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(54) **Title**: COMPOSITIONS AND METHODS RELATED TO PROTEIN A (SPA) ANTIBODIES AS AN ENHANCER OF IMMUNE RESPONSE

(57) **Abstract**: The present invention concerns methods and compositions for treating or preventing a bacterial infection, particularly infection by a Staphylococcus bacterium. The invention provides methods and compositions for stimulating an immune response against the bacteria. In certain embodiments, the methods and compositions involve a non-toxigenic Protein A (SpA) variant or an antibody directed thereto.

COMPOSITIONS AND METHODS RELATED TO PROTEIN A (SpA) ANTIBODIES AS AN ENHANCER OF IMMUNE RESPONSE

DESCRIPTION

BACKGROUND OF THE INVENTION

[0001] This application claims priority to U.S. Provisional Patent Application serial number 61/321,050 filed April 5, 2010, which is incorporated herein by reference in its entirety.

[0002] This invention was made with government support under AI057153, AI75258, AI052474, and GM007281 awarded by the National Institutes of Health. The United States government has certain rights in the invention.

I. FIELD OF THE INVENTION

[0003] The present invention relates generally to the fields of immunology, microbiology, and pathology. More particularly, it concerns methods and compositions for enhancing an immune response against a bacterial antigen.

II. BACKGROUND

[0004] The number of both community acquired and hospital acquired infections have increased over recent years with the increased use of intravascular devices. Hospital acquired (nosocomial) infections are a major cause of morbidity and mortality, more particularly in the United States, where it affects more than 2 million patients annually. The most frequent infections are urinary tract infections (33% of the infections), followed by pneumonia (15.5%), surgical site infections (14.8%) and primary bloodstream infections (13%) (Emorl and Gaynes, 1993).

[0005] The major nosocomial pathogens include *Staphylococcus aureus*, coagulase-negative Staphylococci (mostly *Staphylococcus epidermidis*), *enterococcus* spp., *Escherichia coli* and *Pseudomonas aeruginosa*. Although these pathogens cause approximately the same number of infections, the severity of the disorders they can produce combined with the frequency of antibiotic resistant isolates balance this ranking towards *S. aureus* and *S. epidermidis* as being the most significant nosocomial pathogens.

[0006] Staphylococci can cause a wide variety of diseases in humans and other animals through either toxin production or invasion. Staphylococcal toxins are also a common cause of food poisoning, as the bacteria can grow in improperly-stored food.

[0007] *Staphylococcus epidermidis* is a normal skin commensal, which is also an important opportunistic pathogen responsible for infections of impaired medical devices and infections at sites of surgery. Medical devices infected by *S. epidermidis* include cardiac pacemakers, cerebrospinal fluid shunts, continuous ambulatory peritoneal dialysis catheters, orthopedic devices and prosthetic heart valves.

[0008] *Staphylococcus aureus* is the most common cause of nosocomial infections with a significant morbidity and mortality. It is the cause of some cases of osteomyelitis, endocarditis, septic arthritis, pneumonia, abscesses, and toxic shock syndrome. *S. aureus* can survive on dry surfaces, increasing the chance of transmission. Any *S. aureus* infection can cause the staphylococcal scalded skin syndrome, a cutaneous reaction to exotoxin absorbed into the bloodstream. It can also cause a type of septicemia called pyaemia that can be life-threatening. Problematically, Methicillin-resistant Staphylococcus aureus (MRSA) has become a major cause of hospital-acquired infections.

[0009] *S. aureus* and *S. epidermidis* infections are typically treated with antibiotics, with penicillin being the drug of choice, whereas vancomycin is used for methicillin resistant isolates. The percentage of staphylococcal strains exhibiting wide-spectrum resistance to antibiotics has become increasingly prevalent, posing a threat for effective antimicrobial therapy. In addition, the recent emergence of vancomycin resistant *S. aureus* strain has aroused fear that MRSA strains are emerging and spreading for which no effective therapy is available.

[0010] An alternative to antibiotic treatment for staphylococcal infections is under investigation that uses antibodies directed against staphylococcal antigens. This therapy involves administration of polyclonal antisera (WO00/15238, WO00/12132) or treatment with monoclonal antibodies against lipoteichoic acid (WO98/57994).

[0011] An alternative approach would be the use of active vaccination to generate an immune response against staphylococci. The *S. aureus* genome has been sequenced and many of the coding sequences have been identified (WO02/094868, EP0786519), which can lead to the identification of potential antigens. The same is true for *S. epidermidis* (WO01/34809). As a refinement of this approach, others have identified proteins that are

recognized by hyperimmune sera from patients who have suffered staphylococcal infection (WO01/98499, WO02/059148).

[0012] *S. aureus* secretes a plethora of virulence factors into the extracellular milieu (Archer, 1998; Dinges *et al.*, 2000; Foster, 2005; Shaw *et al.*, 2004; Sibbald *et al.*, 2006). Like most secreted proteins, these virulence factors are translocated by the Sec machinery across the plasma membrane. Proteins secreted by the Sec machinery bear an N-terminal leader peptide that is removed by leader peptidase once the pre-protein is engaged in the Sec translocon (Dalbey and Wickner, 1985; van Wely *et al.*, 2001). Recent genome analysis suggests that Actinobacteria and members of the Firmicutes encode an additional secretion system that recognizes a subset of proteins in a Sec-independent manner (Pallen, 2002). ESAT-6 (early secreted antigen target 6 kDa) and CFP-10 (culture filtrate antigen 10 kDa) of *Mycobacterium tuberculosis* represent the first substrates of this novel secretion system termed ESX-1 or Snm in *M. tuberculosis* (Andersen *et al.*, 1995; Hsu *et al.*, 2003; Pym *et al.*, 2003; Stanley *et al.*, 2003). In *S. aureus,* two ESAT-6 like factors designated EsxA and EsxB are secreted by the Ess pathway (ESAT-6 secretion system) (Burts *et al.*, 2005).

[0013] The first generation of vaccines targeted against *S. aureus* or against the exoproteins it produces have met with limited success (Lee, 1996). There remains a need to develop effective vaccines against staphylococcal infections. Additional compositions for treating staphylococcal infections are also needed.

SUMMARY OF THE INVENTION

[0014] Protein A (SpA) (SEQ ID NO:33), a cell wall anchored surface protein of *Staphylococcus aureus*, provides for bacterial evasion from innate and adaptive immune responses. Protein A binds immunoglobulins at their Fc portion, interacts with the VH3 domain of B cell receptors inappropriately stimulating B cell proliferation and apoptosis, binds to von Willebrand factor A1 domains to activate intracellular clotting, and also binds to the TNF Receptor-1 to contribute to the pathogenesis of staphylococcal pneumonia. Due to the fact that Protein A captures immunoglobulin and displays toxic attributes, the possibility that this surface molecule may function as a vaccine in humans has not been rigorously pursued. Here the inventors demonstrate that antibodies specific for Protein A stimulate or enhance an immune response to other bacterial antigens.

[0015] Embodiments include the use of antibodies that specifically bind Protein A and peptides that elicit such antibodies in methods and compositions for the treatment,

attenuation, or prevention of bacterial and/or staphylococcal infection and/or pathological conditions resulting from such an infection. Furthermore, the present invention provides methods and compositions that can be used to treat (*e.g.*, limiting staphylococcal abscess formation and/or persistence in a subject), attenuate, or prevent bacterial infection or pathological conditions resulting from such infection.

[0016] In certain aspects, methods for stimulating or enhancing an immune response involve administering to the subject an effective amount of an isolated protein A (SpA) specific antibody and a bacterial antigen. The bacterial antigen or immunogenic fragment can be administered before, after, and/or concurrently with the protein A specific antibody. The bacterial antigen or immunogenic fragment and the Protein A specific antibody can be administered in the same or a separate composition.

[0017] In a further aspect, the methods include stimulating or enhancing an immune repsonse involving administering an SpA polypeptide variant prior to or after the administration of one or more bacterial antigens. The SpA polypeptide variant can be administered 12, 24, 48, 72 hours, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 days before or after administration of one or more bacterial antigen. In certain aspects, a subject administered a SpA polypeptide variant can be evalutated for production of SpA specific antibodies prior to administration of one or more bacterial antigens or bacteria. In certain embodiments a SpA polypeptide variant can be administered 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more times prior to or after administration of one or more bacterial antigen or bacteria. In certain embodiments the SpA variant is a full length SpA variant comprising a variant A, B, C, D, and/or E domain. In certain aspects, the SpA variant comprises or consists of the amino acid sequence that is 80, 90, 95, 98, 99, or 100% identical to the amino acid sequence of SEQ ID NO:34. In other embodiments the SpA variant comprises a segment of SpA. The SpA segment can comprise at least or at most 1, 2, 3, 4, 5 or more IgG binding domains. The IgG domains can be at least or at most 1, 2, 3, 4, 5 or more variant A, B, C, D, or E domains. In certain aspects the SpA variant comprises at least or at most 1, 2, 3, 4, 5, or more variant A domains. In a further aspect the SpA variant comprises at least or at most 1, 2, 3, 4, 5, or more variant B domains. In still a further aspect the SpA variant comprises at least or at most 1, 2, 3, 4, 5, or more variant C domains. In yet a further aspect the SpA variant comprises at least or at most 1, 2, 3, 4, 5, or more variant D domains. In certain aspects the SpA variant comprises at least or at most 1, 2, 3, 4, 5, or more variant E domains. In a further aspect the SpA variant comprises a combination of A, B, C, D, and E domains in various combinations and permutations. The

combinations can include all or part of a SpA signal peptide segment, a SpA region X segment, and/or a SpA sorting signal segment. In other aspects the SpA variant does not include a SpA signal peptide segment, a SpA region X segment, and/or a SpA sorting signal segment. In certain aspects a variant A domain comprises a substitution at position(s) 7, 8, 34, and/or 35 of SEQ ID NO:4. In another aspect a variant B domain comprises a substitution at position(s) 7, 8, 34, and/or 35 of SEQ ID NO:6. In still anther aspect a variant C domain comprises a substitution at position(s) 7, 8, 34, and/or 35 of SEQ ID NO:5. In certain aspects a variant D domain comprises a substitution at position(s) 9, 10, 36, and/or 37 of SEQ ID NO:2. In a further aspect a variant E domain comprises a substitution at position(s) 6, 7, 33, and/or 34 of SEQ ID NO:3. In certain aspects, an SpA domain D variant or its equivalent can comprise a mutation at position 9 and 36; 9 and 37; 9 and 10; 36 and 37; 10 and 36; 10 and 37; 9, 36, and 37; 10, 36, and 37, 9, 10 and 36; or 9, 10 and 37 of SEQ ID NO:2. In a further aspect, analogous mutations can be included in one or more of domains A, B, C, or E. In further aspects, the amino acid glutamine (Q) at position 9 of SEQ ID NO:2 (or its analogous amino acid in other SpA domains) can be replaced with an alanine (A), an asparagine (N), an aspartic acid (D), a cysteine (C), a glutamic acid (E), a phenylalanine (F), a glycine (G), a histidine (H), an isoleucine (I), a lysine (K), a leucine (L), a methionine (M), a proline (P), a serine (S), a threonine (T), a valine (V), a tryptophane (W), or a tyrosine (Y). In some aspects the glutamine at position 9 can be substituted with an arginine (R). In a further aspect, the glutamine at position 9 of SEQ ID NO:2, or its equivalent, can be substituted with a lysine or a glycine. Any 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more of the substitutions can be explicitly excluded. In another aspect, the amino acid glutamine (Q) at position 10 of SEQ ID NO:2 (or its analogous amino acid in other SpA domains) can be replaced with an alanine (A), an asparagine (N), an aspartic acid (D), a cysteine (C), a glutamic acid (E), a phenylalanine (F), a glycine (G), a histidine (H), an isoleucine (I), a lysine (K), a leucine (L), a methionine (M), a proline (P), a serine (S), a threonine (T), a valine (V), a tryptophane (W), or a tyrosine (Y). In some aspects the glutamine at position 10 can be substituted with an arginine (R). In a further aspect, the glutamine at position 10 of SEQ ID NO:2, or its equivalent, can be substituted with a lysine or a glycine. Any 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more of the substitutions can be explicitly excluded. In certain aspects, the aspartic acid (D) at position 36 of SEQ ID NO:2 (or its analogous amino acid in other SpA domains) can be replaced with an alanine (A), an asparagine (N), an arginine (R), a cysteine (C), a phenylalanine (F), a glycine (G), a histidine (H), an isoleucine (I), a lysine (K), a leucine (L), a methionine (M), a proline (P), a glutamine (Q), a serine (S), a threonine

(T), a valine (V), a tryptophane (W), or a tyrosine (Y). In some aspects the aspartic acid at position 36 can be substituted with a glutamic acid (E). In certain aspects, an aspartic acid at position 36 of SEQ ID NO:2, or its equivalent, can be substituted with an alanine or a serine. Any 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more of the substitutions can be explicitly excluded. In another aspect, the aspartic acid (D) at position 37 of SEQ ID NO:2 (or its analogous amino acid in other SpA domains) can be replaced with an alanine (A), an asparagine (N), an arginine (R), a cysteine (C), a phenylalanine (F), a glycine (G), a histidine (H), an isoleucine (I), a lysine (K), a leucine (L), a methionine (M), a proline (P), a glutamine (Q), a serine (S), a threonine (T), a valine (V), a tryptophane (W), or a tyrosine (Y). In some aspects the aspartic acid at position 37 can be substituted with a glutamic acid (E). In certain aspects, an aspartic acid at position 37 of SEQ ID NO:2, or its equivalent, can be substituted with an alanine or a serine. Any 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more of the substitutions can be explicitly excluded. In a particular embodiment the amino at position 9 of SEQ ID NO:2 (or an analogous amino acid in another SpA domain) is replaced by an alanine (A), a glycine (G), an isoleucine (I), a leucine (L), a proline (P), a serine (S), or a valine (V). In certain aspects the amino acid at position 9 of SEQ ID NO:2 is replaced by a glycine. In a further aspect the amino acid at position 9 of SEQ ID NO:2 is replaced by a lysine. In a particular embodiment the amino at position 10 of SEQ ID NO:2 (or an analogous amino acid in another SpA domain) is replaced by an alanine (A), a glycine (G), an isoleucine (I), a leucine (L), a proline (P), a serine (S), or a valine (V). In certain aspects the amino acid at position 10 of SEQ ID NO:2 is replaced by a glycine. In a further aspect the amino acid at position 10 of SEQ ID NO:2 is replaced by a lysine. In a particular embodiment the amino at position 36 of SEQ ID NO:2 (or an analogous amino acid in another SpA domain) is replaced by an alanine (A), a glycine (G), an isoleucine (I), a leucine (L), a proline (P), a serine (S), or a valine (V). In certain aspects the amino acid at position 36 of SEQ ID NO:2 is replaced by a serine. In a further aspect the amino acid at position 36 of SEQ ID NO:2 is replaced by an alanine. In a particular embodiment the amino at position 37 of SEQ ID NO:2 (or an analogous amino acid in another SpA domain) is replaced by an alanine (A), a glycine (G), an isoleucine (I), a leucine (L), a proline (P), a serine (S), or a valine (V). In certain aspects the amino acid at position 37 of SEQ ID NO:2 is replaced by a serine. In a further aspect the amino acid at position 37 of SEQ ID NO:2 is replaced by an alanine. In certain aspects the SpA variant includes a substitution of (a) one or more amino acid substitution in an IgG Fc binding sub-domain of SpA domain A, B, C, D, and/or E that disrupts or decreases binding to IgG Fc, and (b) one or more amino acid substitution in a V_H3 binding sub-domain of SpA domain A, B,

C, D, and/or E that disrupts or decreases binding to V_H3. In still further aspects the amino acid sequence of a SpA variant comprises an amino acid sequence that is at least 50%, 60%, 70%, 80%, 90%, 95%, or 100% identical, including all values and ranges there between, to the amino acid sequence of SEQ ID NOs:2-6. In a further aspect the SpA variant includes (a) one or more amino acid substitution in an IgG Fc binding sub-domain of SpA domain D, or at a corresponding amino acid position in other IgG domains, that disrupts or decreases binding to IgG Fc, and (b) one or more amino acid substitution in a V_H3 binding sub-domain of SpA domain D, or at a corresponding amino acid position in other IgG domains, that disrupts or decreases binding to V_H3. In certain aspects amino acid residue F5, Q9, Q10, S11, F13, Y14, L17, N28, I31, and/or K35 (SEQ ID NO:2, QQNNFNKDQQSAFYEILNMPNLNEAQRNGFIQSLKDDPSQSTNVLGEAKKLNES) of the IgG Fc binding sub-domain of domain D are modified or substituted. In certain aspects amino acid residue Q26, G29, F30, S33, D36, D37, Q40, N43, and/or E47 (SEQ ID NO:2) of the V_H3 binding sub-domain of domain D are modified or substituted such that binding to Fc or V_H3 is attenuated. In further aspects corresponding modifications or substitutions can be engineered in corresponding positions of the domain A, B, C, and/or E. Corresponding positions are defined by alignment of the domain D amino acid sequence with one or more of the amino acid sequences from other IgG binding domains of SpA. In certain aspects the amino acid substitution can be any of the other 20 amino acids. In a further aspect conservative amino acid substitutions can be specifically excluded from possible amino acid substitutions. In other aspects only non-conservative substitutions are included. In any event, any substitution or combination of substitutions that reduces the binding of the domain such that SpA toxicity is significantly reduced is contemplated. The significance of the reduction in binding refers to a variant that produces minimal to no toxicity when introduced into a subject and can be assessed using in vitro methods described herein. In certain embodiments, a variant SpA comprises at least or at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more variant SpA domain D peptides. In certain aspects 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 or more amino acid residues of the variant SpA are substituted or modified - including but not limited to amino acids F5, Q9, Q10, S11, F13, Y14, L17, N28, I31, and/or K35 (SEQ ID NO:2) of the IgG Fc binding sub-domain of domain D and amino acid residue Q26, G29, F30, S33, D36, D37, Q40, N43, and/or E47 (SEQ ID NO:2) of the V_H3 binding sub-domain of domain D. In one aspect of the invention glutamine residues at position 9 and/or 10 of SEQ ID NO:2 (or corresponding positions in other domains) are mutated. In another aspect, aspartic acid residues 36 and/or 37 of SEQ ID NO:2 (or

corresponding positions in other domains) are mutated. In a further aspect, glutamine 9 and 10, and aspartic acid residues 36 and 37 are mutated. Purified non-toxigenic SpA or SpA-D mutants/variants described herein are no longer able to significantly bind (i.e., demonstrate attenuated or disrupted binding affinity) Fcγ or $F(ab)_2$ V_H3 and also do not stimulate B cell apoptosis. These non-toxigenic Protein A variants can be used to enhance or stimulate an immune reponse against a bacterial antigen , thereby raising humoral immune responses that confer protective immunity against *S. aureus* challenge. Compared to wild-type full-length Protein A or the wild-type SpA-domain D, immunization with SpA-D variants resulted in an increase in Protein A specific antibody. Using a mouse model of staphylococcal challenge and abscess formation, it was observed that immunization with the non-toxigenic Protein A variants generated significant protection from staphylococcal infection and abscess formation. As virtually all *S. aureus* strains express Protein A, immunization of humans with the non-toxigenic Protein A variants can neutralize this virulence factor and thereby establish protective immunity. In certain aspects the protective immunity protects or ameliorates infection by drug resistant strains of Staphylococcus, such as USA300 and other MRSA strains. In certain embodiments 1, 2, 3, 4, 5, 6,7 ,8 ,9 10 or more SpA variants can be specifically excluded from the claimed invention.

[0018] Bacterial antigens include, but are not limited to (i) a secreted virulence factor, and/or a cell surface protein or peptide, or (ii) a recombinant nucleic acid molecule encoding a secreted virulence factor, and/or a cell surface protein or peptide. The bacterial antigen can include one or more of at least or at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 additional staphylococcal antigen or immunogenic fragment thereof, including, but not limited to FnBpA, FnBpB, LukD (GI:2765304), LukE (GI:2765303), LukF (GI:12231006), SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, 52kDa vitronectin binding protein (WO 01/60852), Aaa (GenBank CAC80837), Aap (GenBank accession AJ249487), Ant (GenBank accession NP_372518), autolysin glucosaminidase, autolysin amidase, Cna, collagen binding protein (US6288214), EFB (FIB), Elastin binding protein (EbpS), EPB, FbpA, fibrinogen binding protein (US6008341), Fibronectin binding protein (US5840846), FnbA, FnbB, GehD (US 2002/0169288), HarA, HBP, Immunodominant ABC transporter, IsaA/PisA, laminin receptor, Lipase GehD, MAP, Mg2+ transporter, MHC II analogue (US5648240), MRPII, Npase, RNA III activating protein (RAP), SasA, SasB, SasC, SasD, SasK,SBI, SdrF(WO

00/12689), SdrG / Fig (WO 00/12689), SdrH (WO 00/12689), SEA exotoxins (WO 00/02523), SEB exotoxins (WO 00/02523), SitC and Ni ABC transporter, SitC/MntC/saliva binding protein (US 5,801,234), SsaA, SSP-1, SSP-2, and/or Vitronectin binding protein (see PCT publications WO2007/113222, WO2007/113223, WO2006/032472, WO2006/032475, WO2006/032500, each of which is incorporated herein by reference in their entirety). In certain aspects, the bacterial antigen is a staphylococcal antigen. The staphylococcal antigen can be selected from the group consisting of: FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh and immunogenic fragments thereof. In certain aspects the bacterial antigens include one or more of sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid (SEQ ID NO:155) polypeptide or immunogenic fragment thereof (see PCT publication WO/2010/119343, which is incorporated herein by reference in its entirety).

[0019] In certain embodiments, the claimed invention specifically excludes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of FnBpA, FnBpB, LukD (GI:2765304), LukE (GI:2765303), LukF (GI:12231006), SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, 52kDa vitronectin binding protein (WO 01/60852), Aaa (GenBank CAC80837), Aap (GenBank accession AJ249487), Ant (GenBank accession NP_372518), autolysin glucosaminidase, autolysin amidase, Cna, collagen binding protein (US6288214), EFB (FIB), Elastin binding protein (EbpS), EPB, FbpA, fibrinogen binding protein (US6008341), Fibronectin binding protein (US5840846), FnbA, FnbB, GehD (US 2002/0169288), HarA, HBP, Immunodominant ABC transporter, IsaA/PisA, laminin receptor, Lipase GehD, MAP, Mg2+ transporter, MHC II analogue (US5648240), MRPII,

Npase, RNA III activating protein (RAP), SasA, SasB, SasC, SasD, SasK,SBI, SdrF(WO 00/12689), SdrG / Fig (WO 00/12689), SdrH (WO 00/12689), SEA exotoxins (WO 00/02523), SEB exotoxins (WO 00/02523), SitC and Ni ABC transporter, SitC/MntC/saliva binding protein (US 5,801,234), SsaA, SSP-1, SSP-2, and/or Vitronectin binding protein (see PCT publications WO2007/113222, WO2007/113223, WO2006/032472, WO2006/032475, WO2006/032500, each of which is incorporated herein by reference in their entirety). In certain aspects, the bacterial antigen is a staphylococcal antigen. The staphylococcal antigen can be selected from the group consisting of: FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh and immunogenic fragments thereof. In certain aspects the bacterial antigens include one or more of sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof

[0020] Certain embodiments are directed to an immunogenic composition comprising an isolated Protein A (SpA) specific antibody and a bacterial antigen, wherein the Protein A specific antibody enhances an immune response to the bacterial antigen. In certain aspects, the antibody is a polyclonal antibody, a monoclonal antibody, or an antibody fragment. In still further aspects, the bacterial antigen is comprised in or on a bacteria. The bacteria can be an attenuated bacteria, in particular an attenuated staphylococcal bacteria.

