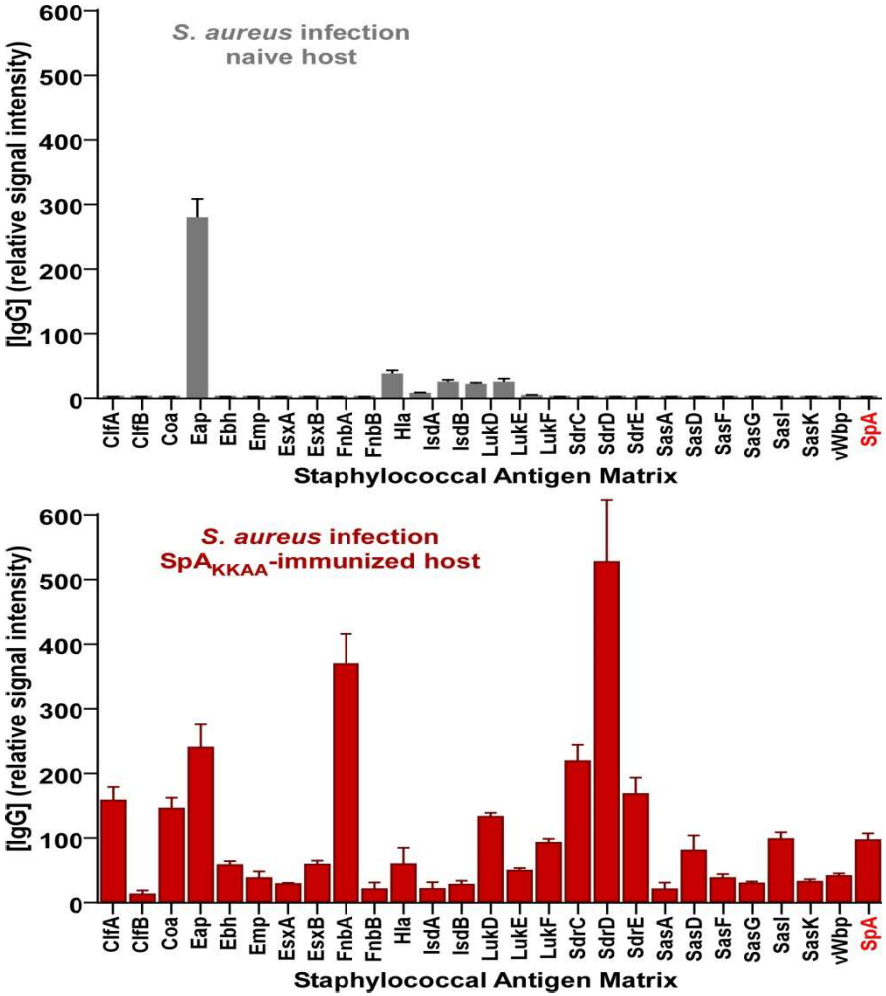
H. K. Kim *et al.* 2010, JEM 207:1863

Efficacy of the SpA_{KKAA} vaccine against *S. aureus* USA300 LAC infection in mice

Antigen	Staphylococcal load and abscess formation in renal tissue					
	log_{10} CFU	P-value	Reduction (log_{10}CFU)	IgG Titer	Number lesions	P-value
Mock	7.20 ± 0.24	–	–	<100	4.0 ± 0.8	–
SpA	6.81 ± 0.26	0.2819	0.39	476	3.3 ± 1.0	0.5969
SpA_{KKAA}	3.66 ± 0.76	0.0001	3.54	10,200	1.2 ± 0.5	0.0109

H. K. Kim *et al.* 2010, JEM 207:1863

Immune responses to *S. aureus* in SpA_{KKAA} vaccinated mice



H. K. Kim *et al.* 2010, JEM 207:1863

Summary

- MRSA, drug-resistant *S. aureus*, is a rising global health threat
- MRSA/*S. aureus* colonizes the nares of about one third of the human population and this increases the risk of infection
- MRSA/*S. aureus* pathogenesis is multifactorial; a clear protective antigen has not been identified; clonal pathogen
- Past (failed) vaccine trials tested single surface antigens (CPS, IsdB, ClfA, Hla) in patients at high risk to prevent MRSA/*S. aureus* infection
- Current vaccine trials test combinations of surface antigens in surgical patients to prevent patients at risk from infection
- SpA modulates human immune responses to MRSA/*S. aureus*; immunization with non-toxigenic SpA improves adaptive immune responses in animal models
- Vaccine testing for MRSA/*S. aureus* colonization should be considered

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