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

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CRUCELL, CONTRAFACT, GSK, MEDIMMUNE, NOVARTIS, PFIZER
Global incidence of community-associated MRSA

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
Why are people not vaccinated against MRSA?
Past & current clinical trials towards for staphylococcal vaccines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Mechanism</th>
<th>Target</th>
<th>Status</th>
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<tr>
<td>StaphVAX</td>
<td>NABI</td>
<td>Vaccine</td>
<td>CP5/CP8</td>
<td>failed phase 3</td>
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<td>Antibody</td>
<td>CP5/CP8</td>
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<td>V710</td>
<td>MERCK</td>
<td>Vaccine</td>
<td>IsdB</td>
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<td>Seb</td>
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<td>CP5+8/ClfA</td>
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<td>MEDI4893</td>
<td>MEDIMMUNE</td>
<td>Antibody</td>
<td>Hla</td>
<td>phase 2b</td>
</tr>
</tbody>
</table>
StaphVAX phase III clinical trial (NABI)

*Is the capsular polysaccharide a protective antigen for MRSA?*

- *Pseudomonas* exotoxin A conjugates to type 5 \([\rightarrow 4]-3\text{-}O\text{-}Ac\text{-}\beta\text{-}D\text{-}ManNAc\text{-}(1\rightarrow 4)\text{-}\alpha\text{-}D\text{-}FucNAc\text{-}(1\rightarrow 3)\text{-}\beta\text{-}D\text{-}FucNAc\text{-}(1\rightarrow)]_n\) and type 8 \([\rightarrow 3]-4\text{-}O\text{-}Ac\text{-}\beta\text{-}D\text{-}ManNAc\text{-}(1\rightarrow 3)\text{-}\alpha\text{-}D\text{-}FucNAc\text{-}(1\rightarrow 3)\text{-}\beta\text{-}D\text{-}FucNAc\text{-}(1\rightarrow)]_n\)
- 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

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?*

- **rmClfA**, 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

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

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

Staphylococcal protein A (SpA)

*Staphylococcus aureus* Infection

S. aureus → protein A (SpA) → IgG

Inhibition of opsonophagocytosis

Neutrophil

Fc-receptor

Inhibition of antibody responses

B cell

IgM


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**

M. Uhlén et al. 1984, JBC 259:1695
O. Schneewind et al. 1992, Cell 70:267
O. Schneewind et al. 1995, Science 268:103
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 \( \text{SpA}_{\text{KKAA}} \) vaccine against \( S. \text{ aureus} \) USA300 LAC infection in mice

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Staphylococcal load and abscess formation in renal tissue</th>
<th>IgG Titer</th>
<th>Number lesions</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mock</strong></td>
<td></td>
<td>&lt;100</td>
<td>4.0 ± 0.8</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>( \log_{10} \text{CFU} ) 7.20 ± 0.24</td>
<td>P-value</td>
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<tr>
<td><strong>SpA</strong></td>
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<td>0.39</td>
<td>3.3 ± 1.0</td>
<td>0.5969</td>
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<tr>
<td></td>
<td>( \log_{10} \text{CFU} ) 6.81 ± 0.26</td>
<td>0.2819</td>
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<tr>
<td><strong>SpA_{KKAA}</strong></td>
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<td>3.54</td>
<td>1.2 ± 0.5</td>
<td>0.0109</td>
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<tr>
<td></td>
<td>( \log_{10} \text{CFU} ) 3.66 ± 0.76</td>
<td>0.0001</td>
<td>10,200</td>
<td></td>
</tr>
</tbody>
</table>

H. K. Kim *et al.* 2010, JEM 207:1863
Immune responses to *S. aureus* in SpA\textsubscript{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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