[0021] In certain embodiments a subject is administered an SpA polypeptide variant (before or after administering one or more bacterial antigens) or administered a protein A specific antibody in combination with one or more bacterial antigens seleted from: FnBpA antigen or immunogenic fragment thereof, FnBpB antigen or immunogenic fragment thereof, LukD antigen or immunogenic fragment thereof, LukE antigen or immunogenic fragment

thereof, LukF antigen or immunogenic fragment thereof, SasA antigen or immunogenic fragment thereof, SasD antigen or immunogenic fragment thereof, SasG antigen or immunogenic fragment thereof, SasI antigen or immunogenic fragment thereof, SasK antigen or immunogenic fragment thereof, SpA (and variants thereof) antigen or immunogenic fragment thereof, Eap antigen or immunogenic fragment thereof, Ebh antigen or immunogenic fragment thereof, Emp antigen or immunogenic fragment thereof, EsaB antigen or immunogenic fragment thereof, EsaC antigen or immunogenic fragment thereof, EsxA antigen or immunogenic fragment thereof, EsxB antigen or immunogenic fragment thereof, SdrC antigen or immunogenic fragment thereof, SdrD antigen or immunogenic fragment thereof, SdrE antigen or immunogenic fragment thereof, IsdA antigen or immunogenic fragment thereof, IsdB antigen or immunogenic fragment thereof, ClfA antigen or immunogenic fragment thereof, ClfB antigen or immunogenic fragment thereof, Coa antigen or immunogenic fragment thereof, Hla (*e.g.*, H35 mutants) antigen or immunogenic fragment thereof, IsdC antigen or immunogenic fragment thereof, SasF antigen or immunogenic fragment thereof, vWbp antigen or immunogenic fragment thereof, vWh antigen or immunogenic fragment thereof, sta001 antigen or immunogenic fragment thereof, sta002 antigen or immunogenic fragment thereof, sta003 antigen or immunogenic fragment thereof, sta004 antigen or immunogenic fragment thereof, sta005 antigen or immunogenic fragment thereof, sta006 antigen or immunogenic fragment thereof, sta007 antigen or immunogenic fragment thereof, sta008 antigen or immunogenic fragment thereof, sta009 antigen or immunogenic fragment thereof, sta010 antigen or immunogenic fragment thereof, sta011 antigen or immunogenic fragment thereof, sta012 antigen or immunogenic fragment thereof, sta013 antigen or immunogenic fragment thereof, sta014 antigen or immunogenic fragment thereof, sta015 antigen or immunogenic fragment thereof, sta016 antigen or immunogenic fragment thereof, sta017 antigen or immunogenic fragment thereof, sta018 antigen or immunogenic fragment thereof, sta019 antigen or immunogenic fragment thereof, sta020 antigen or immunogenic fragment thereof, sta02l antigen or immunogenic fragment thereof, sta022 antigen or immunogenic fragment thereof, sta023 antigen or immunogenic fragment thereof, sta024 antigen or immunogenic fragment thereof, sta025 antigen or immunogenic fragment thereof, sta026 antigen or immunogenic fragment thereof, sta027 antigen or immunogenic fragment thereof, sta028 antigen or immunogenic fragment thereof, sta029 antigen or immunogenic fragment thereof, sta030 antigen or immunogenic fragment thereof, sta03l antigen or immunogenic fragment thereof, sta032 antigen or immunogenic fragment thereof, sta033 antigen or immunogenic fragment thereof, sta034 antigen or immunogenic

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[0022] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with FnBpA and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta021, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta031, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0023] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with FnBpB and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0024] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with LukD and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113,

sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0025] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with LukE and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta021, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta031, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0026] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with LukF and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta021, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta031, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089,

sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0027] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with SasA and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0028] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with SasD and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065,

sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0029] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with SasG and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0030] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with SasI and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041,

sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0031] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with SasK and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0032] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with SpA (and variants thereof) and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017,

sta018, sta019, sta020, sta021, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta031, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0033] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with Eap and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta021, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta031, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0034] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with Ebh and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB,

Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0035] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with Emp and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0036] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with EsaB and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from

FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta021, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta031, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0037] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with EsaC and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta021, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta031, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0038] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before,

concurrently or after one or more bacterial antigens) in combination with EsxA and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0039] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with EsxB and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0040] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with SdrC and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0041] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with SdrD and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113,

sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0042] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with SdrE and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0043] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with IsdA and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089,

sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0044] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with IsdB and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0045] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with ClfA and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065,

sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0046] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with ClfB and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta021, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta031, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0047] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with Coa and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta021, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta031, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041,

sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0048] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with Hla (*e.g.*, H35 mutants) and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0049] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with IsdC and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017,

sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0050] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with SasF and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0051] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with vWbp and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA,

ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWh, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0052] In other aspects, a subject is administered an SpA polypeptide variant (before or after one or more bacterial antigens) or administered a protein A antibody (before, concurrently or after one or more bacterial antigens) in combination with vWh and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more bacterial antigens selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[0053] Certain embodiment are directed to the above listed antibody and bacterial antigen combinations comprised in a vaccine composition having a pharmaceutically acceptable excipient.

[0054] Further embodiments include methods of making a vaccine comprising the steps of mixing antibody and antigens to make the compositions described herein.

[0055] Still further embodiments include methods of preventing or treating staphylococcal infection comprising the step of administering the vaccine as described herein to a patient in need thereof.

[0056] Certain embodiments are directed to use of the compositions described herein in the treatment or prevention of bacterial or staphylococcal infection. Certain embodiments are directed to use of the compositions described herein in the treatment or prevention of pathological conditions resulting from bacterial or staphylococcal infection.

[0057] A further embodiment includes methods for treating a bacterial infection in a subject comprising providing to a subject having, suspected of having or at risk of developing a bacterial infection effective amounts of an isolated Protein A (SpA) specific antibody and one or more bacterial antigens. In certain aspects, the one or more bacterial antigens are comprised in or on a bacteria, or are isolated recombinant polypeptides or peptides. In a further aspect the bacteria comprising the antigens is an attenuated bacteria, in a particular aspect the attenuated bacteria is a staphylococcal bacteria. In certain aspects the subject is diagnosed with a staphylococcal infection. In various aspects described above, the bacterial antigen is a staphylococcal antigen. The staphylococcal antigen can be selected from the group consisting of: FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh and immunogenic fragments thereof.

[0058] The methods further include steps wherein two or more bacterial antigens are provided to the subject. In certain aspects the Protein A (SpA) specific antibody is provided before, after, and/or concurrently with the bacterial antigen. In certain aspects, the Protein A (SpA) specific antibody and the one or more bacterial antigens are provided in the same composition. In a further aspect, the subject is a mammal, particulalry human.

[0059] Embodiments include methods for enhancing an immune response against a bacterium in a subject. In certain aspects the methods include providing to the subject effective amounts of an isolated Protein A (SpA) specific antibody and one or more antigens from the bacterium. In a further aspect the methods include pre-immunization with an SpA polypeptide variant followed by administration of one or more antigens from the bacterium.

Still further aspects include administration of an SpA polypeptide variant after administration of one or more antigens from the bacterium. In certain aspects, one or more bacterial antigens are comprised in or on or produced by a bacteria, or are isolated recombinant polypeptides or peptides. In a further aspect the bacteria comprising the antigens is an attenuated bacteria, in a particular aspect the attenuated bacteria is a staphylococcal bacteria. In certain aspects the subject is diagnosed with a staphylococcal infection. In various aspects described above, the bacterial antigen is a staphylococcal antigen. The staphylococcal antigen can be selected from the group consisting of: FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh and immunogenic fragments thereof. In certain aspects the staphylococcus bacterium is a *S. aureus* bacterium. In a further aspect, the staphylococcus bacterium is resistant to one or more treatments, such as methicillin resistant. In certain aspects the the composition is administered more than one time to the subject.

[0060] In certain aspects, a bacterium delivering a composition of the invention will be limited or attenuated with respect to prolonged or persistent growth or abscess formation. In yet a further aspect, bacterial antigens can be overexpressed in an attenuated bacterium to further enhance or supplement an immune response or vaccine formulation.

[0061] The term "FnBpA protein" refers to a protein that includes isolated wild-type FnBpA polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria FnBpA proteins.

[0062] The term "FnBpB protein" refers to a protein that includes isolated wild-type FnBpB polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria FnBpB proteins.

[0063] The term "LukD protein" refers to a protein that includes isolated wild-type LukD polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria LukD proteins.

[0064] The term "LukE protein" refers to a protein that includes isolated wild-type LukE polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria LukE proteins.

[0065] The term "LukF protein" refers to a protein that includes isolated wild-type LukF polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria LukF proteins.

[0066] The term "SasA protein" refers to a protein that includes isolated wild-type SasA polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria SasA proteins.

[0067] The term "SasD protein" refers to a protein that includes isolated wild-type SasD polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria SasD proteins.

[0068] The term "SasG protein" refers to a protein that includes isolated wild-type SasG polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria SasG proteins.

[0069] The term "SasI protein" refers to a protein that includes isolated wild-type SasI polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria SasI proteins.

[0070] The term "SasK protein" refers to a protein that includes isolated wild-type SasK polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria SasK proteins.

[0071] The term "EsxA protein" refers to a protein that includes isolated wild-type EsxA polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria EsxA proteins.

[0072] The term "EsxB protein" refers to a protein that includes isolated wild-type EsxB polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria EsxB proteins.

[0073] The term "SdrD protein" refers to a protein that includes isolated wild-type SdrD polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria SdrD proteins.

[0074] The term "SdrE protein" refers to a protein that includes isolated wild-type SdrE polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria SdrE proteins.

[0075] The term "IsdA protein" refers to a protein that includes isolated wild-type IsdA polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria IsdA proteins.

[0076] The term "IsdB protein" refers to a protein that includes isolated wild-type IsdB polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria IsdB proteins.

[0077] The term "Eap protein" refers to a protein that includes isolated wild-type Eap polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria Eap proteins.

[0078] The term "Ebh protein" refers to a protein that includes isolated wild-type Ebh polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria Ebh proteins.

[0079] The term "Emp protein" refers to a protein that includes isolated wild-type Emp polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria Emp proteins.

[0080] The term "EsaB protein" refers to a protein that includes isolated wild-type EsaB polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria EsaB proteins.

[0081] The term "EsaC protein" refers to a protein that includes isolated wild-type EsaC polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria EsaC proteins.

[0082] The term "SdrC protein" refers to a protein that includes isolated wild-type SdrC polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria SdrC proteins.

[0083] The term "ClfA protein" refers to a protein that includes isolated wild-type ClfA polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria ClfA proteins.

[0084] The term "ClfB protein" refers to a protein that includes isolated wild-type ClfB polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria ClfB proteins.

[0085] The term "Coa protein" refers to a protein that includes isolated wild-type Coa polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria Coa proteins.

[0086] The term "Hla protein" refers to a protein that includes isolated wild-type Hla polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria Hla proteins.

[0087] The term "IsdC protein" refers to a protein that includes isolated wild-type IsdC polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria IsdC proteins.

[0088] The term "SasF protein" refers to a protein that includes isolated wild-type SasF polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria SasF proteins.

[0089] The term "vWbp protein" refers to a protein that includes isolated wild-type vWbp (von Willebrand factor binding protein) polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria vWbp proteins.

[0090] The term "vWh protein" refers to a protein that includes isolated wild-type vWh (von Willebrand factor binding protein homolog) polypeptides from staphylococcus bacteria and segments thereof, as well as variants that stimulate an immune response against staphylococcus bacteria vWh proteins.

[0091] An immune response refers to a humoral response, a cellular response, or both a humoral and cellular response in an organism. An immune response can be measured by assays that include, but are not limited to, assays measuring the presence or amount of antibodies that specifically recognize a protein or cell surface protein, assays measuring T-cell activation or proliferation, and/or assays that measure modulation in terms of activity or expression of one or more cytokines.

[0092] In still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to a FnBpA protein. In certain aspects the FnBpA protein will have all or part of the amino acid sequence of accession number A32192 / GI:97812.

[0093] In still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an FnBpB protein. In certain aspects the FnBpB protein will have all or part of the amino acid sequence of accession number A32192 / GI:97812.

[0094] In still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an LukD protein. In certain aspects the LukD protein will have all or part of the amino acid sequence of accession number CAA73668 / GI:2765304.

[0095] In still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an LukE protein. In certain aspects the LukE protein will have all or part of the amino acid sequence of accession number CAA73667.1 / GI:2765303.

[0096] In still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an LukF protein. In certain aspects the LukF protein will have all or part of the amino acid sequence of accession number AAC60446.1 / GI:410007.

[0097] In still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an SasA protein. In certain aspects the SasA protein will have all or part of the amino acid sequence of accession number Q06904.2 / GI:93141309.

[0098] In still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an SasD protein. In certain aspects the SasD protein will have all or part of the amino acid sequence of accession number AAR15215.1 / GI:38259745.

[0099] In still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%,

97%, 98%, or 99% identical or similar to an SasG protein. In certain aspects the SasG protein will have all or part of the amino acid sequence of accession number Q2G2B2.1 / GI:122540575.

[00100] In still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an SasI protein. In certain aspects the SasI protein will have all or part of the amino acid sequence of accession number AAR15295.1 / GI:38259905.

[00101] In still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an SasK protein. In certain aspects the SasK protein will have all or part of the amino acid sequence of accession number ZP_06340589.1 / GI:283767674.

[00102] In still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an EsxA protein. In certain aspects the EsxA protein will have all or part of the amino acid sequence of SEQ ID NO:11.

[00103] In still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an EsxB protein. In certain aspects the EsxB protein will have all or part of the amino acid sequence of SEQ ID NO:12.

[00104] In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an SdrD protein. In certain aspects the SdrD protein will have all or part of the amino acid sequence of SEQ ID NO:13.

[00105] In further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an SdrE protein. In certain aspects the SdrE protein will have all or part of the amino acid sequence of SEQ ID NO:14.

[00106] In still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%,

97%, 98%, or 99% identical or similar to an IsdA protein. In certain aspects the IsdA protein will have all or part of the amino acid sequence of SEQ ID NO:15.

[00107] In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an IsdB protein. In certain aspects the IsdB protein will have all or part of the amino acid sequence of SEQ ID NO:16.

[00108] Embodiments of the invention include compositions that include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to a EsaB protein. In certain aspects the EsaB protein will have all or part of the amino acid sequence of SEQ ID NO:17.

[00109] In a further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to a ClfB protein. In certain aspects the ClfB protein will have all or part of the amino acid sequence of SEQ ID NO:18.

[00110] In still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an IsdC protein. In certain aspects the IsdC protein will have all or part of the amino acid sequence of SEQ ID NO:19.

[00111] In yet further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to a SasF protein. In certain aspects the SasF protein will have all or part of the amino acid sequence of SEQ ID NO:20.

[00112] In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to a SdrC protein. In certain aspects the SdrC protein will have all or part of the amino acid sequence of SEQ ID NO:21.

[00113] In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to a ClfA protein. In certain aspects the ClfA protein will have all or part of the amino acid sequence of SEQ ID NO:22.

[00114] In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an Eap protein. In certain aspects the Eap protein will have all or part of the amino acid sequence of SEQ ID NO:23.

[00115] In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an Ebh protein. In certain aspects the Ebh protein will have all or part of the amino acid sequence of SEQ ID NO:24.

[00116] In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an Emp protein. In certain aspects the Emp protein will have all or part of the amino acid sequence of SEQ ID NO:25.

[00117] In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to an EsaC protein. In certain aspects the EsaC protein will have all or part of the amino acid sequence of SEQ ID NO:26. Sequence of EsaC polypeptides can be found in the protein databases and include, but are not limited to accession numbers ZP_02760162 (GI:168727885), NP_645081.1 (GI:21281993), and NP_370813.1 (GI:15923279), each of which is incorporated herein by reference as of the priority date of this application.

[00118] In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to a Coa protein. In certain aspects the Coa protein will have all or part of the amino acid sequence of SEQ ID NO:27.

[00119] In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to a Hla protein. In certain aspects the Hla protein will have all or part of the amino acid sequence of SEQ ID NO:28.

[00120] In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to a vWa protein. In certain aspects the vWa protein will have all or part of the amino acid sequence of SEQ ID NO:29.

[00121] In yet still further embodiments of the invention a composition may include a polypeptide, peptide, or protein that is or is at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical or similar to a vWbp protein. In certain aspects the vWbp protein will have all or part of the amino acid sequence of SEQ ID NO:32.

[00122] In certain aspects, a polypeptide or segment/fragment can have a sequence that is at least 85%, at least 90%, at least 95%, at least 98%, or at least 99% or more identical to the amino acid sequence of the reference polypeptide. The term "similarity" refers to a polypeptide that has a sequence that has a certain percentage of amino acids that are either identical with the reference polypeptide or constitute conservative substitutions with the reference polypeptides.

[00123] The 'sta001' antigen is annotated as '5'-nucleotidase family protein'. In the NCTC 8325 strain sta001 is SAOUHSC_00025 and has amino acid sequence SEQ ID NO:35 (GI:88193846). In the Newman strain it is nwmn_0022 (GI:151220234). It has also been referred to as AdsA and SasH and SA0024.

[00124] Useful sta001 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:35 and/or may comprise an amino acid sequence: (a) having 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more identity to SEQ ID NO: 35; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO: 35, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta001 proteins include variants of SEQ ID NO: 35. Preferred fragments of (b) comprise an epitope from SEQ ID NO: 35. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO: 35 while retaining at least one epitope of SEQ ID NO: 35. The final 34 C-terminal amino acids of SEQ ID NO: 35 can usefully be omitted. The first 38 N-terminal amino acids of SEQ ID NO: 35 can usefully be omitted. Other fragments omit one or more protein domains.

[00125] The sta002 antigen is annotated as 'lipoprotein'. In the NCTC• 8325 strain sta002 is SAOUHSC 00356 and has amino acid sequence SEQ ID NO:36 (GI:88194155). In the Newman strain it is nwmn_0364 (GI:151220576).

[00126] Useful sta002 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:36 and/or may comprise an amino acid sequence: (a) having

50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more identity to SEQ ID NO:36; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:36, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150 or more). These sta002 proteins include variants of SEQ ID *NO:36*. Preferred fragments of (b) comprise an epitope from SEQ ID NO:36. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:36 while retaining at least one epitope of SEQ ID NO:36. The first 18 N-terminal amino acids of SEQ ID NO:36 can usefully be omitted. Other fragments omit one or more protein domains. $sta002_{19\text{-}187}$ and $sta002_{19_124}$ are two useful fragments of SEQ ID NO:36 which reduce the antigen's similarity with human proteins.

[00127] The 'sta003' antigen is annotated as 'surface protein'. In the NCTC 8325 strain sta003 is SAOUHSC_00400 and has amino acid sequence SEQ ID NO:37 (GI:88194195). In the Newman strain it is nwmn_0401 (GI:151220613).

[00128] Useful sta003 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:37 and/or may comprise an amino acid sequence: (a) having 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more identity to SEQ ID NO:37; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:37, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta003 proteins include variants of SEQ ID NO:37. Preferred fragments of (b) comprise an epitope from SEQ ID NO:37. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:37 while retaining at least one epitope of SEQ ID NO:37. The first 32 N-terminal amino acids of SEQ ID NO:37 can usefully be omitted. Other fragments omit one or more protein domains.

[00129] The 'sta004' antigen is annotated as 'Siderophore binding protein FatB'. In the NCTC 8325 strain sta004 is SAOUHSC_00749 and has amino acid sequence SEQ ID NO:38 (GI:88194514). In the Newman strain it is nwmn_0705 (GI:151220917).

[00130] Useful sta004 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:38 and/or may comprise an amino acid sequence: (a) having 50%

or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:38; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:38, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta004 proteins include variants of SEQ ID NO:38. Preferred fragments of (b) comprise an epitope from SEQ ID NO:38. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:38 while retaining at least one epitope of SEQ ID NO:38. The first 18 N-terminal amino acids of SEQ ID NO:38 can usefully be omitted. Other fragments omit one or more protein domains.

[00131] The 'sta005' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta005 is 10 SAOUHSC_01127 and has amino acid sequence SEQ ID NO:39 (GI:88194870). In the Newman strain it is nwmn_1077 (GI:151221289).

[00132] Useful sta005 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:39 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:39; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:39, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta005 proteins include variants of SEQ ID NO:39. Preferred fragments of (b) comprise an epitope from SEQ ID NO:39. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:39 while retaining at least one epitope of SEQ ID NO:39. The first 18 N-terminal amino acids of SEQ ID NO:39 can usefully be omitted. Other fragments omit one or more protein domains.

[00133] The 'sta006' antigen is annotated as 'ferrichrome-binding protein', and has also been referred to as 25 'FhuD2' in the literature. In the NCTC 8325 strain sta006 is SAOUHSC_02554 and has amino acid sequence SEQ ID NO:40 (GI:88196199). In the Newman strain it is nwmn 2185 (GI:151222397).

[00134] Useful sta006 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:40 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 30, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:40; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:40, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta006 proteins include variants of SEQ ID NO:40. Preferred fragments of (b) comprise an epitope from SEQ ID NO:40. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:40 while retaining at least one epitope of SEQ ID NO:40. The first 17 N-terminal amino acids of SEQ ID NO:40 can usefully be omitted. Other fragments omit one or more protein domains. A sta006 antigen may be lipidated *e.g.* with an acylated N-terminus cysteine. One useful sta006 sequence has a Met-Ala-Ser- sequence at the N-terminus.

[00135] The 'sta007' antigen is annotated as 'secretory antigen precursor'. In the NCTC 8325 strain sta007 is SAOUHSC_02571 and has amino acid sequence SEQ ID NO:41 (GI:88196215). In the Newman strain it is nwmn_2199 (GI:151222411). Proteomic analysis has revealed that this protein is secreted or surface-exposed.

[00136] Useful sta007 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:41 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:41; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:41, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta007 proteins include variants of SEQ ID NO:41. Preferred fragments of (b) comprise an epitope from SEQ ID NO:41. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:41 while retaining at least one epitope of SEQ ID NO:41. The first 27 N-terminal amino acids of SEQ ID NO:41 can usefully be omitted. Other fragments omit one or more protein domains.

[00137] The 'sta008' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta008 is SAOUHSC_02650 and has amino acid sequence SEQ ID NO:42 (GI:88196290). In the Newman strain it is nwmn_2270 (GI:151222482).

[00138] Useful sta008 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:42 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:42; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:42, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta008 proteins include variants of SEQ ID NO:42. Preferred fragments of (b) comprise an epitope from SEQ ID NO:42. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:42 while retaining at least one epitope of SEQ ID NO:42. The first 17 N-terminal amino acids of SEQ ID NO:42 can usefully be omitted. Other fragments omit one or more protein domains.

[00139] The 'sta009' antigen is annotated as 'immunoglobulin G-binding protein Sbi'. In the NCTC 8325 strain sta009 is SAOUHSC_02706 and has amino acid sequence SEQ ID NO:43 (GI:88196346). In the Newman strain it is nwmn_2317 (GI:151222529).

[00140] Useful sta009 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:43 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:43; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:43, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta009 proteins include variants of SEQ ID NO:43. Preferred fragments of (b) comprise an epitope from SEQ ID NO:43. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:43 while retaining at least one epitope of SEQ ID NO:43. The first 29 N-terminal amino acids of SEQ ID NO:43 can usefully be omitted. Other fragments omit one or more protein domains.

[00141] The 'sta010' antigen is annotated as 'immunodominant antigen A'. In the NCTC 8325 strain sta010 is SAOUHSC_02887 and has amino acid sequence SEQ ID NO:44 (GI:88196515). In the Newman strain it is nwmn_2469 (GI:151222681). Proteomic analysis has revealed that this protein is secreted or surface-exposed.

[00142] Useful sta010 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:44 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:44; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:44, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta010 proteins include variants of SEQ ID NO:44. Preferred fragments of (b) comprise an epitope from SEQ ID NO:44. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:44 while retaining at least one epitope of SEQ ID NO:44. The first 29 N-terminal amino acids of SEQ ID NO:44 can usefully be omitted. Other fragments omit one or more protein domains.

[00143] The 'sta011' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta011 is SAOUHSC_00052 and has amino acid sequence SEQ ID NO:45 (GI:88193872).

[00144] Useful sta011 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:45 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:45; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:45, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta011 proteins include variants of SEQ ID NO:45. Preferred fragments of (b) comprise an epitope from SEQ ID NO:45. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:45 while retaining at least one epitope of SEQ ID NO:45. The first 23 N-terminal amino acids of SEQ ID NO:45 can usefully be omitted. Other fragments omit one or more protein domains. A sta011 antigen may be lipidated *e.g.* with an acylated N-terminus cysteine.

[00145] The 'sta012' antigen is annotated as 'protein with leader'. In the NCTC 8325 strain sta012 is SAOUHSC_00106 and has amino acid sequence SEQ ID NO:46 (GI:88193919).

[00146] Useful sta012 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:46 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:46; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:46, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta012 proteins include variants of SEQ ID NO:46. Preferred fragments of (b) comprise an epitope from SEQ ID NO:46. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:46 while retaining at least one epitope of SEQ ID NO:46. The first 21 N-terminal amino acids of SEQ ID NO:46 can usefully be omitted. Other fragments omit one or more protein domains.

[00147] The 'sta013' antigen is annotated as 'poly-gamma-glutamate capsule biosynthesis protein'. In the NCTC 8325 strain staOB is SAOUHSC_00107 and has amino acid sequence SEQ ID NO:47 (GI:88193920).

[00148] Useful sta013 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:47 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:47; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:47, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta013 proteins include variants of SEQ ID NO:47. Preferred fragments of (b) comprise an epitope from SEQ ID NO:47. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:47 while retaining at least one epitope of SEQ ID NO:47. Other fragments omit one or more protein domains.

[00149] The 'sta014' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta014 is SAOUHSC_00137 and has amino acid sequence SEQ ID NO:48 (GI:88193950).

[00150] Useful sta014 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:48 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:48; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:48, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta014 proteins include variants of SEQ ID NO:48. Preferred fragments of (b) comprise an epitope from SEQ ID NO:48. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:48 while retaining at least one epitope of SEQ ID NO:48. The first 17 N-terminal amino acids of SEQ ID NO:48 can usefully be omitted. Other fragments omit one or more protein domains.

[00151] The 'sta015' antigen is annotated as 'extracellular solute-binding protein; ROD containing lipoprotein'. In the NCTC 8325 strain sta015 is SAOUHSC_00170 and has amino acid sequence SEQ ID NO:49 (GI:88193980).

[00152] Useful sta015 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:49 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:49; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:49, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta015 proteins include variants of SEQ ID NO:49. Preferred fragments of (b) comprise an epitope from SEQ ID NO:49. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:49 while retaining at least one epitope of SEQ ID NO:49. The first 18 N-terminal amino acids of SEQ ID NO:49 can usefully be omitted. Other fragments omit one or more protein domains.

[00153] The 'sta016' antigen is annotated as 'gamma-glutamyltranspeptidase'. In the NCTC 8325 strain sta016 is SAOUHSC_00171 and has amino acid sequence SEQ ID NO:50 (GI:88193981).

[00154] Useful sta016 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:50 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:50; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:50, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta016 proteins include variants of SEQ ID NO:50. Preferred fragments of (b) comprise an epitope from SEQ ID NO:50. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:50 while retaining at least one epitope of SEQ ID NO:50. Other fragments omit one or more protein domains.

[00155] The 'sta017' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta017 is SAOUHSC_00186 and has amino acid sequence SEQ ID NO:51 (GI:88193996).

[00156] Useful sta017 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:51 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:51; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:51, wherein In' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta017 proteins include variants of SEQ ID NO:51. Preferred fragments of (b) comprise an epitope from SEQ ID NO:51. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:51 while retaining at least one epitope of SEQ ID NO:51. The first 17 N-terminal amino acids of SEQ ID NO:51 can usefully be omitted. Other fragments omit one or more protein domains.

[00157] The 'sta018' antigen is annotated as 'extracellular solute-binding protein'. In the NCTC 8325 strain sta018 is SAOUHSC_00201 and has amino acid sequence SEQ ID NO:52 (GI:88194011).

[00158] Useful sta018 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:52 and/or may comprise an amino acid sequence: (a) having

50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more identity to SEQ ID NO:52; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:52, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta018 proteins include variants of SEQ ID NO:52. Preferred fragments of (b) comprise an epitope from SEQ ID NO:52. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:52 while retaining at least one epitope of SEQ ID NO:52. Other fragments omit one or more protein domains.

[00159] The 'sta019' antigen is annotated as 'peptidoglycan hydrolase'. In the NCTC 8325 strain sta019 is SAOUHSC_00248 and has amino acid sequence SEQ ID NO:53 (GI:88194055). In the Newman strain it is nwmn_0210 (GI:151220422).

[00160] Useful sta019 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:53 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.*60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:53; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:53, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta019 proteins include variants of SEQ ID NO:53. Preferred fragments of (b) comprise an epitope from SEQ ID NO:53. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:53 while retaining at least one epitope of SEQ ID NO:53. The first 25 N-terminal amino acids of SEQ ID NO:53 can usefully be omitted. Other fragments omit one or more protein domains.

[00161] Sta019 does not adsorb well to aluminium hydroxide adjuvants, so Sta019 present in a composition may be unadsorbed or may be adsorbed to an alternative adjuvant *e.g.* to an aluminium phosphate.

[00162] The 'sta020' antigen is annotated as 'exported protein'. In the NCTC 8325 strain sta020 is SAOUHSC_00253 and has amino acid sequence SEQ ID NO:54 (GI:88 194059).

[00163] Useful sta020 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:54 and/or may comprise an amino acid sequence: (a) having 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more identity to SEQ ID NO:54; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:54, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta020 proteins include variants of SEQ ID NO:54. Preferred fragments of (b) comprise an epitope from SEQ ID NO:54. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:54 while retaining at least one epitope of SEQ ID NO:54. The first 30 N-terminal amino acids of SEQ ID NO:54 can usefully be omitted. Other fragments omit one or more protein domains.

[00164] The 'sta021' antigen is annotated as 'secretory antigen SsaA-like protein'. In the NCTC 8325 strain sta021 is SAOUHSC_00256 and has amino acid sequence SEQ ID NO:55 (GI:88194062).

[00165] Useful sta021 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:55 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:55; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:55, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta021 proteins include variants of SEQ ID NO:55. Preferred fragments of (b) comprise an epitope from SEQ ID NO:55. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:55 while retaining at least one epitope of SEQ ID NO:55. The first 24 N-terminal amino acids of SEQ ID NO:55 can usefully be omitted. Other fragments omit one or more protein domains.

[00166] The 'sta022' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta022 is SAOUHSC_00279 and has amino acid sequence SEQ ID NO:56 (GI:88194083).

[00167] Useful sta022 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:56 and/or may comprise an amino acid sequence: (a) having 50%

or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:56; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:56, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100 or more). These sta022 proteins include variants of SEQ ID NO:56. Preferred fragments of (b) comprise an epitope from SEQ ID NO:56. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:56 while retaining at least one epitope of SEQ ID NO:56. The first 17 N-terminal amino acids of SEQ ID NO:56 can usefully be omitted. Other fragments omit one or more protein domains.

[00168] The 'sta023' antigen is annotated as '5'-nucleotidase; lipoprotein e(P4) family'. In the NCTC 8325 strain sta023 is SAOUHSC_00284 and has amino acid sequence SEQ ID NO:57 (GI:88194087).

[00169] Useful sta023 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:57 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:57; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:57, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta023 proteins include variants of SEQ ID NO:57. Preferred fragments of (b) comprise an epitope from SEQ ID NO:57. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:57 while retaining at least one epitope of SEQ ID NO:57. The first 31 N-terminal amino acids of SEQ ID NO:57 can usefully be omitted. Other fragments omit one or more protein domains.

[00170] The 'sta024' antigen is annotated as 'lipase precursor'. In the NCTC 8325 strain sta024 is SAOUHSC_00300 and has amino acid sequence SEQ ID NO:58 (GI:88194101).

[00171] Useful sta024 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:58 and/or may comprise an amino acid sequence: (a) having 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more identity to SEQ ID NO:58; and/or (b) comprising a fragment of at least

'n' consecutive amino acids of SEQ ID NO:58, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta024 proteins include variants of SEQ ID NO:58. Preferred fragments of (b) comprise an epitope from SEQ ID NO:58. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:58 while retaining at least one epitope of SEQ ID NO:58. The first 37 N-terminal amino acids of SEQ ID NO:58 can usefully be omitted. Other fragments omit one or moreprotein domains.

[00172] The 'sta025' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta025 is SAOUHSC_00362 and has amino acid sequence SEQ ID NO:59 (GI:88194160).

[00173] Useful sta025 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:59 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:59; and/or (b) comprising a fragment of at least In' consecutive amino acids of SEQ ID NO:59, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta025 proteins include variants of SEQ ID NO:59. Preferred fragments of (b) comprise an epitope from SEQ ID NO:59. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:59 while retaining at least one epitope of SEQ ID NO:59. The first 19 N-terminal amino acids of SEQ ID NO:59 can usefully be omitted. Other fragments omit one or more protein domains.

[00174] The 'sta026' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta026 is SAOUHSC_00404 and has amino acid sequence SEQ ID NO:60 (GI:88194198).

[00175] Useful sta026 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:60 and/or may comprise an amino acid sequence: (a) having 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more identity to SEQ ID NO:60; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:60, wherein In' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta026 proteins include variants of SEQ ID NO:60. Preferred fragments of (b) comprise an epitope from SEQ ID NO:60. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6,

7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:60 while retaining at least one epitope of SEQ ID NO:60. The first 22 N-terminal amino acids of SEQ ID NO:60 can usefully be omitted. Other fragments omit one or more protein domains.

[00176] The 'sta027' antigen is annotated as 'probable lipase'. In the NCTC 8325 strain sta027 is SAOUHSC_00661 and has amino acid sequence SEQ ID NO:61 (GI:88194426).

[00177] Useful sta027 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:61 and/or may comprise an amino acid sequence: (a) having 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more identity to SEQ ID NO:61; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:61, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta027 proteins include variants of SEQ ID NO:61. Preferred fragments of (b) comprise an epitope from SEQ ID NO:61. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:61 while retaining at least one epitope of SEQ ID NO:61. The first 23 N-terminal amino acids of SEQ ID NO:61 can usefully be omitted. Other fragments omit one or more protein domains.

[00178] The 'sta028' antigen is annotated as 'secretory antigen SsaA-like protein'. In the NCTC 8325 strain sta028 is SAOUHSC_00671 and has amino acid sequence SEQ ID NO:62 (GI:88194436). In the Newman strain it is nwmn_0634 (GI:151220846).

[00179] Useful sta028 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:62 and/or may comprise an amino acid sequence: (a) having 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more identity to SEQ ID NO:62; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:62, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta028 proteins include variants of SEQ ID NO:62. Preferred fragments of (b) comprise an epitope from SEQ ID NO:62. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:62 while

retaining at least one epitope of SEQ ID NO:62. The first 25 N-terminal amino acids of SEQ ID NO:62 can usefully be omitted. Other fragments omit one or more protein domains.

[00180] The 'sta029' antigen is annotated as 'ferrichrome binding protein'. In the NCTC 8325 strain sta029 is SAOUHSC_00754 and has amino acid sequence SEQ ID NO:63 (GI:88194518).

[00181] Useful sta029 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:63 and/or may comprise an amino acid sequence: (a) having 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more identity to SEQ ID NO:63; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:63, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta029 proteins include variants of SEQ ID NO:63. Preferred fragments of (b) comprise an epitope from SEQ ID NO:63. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:63 while retaining at least one epitope of SEQ ID NO:63. The final 25 C-terminal amino acids of SEQ ID NO:63 can usefully be omitted. The first 19 N-terminal amino acids of SEQ ID NO:63 can usefully be omitted. Other fragments omit one or more protein domains.

[00182] The 'sta030' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta030 is SAOUHSC_00808 and has amino acid sequence SEQ ID NO:64 (GI:88194568).

[00183] Useful sta030 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:64 and/or may comprise an amino acid sequence: (a) having 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more identity to SEQ ID NO:64; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:64, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta030 proteins include variants of SEQ ID NO:64. Preferred fragments of (b) comprise an epitope from SEQ ID NO:64. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:64 while retaining at least one epitope of SEQ ID NO:64. The first 17 N-terminal amino acids of SEQ ID NO:64 can usefully be omitted. Other fragments omit one or more protein domains.

[00184] The 'sta03I' antigen is annotated as '5-nucleotidase family protein'. In the NCTC 8325 strain sta031 is SAOUHSC_00860 and has amino acid sequence SEQ ID NO:65 (GI:88194617).

[00185] Useful sta031 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:65 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:65; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:65, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta031 proteins include variants of SEQ ID NO:65. Preferred fragments of (b) comprise an epitope from SEQ ID NO:65. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:65 while retaining at least one epitope ofSEQ ID NO:65. Other fragments omit one or more protein domains.

[00186] The 'sta032' antigen is annotated as 'serine protease HtrA'. In the NCTC 8325 strain sta032 is SAOUHSC 00958 and has amino acid sequence SEQ ID NO:66 (GI:88194715).

[00187] Useful sta032 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:66 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:66; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:66, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta032 proteins include variants of SEQ ID NO:66. Preferred fragments of (b) comprise an epitope from SEQ ID NO:66. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:66 while retaining at least one epitope of SEQ ID NO:66. Other fragments omit one or more protein domains.

[00188] The 'sta033' antigen is annotated as 'cysteine protease precursor'. In the NCTC 8325 strain sta033 is SAOUHSC_00987 and has amino acid sequence SEQ ID NO:67 (GI:88194744).

[00189] Useful sta033 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:67 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:67; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:67, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta033 proteins include variants of SEQ ID NO:67. Preferred fragments of (b) comprise an epitope from SEQ ID NO:67. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:67 while retaining at least one epitope of SEQ ID NO:67. The first 29 N-terminal amino acids of SEQ ID NO:67 can usefully be omitted. Other fragments omit one or more protein domains.

[00190] The 'sta034' antigen is annotated as 'glutamyl endopeptidase precursor'. In the NCTC 8325 strain sta034 is SAOUHSC_00988 and has amino acid sequence SEQ ID NO:68 (GI:88194745).

[00191] Useful sta034 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:68 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:68; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:68, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta034 proteins include variants of SEQ ID NO:68. Preferred fragments of (b) comprise an epitope from SEQ ID NO:68. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:68 while retaining at least one epitope of SEQ ID NO:68. The first 29 N-terminal amino acids of SEQ ID NO:68 can usefully be omitted. Other fragments omit one or more protein domains.

[00192] The 'sta035' antigen is annotated as 'fmt protein'. In the NCTC 8325 strain sta035 is SAOUHSC_00998 and has amino acid sequence SEQ ID NO:69 (GI:88194754).

[00193] Useful sta035 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:69 and/or may comprise an amino acid sequence: (a) having 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more identity to SEQ ID NO:69; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:69, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta035 proteins include variants of SEQ ID NO:69. Preferred fragments of (b) comprise an epitope from SEQ ID NO:69. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:69 while retaining at least one epitope of SEQ ID NO:69. The first 25 N-terminal amino acids of SEQ ID NO:69 can usefully be omitted. Other fragments omit one or more protein domains.

[00194] The 'sta036' antigen is annotated as 'iron-regulated protein with leader'. In the NCTC 8325 strain sta036 is SAOUHSC_01084 and has amino acid sequence SEQ ID NO:70 (GI:88194831).

[00195] Useful sta036 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:70 and/or may comprise an amino acid sequence: (a) having 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more identity to SEQ ID NO:70; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:70, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta036 proteins include variants of SEQ ID NO:70. Preferred fragments of (b) comprise an epitope from SEQ ID NO:70. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:70 while retaining at least one epitope of SEQ ID NO:70. The first 27 C-terminal amino acids of SEQ ID NO:70 can usefully be omitted. The first 32 N-terminal amino acids of SEQ ID NO:70 can usefully be omitted. Other fragments omit one or more protein domains.

[00196] The 'sta037' antigen is annotated as 'iron ABC transporter; iron-binding protein IsdE'. In the NCTC 8325 strain sta037 is SAOUHSC 01085 and has amino acid sequence SEQ ID NO:71 (GI:88194832).

[00197] Useful sta037 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:71 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:71; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:71, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta037 proteins include variants of SEQ ID NO:71. Preferred fragments of (b) comprise an epitope from SEQ ID NO:71. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:71 while retaining at least one epitope of SEQ ID NO:71. The first 9 N-terminal amino acids of SEQ ID NO:71 can usefully be omitted. Other fragments omit one or more protein domains.

[00198] The 'sta038' antigen is annotated as 'NPQTN specifIc sortase B'. In the NCTC 8325 strain sta038 is SAOUHSC_01088 and has amino acid sequence SEQ ID NO:72 (GI:88194835).

[00199] Useful sta038 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:72 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:72; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:72, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta038 proteins include variants of SEQ ID NO:72. Preferred fragments of (b) comprise an epitope from SEQ ID NO:72. Other preferred fragments lack one or more amino acids)(*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:72 while retaining at least one epitope of SEQ ID NO:72. The first 21 N-terminal amino acids of SEQ ID NO:72 can usefully be omitted. Other fragments omit one or more protein domains.

[00200] The 'sta039' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta039 is SAOUHSC_01124 and has amino acid sequence SEQ ID NO:73 (GI:88194868).

[00201] Useful sta039 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:73 and/or may comprise an amino acid sequence: (a) having 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more identity to SEQ ID NO:73; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:73, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta039 proteins include variants of SEQ ID NO:73. Preferred fragments of (b) comprise an epitope from SEQ ID NO:73. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:73 while retaining at least one epitope of SEQ ID NO:73. The first 22 N-terminal amino acids of SEQ ID NO:73 can usefully be omitted. Other fragments omit one or more protein domains.

[00202] The 'sta040' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta040 is SAOUHSC_011125 and has amino acid sequence SEQ ID NO:74 (GI:88194869). In the Newman strain it is nwmn_1076 (GI:151221288).

[00203] Useful sta040 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:74 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:74; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:74, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta040 proteins include variants of SEQ ID NO:74. Preferred fragments of (b) comprise an epitope from SEQ ID NO:74. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:74 while retaining at least one epitope of SEQ ID NO:74. The first 21 N-terminal amino acids of SEQ ID NO:74 can usefully be omitted. Other fragments omit one or more protein domains.

[00204] The 'sta041' antigen is annotated as 'fibronectin-binding protein A-related'. In the NCTC 8325 strain sta041 is SAOUHSC_01175 and has amino acid sequence SEQ ID NO:75 (GI:88194914).

[00205] Useful sta041 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:75 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:75; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:75, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta041 proteins include variants of SEQ ID NO:75. Preferred fragments of (b) comprise an epitope from SEQ ID NO:75. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:75 while retaining at least one epitope of SEQ ID NO:75. Other fragments omit one or more protein domains.

[00206] The 'sta042, antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta042 is SAOUHSC_01180 and has amino acid sequence SEQ ID NO:76 (GI:88194919).

[00207] Useful sta042 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:76 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:76; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:76, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta042 proteins include variants of SEQ ID NO:76. Preferred fragments of (b) comprise an epitope from SEQ ID NO:76. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:76 while retaining at least one epitope of SEQ ID NO:76. The first 18 N-terminal amino acids of SEQ ID NO:76 can usefully be omitted. Other fragments omit one or more protein domains.

[00208] The 'sta043', antigen is annotated as 'cell wall hydrolase'. In the NCTC 8325 strain sta043 is SAOUHSC_01219 and has amino acid sequence SEQ ID NO:77 (GI:88194955).

[00209] Useful sta043 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:77 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:77; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:77, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta043 proteins include variants of SEQ ID NO:77. Preferred fragments of (b) comprise an epitope from SEQ ID NO:77. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:77 while retaining at least one epitope of SEQ ID NO:77. The first 38 N-terminal amino acids of SEQ ID NO:77 can usefully be omitted. Other fragments omit one or more protein domains.

[00210] The 'sta044' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta044 is SAOUHSC_01508 and has amino acid sequence SEQ ID NO:78 (GI:88195223).

[00211] Useful sta044 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:78 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:78; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:78, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta044 proteins include variants of SEQ ID NO:78. Preferred fragments of (b) comprise an epitope from SEQ ID NO:78. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:78 while retaining at least one epitope of SEQ ID NO:78. The first 17 N-terminal amino acids of SEQ ID NO:78 can usefully be omitted. Other fragments omit one or more protein domains.

[00212] The 'sta045' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta045 is SAOUHSC_01627 and has amino acid sequence SEQ ID NO:79 (GI:88195337).

[00213] Useful sta045 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:79 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:79; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:79, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150 or more). These sta045 proteins include variants of SEQ ID NO:79. Preferred fragments of (b) comprise an epitope from SEQ ID NO:79. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:79 while retaining at least one epitope of SEQ ID NO:79. The first 16 N-terminal amino acids of SEQ ID NO:79 can usefully be omitted. Other fragments omit one or more protein domains.

[00214] The 'sta046' antigen is annotated as 'Excalibur protein'. In the NCTC 8325 strain sta046 is SAOUHSC_01918 and has amino acid sequence SEQ ID NO:80 (GI:88195613).

[00215] Useful sta046 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:80 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:80; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:80, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta046 proteins include variants of SEQ ID NO:80. Preferred fragments of (b) comprise an epitope from SEQ ID NO:80. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:80 while retaining at least one epitope of SEQ ID NO:80. The first 53 N-terminal amino acids of SEQ ID NO:80 can usefully be omitted. Other fragments omit one or more protein domains.

[00216] The 'sta047' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta047 is SAOUHSC_01920 and has amino acid sequence SEQ ID NO:81 (GI:88195615).

[00217] Useful sta047 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:81 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:81; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:81, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta047 proteins include variants of SEQ ID NO:81. Preferred fragments of (b) comprise an epitope from SEQ ID NO:81. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:81 while retaining at least one epitope of SEQ ID NO:81. The first 18 N-terminal amino acids of SEQ ID NO:81 can usefully be omitted. Other fragments omit one or more protein domains.

[00218] The 'sta048' antigen is annotated as 'intracellular serine protease'. In the NCTC 8325 strain sta048 is SAOUHSC_01949 and has amino acid sequence SEQ ID NO:82 (GI:88195642).

[00219] Useful sta048 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:82 and/or may comprise an amino acid sequence: (a) having 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more identity to SEQ ID NO:82; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:82, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta048 proteins include variants of SEQ ID NO:82. Preferred fragments of (b) comprise an epitope from SEQ ID NO:82. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:82 while retaining at least one epitope of SEQ ID NO:82. The first 27 N-terminal amino acids of SEQ ID NO:82 can usefully be omitted. Other fragments omit one or more protein domains.

[00220] The 'sta049' antigen is annotated as 'protein export protein PrsA'. In the NCTC 8325 strain sta049 is SAOUHSC_01972 and has amino acid sequence SEQ ID NO:83 (GI:88195663). In the Newman strain it is nwmn_I733 (GI:I51221945).

[00221] Useful sta049 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:83 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:83; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:83, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta049 proteins include variants of SEQ ID NO:83. Preferred fragments of (b) comprise an epitope from SEQ ID NO:83. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:83 while retaining at least one epitope of SEQ ID NO:83. The first 25 N-terminal amino acids of SEQ ID NO:83 can usefully be omitted. Other fragments omit one or more protein domains.

[00222] The 'sta050' antigen is annotated as 'staphopain thiol proteinase'. In the NCTC 8325 strain sta050 is SAOUHSC_02127 and has amino acid sequence SEQ ID NO:84 (GI:88195808).

[00223] Useful sta050 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:84 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:84; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:84, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta050 proteins include variants of SEQ ID NO:84. Preferred fragments of (b) comprise an epitope from SEQ ID NO:84. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:84 while retaining at least one epitope of SEQ ID NO:84. The first 25 N-terminal amino acids of SEQ ID NO:84 can usefully be omitted. Other fragments omit one or more protein domains.

[00224] The 'sta051' antigen is annotated as 'protein with leader'. In the NCTC 8325 strain sta051 is SAOUHSC_02147 and has amino acid sequence SEQ ID NO:85 (GI:88195827).

[00225] Useful sta051 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:85 and/or may comprise an amino acid sequence: (a) having 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more identity to SEQ ID NO:85; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:85, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta051 proteins include variants of SEQ ID NO:85. Preferred fragments of (b) comprise an epitope from SEQ ID NO:85. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:85 while retaining at least one epitope of SEQ ID NO:85. The first 24 N-terminal amino acids of SEQ ID NO:85 can usefully be omitted. Other fragments omit one or more protein domains.

[00226] The 'sta052' antigen is annotated as 'ferric hydroxamate receptor I'. In the NCTC 8325 strain sta052 is SAOUHSC_02246 and has amino acid sequence SEQ ID NO:86 (GI:88195918).

[00227] Useful sta052 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:86 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:86; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:86, wherein In' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta052 proteins include variants of SEQ ID NO:86. Preferred fragments of (b) comprise an epitope from SEQ ID NO:86. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:86 while retaining at least one epitope of SEQ ID NO:86. The first 17 N-terminal amino acids of SEQ ID NO:86 can usefully be omitted. Other fragments omit one or more protein domains.

[00228] The 'sta053' antigen is annotated as 'srdH family protein'. In the NCTC 8325 strain sta053 is SAOUHSC_02257 and has amino acid sequence SEQ ID NO:87 (GI:88195928).

[00229] Useful sta053 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:87 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:87; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:87, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta053 proteins include variants of SEQ ID NO:87. Preferred fragments of (b) comprise an epitope from SEQ ID NO:87. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:87 while retaining at least one epitope of SEQ ID NO:87. The first 26 N-terminal amino acids of SEQ ID NO:87 can usefully be omitted. Other fragments omit one or more protein domains.

[00230] The 'sta054' antigen is annotated as 'Probable transglycosylase isaA precursor'. In the NCTC 8325 strain sta054 is SAOUHSC_02333 and has amino acid sequence SEQ ID NO:88 (GI:88195999).

[00231] Useful sta054 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:88 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:88; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:88, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta054 proteins include variants of SEQ ID NO:88. Preferred fragments of (b) comprise an epitope from SEQ ID NO:88. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:88 while retaining at least one epitope of SEQ ID NO:88. The first 27 N-terminal amino acids of SEQ ID NO:88 can usefully be omitted. Other fragments omit one or more protein domains.

[00232] The 'sta055' antigen is annotated as 'surface hydrolase'. In the NCTC 8325 strain sta055 is SAOUHSC_02448 and has amino acid sequence SEQ ID NO:89 (GI:88196100).

[00233] Useful sta055 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:89 and/or may comprise an amino acid sequence: (a) having 50%

or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:89; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:89, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta055 proteins include variants of SEQ ID NO:89. Preferred fragments of (b) comprise an epitope from SEQ ID NO:89. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:89 while retaining at least one epitope of SEQ ID NO:89. The first 31 N-terminal amino acids of SEQ ID NO:89 can usefully be omitted. Other fragments omit one or more protein domains.

[00234] The 'sta056' antigen is annotated as 'hyaluronate lyase'. In the NCTC 8325 strain sta056 is SAOUHSC_02463 and has amino acid sequence SEQ ID NO:90 (GI:88196115).

[00235] Useful sta056 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:90 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:90; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:90, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta056 proteins include variants of SEQ ID NO:90. Preferred fragments of (b) comprise an epitope from SEQ ID NO:90. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:90 while retaining at least one epitope of SEQ ID NO:90. The first 24 N-terminal amino acids of SEQ ID NO:90 can usefully be omitted. Other fragments omit one or more protein domains.

[00236] The 'sta057' antigen is annotated as 'secretory antigen precursor SsaA'. In the NCTC 8325 strain sta057 is SAOUHSC_02576 and has amino acid sequence SEQ ID NO:91 (GI:88 196220). In the Newman strain it is nwmn_2203 (GI:I51222415).

[00237] Useful sta057 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:91 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%,

96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:91; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:91, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150 or more). These sta057 proteins include variants of SEQ ID NO:91. Preferred fragments of (b) comprise an epitope from SEQ ID NO:91. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:91 while retaining at least one epitope of SEQ ID NO:91. The first 27 N-terminal amino acids ofSEQ ID NO:91 can usefully be omitted. Other fragments omit one or more protein domains.

[00238] The 'sta058' antigen is annotated as 'Zn-binding lipoprotein adcA-like'. In the NCTC 8325 strain sta058 is SAOUHSC_02690 and has amino acid sequence SEQ ID NO:92 (GI:88196330).

[00239] Useful sta058 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:92 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:92; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:92, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta058 proteins include variants of SEQ ID NO:92. Preferred fragments of (b) comprise an epitope from SEQ ID NO:92. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:92 while retaining at least one epitope of SEQ ID NO:92. The first 20 N-terminal amino acids of SEQ ID NO:92 can usefully be omitted. Other fragments omit one or more protein domains.

[00240] The 'sta059' antigen is annotated as 'gamma-hemolysin h-gamma-ii subunit'. In the NCTC 8325 strain sta059 is SAOUHSC_02708 and has amino acid sequence SEQ ID NO:93 (GI:88196348).

[00241] Useful sta059 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:93 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ In NO:93; and/or (b) comprising a fragment

of at least 'n' consecutive amino acids of SEQ In NO:93, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta059 proteins include variants of SEQ ID NO:93. Preferred fragments of (b) comprise an epitope from SEQ ID NO:93. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ In NO:93 while retaining at least one epitope of SEQ ID NO:93. The first 20 N-terminal amino acids of SEQ In NO:93 can usefully be omitted. Other fragments omit one or more protein domains.

[00242] The 'sta060' antigen is annotated as 'peptide ABC transporter; peptide-binding protein'. In the NCTC 8325 strain sta060 IS SAOUHSC 02767 and has amino acid sequence SEQ ID NO:94 (GI:88196403).

[00243] Useful sta060 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:94 and/or may comprise an amino acid sequence: (a) having 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more identity to SEQ In NO:94; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ In NO:94, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta060 proteins include variants of SEQ ID NO:94. Preferred fragments of (b) comprise an epitope from SEQ In NO:94. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:94 while retaining at least one epitope of SEQ In NO:94. The first 20 N-terminal amino acids of SEQ In NO:94 can usefully be omitted. Other fragments omit one or more protein domains.

[00244] The 'sta061' antigen is annotated as 'protein with leader'. In the NCTC 8325 strain sta061 is SAOUHSC_02783 and has amino acid sequence SEQ ID NO:95 (GI:88196419).

[00245] Useful sta061 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ In NO:95 and/or may comprise an amino acid sequence: (a) having 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more identity to SEQ ID NO:95; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:95, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta061 proteins

include variants of SEQ ID NO:95. Preferred fragments of (b) comprise an epitope from SEQ ID NO:95. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:95 while retaining at least one epitope of SEQ ID NO:95. The first 21 N-terminal amino acids of SEQ ID NO:95 can usefully be omitted. Other fragments omit one or more protein domains.

[00246] The 'sta062' antigen is annotated as 'protein with leader'. In the NCTC 8325 strain sta062 is SAOUHSC_02788 and has amino acid sequence SEQ ID NO:96 (GI:88 196424).

[00247] Useful sta062 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:96 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:96; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:96, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta062 proteins include variants of SEQ ID NO:96. Preferred fragments of (b) comprise an epitope from SEQ ID NO:96. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:96 while retaining at least one epitope of SEQ ID NO:96. The first 22 N-terminal amino acids of SEQ ID NO:96 can usefully be omitted. Other fragments omit one or more protein domains.

[00248] The 'sta063, antigen is annotated as 'aureolysin'. In the NCTC 8325 strain sta063 is SAOUHSC_02971 and has amino acid sequence SEQ ID NO:97 (GI:88196592).

[00249] Useful sta063 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:97 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:97; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:97, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta063 proteins include variants of SEQ ID NO:97. Preferred fragments of (b) comprise an epitope from SEQ ID NO:97. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino

acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:97 while retaining at least one epitope of SEQ ID NO:97. The first 16 N-terminal amino acids of SEQ ID NO:97 can usefully be omitted. Other fragments omit one or more protein domains.

[00250] The 'sta064' antigen is annotated as 'lipase'. In the NCTC 8325 strain sta064 is SAOUHSC_03006 and has amino acid sequence SEQ ID NO:98 (GI:88 196625). In the Newman strain it is nwmn 2569 (GI:151222781).

[00251] Useful sta064 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:98 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:98; and/or (b) comprising a fragment of at least In' consecutive amino acids of SEQ ID NO:98, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta064 proteins include variants of SEQ ID NO:98. Preferred fragments of (b) comprise an epitope from SEQ ID NO:98. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:98 while retaining at least one epitope of SEQ ID NO:98. The first 34 N-terminal amino acids of SEQ ID NO:98 can usefully be omitted. Other fragments omit one or more protein domains.

[00252] The 'sta065' antigen is annotated as 'l-phosphatidylinositol phosphodiesterase precursor'. In the NCTC 8325 strain sta065 is SAOUHSC 00051 and has amino acid sequence SEQ ID NO:99 (GI:88193871).

[00253] Useful sta065 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:99 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:99; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:99, wherein In' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta065 proteins include variants of SEQ ID NO:99. Preferred fragments of (b) comprise an epitope from SEQ ID NO:99. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino

acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:99 while retaining at least one epitope ofSEQ ID NO:99. The first 26 N-terminal amino acids of SEQ ID NO:99 can usefully be omitted. Other fragments omit one or more protein domains.

[00254] The 'sta066' antigen is annotated as 'protein'. In the NCTC 8325 strain sta066 is SAOUHSC_00172 and has amino acid sequence SEQ ID NO:100 (GI:88193982).

[00255] Useful sta066 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:100 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:100; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:100, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta066 proteins include variants of SEQ ID NO:100. Preferred fragments of (b) comprise an epitope from SEQ ID NO:100. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:100 while retaining at least one epitope of SEQ ID NO:100. The first 21 N-terminal amino acids of SEQ ID NO:100 can usefully be omitted. Other fragments omit one or more protein domains.

[00256] The 'sta067' antigen is annotated as 'bacterial extracellular solute-binding protein'. In the NCTC 8325 strain sta067 is SAOUHSC_00176 and has amino acid sequence SEQ ID NO:101 (GI:88 193986).

[00257] Useful sta067 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:101 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:101; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:101, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta067 proteins include variants of SEQ ID NO:101. Preferred fragments of (b) comprise an epitope from SEQ ID NO:101. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-

terminus of SEQ ID NO:101 while retaining at least one epitope of SEQ ID NO:101. The first 20 N-terminal amino acids of SEQ ID NO:101 can usefully be omitted. Other fragments omit one or more protein domains.

[00258] The 'sta068' antigen is annotated as 'iron permease FTRI'. In the NCTC 8325 strain sta068 is SAOUHSC_00327 and has amino acid sequence SEQ ID NO:102 (GI:88194127).

[00259] Useful sta068 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:102 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:102; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:102, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta068 proteins include variants of SEQ ID NO:102. Preferred fragments of (b) comprise an epitope from SEQ ID NO:102. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:102 while retaining at least one epitope of SEQ ID NO:102. The final 20 C-terminal amino acids of SEQ ID NO:102 can usefully be omitted. The first 14 N-terminal amino acids of SEQ ID NO:102 can usefully be omitted. Other fragments omit one or more protein domains.

[00260] The 'sta069' antigen is annotated as 'autolysin precursor'. In the NCTC 8325 strain sta069 is SAOUHSC_00427 and has amino acid sequence SEQ ID NO:103 (GI:88194219).

[00261] Useful sta069 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:103 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:103; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:103, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta069 proteins include variants of SEQ ID NO:103. Preferred fragments of (b) comprise an epitope from SEQ ID NO:103. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-

terminus of SEQ ID NO:103 while retaining at least one epitope of SEQ ID NO:103. The first 25 N-terminal amino acids of SEQ ID NO:103 can usefully be omitted. Other fragments omit one or more protein domains.

[00262] The 'sta070' antigen is annotated as 'immunogenic secreted precursor-like protein (truncated)'. In the NCTC 8325 strain sta070 is SAOUHSC_00773 and has amino acid sequence SEQ ID NO:104 (GI:88194535).

[00263] Useful sta070 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:104 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:104; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:104, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta070 proteins include variants of SEQ ID NO:104. Preferred fragments of (b) comprise an epitope from SEQ ID NO:104. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:104 while retaining at least one epitope of SEQ ID NO:104. The first 24 N-terminal amino acids of SEQ ID NO:104 can usefully be omitted. Other fragments omit one or more protein domains.

[00264] The 'sta071' antigen is annotated as 'hemolysin'. In the NCTC 8325 strain sta071 is SAOUHSC_00854 and has amino acid sequence SEQ ID NO:105 (GI:88194612).

[00265] Useful sta071 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:105 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:105; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:105, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta071 proteins include variants of SEQ ID NO:105. Preferred fragments of (b) comprise an epitope from SEQ ID NO:105. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:105 while retaining at least one epitope of SEQ ID NO:105. The

first 24 N-terminal amino acids of SEQ ID NO:105 can usefully be omitted. Other fragments omit one or more protein domains.

[00266] The 'sta072' antigen is annotated as 'extramembranal protein'. In the NCTC 8325 strain sta072 is SAOUHSC_00872 and has amino acid sequence SEQ ID NO:106 (GI:88194629).

[00267] Useful sta072 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:106 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:106; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:106, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta072 proteins include variants of SEQ ID NO:106. Preferred fragments of (b) comprise an epitope from SEQ ID NO:106. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:106 while retaining at least one epitope of SEQ ID NO:106. The first 24 N-terminal amino acids of SEQ ID NO:106 can usefully be omitted. Other fragments omit one or more protein domains.

[00268] The 'sta073' antigen is annotated as 'bifunctional autolysin precursor'. In the NCTC 8325 strain sta073 is SAOUHSC_00994 and has amino acid sequence SEQ ID NO:107 (GI:88194750). In the Newman strain it is nwmn_0922 (GI:151221134). Proteomic analysis has revealed that this protein is secreted or surface-exposed.

[00269] Useful sta073 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:107 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:107; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:107, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta073 proteins include variants of SEQ ID NO:107. Preferred fragments of (b) comprise an epitope from SEQ ID NO:107. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-

terminus of SEQ ID NO:107 while retaining at least one epitope of SEQ ID NO:107. The first 24 N-terminal amino acids of SEQ ID NO:107 can usefully be omitted. Other fragments omit one or more protein domains.

[00270] A Sta073 antigen can usefully be included in a composition in combination with a Sta112. Sta073 does not adsorb well to aluminium hydroxide adjuvants, so Sta073 present in a composition may be unadsorbed or may be adsorbed to an alternative adjuvant *e.g.* to an aluminium phosphate.

[00271] The 'sta074' antigen is annotated as 'factor essential for methicillin resistance'. In the NCTC 8325 strain sta074 is SAOUHSC_01220 and has amino acid sequence SEQ ID NO:108 (GI:88194956).

[00272] Useful sta074 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:108 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:108; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:108, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta074 proteins include variants of SEQ ID NO:108. Preferred fragments of (b) comprise an epitope from SEQ ID NO:108. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:108 while retaining at least one epitope of SEQ ID NO:108. Other fragments omit one or more protein domains.

[00273] The 'sta075' antigen is annotated as 'insulysin; peptidase family M16'. In the NCTC 8325 strain sta075 is SAOUHSC_01256 and has amino acid sequence SEQ ID NO:109 (GI:88194989).

[00274] Useful sta075 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:109 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:109; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:109, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta075 proteins include variants of SEQ ID 10 NO:109. Preferred fragments of (b)

comprise an epitope from SEQ ID NO:109. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:109 while retaining at least one epitope of SEQ ID NO:109. Other fragments omit one or more protein domains.

[00275] The 'sta076' antigen is annotated as 'hydrolase'. In the NCTC 8325 strain sta076 is SAOUHSC_01263 and has amino acid sequence SEQ ID NO:110 (GI:88194996).

[00276] Useful sta076 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:110 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:110; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:110, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta076 proteins include variants of SEQ ID NO:110. Preferred fragments of (b) comprise an epitope from SEQ ID NO:110. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:110 while retaining at least one epitope of SEQ ID NO:110. The first 24 N-terminal amino acids of SEQ ID NO:110 can usefully be omitted. Other fragments omit one or more protein domains.

[00277] The 'sta077' antigen is annotated as 'protein'. In the NCTC 8325 strain sta077 is SAOUHSC_01317 and has amino acid sequence SEQ ID NO:111 (GI:88195047). Proteomic analysis has revealed that this protein is secreted or surface-exposed.

[00278] Useful sta077 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:111 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:111; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:111, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta077 proteins include variants of SEQ ID NO:111. Preferred fragments of (b) comprise an epitope from SEQ ID NO:111. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or

one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:111 while retaining at least one epitope of SEQ ID NO:111. The first 20 N-terminal amino acids of SEQ ID NO:111 can usefully be omitted. Other fragments omit one or more protein domains.

[00279] The 'sta078' antigen is annotated as 'FtsK/SpoIIIE family protein'. In the NCTC 8325 strain sta078 is SAOUHSC_01857 and has amino acid sequence SEQ ID NO:112 (GI:88195555).

[00280] Useful sta078 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:112 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:112; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:112, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta078 proteins include variants of SEQ ID NO:112. Preferred fragments of (b) comprise an epitope from SEQ ID NO:112. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:112 while retaining at least one epitope of SEQ ID NO:112. Other fragments omit one or more protein domains.

[00281] The 'sta079' antigen is annotated as 'serine protease SpIF'. In the NCTC 8325 strain sta079 is SAOUHSC_01935 and has amino acid sequence SEQ ID NO:113 (GI:88195630).

[00282] Useful sta079 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:113 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 30 99.5% or more) to SEQ ID NO:113; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:113, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta079 proteins include variants of SEQ ID NO:113. Preferred fragments of (b) comprise an epitope from SEQ ID NO:113. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the 35 C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the

N-terminus of SEQ ID NO:113 while retaining at least one epitope of SEQ ID NO:113. The first 36 N-terminal amino acids of SEQ ID NO:113 can usefully be omitted. Other fragments omit one or more protein domains.

[00283] The 'sta080' antigen is annotated as 'serine protease SpIE'. In the NCTC 8325 strain sta080 is SAOUHSC_01936 and has amino acid sequence SEQ ID NO:114 (GI:88195631).

[00284] Useful sta080 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:114 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:114; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:114, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta080 proteins include variants of SEQ ID NO:114. Preferred fragments of (b) comprise an epitope from SEQ ID NO:114. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:114 while retaining at least one epitope of SEQ ID NO:114. The first 36 N-terminal amino acids of SEQ ID NO:114 can usefully be omitted. Other fragments omit one or more protein domains.

[00285] The 'sta081' antigen is annotated as 'serine protease SplD (EC:3.4.21.19)'. In the NCTC 8325 strain sta081 is SAOUHSC_01938 and has amino acid sequence SEQ ID NO:154 (GI:88195633).

[00286] Useful sta081 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:154 and/or may comprise an amino acid sequence: (a) having 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more identity to SEQ ID NO:154; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:154, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta081 proteins include variants of SEQ ID NO:154. Preferred fragments of (b) comprise an epitope from SEQ ID NO:154. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from 30 the N-terminus of SEQ ID NO:154 while

retaining at least one epitope of SEQ ID NO:154. The first 36 N-terminal amino acids of SEQ ID NO:154 can usefully be omitted. Other fragments omit one or more protein domains.

[00287] The 'sta082' antigen is annotated as 'serine protease SplC'. In the NCTC 8325 strain sta082 is SAOUHSC_01939 and has amino acid sequence SEQ ID NO:115 (GI:88195634).

[00288] Useful sta082 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:115 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:115; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:115, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta082 proteins include variants of SEQ ID NO:115. Preferred fragments of (b) comprise an epitope from SEQ ID NO:115. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:115 while retaining at least one epitope of SEQ ID NO:115. The first 36 N-terminal amino acids of SEQ ID NO:115 can usefully be omitted. Other fragments omit one or more protein domains.

[00289] The 'sta083' antigen is annotated as 'serine protease SplB'. In the NCTC 8325 strain sta083 is SAOUHSC_01941 and has amino acid sequence SEQ ID NO:116 (GI:88195635).

[00290] Useful sta083 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:116 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:116; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:116, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta083 proteins include variants of SEQ ID NO:116. Preferred fragments of (b) comprise an epitope from SEQ ID NO:116. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:116 while retaining at least one epitope of SEQ ID NO:116. The

first 36 N-terminal amino acids of SEQ ID NO:116 can usefully be omitted. Other fragments omit one or more protein domains.

[00291] The 'sta084' antigen is annotated as 'serine protease SplA'. In the NCTC 8325 strain sta084 is SAOUHSC_01942 and has amino acid sequence SEQ ID NO:117 (GI:88195636).

[00292] Useful sta084 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:117 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:117; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:117, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta084 proteins include variants of SEQ ID NO:117. Preferred fragments of (b) comprise an epitope from SEQ ID NO:117. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:117 while retaining at least one epitope of SEQ ID NO:117. The first N-terminal amino acids of SEQ ID NO:117 can usefully be omitted. Other fragments omit one or more protein domains.

[00293] The 'sta085' antigen is annotated as 'staphylokinase precursor'. In the NCTC 8325 strain sta085 is SAOUHSC_02171 and has amino acid sequence SEQ ID NO:118 (GI:88195848).

[00294] Useful sta085 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:118 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:118; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:118, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150 or more). These sta085 proteins include variants of SEQ ID NO:118. Preferred fragments of (b) comprise an epitope from SEQ ID NO:118. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:118 while retaining at least one epitope of SEQ ID NO:118. The first 27 N-terminal

amino acids of SEQ ID NO:118 can usefully be omitted. Other fragments omit one or 20 more protein domains.

[00295] The 'sta086' antigen is annotated as 'OxaA-like protein'. In the NCTC 8325 strain sta086 is SAOUHSC_02327 and has amino acid sequence SEQ ID NO:119 (GI:88195993).

[00296] Useful sta086 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:119 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:119; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:119, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta086 proteins include variants of SEQ ID NO:119. Preferred fragments of (b) comprise an epitope from SEQ ID NO:119. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:119 while retaining at least one epitope of SEQ ID NO:119. The first 19 N-terminal amino acids of SEQ ID NO:119 can usefully be omitted. Other fragments omit one or more protein domains.

[00297] The 'sta087' antigen is annotated as 'teicoplanin resistance protein TcaA'. In the NCTC 8325 strain sta087 is SAOUHSC_02635 and has amino acid sequence SEQ ID NO:120 (GI:88196276).

[00298] Useful sta087 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:120 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:120; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:120, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta087 proteins include variants of SEQ ID NO:120. Preferred fragments of (b) comprise an epitope from SEQ ID NO:120. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:120 while retaining at least one epitope of SEQ ID NO:120. Other fragments omit one or more protein domains.

[00299] The 'sta088' antigen is annotated as 'esterase'. In the NCTC 8325 strain sta088 is SAOUHSC_02844 and has amino acid sequence SEQ ID NO:121 (GI:88196477).

[00300] Useful sta088 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:121 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:121; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:121, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta088 proteins include variants of SEQ ID NO:121. Preferred fragments of (b) comprise an epitope from SEQ ID NO:121. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:121 while retaining at least one epitope of SEQ ID NO:121. The first 18 N-terminal amino acids of SEQ ID NO:121 can usefully be omitted. Other fragments omit one or more protein domains.

[00301] The 'sta089' antigen is annotated as 'LysM domain protein'. In the NCTC 8325 strain sta089 is SAOUHSC_02855 and has amino acid sequence SEQ ID NO:122 (GI:88196486).

[00302] Useful sta089 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:122 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:122; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:122, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100 or more). These sta089 proteins include variants of SEQ ID NO:122. Preferred fragments of (b) comprise an epitope from SEQ ID NO:122. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:122 while retaining at least one epitope of SEQ ID NO:122. The first 20 N-terminal amino acids of SEQ ID NO:122 can usefully be omitted. Other fragments omit one or more protein domains.

[00303] The 'sta090' antigen is annotated as 'LysM domain protein'. In the NCTC 8325 strain sta090 is SAOUHSC_02883 and has amino acid sequence SEQ ID NO:123 (GI:88196512).

[00304] Useful sta090 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:123 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:123; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:123, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta090 proteins include variants of SEQ ID NO:123. Preferred fragments of (b) comprise an epitope from SEQ ID NO:123. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:123 while retaining at least one epitope of SEQ ID NO:123. The first 26 N-terminal amino acids of SEQ ID NO:123 can usefully be omitted. Other fragments omit one or more protein domains.

[00305] The 'sta091' antigen is annotated as 'lipoprotein'. In the NCTC 8325 strain sta091 is SAOUHSC_00685 and has amino acid sequence SEQ ID NO:124 (GI:88194450).

[00306] Useful sta091 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:124 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:124; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:124, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100 or more). These sta091 proteins include variants of SEQ ID NO:124. Preferred fragments of (b) comprise an epitope from SEQ ID NO:124. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:124 while retaining at least one epitope of SEQ ID NO:124. The first 15 N-terminal amino acids of SEQ ID NO:124 can usefully be omitted. Other fragments omit one or more protein domains.

[00307] The 'sta092' antigen is annotated as 'M23/M37 peptidase domain protein'. In the NCTC 8325 strain sta092 is SAOUHSC_00174 and has amino acid sequence SEQ ID NO:125 (GI:88193984).

[00308] Useful sta092 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:125 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:125; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:125, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150 or more). These sta092 proteins include variants of SEQ ID NO:125. Preferred fragments of (b) comprise an epitope from SEQ ID NO:125. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:125 while retaining at least one epitope of SEQ ID NO:125. The first 25 N-terminal amino acids of SEQ ID NO:125 can usefully be omitted. Other fragments omit one or more protein domains.

[00309] The 'sta093, antigen is annotated as 'protein'. In the NCTC 8325 strain sta093 is SAOUHSC_01854 and has amino acid sequence SEQ ID NO:126 (GI:88195552).

[00310] Useful sta093 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:126 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:126; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:126, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta093 proteins include variants of SEQ ID NO:126. Preferred fragments of (b) comprise an epitope from SEQ ID NO:126. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:126 while retaining at least one epitope of SEQ ID NO:126. Other fragments omit one or more protein domains.

[00311] The 'sta094' antigen is annotated as 'protein'. In the NCTC 8325 strain sta094 is SAOUHSC_01512 and has amino acid sequence SEQ ID NO:127 (GI:88195226).

[00312] Useful sta094 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:127 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:127; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:127, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta094 proteins include variants of SEQ ID NO:127. Preferred fragments of (b) comprise an epitope from SEQ ID NO:127. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:127 while retaining at least one epitope of SEQ ID NO:127. The first 17 N-terminal amino acids of SEQ ID NO:127 can usefully be omitted. Other fragments omit one or more protein domains.

[00313] The 'sta095' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta095 is SAOUHSC_00383 and has amino acid sequence SEQ ID NO:128 (GI:88194180). In the Newman strain it is nwmn_0388 (GI:151220600).

[00314] Useful sta095 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:128 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:128; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:128, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 20 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta095 proteins include variants of SEQ ID NO:128. Preferred fragments of (b) comprise an epitope from SEQ ID NO:128. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:128 while retaining at least one epitope of SEQ ID NO:128. The first 32 N-terminal amino acids of SEQ ID NO:128 can usefully be omitted. Other fragments omit one or more protein domains.

[00315] The 'sta096' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta096 is SAOUHSC_00384 and has amino acid sequence SEQ ID NO:129 (GI:88194181). Useful sta096 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:129 and/or may comprise an amino acid sequence: (a)

having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:129; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:129, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 35 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta096 proteins include variants of SEQ ID NO:129. Preferred fragments of (b) comprise an epitope from SEQ ID NO:129. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:129 while retaining at least one epitope of SEQ ID NO:129. The first 30 N-terminal amino acids of SEQ ID NO:129 can usefully be omitted. Other fragments omit one or more protein domains.

[00316] The 'sta097' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta097 is SAOUHSC_00386 and has amino acid sequence SEQ ID NO:130 (GI:88194182).

[00317] Useful sta097 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:130 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:130; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:130, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta097 proteins include variants of SEQ ID NO:130. Preferred fragments of (b) comprise an epitope from SEQ ID NO:130. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:130 while retaining at least one epitope of SEQ ID NO:130. The first 30 N-terminal amino acids of SEQ ID NO:130 can usefully be omitted. Other fragments omit one or more protein domains.

[00318] The 'sta098' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta098 is SAOUHSC_00389 and has amino acid sequence SEQ ID NO:131 (GI:88194184). In the Newman strain it is nwmn_0391 (GI:151220603).

[00319] Useful sta098 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:131 and/or may comprise an amino acid sequence: (a) having

50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:131; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:131, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta098 proteins include variants of SEQ ID NO:131. Preferred fragments of (b) comprise an epitope from SEQ ID NO:131. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:131 while retaining at least one epitope of SEQ ID NO:131. The first 30 N-terminal amino acids of SEQ ID NO:131 can usefully be omitted. Other fragments omit one or more protein domains.

[00320] The 'sta099' antigen is annotated as 'superantigen-like protein 5'. In the NCTC 8325 strain sta099 is SAOUHSC_00390 and has amino acid sequence SEQ ID NO:132 (GI:88194185).

[00321] Useful sta099 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:132 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:132; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:132, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta099 proteins include variants of SEQ ID NO:132. Preferred fragments of (b) comprise an epitope from SEQ ID NO:132. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:132 while retaining at least one epitope of SEQ ID NO:132. The first 30 N-terminal amino acids of SEQ ID NO:132 can usefully be omitted. Other fragments omit one or more protein domains.

[00322] The 'sta100' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta100 is SAOUHSC_00391 and has amino acid sequence SEQ ID NO:133 (GI:88194186).

[00323] Useful sta100 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:133 and/or may comprise an amino acid sequence: (a) having

50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:133; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:133, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta100 proteins include variants of SEQ ID NO:133. Preferred fragments of (b) comprise an epitope from SEQ ID NO:133. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:133 while retaining at least one epitope of SEQ ID NO:133. The first 30 N-terminal amino acids of SEQ ID NO:133 can usefully be omitted. Other fragments omit one or more protein domains.

[00324] The 'sta101' antigen is annotated as 'superantigen-like protein 7'. In the NCTC 8325 strain sta101 is SAOUHSC_00392 and has amino acid sequence SEQ ID NO:134 (GI:88194187). In the Newman strain it is nwrnn_0394 (GI:151220606).

[00325] Useful sta101 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:134 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:134; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:134, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta101 proteins include variants of SEQ ID NO:134. Preferred fragments of (b) comprise an epitope from SEQ ID NO:134. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:134 while retaining at least one epitope of SEQ ID NO:134. The first 30 N-terminal amino acids of SEQ ID NO:134 can usefully be omitted. Other fragments omit one or more protein domains.

[00326] The 'sta102' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta102 is SAOUHSC_00393 and has amino acid sequence SEQ ID NO:135 (GI:88194188).

[00327] Useful sta102 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:135 and/or may comprise an amino acid sequence: (a) having

50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:135; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:135, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta102 proteins include variants of SEQ ID NO:135. Preferred fragments of (b) comprise an epitope from SEQ ID NO:135. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:135 while retaining at least one epitope of SEQ ID NO:135. The first 17 N-terminal amino acids of SEQ ID NO:135 can usefully be omitted. Other fragments omit one or more protein domains.

[00328] The 'sta103' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta103 is SAOUHSC_00394 and has amino acid sequence SEQ ID NO:136 (GI:88194189).

[00329] Useful sta103 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:136 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:136; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:136, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta103 proteins include variants of SEQ ID NO:136. Preferred fragments of (b) comprise an epitope from SEQ ID NO:136. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:136 while retaining at least one epitope of SEQ ID NO:136. The first 23 N-terminal amino acids of SEQ ID NO:136 can usefully be omitted. Other fragments omit one or more protein domains.

[00330] The 'sta104' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta104 is SAOUHSC_00395 and has amino acid sequence SEQ ID NO:137 (GI:88194190).

[00331] Useful sta104 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:137 and/or may comprise an amino acid sequence: (a) having

50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:137; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:137, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta104 proteins include variants of SEQ ID NO:137. Preferred fragments of (b) comprise an epitope from SEQ ID NO:137. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:137 while retaining at least one epitope of SEQ ID NO:137. Other fragments omit one or more protein domains.

[00332] The 'sta105' antigen is annotated as 'superantigen-like protein'. In the NCTC 8325 strain sta105 is 20 SAOUHSC_00399 and has amino acid sequence SEQ ID NO:138 (GI:88194194). In the Newman strain it is nwmn_0400 (GI:151220612).

[00333] Useful sta105 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:138 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:138; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:138, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta105 proteins include variants of SEQ ID NO:138. Preferred fragments of (b) comprise an epitope from SEQ ID NO:138. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:138 while retaining at least one epitope of SEQ ID NO:138. The first 30 N-terminal amino acids of SEQ ID NO:138 can usefully be omitted. Other fragments omit one or more protein domains.

[00334] The 'sta106' antigen is annotated as 'hypothetical protein'. In the NCTC 8325 strain sta106 is SAOUHSC_01115 and has amino acid sequence SEQ ID NO:139 (GI:88194861).

[00335] Useful sta106 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:139 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%,

95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:139; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:139, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100 or more). These sta106 proteins include variants of SEQ ID NO:139. Preferred fragments of (b) comprise an epitope from SEQ ID NO:139. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:139 while retaining at least one epitope of SEQ ID NO:139. The first 16 N-terminal amino acids of SEQ ID NO:139 can usefully be omitted. Other fragments omit one or more protein domains.

[00336] The 'sta107' antigen is annotated as 'hypothetical protein'. In the NCTC 8325 strain sta107 is SAOUHSC_00354 and has amino acid sequence SEQ ID NO:140 (GI:88194153).

[00337] Useful sta107 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:140 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:140; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:140, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta107 proteins include variants of SEQ ID NO:140. Preferred fragments of (b) comprise an epitope from SEQ ID NO:140. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:140 while retaining at least one epitope of SEQ ID NO:140. The first 35 N-terminal amino acids of SEQ ID NO:140 can usefully be omitted. Other fragments omit one or more protein domains.

[00338] The 'sta108' antigen is annotated as 'hypothetical protein'. In the NCTC 8325 strain sta108 is SAOUHSC_00717 and has amino acid sequence SEQ ID NO:141 (GI:88194482).

[00339] Useful sta108 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:141 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%,

95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:141; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:141, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100 or more). These sta108 proteins include variants of SEQ ID NO:141. Preferred fragments of (b) comprise an epitope from SEQ ID NO:141. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:141 while retaining at least one epitope of SEQ ID NO:141. The first 20 N-terminal amino acids of SEQ ID NO:141 can usefully be omitted. Other fragments omit one or more protein domains.

[00340] The 'sta109' antigen is annotated as 'N-acetylmuramoyl-L-alanine amidase '. In the NCTC 8325 strain sta109 is SAOUHSC_02979 and has amino acid sequence SEQ ID NO:142 (GI:88196599).

[00341] Useful sta109 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:142 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:142; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:142, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta109 proteins include variants of SEQ ID NO:142. Preferred fragments of (b) comprise an epitope from SEQ ID NO:142. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:142 while retaining at least one epitope of SEQ ID NO:142. The first 27 N-terminal amino acids of SEQ ID NO:142 can usefully be omitted. Other fragments omit one or more protein domains.

[00342] The 'sta110' antigen is annotated as 'hypothetical protein'. In the NCTC 8325 strain sta110 is SAOUHSC_01039 and has amino acid sequence SEQ ID NO:143 (GI:88194791).

[00343] Useful sta110 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:143 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%,

95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:143; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:143, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200 or more). These sta110 proteins include variants of SEQ ID NO:143. Preferred fragments of (b) comprise an epitope from SEQ ID NO:143. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:143 while retaining at least one epitope ofSEQ ID NO:143. The first 19 N-terminal amino acids of SEQ ID NO:143 can usefully be omitted. Other fragments omit one or more protein domains.

[00344] The 'sta111' antigen is annotated as 'hypothetical protein'. In the NCTC 8325 strain sta111 is SAOUHSC_01005 and has amino acid sequence SEQ ID NO:144 (GI:88194760).

[00345] Useful sta111 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:144 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:144; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:144, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100 or more). These sta111 proteins include variants of SEQ ID NO:144. Preferred fragments of (b) comprise an epitope from SEQ ID NO:144. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:144 while retaining at least one epitope of SEQ ID NO:144. The first 20 N-terminal amino acids of SEQ ID NO:144 can usefully be omitted. Other fragments omit one or more protein domains.

[00346] The 'sta112' antigen is annotated as a putative 'ABC transporter, substrate-binding protein'. In the NCTC 8325 strain sta112 is SAOUHSC_00634 and has amino acid sequence SEQ ID NO:145 (GI:88194402).

[00347] Useful sta112 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:145 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%,

95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:145; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:145, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta112 proteins include variants of SEQ ID NO:145. Preferred fragments of (b) comprise an epitope from SEQ ID NO:145. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:145 while retaining at least one epitope of SEQ ID NO:145. The first 17 N-terminal amino acids of SEQ ID NO:145 can usefully be omitted. Other fragments omit one or more protein domains.

[00348] The 'sta113' antigen is annotated as 'hypothetical protein'. In the NCTC 8325 strain stal13 is SAOUHSC_00728 and has amino acid sequence SEQ ID NO:146 (GI:88194493).

[00349] Useful sta113 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:146 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:146; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:146, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta113 proteins include variants of SEQ ID NO:146. Preferred fragments of (b) comprise an epitope from SEQ ID NO:146. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from 10 the N-terminus of SEQ ID NO:146 while retaining at least one epitope of SEQ ID NO:146. The first 173 N-terminal amino acids of SEQ ID NO:146 can usefully be omitted. Other fragments omit one or more protein domains.

[00350] The 'sta114' antigen is annotated as 'hypothetical protein'. In the NCTC 8325 strain sta114 is SAOUHSC_00810 and has amino acid sequence SEQ ID NO:147 (GI:88194570).

[00351] Useful sta114 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:147 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%,

95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:147; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:147, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150 or more). These sta114 proteins include variants of SEQ ID NO:147. Preferred fragments of (b) comprise an epitope from SEQ ID NO:147. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:147 while retaining at least one epitope of SEQ ID NO:147. Other fragments omit one or more protein domains.

[00352] The 'sta115' antigen is annotated as 'hypothetical protein'. In the NCTC 8325 strain sta115 is SAOUHSC_00817 and has amino acid sequence SEQ ID NO:148 (GI:88194576).

[00353] Useful sta115 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:148 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:148; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:148, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 35 40, 50, 60, 70, 80, 90, 100, 150 or more). These sta115 proteins include variants of SEQ ID NO:148. Preferred fragments of (b) comprise an epitope from SEQ ID NO:148. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:148 while retaining at least one epitope of SEQ ID NO:148. The first 18 N-terminal amino acids of SEQ ID NO:148 can usefully be omitted. Other fragments omit one or more protein domains.

[00354] The 'sta116' antigen is annotated as 'formyl peptide receptor-like 1 inhibitory protein '. In the NCTC 8325 strain sta116 IS SAOUHSC 01112 and has amino acid sequence SEQ ID NO:149 (GI:88194858).

[00355] Useful sta116 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:149 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:149; and/or (b) comprising a

fragment of at least 'n' consecutive amino acids of SEQ ID NO:149, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100 or more). These sta116 proteins include variants of SEQ ID NO:149. Preferred fragments of (b) comprise an epitope from SEQ ID NO:149. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:149 while retaining at least one epitope of SEQ ID NO:149. The first 20 N-terminal amino acids of SEQ ID NO:149 can usefully be omitted. Other fragments omit one or more protein domains.

[00356] The 'sta117' antigen is annotated as 'truncated beta-hemolysin'. In the NCTC 8325 strain sta117 is SAOUHSC_02240 and has amino acid sequence SEQ ID NO:150 (GI:88195913).

[00357] Useful sta117 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:150 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:150; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:150, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta117 proteins include variants of SEQ ID NO:150. Preferred fragments of (b) comprise an epitope from SEQ ID NO:150. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:150 while retaining at least one epitope of SEQ ID NO:150. Other fragments omit one or more protein domains.

[00358] The 'sta118' antigen is annotated as 'cell division protein FtsZ'. In the NCTC 8325 strain sta118 is SAOUHSC_01150 and has amino acid sequence SEQ ID NO:151 (GI:88194892).

[00359] Useful sta118 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:151 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:151; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:151, wherein 'n' is 7 or more

(*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150, 200, 250 or more). These sta118 proteins include variants of SEQ ID NO:151. Preferred fragments of (b) comprise an epitope from SEQ ID NO:151. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:151 while retaining at least one epitope of SEQ ID NO:151. Other fragments omit one or more protein domains.

[00360] The 'sta119' antigen is annotated as 'thioredoxin'. In the NCTC 8325 strain sta119 is SAOUHSC_01100 and has amino acid sequence SEQ ID NO:152 (GI:88194846).

[00361] Useful sta119 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:152 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more) to SEQ ID NO:152; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:152, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100 or more). These sta119 proteins include variants of SEQ ID NO:152. Preferred fragments of (b) comprise an epitope from SEQ ID NO:152. Other preferred fragments lack one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:152 while retaining at least one epitope of SEQ ID NO:152. Other fragments omit one or more protein domains.

[00362] The 'sta120' antigen is annotated as 'alkyl hydroperoxide reductase subunit c'. In the NCTC 8325 strain sta120 is SAOUHSC_00365 and has amino acid sequence SEQ ID NO:153 (GI:88194163).

[00363] Useful sta120 antigens can elicit an antibody (*e.g.* when administered to a human) that recognizes SEQ ID NO:153 and/or may comprise an amino acid sequence: (a) having 50% or more identity (*e.g.* 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 35 99.5% or more) to SEQ ID NO:153; and/or (b) comprising a fragment of at least 'n' consecutive amino acids of SEQ ID NO:153, wherein 'n' is 7 or more (*e.g.* 8, 10, 12, 14, 16, 18, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 150 or more). These sta120 proteins include variants of SEQ ID NO:153. Preferred fragments of (b) comprise an epitope from SEQ ID NO:153. Other preferred fragments lack one or more amino acids (*e.g.*

1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the C-terminus and/or one or more amino acids (*e.g.* 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25 or more) from the N-terminus of SEQ ID NO:153 while retaining at least one epitope of SEQ ID NO:153. Other fragments omit one or more protein domains.

[00364] The polypeptides described herein may include 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or more variant amino acids within at least, or at most 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 300, 400, 500, 550, 1000 or more contiguous amino acids, or any range derivable therein, of SEQ ID NO:2-30, or SEQ ID NO:32-155.

[00365] A polypeptide segment or immunogenic fragment as described herein may include 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246,

247, 248, 249, 250, 300, 400, 500, 550, 1000 or more contiguous amino acids, or any range derivable therein, of SEQ ID NO:2-30, or SEQ ID NO:33-155.

[00366] The immunogenic compositions of the invention may further comprise capsular polysaccharides including one or more of PIA (also known as PNAG) and/or *S. aureus* Type V and/or type VIII capsular polysaccharide and/or *S. epidermidis* Type I, and/or Type II and/or Type III capsular polysaccharide.

[00367] The compositions may be formulated in a pharmaceutically acceptable composition. In certain aspects of the invention the staphylococcus bacterium is an *S. aureus* bacterium.

[00368] In further aspects, a composition may be administered more than one time to the subject, and may be administered 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20 or more times. The administration of the compositions include, but is not limited to oral, parenteral, subcutaneous, intramuscular, intravenous, or various combinations thereof, including inhalation or aspiration.

[00369] In still further embodiments, a composition comprises a recombinant nucleic acid molecule encoding a polypeptide described herein or segments/fragments thereof. Typically a recombinant nucleic acid molecule encoding a polypeptide described herein contains a heterologous promoter. In certain aspects, a recombinant nucleic acid molecule of the invention is a vector, in still other aspects the vector is a plasmid. In certain embodiments the vector is a viral vector. In certain aspects a composition includes a recombinant, non-staphylococcus bacterium containing or expressing a polypeptide described herein. In particular aspects the recombinant non-staphylococcus bacteria is *Salmonella* or another gram-positive bacteria. A composition is typically administered to mammals, such as human subjects, but administration to other animals that are capable of eliciting an immune response is contemplated. In further aspects the staphylococcus bacterium containing or expressing the polypeptide is *Staphylococcus aureus*. In further embodiments the immune response is a protective immune response.

[00370] In further embodiments a composition comprises a recombinant nucleic acid molecule encoding all or part of one or more of a SpA, SpA polypeptide variant, Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla, IsdC, SasF, SpA, vWbp, or vWh protein or peptide or variant thereof. Additional staphylococcal antigens that can be used in combination with the polypeptides described herein include, but

are not limited to 52kDa vitronectin binding protein (WO 01/60852), Aaa, Aap, Ant, autolysin glucosaminidase, autolysin amidase, Cna, collagen binding protein (US6288214), EFB (FIB), Elastin binding protein (EbpS), EPB, FbpA, fibrinogen binding protein (US6008341), Fibronectin binding protein (US5840846), FnbA, FnbB, GehD (US 2002/0169288), HarA, HBP, Immunodominant ABC transporter, IsaA/PisA, laminin receptor, Lipase GehD, MAP, Mg2+ transporter, MHC II analogue (US5648240), MRPII, Npase, RNA III activating protein (RAP), SasA, SasB, SasC, SasD, SasK,SBI, SdrF(WO 00/12689), SdrG / Fig (WO 00/12689), SdrH (WO 00/12689), SEA exotoxins (WO 00/02523), SEB exotoxins (WO 00/02523), SitC and Ni ABC transporter, SitC/MntC/saliva binding protein (US 5,801,234), SsaA, SSP-1, SSP-2, and/or Vitronectin binding protein. In particular aspects, a bacteria is a recombinant non-staphylococcus bacteria, such as a *Salmonella* or other gram-positive bacteria. Certain embodiments include compositions comprising recombinant nucleic acid molecules encoding all or part of one or more of , sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof.

[00371] Compositions of the invention are typically administered to human subjects, but administration to other animals that are capable of eliciting an immune response to a bacterium, *e.g.*, a staphylococcus bacterium, is contemplated, particularly cattle, horses, goats, sheep and other domestic animals, *i.e.*, mammals.

[00372] In certain aspects the staphylococcus bacterium is a *Staphylococcus aureus*. In further embodiments the immune response is a protective immune response. In still further aspects, the methods and compositions of the invention can be used to prevent, ameliorate, reduce, or treat infection of tissues or glands, *e.g.*, mammary glands, particularly mastitis and other infections. Other methods include, but are not limited to prophylactically reducing

bacterial burden in a subject not exhibiting signs of infection, particularly those subjects suspected of or at risk of being colonized by a target bacteria, *e.g.*, patients that are or will be at risk or susceptible to infection during a hospital stay, treatment, and/or recovery.

[00373] Any embodiment discussed with respect to one aspect of the invention applies to other aspects of the invention as well. In particular, any embodiment discussed in the context of a SpA variant polypeptide, peptide, nucleic acid, or antibody may specifically exlcude one or more of Eap, Ebh, Emp, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla, IsdC, SasF, vWbp, vWh, 52kDa vitronectin binding protein (WO 01/60852), Aaa, Aap, Ant, autolysin glucosaminidase, autolysin amidase, Cna, collagen binding protein (US6288214), EFB (FIB), Elastin binding protein (EbpS), EPB, FbpA, fibrinogen binding protein (US6008341), Fibronectin binding protein (US5840846), FnbA, FnbB, GehD (US 2002/0169288), HarA, HBP, Immunodominant ABC transporter, IsaA/PisA, laminin receptor, Lipase GehD, MAP, Mg2+ transporter, MHC II analogue (US5648240), MRPII, Npase, RNA III activating protein (RAP), SasA, SasB, SasC, SasD, SasK,SBI, SdrF(WO 00/12689), SdrG / Fig (WO 00/12689), SdrH (WO 00/12689), SEA exotoxins (WO 00/02523), SEB exotoxins (WO 00/02523), SitC and Ni ABC transporter, SitC/MntC/saliva binding protein (US 5,801,234), SsaA, SSP-1, SSP-2, and/or Vitronectin binding protein (or nucleic acids), sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta02l, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta03l, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093, sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof and vice versa.

[00374] Embodiments of the invention include compositions that contain or do not contain a bacterium. A composition may or may not include an attenuated or viable or intact staphylococcal bacterium. In certain aspects, the composition comprises a bacterium that is not a staphylococcal bacterium or does not contain staphylococcal bacteria. In certain embodiments a bacterial composition comprises an isolated or recombinantly expressed

staphylococcal Protein A variant or a nucleotide encoding the same. The composition may be or include a recombinantly engineered staphylococcus bacterium that has been altered in a way that comprises specifically altering the bacterium with respect to a secreted virulence factor or cell surface protein. For example, the bacteria may be recombinantly modified to express more of the virulence factor or cell surface protein than it would express if unmodified.

[00375] The term "isolated" can refer to a nucleic acid or polypeptide that is substantially free of cellular material, bacterial material, viral material, or culture medium (when produced by recombinant DNA techniques) of their source of origin, or chemical precursors or other chemicals (when chemically synthesized). Moreover, an isolated compound refers to one that can be administered to a subject as an isolated compound; in other words, the compound may not simply be considered "isolated" if it is adhered to a column or embedded in an agarose gel. Moreover, an "isolated nucleic acid fragment" or "isolated peptide" is a nucleic acid or protein fragment that is not naturally occurring as a fragment and/or is not typically in the functional state.

[00376] Moieties of the invention, such as polypeptides, peptides, antigens, or immunogens, may be conjugated or linked covalently or noncovalently to other moieties such as adjuvants, proteins, peptides, supports, fluorescence moieties, or labels. The term "conjugate" or "immunoconjugate" is broadly used to define the operative association of one moiety with another agent and is not intended to refer solely to any type of operative association, and is particularly not limited to chemical "conjugation." Recombinant fusion proteins are particularly contemplated. Compositions of the invention may further comprise an adjuvant or a pharmaceutically acceptable excipient. An adjuvant may be covalently or non-covalently coupled to a polypeptide or peptide of the invention. In certain aspects, the adjuvant is chemically conjugated to a protein, polypeptide, or peptide.

[00377] The term "providing" is used according to its ordinary meaning to indicate "to supply or furnish for use." In some embodiments, the protein is provided directly by administering the protein, while in other embodiments, the protein is effectively provided by administering a nucleic acid that encodes the protein. In certain aspects the invention contemplates compositions comprising various combinations of nucleic acid, antigens, peptides, and/or epitopes.

[00378] The subject will have (*e.g.*, are diagnosed with a staphylococcal infection), will be suspected of having, or will be determined to be at risk of developing a staphylococcal infection. Compositions of the present invention include immunogenic compositions wherein the antigen(s) or epitope(s) are contained in an amount effective to achieve the intended purpose. More specifically, an effective amount means an amount of active ingredients necessary to stimulate or elicit an immune response, or provide resistance to, amelioration of, or mitigation of infection. In more specific aspects, an effective amount prevents, alleviates or ameliorates symptoms of disease or infection, or prolongs the survival of the subject being treated. Determination of the effective amount is well within the capability of those skilled in the art, especially in light of the detailed disclosure provided herein. For any preparation used in the methods of the invention, an effective amount or dose can be estimated initially from *in vitro* studies, cell culture, and/or animal model assays. For example, a dose can be formulated in animal models to achieve a desired immune response or circulating antibody concentration or titer. Such information can be used to more accurately determine useful doses in humans.

[00379] The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or." It is also contemplated that anything listed using the term "or" may also be specifically excluded.

[00380] Throughout this application, the term "about" is used to indicate that a value includes the standard deviation of error for the device or method being employed to determine the value.

[00381] Following long-standing patent law, the words "a" and "an," when used in conjunction with the word "comprising" in the claims or specification, denotes one or more, unless specifically noted.

[00382] Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

DESCRIPTION OF THE DRAWINGS

[00383] So that the matter in which the above-recited features, advantages and objects of the invention as well as others which will become clear are attained and can be understood in detail, more particular descriptions and certain embodiments of the invention briefly summarized above are illustrated in the appended drawings. These drawings form a part of the specification. It is to be noted, however, that the appended drawings illustrate certain embodiments of the invention and therefore are not to be considered limiting in their scope.

[00384] **FIG. 1 Immunization with SpA_{KKAA} modifies host immune responses to staphylococcal infection.** Cohorts of BALB/c mice (n=15) were immunized with SpA_{KKAA} or with PBS/adjuvant control (mock) and then challenged by intravenous inoculation with 5×10^6 CFU *S. aureus* USA300 LAC. Thirty days after infection, animals were bled and serum samples were analyzed for antibody responses to staphylococcal antigens. Twenty-seven recombinant, six-histidyl tagged staphylococcal proteins (ClfA, ClfB, Coa, Eap, Ebh, Emp, EsxA, EsxB, FnbpA, FnbpB, Hla, IsdA, IsdB, LukD, LukE, LukF, SdrC, SdrD, SdrE, SasA, SasD, SasF, SasG, SasI, SasK, SpA_{KKAA} and vWbp) were purified by Ni-NTA affinity chromatography and immobilized on nitrocellulose membrane at 2 μg. Signal intensities in sera from mice were quantified and normalized by infrared imaging. Data are the means, and error bars represent SEM (±).

DETAILED DESCRIPTION

[00385] *Staphylococcus aureus* is a commensal of the human skin and nares, and the leading cause of bloodstream, skin and soft tissue infections (Klevens *et al.*, 2007). Recent dramatic increases in the mortality of staphylococcal diseases are attributed to the spread of methicillin-resistant *S. aureus* (MRSA) strains often not susceptible to antibiotics (Kennedy *et al.*, 2008). In a large retrospective study, the incidence of MRSA infections was 4.6% of all hospital admissions in the United States (Klevens *et al.*, 2007). The annual health care costs for 94,300 MRSA infected individuals in the United States exceed $2.4 billion (Klevens *et al.*, 2007). The current MRSA epidemic has precipitated a public health crisis that needs to be addressed by development of a preventive vaccine (Boucher and Corey, 2008). To date, an FDA licensed vaccine that prevents *S. aureus* diseases is not available.

[00386] The inventors describe here the use of Protein A, a cell wall anchored surface protein of staphylococci, for the generation of variants that can serve as subunit vaccines. The pathogenesis of staphylococcal infections is initiated as bacteria invade the skin or blood

stream via trauma, surgical wounds, or medical devices (Lowy, 1998). Although the invading pathogen may be phagocytosed and killed, staphylococci can also escape innate immune defenses and seed infections in organ tissues, inducing inflammatory responses that attract macrophages, neutrophils, and other phagocytes (Lowy, 1998). The responsive invasion of immune cells to the site of infection is accompanied by liquefaction necrosis as the host seeks to prevent staphylococcal spread and allow for removal of necrotic tissue debris (Lam *et al.*, 1963). Such lesions can be observed by microscopy as hypercellular areas containing necrotic tissue, leukocytes, and a central nidus of bacteria (Lam *et al.*, 1963). Unless staphylococcal abscesses are surgically drained and treated with antibiotics, disseminated infection and septicemia produce a lethal outcome (Sheagren, 1984).

I. STAPHYLOCOCCAL ANTIGENS

A. Staphylcoccal Protein A (SpA)

[00387] All *Staphylococcus aureus* strains express the structural gene for Protein A (spa) (Jensen, 1958 ; Said-Salim *et al.*, 2003), a well characterized virulence factor whose cell wall anchored surface protein product (SpA) encompasses five highly homologous immunoglobulin binding domains designated E, D, A, B, and C (Sjodahl, 1977). These domains display ~ 80% identity at the amino acid level, are 56 to 61 residues in length, and are organized as tandem repeats (Uhlen *et al.*, 1984). SpA is synthesized as a precursor protein with an N-terminal YSIRK/GS signal peptide and a C-terminal LPXTG motif sorting signal (DeDent *et al.*, 2008; Schneewind *et al.*, 1992). Cell wall anchored Protein A is displayed in great abundance on the staphylococcal surface (DeDent *et al.*, 2007; Sjoquist *et al.*, 1972). Each of its immunoglobulin binding domains is composed of anti-parallel α-helices that assemble into a three helix bundle and bind the Fc domain of immunoglobulin G (IgG) (Deisenhofer, 1981; Deisenhofer *et al.*, 1978), the VH3 heavy chain (Fab) of IgM (*i.e.*, the B cell receptor) (Graille *et al.*, 2000), the von Willebrand factor at its A1 domain [vWF AI is a ligand for platelets] (O'Seaghdha *et al.*, 2006) and the tumor necrosis factor α (TNF-α) receptor I (TNFRI) (Gomez *et al.*, 2006), which is displayed on surfaces of airway epithelia (Gomez *et al.*, 2004; Gomez *et al.*, 2007).

[00388] SpA impedes neutrophil phagocytosis of staphylococci through its attribute of binding the Fc component of IgG (Jensen, 1958; Uhlen *et al.*, 1984). Moreover, SpA is able to activate intravascular clotting via its binding to von Willebrand factor AI domains (Hartleib *et al.*, 2000). Plasma proteins such as fibrinogen and fibronectin act as bridges

between staphylococci (ClfA and ClfB) and the platelet integrin GPIIb/IIIa (O'Brien *et al.*, 2002), an activity that is supplemented through Protein A association with vWF AI, which allows staphylococci to capture platelets via the GPIb-α platelet receptor (Foster, 2005; O'Seaghdha *et al.*, 2006). SpA also binds TNFRI and this interaction contributes to the pathogenesis of staphylococcal pneumonia (Gomez *et al.*, 2004). SpA activates proinflammatory signaling through TNFR1 mediated activation of TRAF2, the p38/c-Jun kinase, mitogen activate protein kinase (MAPK) and the Rel-transcription factor NF-KB. SpA binding further induces TNFR1 shedding, an activity that appears to require the TNF-converting enzyme (TACE)(Gomez *et al.*, 2007). All of the aforementioned SpA activities are mediated through its five IgG binding domains and can be perturbed by the same amino acid substitutions, initially defined by their requirement for the interaction between Protein A and human IgG1 (Cedergren *et al.*, 1993.

[00389] SpA also functions as a B cell superantigen by capturing the Fab region of VH3 bearing IgM, the B cell receptor (Gomez *et al.*, 2007; Goodyear *et al.*, 2003; Goodyear and Silverman, 2004; Roben *et al.*, 1995). Following intravenous challenge, staphylococcal Protein A (SpA) mutations show a reduction in staphylococcal load in organ tissues and dramatically diminished ability to form abscesses (described herein). During infection with wildtype *S. aureus*, abscesses are formed within forty-eight hours and are detectable by light microscopy of hematoxylin-eosin stained, thin-sectioned kidney tissue, initially marked by an influx of polymorphonuclear leukocytes (PMNs). On day 5 of infection, abscesses increase in size and enclosed a central population of staphylococci, surrounded by a layer of eosinophilic, amorphous material and a large cuff of PMNs. Histopathology revealed massive necrosis of PMNs in proximity to the staphylococcal nidus at the center of abscess lesions as well as a mantle of healthy phagocytes. The inventors also observed a rim of necrotic PMNs at the periphery of abscess lesions, bordering the eosinophilic pseudocapsule that separated healthy renal tissue from the infectious lesion. Staphylococcal variants lacking Protein A are unable to establish the histopathology features of abscesses and are cleared during infection.

[00390] In previous studies, Cedergren *et al.* (1993) engineered five individual substitutions in the Fc frgament binding sub-domain of the B domain of SpA, L17D, N28A, I31A and K35A. These authors created these proteins to test data gathered from a three dimensional structure of a complex between one domain of SpA and Fc_1. Cedergren *et al.*

determined the effects of these mutations on stability and binding, but did not contemplate use of such substitutions for the production of a vaccine antigen.

[00391] Brown *et al.* (1998) describe studies designed to engineer new proteins based on SpA that allow the use of more favorable elution conditions when used as affinity ligands. The mutations studied included single mutations of Q13A, Q14H, N15A, N15H, F17H, Y18F, L21H, N32H, or K39H. Brown *et al.* report that Q13A, N15A, N15H, and N32H substitutions made little difference to the dissociation constant values and that the Y18F substitution resulted in a 2 fold decrease in binding affinity as compared to wild type SpA. Brown *et al.* also report that L21H and F17H substitutions decrease the binding affinity by five-fold and a hundred-fold respectively. The authors also studied analogous substitutions in two tandem domains. Thus, the Brown *et al.* studies were directed to generating a SpA with a more favorable elution profile, hence the use of His substitutions to provide a pH sensitive alteration in the binding affinity. Brown *et al.* ia silent on the use of SpA as a vaccine antigen.

[00392] Graille *et al.* (2000) describe a crystal structure of domain D of SpA and the Fab fragment of a human IgM antibody. Graille *et al.* define by analysis of a crystal structure the D domain amino acid residues that interact with the Fab fragment as residues Q26, G29, F30, Q32, S33, D36, D37, Q40, N43, E47, or L51, as well as the amino acid residues that form the interface between the domain D sub-domains. Graille *et al.* define the molecular interactions of these two proteins, but is silent in regard to any use of substitutions in the interacting residues in producing a vaccine antigen.

[00393] O'Seaghdha *et al.* (2006) describe studies directed at elucidating which sub-domain of domain D binds vWF. The authors generated single mutations in either the Fc or VH3 binding sub-domains, i.e., amino acid residues F5A, Q9A, Q10A, F13A, Y14A, L17A, N28A, I31A, K35A, G29A, F30A, S33A, D36A, D37A, Q40A, E47A, or Q32A.. The authors discovered that vWF binds the same sub-domain that binds Fc. O'Seaghda *et al.* define the sub-domain of domain D responsible for binding vWF, but is silent in regard to any use of substitutions in the interacting residues in producing a vaccine antigen.

[00394] Gomez *et al.* (2006) describe the identifcation of residues responsible for activation of the TNFR1 by using single mutations of F5A, F13A, Y14A, L17A, N21A, I31A, Q32A, and K35A. Gomez *et al.* is silent in regard to any use of substitutions in the interacting residues in producing a vaccine antigen.

[00395] Recombinant affinity tagged Protein A, a polypeptide encompassing the five IgG domains (EDCAB) (Sjodahl, 1977) but lacking the C-terminal Region X (Guss *et al.*, 1984), was purified from recombinant *E. coli* and used as a vaccine antigen (Stranger-Jones *et al.*, 2006). Because of the attributes of SpA in binding the Fc portion of IgG, a specific humoral immune response to Protein A could not be measured (Stranger-Jones *et al.*, 2006). The inventors have overcome this obstacle through the generation of SpA-DQ9,10K;D36,37A. BALB/c mice immunized with recombinant Protein A (SpA) displayed significant protection against intravenous challenge with *S. aureus* strains: a 2.951 log reduction in staphylococcal load as compared to the wild-type ($P > 0.005$; Student's t-test) (Stranger-Jones *et al.*, 2006). SpA specific antibodies may cause phagocytic clearance prior to abscess formation and/or impact the formation of the aforementioned eosinophilic barrier in abscesses that separate staphylococcal communities from immune cells since these do not form during infection with Protein A mutant strains. Each of the five SpA domains (*i.e.*, domains formed from three helix bundles designated E, D, A, B, and C) exerts similar binding properties (Jansson *et al.*, 1998). The solution and crystal structure of the domain D has been solved both with and without the Fc and VH3 (Fab) ligands, which bind Protein A in a non-competitive manner at distinct sites (Graille *et al.*, 2000). Mutations in residues known to be involved in IgG binding (FS, Q9, Q10, S11, F13, Y14, L17, N28, I31 and K35) are also required for vWF AI and TNFR1 binding (Cedergren *et al.*, 1993; Gomez *et al.*, 2006; O'Seaghdha *et al.*, 2006), whereas residues important for the VH3 interaction (Q26, G29, F30, S33, D36, D37, Q40, N43, E47) appear to have no impact on the other binding activities (Graille *et al.*, 2000; Jansson *et al.*, 1998). SpA specifically targets a subset of B cells that express VH3 family related IgM on their surface, *i.e.*, VH3 type B cell receptors (Roben *et al.*, 1995). Upon interaction with SpA, these B cells proliferate and commit to apoptosis, leading to preferential and prolonged deletion of innate-like B lymphocytes (*i.e.*, marginal zone B cells and follicular B2 cells)(Goodyear *et al.*, 2003; Goodyear *et al.*, 2004).

[00396] ***Molecular basis of Protein A surface display and function.*** Protein A is synthesized as a precursor in the bacterial cytoplasm and secreted via its YSIRK signal peptide at the cross wall, *i.e.* the cell division septum of staphylococci (FIG. 1) (DeDent *et al.*, 2007; DeDent *et al.*, 2008). Following cleavage of the C-terminal LPXTG sorting signal, Protein A is anchored to bacterial peptidoglycan crossbridges by sortase A (Mazmanian *et al.*, 1999; Schneewind *et al.*, 1995; Mazmanian *et al.*, 2000). Protein A is the most abundant surface protein of staphylococci; the molecule is expressed by virtually all *S. aureus* strains

(Cespedes *et al.*, 2005; Kennedy *et al.*, 2008; Said-Salim *et al.*, 2003). Staphylococci turn over 15-20% of their cell wall per division cycle (Navarre and Schneewind, 1999). Murine hydrolases cleave the glycan strands and wall peptides of peptidoglycan, thereby releasing Protein A with its attached C-terminal cell wall disaccharide tetrapeptide into the extracellular medium (Ton-That *et al.*, 1999). Thus, by physiological design, Protein A is both anchored to the cell wall and displayed on the bacterial surface but also released into surrounding tissues during host infection (Marraffini *et al.*, 2006).

[00397] Protein A captures immunoglobulins on the bacterial surface and this biochemical activity enables staphylococcal escape from host innate and acquired immune responses (Jensen, 1958; Goodyear *et al.*, 2004). Interestingly, region X of Protein A (Guss *et al.*, 1984), a repeat domain that tethers the IgG binding domains to the LPXTG sorting signal / cell wall anchor, is perhaps the most variable portion of the staphylococcal genome (Said-Salim, 2003; Schneewind *et al.*, 1992). Each of the five immunoglobulin binding domains of Protein A (SpA), formed from three helix bundles and designated E, D, A, B, and C, exerts similar structural and functional properties (Sjodahl, 1977; Jansson *et al.*, 1998). The solution and crystal structure of the domain D has been solved both with and without the Fc and V_H3 (Fab) ligands, which bind Protein A in a non-competitive manner at distinct sites (Graille 2000).

[00398] In the crystal structure complex, the Fab interacts with helix II and helix III of domain D via a surface composed of four VH region β-strands (Graille 2000). The major axis of helix II of domain D is approximately 50° to the orientation of the strands, and the interhelical portion of domain D is most proximal to the C0 strand. The site of interaction on Fab is remote from the Ig light chain and the heavy chain constant region. The interaction involves the following domain D residues: Asp-36 of helix II, Asp-37 and Gln-40 in the loop between helix II and helix III and several other residues (Graille 2000). Both interacting surfaces are composed predominantly of polar side chains, with three negatively charged residues on domain D and two positively charged residues on the 2A2 Fab buried by the interaction, providing an overall electrostatic attraction between the two molecules. Of the five polar interactions identified between Fab and domain D, three are between side chains. A salt bridge is formed between Arg-H19 and Asp-36 and two hydrogen bonds are made between Tyr-H59 and Asp-37 and between Asn-H82a and Ser-33. Because of the conservation of Asp-36 and Asp-37 in all five IgG binding domains of Protein A, the inventors mutated these residues.

[00399] The SpA-D sites responsible for Fab binding are structurally separate from the domain surface that mediates Fcγ binding. The interaction of Fcγ with domain D primarily involves residues in helix I with lesser involvement of helix II (Gouda *et al.*, 1992; Deisenhofer, 1981). With the exception of the Gln-32, a minor contact in both complexes, none of the residues that mediate the Fcγ interaction are involved in Fab binding. To examine the spatial relationship between these different Ig-binding sites, the SpA domains in these complexes have been superimposed to construct a model of a complex between Fab, the SpA-domain D, and the Fcγ molecule. In this ternary model, Fab and Fcγ form a sandwich about opposite faces of the helix II without evidence of steric hindrance of either interaction. These findings illustrate how, despite its small size (*i.e.*, 56–61 aa), an SpA domain can simultaneously display both activities, explaining experimental evidence that the interactions of Fab with an individual domain are noncompetitive. Residues for the interaction between SpA-D and Fcγ are Gln-9 and Gln-10.

[00400] In contrast, occupancy of the Fc portion of IgG on the domain D blocks its interaction with vWF A1 and probably also TNFR1 (O'Seaghdha *et al.*, 2006). Mutations in residues essential for IgG Fc binding (F5, Q9, Q10, S11, F13, Y14, L17, N28, I31 and K35) are also required for vWF A1 and TNFR1 binding (O'Seaghdha *et al.*, 2006; Cedergren *et al.*, 1993; Gomez *et al.*, 2006), whereas residues critical for the VH3 interaction (Q26, G29, F30, S33, D36, D37, Q40, N43, E47) have no impact on the binding activities of IgG Fc, vWF A1 or TNFR1 (Jansson *et al.*, 1998; Graille *et al.*, 2000). The Protein A immunoglobulin Fab binding activity targets a subset of B cells that express V_H3 family related IgM on their surface, *i.e.*, these molecules function as VH3type B cell receptors (Roben *et al.*, 1995). Upon interaction with SpA, these B cells rapidly proliferate and then commit to apoptosis, leading to preferential and prolonged deletion of innate-like B lymphocytes (*i.e.*, marginal zone B cells and follicular B2 cells) (Goodyear and Silverman, 2004; Goodyear and Silverman, 2003). More than 40% of circulating B cells are targeted by the Protein A interaction and the V_H3 family represents the largest family of human B cell receptors to impart protective humoral responses against pathogens (Goodyear and Silverman, 2004; Goodyear and Silverman, 2003). Thus, Protein A functions analogously to staphylococcal superantigens (Roben *et al.*, 1995), albeit that the latter class of molecules, for example SEB, TSST-1, TSST-2, form complexes with the T cell receptor to inappropriately stimulate host immune responses and thereby precipitating characteristic disease features of staphylococcal infections (Roben *et al.*, 1995; Tiedemann *et al.*, 1995). Together these findings document

the contributions of Protein A in establishing staphylococcal infections and in modulating host immune responses.

[00401] In sum, Protein A domains can viewed as displaying two different interfaces for binding with host molecules and any development of Protein A based vaccines must consider the generation of variants that do not perturb host cell signaling, platelet aggregation, sequestration of immunoglobulins or the induction of B cell proliferation and apoptosis. Such Protein A variants should also be useful in analyzing vaccines for the ability of raising antibodies that block the aforementioned SpA activities and occupy the five repeat domains at their dual binding interfaces. This goal is articulated and pursued here for the first time and methods are described in detail for the generation of Protein A variants that can be used as a safe vaccine for humans. To perturb IgG Fcγ, vWF AI and TNFR1 binding, glutamine (Q) 9 and 10 [numbering derived from the SpA domain D as described in Uhlen *et al.*, 1984] were mutated, and generated lysine substitutions for both glutamines with the expectation that these abolish the ligand attributes at the first binding interface. To perturb IgM Fab VH3 binding, aspartate (D) 36 and 37 were mutated, each of which is required for the association with the B cell receptor. D36 and D37 were both substituted with alanine. Q9,10K and D36,37A mutations are here combined in the recombinant molecule SpA-DQ9,10K;D36,37A and tested for the binding attributes of Protein A. Further, SpA-D and SpA-DQ9,10K;D36,37A are subjected to immunization studies in mice and rabbits and analyzed for [1] the production of specific antibodies (SpA-D Ab); [2] the ability of SpA-D Ab to block the association between Protein A and its four different ligands; and, [3] the attributes of SpA-D Ab to generate protective immunity against staphylococcal infections.

[00402] In certain embodiments the SpA variant is a full length SpA variant comprising a variant A, B, C, D, and E domain. In certain aspects, the SpA variant comprises or consists of the amino acid sequence that is 80, 90, 95, 98, 99, or 100% identical to the amino acid sequence of SEQ ID NO:34 In other embodiments the SpA variant comprises a segment of SpA. The SpA segment can comprise at least or at most 1, 2, 3, 4, 5 or more IgG binding domains. The IgG domains can be at least or at most 1, 2, 3, 4, 5 or more variant A, B, C, D, or E domains. In certain aspects the SpA variant comprises at least or at most 1, 2, 3, 4, 5, or more variant A domains. In a further aspect the SpA variant comprises at least or at most 1, 2, 3, 4, 5, or more variant B domains. In still a further aspect the SpA variant comprises at least or at most 1, 2, 3, 4, 5, or more variant C domains. In yet a further aspect the SpA variant comprises at least or at most 1, 2, 3, 4, 5, or more variant D domains. In certain

aspects the SpA variant comprises at least or at most 1, 2, 3, 4, 5, or more variant E domains. In a further aspect the SpA variant comprises a combination of A, B, C, D, and E domains in various combinations and permutations. The combinations can include all or part of a SpA signal peptide segment, a SpA region X segment, and/or a SpA sorting signal segment. In other aspects the SpA variant does not include a SpA signal peptide segment, a SpA region X segment, and/or a SpA sorting signal segment. In certain aspects a variant A domain comprises a substitution at position(s) 7, 8, 34, and/or 35 of SEQ ID NO:4. In another aspect a variant B domain comprises a substitution at position(s) 7, 8, 34, and/or 35 of SEQ ID NO:6. In still anther aspect a variant C domain comprises a substitution at position(s) 7, 8, 34, and/or 35 of SEQ ID NO:5. In certain aspects a variant D domain comprises a substitution at position(s) 9, 10, 37, and/or 38 of SEQ ID NO:2. In a further aspect a variant E domain comprises a substitution at position(s) 6, 7, 33, and/or 34 of SEQ ID NO:3.

[00403] In certain aspects the SpA variant includes a substitution of (a) one or more amino acid substitution in an IgG Fc binding sub-domain of SpA domain A, B, C, D, and/or E that disrupts or decreases binding to IgG Fc, and (b) one or more amino acid substitution in a V_H3 binding sub-domain of SpA domain A, B, C, D, and/or E that disrupts or decreases binding to V_H3. In still further aspects the amino acid sequence of a SpA variant comprises an amino acid sequence that is at least 50%, 60%, 70%, 80%, 90%, 95%, or 100% identical, including all values and ranges there between, to the amino acid sequence of SEQ ID NOs:2-6.

[00404] In a further aspect the SpA variant includes (a) one or more amino acid substitution in an IgG Fc binding sub-domain of SpA domain D, or at a corresponding amino acid position in other IgG domains, that disrupts or decreases binding to IgG Fc, and (b) one or more amino acid substitution in a V_H3 binding sub-domain of SpA domain D, or at a corresponding amino acid position in other IgG domains, that disrupts or decreases binding to V_H3. In certain aspects amino acid residue F5, Q9, Q10, S11, F13, Y14, L17, N28, I31, and/or K35 (SEQ ID NO:2, QQNNFNKDQQSAFYEILNMPNLNEAQRNGFIQSLKDDPSQSTNVLGEAKKLNES) of the IgG Fc binding sub-domain of domain D are modified or substituted. In certain aspects amino acid residue Q26, G29, F30, S33, D36, D37, Q40, N43, and/or E47 (SEQ ID NO:2) of the V_H3 binding sub-domain of domain D are modified or substituted such that binding to Fc or V_H3 is attenuated. In further aspects corresponding modifications or substitutions can be engineered in corresponding positions of the domain A, B, C, and/or E. Corresponding positions are defined by alignment of the domain D amino acid sequence with one or more of

the amino acid sequences from other IgG binding domains of SpA. In certain aspects the amino acid substitution can be any of the other 20 amino acids. In a further aspect conservative amino acid substitutions can be specifically excluded from possible amino acid substitutions. In other aspects only non-conservative substitutions are included. In any event, any substitution or combination of substitutions that reduces the binding of the domain such that SpA toxicity is significantly reduced is contemplated. The significance of the reduction in binding refers to a variant that produces minimal to no toxicity when introduced into a subject and can be assessed using in vitro methods described herein.

[00405] In certain embodiments, a variant SpA comprises at least or at most 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more variant SpA domain D peptides. In certain aspects 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, or 19 or more amino acid residues of the variant SpA are substituted or modified - including but not limited to amino acids F5, Q9, Q10, S11, F13, Y14, L17, N28, I31, and/or K35 (SEQ ID NO:2) of the IgG Fc binding sub-domain of domain D and amino acid residue Q26, G29, F30, S33, D36, D37, Q40, N43, and/or E47 (SEQ ID NO:2) of the V_H3 binding sub-domain of domain D. In one aspect of the invention glutamine residues at position 9 and/or 10 of SEQ ID NO:2 (or corresponding positions in other domains) are mutated. In another aspect, aspartic acid residues 36 and/or 37 of SEQ ID NO:2 (or corresponding positions in other domains) are mutated. In a further aspect, glutamine 9 and 10, and aspartic acid residues 36 and 37 are mutated. Purified non-toxigenic SpA or SpA-D mutants/variants described herein are no longer able to significantly bind (i.e., demonstrate attenuated or disrupted binding affinity) Fcγ or $F(ab)_2$ V_H3 and also do not stimulate B cell apoptosis. These non-toxigenic Protein A variants can be used as subunit vaccines and raise humoral immune responses and confer protective immunity against *S. aureus* challenge. Compared to wild-type full-length Protein A or the wild-type SpA-domain D, immunization with SpA-D variants resulted in an increase in Protein A specific antibody. Using a mouse model of staphylococcal challenge and abscess formation, it was observed that immunization with the non-toxigenic Protein A variants generated significant protection from staphylococcal infection and abscess formation. As virtually all *S. aureus* strains express Protein A, immunization of humans with the non-toxigenic Protein A variants can neutralize this virulence factor and thereby establish protective immunity. In certain aspects the protective immunity protects or ameliorates infection by drug resistant strains of Staphylococcus, such as USA300 and other MRSA strains.

[00406] In still further aspects, the bacterial antigen is multimerized, *e.g.*, dimerized or a linear fusion of two or more polypeptides or peptide segments. In certain aspects of the invention, a composition comprises multimers or concatamers of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 or more isolated cell surface proteins or segments thereof. Concatamers are linear polypeptides having one or more repeating peptide units. Bacterial antigens or fragments can be consecutive or separated by a spacer or other peptide sequences, *e.g.*, one or more additional bacterial peptide. In a further aspect, the other polypeptides or peptides contained in the multimer or concatamer can include, but are not limited to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 of FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, or vWh or immunogenic fragments thereof. Additional staphylococcal antigens that can be used including, but are not limited to 52kDa vitronectin binding protein (WO 01/60852), Aaa, Aap, Ant, autolysin glucosaminidase, autolysin amidase, Cna, collagen binding protein (US6288214), EFB (FIB), Elastin binding protein (EbpS), EPB, FbpA, fibrinogen binding protein (US6008341), Fibronectin binding protein (US5840846), FnbA, FnbB, GehD (US 2002/0169288), HarA, HBP, Immunodominant ABC transporter, IsaA/PisA, laminin receptor, Lipase GehD, MAP, Mg2+ transporter, MHC II analogue (US5648240), MRPII, Npase, RNA III activating protein (RAP), SasA, SasB, SasC, SasD, SasK,SBI, SdrF(WO 00/12689), SdrG / Fig (WO 00/12689), SdrH (WO 00/12689), SEA exotoxins (WO 00/02523), SEB exotoxins (WO 00/02523), SitC and Ni ABC transporter, SitC/MntC/saliva binding protein (US 5,801,234), SsaA, SSP-1, SSP-2, and/or Vitronectin binding protein.

[00407] Yet still further embodiments include vaccines comprising a pharmaceutically acceptable composition having a combination or permutation of protein(s) or peptide(s) described herein, wherein the composition is capable of stimulating and/or enhancing an immune response against a staphylococcus bacterium. The vaccine may comprise an isolated protein(s) or peptide(s) described. In certain aspects of the invention the bacterial antigen, or any other combination or permutation of protein(s) or peptide(s) described are multimerized, *e.g.*, dimerized or concatamerized. In a further aspect, the vaccine composition is contaminated by less than about 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0.5, 0.25, 0.05% (or any range derivable therein) of other Staphylococcal proteins. A composition may further comprise an isolated protein A specific antibody or fragment thereof.

B. Staphylococcal Coagulases

[00408] Coagulases are enzymes produced by *Staphylococcus* bacteria that convert fibrinogen to fibrin. Coa and vW_h activate prothrombin without proteolysis (Friedrich *et al.*, 2003). The coagulase·prothrombin complex recognizes fibrinogen as a specific substrate, converting it directly into fibrin. The crystal structure of the active complex revealed binding of the D1 and D2 domains to prothrombin and insertion of its Ile1-Val^2 N-terminus into the Ile^{16} pocket, inducing a functional active site in the zymogen through conformational change (Friedrich *et al.*, 2003). Exosite I of α-thrombin, the fibrinogen recognition site, and proexosite I on prothrombin are blocked by the D2 of Coa (Friedrich *et al.*, 2003). Nevertheless, association of the tetrameric (Coa·prothrombin)$_2$ complex binds fibrinogen at a new site with high affinity (Panizzi *et al.*, 2006). This model explains the coagulant properties and efficient fibrinogen conversion by coagulase (Panizzi *et al.*, 2006).

[00409] Fibrinogen is a large glycoprotein (*Mr* ~340,000), formed by three pairs of Aα-, Bβ-, and γ-chains covalently linked to form a "dimer of trimers," where A and B designate the fibrinopeptides released by thrombin cleavage (Panizzi *et al.*, 2006). The elongated molecule folds into three separate domains, a central fragment E that contains the N-termini of all six chains and two flanking fragments D formed mainly by the C-termini of the Bβ- and γ-chains. These globular domains are connected by long triple-helical structures. Coagulase-prothrombin complexes, which convert human fibrinogen to the self-polymerizing fibrin, are not targeted by circulating thrombin inhibitors (Panizzi *et al.*, 2006). Thus, staphylococcal coagulases bypass the physiological blood coagulation pathway.

[00410] All *S. aureus* strains secrete coagulase and vWbp (Bjerketorp *et al.*, 2004; Field and Smith, 1945). Although early work reported important contributions of coagulase to the pathogenesis of staphylococcal infections (Ekstedt and Yotis, 1960; Smith et al., 1947), more recent investigations with molecular genetics tools challenged this view by observing no virulence phenotypes with endocarditis, skin abscess and mastitis models in mice (Moreillon *et al.*, 1995; Phonimdaeng *et al.*, 1990). Generating isogenic variants of *S. aureus* Newman, a fully virulent clinical isolate (Duthie *et al.*, 1952), it is described herein that *coa* mutants indeed display virulence defects in a lethal bacteremia and renal abscess model in mice. In the inventors experience, *S. aureus* 8325-4 is not fully virulent and it is presumed that mutational lesions in this strain may not be able to reveal virulence defects *in vivo*. Moreover, antibodies raised against Coa or vWbp perturb the pathogenesis of *S. aureus* Newman infections to a degree mirroring the impact of gene deletions. Coa and vWbp

contribute to staphylococcal abscess formation and lethal bacteremia and may also function as protective antigens in subunit vaccines.

[00411] Biochemical studies document the biological value of antibodies against Coa and vWbp. By binding to antigen and blocking its association with clotting factors, the antibodies prevent the formation of Coa·prothrombin and vWbp·prothrombin complexes. Passive transfer studies revealed protection of experimental animals against staphylococcal abscess formation and lethal challenge by Coa and vWbp antibodies. Thus, Coa and vWbp neutralizing antibodies generate immune protection against staphylococcal disease.

[00412] Earlier studies revealed a requirement of coagulase for resisting phagocytosis in blood (Smith *et al.*, 1947) and the inventors observed a similar phenotype for Δ*coa* mutants in lepirudin-treated mouse blood (see Example 3 below). As vWbp displays higher affinity for human prothrombin than the mouse counterpart, it is suspected the same may be true for Δ*vWbp* variants in human blood. Further, expression of Coa and vWbp in abscess lesions as well as their striking distribution in the eosinophilic pseudocapsule surrounding (staphylococcal abscess communities (SACs) or the peripheral fibrin wall, suggest that secreted coagulases contribute to the establishment of these lesions. This hypothesis was tested and, indeed, Δ*coa* mutants were defective in the establishment of abscesses. A corresponding test, blocking Coa function with specific antibodies, produced the same effect. Consequently, it is proposed that the clotting of fibrin is a critical event in the establishment of staphylococcal abscesses that can be targeted for the development of protective vaccines. Due to their overlapping function on human prothrombin, both Coa and vWbp are considered excellent candidates for vaccine development.

C. Other Staphylococcal Antigens

[00413] Research over the past several decades identified *S. aureus* exotoxins, surface proteins and regulatory molecules as important virulence factors (Foster, 2005; Mazmanian *et al.*, 2001; Novick, 2003). Much progress has been achieved regarding the regulation of these genes. For example, staphylococci perform a bacterial census via the secretion of auto-inducing peptides that bind to a cognate receptor at threshold concentration, thereby activating phospho-relay reactions and transcriptional activation of many of the exotoxin genes (Novick, 2003). The pathogenesis of staphylococcal infections relies on these virulence factors (secreted exotoxins, exopolysaccharides, and surface adhesins). The development of staphylococcal vaccines is hindered by the multifaceted nature of

staphylococcal invasion mechanisms. It is well established that live attenuated micro-organisms are highly effective vaccines; immune responses elicited by such vaccines are often of greater magnitude and of longer duration than those produced by non-replicating immunogens. One explanation for this may be that live attenuated strains establish limited infections in the host and mimic the early stages of natural infection. Embodiments of the invention are directed to compositions and methods including variant SpA polypeptides and peptides, as well as other immunogenic extracellular proteins, polypeptides, and peptides (including both secreted and cell surface proteins or peptides) of gram positive bacteria for the use in mitigating or immunizing against infection. In particular embodiments the bacteria is a staphylococcus bacteria. Extracellular proteins, polypeptides, or peptides include, but are not limited to secreted and cell surface proteins of the targeted bacteria.

[00414] The human pathogen *S. aureus* secretes EsxA and EsxB, two ESAT-6 like proteins, across the bacterial envelope (Burts *et al.*, 2005, which is incorporated herein by reference). Staphylococcal *esxA* and *esxB* are clustered with six other genes in the order of transcription: *esxA esaA essA esaB essB essC esaC esxB*. The acronyms esa, ess, and esx stand for ESAT-6 secretion accessory, system, and extracellular, respectively, depending whether the encoded proteins play an accessory (esa) or direct (ess) role for secretion, or are secreted (esx) in the extracellular milieu. The entire cluster of eight genes is herein referred to as the Ess cluster. EsxA, esxB, essA, essB, and essC are all required for synthesis or secretion of EsxA and EsxB. Mutants that fail to produce EsxA, EsxB, and EssC display defects in the pathogenesis of *S. aureus* murine abscesses, suggesting that this specialized secretion system may be a general strategy of human bacterial pathogenesis. Secretion of non-WXG100 substrates by the ESX-1 pathway has been reported for several antigens including EspA, EspB, Rv3483c, and Rv3615c (Fortune *et al.*, 2005; MacGurn *et al.*, 2005; McLaughlin *et al.*, 2007; Xu *et al.*, 2007). The alternate ESX-5 pathway has also been shown to secrete both WXG100 and non-WXG100 proteins in pathogenic mycobacteria (Abdallah *et al.*, 2007; Abdallah *et al.*, 2006).

[00415] The *Staphylococcus aureus* Ess pathway can be viewed as a secretion module equipped with specialized transport components (Ess), accessory factors (Esa) and cognate secretion substrates (Esx). EssA, EssB and EssC are required for EsxA and EsxB secretion. Because EssA, EssB and EssC are predicted to be transmembrane proteins, it is contemplated that these proteins form a secretion apparatus. Some of the proteins in the *ess* gene cluster may actively transport secreted substrates (acting as motor) while others may regulate

transport (regulator). Regulation may be achieved, but need not be limited to, transcriptional or post-translational mechanisms for secreted polypeptides, sorting of specific substrates to defined locations (*e.g.,* extracellular medium or host cells), or timing of secretion events during infection. At this point, it is unclear whether all secreted Esx proteins function as toxins or contribute indirectly to pathogenesis.

[00416] Staphylococci rely on surface protein mediated-adhesion to host cells or invasion of tissues as a strategy for escape from immune defenses. Furthermore, *S. aureus* utilize surface proteins to sequester iron from the host during infection. The majority of surface proteins involved in staphylococcal pathogenesis carry C-terminal sorting signals, *i.e.*, they are covalently linked to the cell wall envelope by sortase. Further, staphylococcal strains lacking the genes required for surface protein anchoring, *i.e.,* sortase A and B, display a dramatic defect in the virulence in several different mouse models of disease. Thus, surface protein antigens represent a validated vaccine target as the corresponding genes are essential for the development of staphylococcal disease and can be exploited in various embodiments of the invention. The sortase enzyme superfamily are Gram-positive transpeptidases responsible for anchoring surface protein virulence factors to the peptidoglycan cell wall layer. Two sortase isoforms have been identified in *Staphylococcus aureus*, SrtA and SrtB. These enzymes have been shown to recognize a LPXTG motif in substrate proteins. The SrtB isoform appears to be important in heme iron acquisition and iron homeostasis, whereas the SrtA isoform plays a critical role in the pathogenesis of Gram-positive bacteria by modulating the ability of the bacterium to adhere to host tissue via the covalent anchoring of adhesins and other proteins to the cell wall peptidoglycan. In certain embodiments the SpA variants described herein can be used in combination with other staphylococcal proteins such as Coa, Eap, Ebh, Emp, EsaC, EsaB, EsxA, EsxB, Hla, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, IsdC, SasF, vWbp, and/or vWh proteins.

[00417] Certain aspects of the invention include methods and compositions concerning proteinaceous compositions including polypeptides, peptides, or nucleic acid encoding SpA variant(s) and other staphylococcal antigens such as other proteins transported by the Ess pathway, or sortase substrates. These proteins may be modified by deletion, insertion, and/or substitution.

[00418] The Esx polypeptides include the amino acid sequence of Esx proteins from bacteria in the Staphylococcus genus. The Esx sequence may be from a particular staphylococcus species, such as *Staphylococcus aureus*, and may be from a particular strain,

such as Newman. In certain embodiments, the EsxA sequence is SAV0282 from strain Mu50 (which is the same amino acid sequence for Newman) and can be accessed using Genbank Accession Number Q99WU4 (gi|68565539), which is hereby incorporated by reference. In other embodiments, the EsxB sequence is SAV0290 from strain Mu50 (which is the same amino acid sequence for Newman) and can be accessed using Genbank Accession Number Q99WT7 (gi|68565532), which is hereby incorporated by reference. In further embodiments, other polypeptides transported by the Ess pathway may be used, the sequences of which may be identified by one of skill in the art using databases and internet accessible resources.

[00419] The sortase substrate polypeptides include, but are not limited to the amino acid sequence of SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, IsdC or SasF proteins from bacteria in the Staphylococcus genus. The sortase substrate polypeptide sequence may be from a particular staphylococcus species, such as *Staphylococcus aureus*, and may be from a particular strain, such as Newman. In certain embodiments, the SdrD sequence is from strain N315 and can be accessed using Genbank Accession Number NP_373773.1 (gi|15926240), which is incorporated by reference. In other embodiments, the SdrE sequence is from strain N315 and can be accessed using Genbank Accession Number NP_373774.1 (gi|15926241), which is incorporated by reference. In other embodiments, the IsdA sequence is SAV1130 from strain Mu50 (which is the same amino acid sequence for Newman) and can be accessed using Genbank Accession Number NP_371654.1 (gi|15924120), which is incorporated by reference. In other embodiments, the IsdB sequence is SAV1129 from strain Mu50 (which is the same amino acid sequence for Newman) and can be accessed using Genbank Accession Number NP_371653.1 (gi|15924119), which is incorporated by reference. In further embodiments, other polypeptides transported by the Ess pathway or processed by sortase may be used, the sequences of which may be identified by one of skill in the art using databases and internet accessible resources.

[00420] Examples of various proteins that can be used in the context of the present invention can be identified by analysis of database submissions of bacterial genomes, including but not limited to accession numbers NC_002951 (GI:57650036 and GenBank CP000046), NC_002758 (GI:57634611 and GenBank BA000017), NC_002745 (GI:29165615 and GenBank BA000018), NC_003923 (GI:21281729 and GenBank BA000033), NC_002952 (GI:49482253 and GenBank BX571856), NC_002953 (GI:49484912 and GenBank BX571857), NC_007793 (GI:87125858 and GenBank

CP000255), NC_007795 (GI:87201381 and GenBank CP000253) each of which are incorporated by reference.

[00421] As used herein, a "protein" or "polypeptide" refers to a molecule comprising at least ten amino acid residues. In some embodiments, a wild-type version of a protein or polypeptide are employed, however, in many embodiments of the invention, a modified protein or polypeptide is employed to generate an immune response. The terms described above may be used interchangeably. A "modified protein" or "modified polypeptide" or a "variant" refers to a protein or polypeptide whose chemical structure, particularly its amino acid sequence, is altered with respect to the wild-type protein or polypeptide. In some embodiments, a modified/variant protein or polypeptide has at least one modified activity or function (recognizing that proteins or polypeptides may have multiple activities or functions). It is specifically contemplated that a modified/variant protein or polypeptide may be altered with respect to one activity or function yet retain a wild-type activity or function in other respects, such as immunogenicity.

[00422] In certain embodiments the size of a protein or polypeptide (wild-type or modified) may comprise, but is not limited to, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 625, 650, 675, 700, 725, 750, 775, 800, 825, 850, 875, 900, 925, 950, 975, 1000, 1100, 1200, 1300, 1400, 1500, 1750, 2000, 2250, 2500 amino molecules or greater, and any range derivable therein, or derivative of a corresponding amino sequence described or referenced herein. It is contemplated that polypeptides may be mutated by truncation, rendering them shorter than their corresponding wild-type form, but also they might be altered by fusing or conjugating a heterologous protein sequence with a particular function (*e.g.*, for targeting or localization, for enhanced immunogenicity, for purification purposes, *etc.*).

[00423] As used herein, an "amino molecule" refers to any amino acid, amino acid derivative, or amino acid mimic known in the art. In certain embodiments, the residues of the proteinaceous molecule are sequential, without any non-amino molecule interrupting the sequence of amino molecule residues. In other embodiments, the sequence may comprise one or more non-amino molecule moieties. In particular embodiments, the sequence of

residues of the proteinaceous molecule may be interrupted by one or more non-amino molecule moieties.

[00424] Accordingly, the term "proteinaceous composition" encompasses amino molecule sequences comprising at least one of the 20 common amino acids in naturally synthesized proteins, or at least one modified or unusual amino acid.

[00425] Proteinaceous compositions may be made by any technique known to those of skill in the art, including (i) the expression of proteins, polypeptides, or peptides through standard molecular biological techniques, (ii) the isolation of proteinaceous compounds from natural sources, or (iii) the chemical synthesis of proteinaceous materials. The nucleotide as well as the protein, polypeptide, and peptide sequences for various genes have been previously disclosed, and may be found in the recognized computerized databases. One such database is the National Center for Biotechnology Information's Genbank and GenPept databases (on the World Wide Web at ncbi.nlm.nih.gov/). The coding regions for these genes may be amplified and/or expressed using the techniques disclosed herein or as would be known to those of ordinary skill in the art.

[00426] Amino acid sequence variants of SpA, coagulases and other polypeptides of the invention can be substitutional, insertional, or deletion variants. A variation in a polypeptide of the invention may affect 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, or more non-contiguous or contiguous amino acids of the polypeptide, as compared to wild-type. A variant can comprise an amino acid sequence that is at least 50%, 60%, 70%, 80%, or 90%, including all values and ranges there between, identical to any sequence provided or referenced herein, *e.g.*, SEQ ID NO:2-8 or SEQ ID NO:11-30, A variant can include 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more substitute amino acids. A polypeptide processed or secreted by the Ess pathway or other surface proteins (see Table 1) or sortase substrates from any staphylococcus species and strain are contemplated for use in compositions and methods described herein.

[00427] Deletion variants typically lack one or more residues of the native or wild-type protein. Individual residues can be deleted or a number of contiguous amino acids can be deleted. A stop codon may be introduced (by substitution or insertion) into an encoding nucleic acid sequence to generate a truncated protein. Insertional mutants typically involve the addition of material at a non-terminal point in the polypeptide. This may include the

insertion of one or more residues. Terminal additions, called fusion proteins, may also be generated. These fusion proteins include multimers or concatamers of one or more peptide or polypeptide described or referenced herein.

[00428] Substitutional variants typically contain the exchange of one amino acid for another at one or more sites within the protein, and may be designed to modulate one or more properties of the polypeptide, with or without the loss of other functions or properties. Substitutions may be conservative, that is, one amino acid is replaced with one of similar shape and charge. Conservative substitutions are well known in the art and include, for example, the changes of: alanine to serine; arginine to lysine; asparagine to glutamine or histidine; aspartate to glutamate; cysteine to serine; glutamine to asparagine; glutamate to aspartate; glycine to proline; histidine to asparagine or glutamine; isoleucine to leucine or valine; leucine to valine or isoleucine; lysine to arginine; methionine to leucine or isoleucine; phenylalanine to tyrosine, leucine or methionine; serine to threonine; threonine to serine; tryptophan to tyrosine; tyrosine to tryptophan or phenylalanine; and valine to isoleucine or leucine. Alternatively, substitutions may be non-conservative such that a function or activity of the polypeptide is affected. Non-conservative changes typically involve substituting a residue with one that is chemically dissimilar, such as a polar or charged amino acid for a nonpolar or uncharged amino acid, and vice versa.

Table 1. Exemplary surface proteins of *S. aureus* strains.

SAV #	SA#	Surface	MW2	Mu50	N315	Newman	MRSA252*	MSSA476*
SAV0111	SA0107	Spa	492	450	450	520	516	492
SAV2503	SA2291	FnBPA	1015	1038	1038	741	-	1015
SAV2502	SA2290	FnBPB	943	961	961	677	965	957
SAV0811	SA0742	ClfA	946	935	989	933	1029	928
SAV2630	SA2423	ClfB	907	877	877	913	873	905
Np	Np	Cna	1183	-	-	-	1183	1183
SAV0561	SA0519	SdrC	955	953	953	947	906	957
SAV0562	SA0520	SdrD	1347	1385	1385	1315	-	1365
SAV0563	SA0521	SdrE	1141	1141	1141	1166	1137	1141
Np	Np	Pls	-	-	-	-	-	-
SAV2654	SA2447	SasA	2275	2271	2271	2271	1351	2275
SAV2160	SA1964	SasB	686	2481	2481	2481	2222	685
	SA1577	SasC	2186	213	2186	2186	2189	2186
SAV0134	SA0129	SasD	241	241	241	241	221	241
SAV1130	SA0977	SasE/IsdA	350	350	350	350	354	350
SAV2646	SA2439	SasF	635	635	635	635	627	635
SAV2496		SasG	1371	525	927	-	-	1371
SAV0023	SA0022	SasH	772	-	772	772	786	786
SAV1731	SA1552	SasI	895	891	891	891	534	895
SAV1129	SA0976	SasJ/IsdB	645	645	645	645	652	645
	SA2381	SasK	198	211	211	-	-	197
	Np	SasL	-	232	-	-	-	-
SAV1131	SA0978	IsdC	227	227	227	227	227	227

[00429] Proteins of the invention may be recombinant, or synthesized *in vitro*. Alternatively, a non-recombinant or recombinant protein may be isolated from bacteria. It is also contemplated that a bacteria containing such a variant may be implemented in compositions and methods of the invention. Consequently, a protein need not be isolated.

[00430] The term "functionally equivalent codon" is used herein to refer to codons that encode the same amino acid, such as the six codons for arginine or serine, and also refers to codons that encode biologically equivalent amino acids (see Table 2, below).

Table 2 Codon Table

Amino Acids			Codons
Alanine	Ala	A	GCA GCC GCG GCU
Cysteine	Cys	C	UGC UGU
Aspartic acid	Asp	D	GAC GAU
Glutamic acid	Glu	E	GAA GAG
Phenylalanine	Phe	F	UUC UUU
Glycine	Gly	G	GGA GGC GGG GGU
Histidine	His	H	CAC CAU
Isoleucine	Ile	I	AUA AUC AUU
Lysine	Lys	K	AAA AAG
Leucine	Leu	L	UUA UUG CUA CUC CUG CUU
Methionine	Met	M	AUG
Asparagine	Asn	N	AAC AAU
Proline	Pro	P	CCA CCC CCG CCU
Glutamine	Gln	Q	CAA CAG
Arginine	Arg	R	AGA AGG CGA CGC CGG CGU
Serine	Ser	S	AGC AGU UCA UCC UCG UCU
Threonine	Thr	T	ACA ACC ACG ACU
Valine	Val	V	GUA GUC GUG GUU
Tryptophan	Trp	W	UGG
Tyrosine	Tyr	Y	UAC UAU

[00431] It also will be understood that amino acid and nucleic acid sequences may include additional residues, such as additional N- or C-terminal amino acids, or 5' or 3' sequences, respectively, and yet still be essentially as set forth in one of the sequences disclosed herein, so long as the sequence meets the criteria set forth above, including the maintenance of biological protein activity (*e.g.*, immunogenicity) where protein expression is concerned. The addition of terminal sequences particularly applies to nucleic acid sequences that may, for example, include various non-coding sequences flanking either of the 5' or 3' portions of the coding region.

[00432] The following is a discussion based upon changing of the amino acids of a protein to create a variant polypeptide or peptide. For example, certain amino acids may be substituted for other amino acids in a protein structure with or without appreciable loss of interactive binding capacity with structures such as, for example, antigen-binding regions of antibodies or binding sites on substrate molecules. Since it is the interactive capacity and nature of a protein that defines that protein's functional activity, certain amino acid substitutions can be made in a protein sequence, and in its underlying DNA coding sequence, and nevertheless produce a protein with a desirable property. It is thus contemplated by the inventors that various changes may be made in the DNA sequences of genes.

[00433] It is contemplated that in compositions of the invention, there is between about 0.001 mg and about 10 mg of total polypeptide, peptide, and/or protein per ml. The concentration of protein in a composition can be about, at least about or at most about 0.001, 0.010, 0.050, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0 mg/ml or more (or any range derivable therein). Of this, about, at least about, or at most about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100% may be an SpA variant or a coagulase, and may be used in combination with other peptides or polypeptides, such as other bacterial peptides and/or antigens.

[00434] The present invention contemplates the administration of variant SpA polypeptides or peptides to effect a preventative therapy or therapeutic effect against the development of a disease or condition associated with infection by a staphylococcus pathogen.

[00435] In certain aspects, combinations of staphylococcal antigens are used in the production of an immunogenic composition that is effective at treating or preventing staphylococcal infection. Staphylococcal infections progress through several different stages. For example, the staphylococcal life cycle involves commensal colonization, initiation of infection by accessing adjoining tissues or the bloodstream, and/or anaerobic multiplication in the blood. The interplay between *S. aureus* virulence determinants and the host defense mechanisms can induce complications such as endocarditis, metastatic abscess formation, and sepsis syndrome. Different molecules on the surface of the bacterium are involved in different steps of the infection cycle. Combinations of certain antigens can elicit an immune response which protects against multiple stages of staphylococcal infection. The effectiveness of the immune response can be measured either in animal model assays and/or using an opsonophagocytic assay.

D. Polypeptides and Polypeptide Production

[00436] The present invention describes polypeptides, peptides, and proteins and immunogenic fragments thereof for use in various embodiments of the present invention. For example, specific polypeptides are assayed for or used to elicit an immune response. In

specific embodiments, all or part of the proteins of the invention can also be synthesized in solution or on a solid support in accordance with conventional techniques. Various automatic synthesizers are commercially available and can be used in accordance with known protocols. See, for example, Stewart and Young, (1984); Tam *et al.*, (1983); Merrifield, (1986); and Barany and Merrifield (1979), each incorporated herein by reference.

[00437] Alternatively, recombinant DNA technology may be employed wherein a nucleotide sequence which encodes a peptide of the invention is inserted into an expression vector, transformed or transfected into an appropriate host cell and cultivated under conditions suitable for expression.

[00438] One embodiment of the invention includes the use of gene transfer to cells, including microorganisms, for the production and/or presentation of polypeptides or peptides. The gene for the polypeptide or peptide of interest may be transferred into appropriate host cells followed by culture of cells under the appropriate conditions. The generation of recombinant expression vectors, and the elements included therein, are well known in the art and briefly discussed herein. Alternatively, the protein to be produced may be an endogenous protein normally synthesized by the cell that is isolated and purified.

[00439] Another embodiment of the present invention uses autologous B lymphocyte cell lines, which are transfected with a viral vector that expresses an immunogen product, and more specifically, a protein having immunogenic activity. Other examples of mammalian host cell lines include, but are not limited to Vero and HeLa cells, other B- and T- cell lines, such as CEM, 721.221, H9, Jurkat, Raji, as well as cell lines of Chinese hamster ovary, W138, BHK, COS-7, 293, HepG2, 3T3, RIN and MDCK cells. In addition, a host cell strain may be chosen that modulates the expression of the inserted sequences, or that modifies and processes the gene product in the manner desired. Such modifications (*e.g.*, glycosylation) and processing (*e.g.*, cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed.

[00440] A number of selection systems may be used including, but not limited to HSV thymidine kinase, hypoxanthine-guanine phosphoribosyltransferase, and adenine phosphoribosyltransferase genes, in tk-, hgprt- or aprt- cells, respectively. Also, anti-

metabolite resistance can be used as the basis of selection: for dhfr, which confers resistance to trimethoprim and methotrexate; gpt, which confers resistance to mycophenolic acid; neo, which confers resistance to the aminoglycoside G418; and hygro, which confers resistance to hygromycin.

[00441] Animal cells can be propagated *in vitro* in two modes: as non-anchorage-dependent cells growing in suspension throughout the bulk of the culture or as anchorage-dependent cells requiring attachment to a solid substrate for their propagation (*i.e.*, a monolayer type of cell growth).

[00442] Non-anchorage dependent or suspension cultures from continuous established cell lines are the most widely used means of large scale production of cells and cell products. However, suspension cultured cells have limitations, such as tumorigenic potential and lower protein production than adherent cells.

[00443] Where a protein is specifically mentioned herein, it is preferably a reference to a native or recombinant protein or optionally a protein in which any signal sequence has been removed. The protein may be isolated directly from the staphylococcal strain or produced by recombinant DNA techniques. Immunogenic fragments of the protein may be incorporated into the immunogenic composition of the invention. These are fragments comprising at least 10 amino acids, 20 amino acids, 30 amino acids, 40 amino acids, 50 amino acids, or 100 amino acids, including all values and ranges there between, taken contiguously from the amino acid sequence of the protein. In addition, such immunogenic fragments are immunologically reactive with antibodies generated against the Staphylococcal proteins or with antibodies generated by infection of a mammalian host with Staphylococci. Immunogenic fragments also include fragments that when administered at an effective dose, (either alone or as a hapten bound to a carrier), elicit a protective or therapeutic immune response against Staphylococcal infection, in certain aspects it is protective against *S. aureus* and/or *S. epidermidis* infection. Such an immunogenic fragment may include, for example, the protein lacking an N-terminal leader sequence, and/or a transmembrane domain and/or a C-terminal anchor domain. In a preferred aspect the immunogenic fragment according to the invention comprises substantially all of the extracellular domain of a protein which has at least 80% identity, at least 85% identity, at least 90% identity, at least 95% identity, or at least 97-99% identity, including all values and ranges there between, to a sequence selected segment of a polypeptide described or referenced herein.

[00444] Also included in immunogenic compositions of the invention are fusion proteins composed of one or more Staphylococcal proteins, or immunogenic fragments of staphylococcal proteins. Such fusion proteins may be made recombinantly and may comprise one portion of at least 1, 2, 3, 4, 5, or 6 staphylococcal proteins or segments. Alternatively, a fusion protein may comprise multiple portions of at least 1, 2, 3, 4 or 5 staphylococcal proteins. These may combine different Staphylococcal proteins and/or multiples of the same protein or proten fragment, or immunogenic fragments in the same protein (forming a multimer or a concatamer). Alternatively, the invention also includes individual fusion proteins of Staphylococcal proteins or immunogenic fragments thereof, as a fusion protein with heterologous sequences such as a provider of T-cell epitopes or purification tags, for example: β-galactosidase, glutathione-S-transferase, green fluorescent proteins (GFP), epitope tags such as FLAG, myc tag, poly histidine, or viral surface proteins such as influenza virus haemagglutinin, or bacterial proteins such as tetanus toxoid, diphtheria toxoid, or CRM197.

II. NUCLEIC ACIDS

[00445] In certain embodiments, the present invention concerns recombinant polynucleotides encoding the proteins, polypeptides, peptides of the invention. The nucleic acid sequences for SpA, coagulases and other bacterial proteins are included, all of which are incorporated by reference, and can be used to prepare peptides or polypeptides.

[00446] As used in this application, the term "polynucleotide" refers to a nucleic acid molecule that either is recombinant or has been isolated free of total genomic nucleic acid. Included within the term "polynucleotide" are oligonucleotides (nucleic acids of 100 residues or less in length), recombinant vectors, including, for example, plasmids, cosmids, phage, viruses, and the like. Polynucleotides include, in certain aspects, regulatory sequences, isolated substantially away from their naturally occurring genes or protein encoding sequences. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be RNA, DNA (genomic, cDNA or synthetic), analogs thereof, or a combination thereof. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide.

[00447] In this respect, the term "gene," "polynucleotide," or "nucleic acid" is used to refer to a nucleic acid that encodes a protein, polypeptide, or peptide (including any sequences required for proper transcription, post-translational modification, or localization).

As will be understood by those in the art, this term encompasses genomic sequences, expression cassettes, cDNA sequences, and smaller engineered nucleic acid segments that express, or may be adapted to express, proteins, polypeptides, domains, peptides, fusion proteins, and mutants. A nucleic acid encoding all or part of a polypeptide may contain a contiguous nucleic acid sequence of: 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 441, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, 1000, 1010, 1020, 1030, 1040, 1050, 1060, 1070, 1080, 1090, 1095, 1100, 1500, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, 8000, 9000, 10000, or more nucleotides, nucleosides, or base pairs, including all values and ranges therebetween, of a polynucleotide encoding one or more amino acid sequence described or referenced herein. It also is contemplated that a particular polypeptide may be encoded by nucleic acids containing variations having slightly different nucleic acid sequences but, nonetheless, encode the same or substantially similar protein (see Table 2 above).

[00448] In particular embodiments, the invention concerns isolated nucleic acid segments and recombinant vectors incorporating nucleic acid sequences that encode a variant SpA or coagulase. The term "recombinant" may be used in conjunction with a polynucleotide or polypeptide and generally refers to a polypeptide or polynucleotide produced and/or manipulated *in vitro* or that is a replication product of such a molecule.

[00449] In other embodiments, the invention concerns isolated nucleic acid segments and recombinant vectors incorporating nucleic acid sequences that encode a variant SpA or coagulase polypeptide or peptide to generate an immune response in a subject. In various embodiments the nucleic acids of the invention may be used in genetic vaccines.

[00450] The nucleic acid segments used in the present invention can be combined with other nucleic acid sequences, such as promoters, polyadenylation signals, additional restriction enzyme sites, multiple cloning sites, other coding segments, and the like, such that their overall length may vary considerably. It is therefore contemplated that a nucleic acid fragment of almost any length may be employed, with the total length preferably being limited by the ease of preparation and use in the intended recombinant nucleic acid protocol. In some cases, a nucleic acid sequence may encode a polypeptide sequence with additional

heterologous coding sequences, for example to allow for purification of the polypeptide, transport, secretion, post-translational modification, or for therapeutic benefits such as targeting or efficacy. As discussed above, a tag or other heterologous polypeptide may be added to the modified polypeptide-encoding sequence, wherein "heterologous" refers to a polypeptide that is not the same as the modified polypeptide.

[00451] In certain other embodiments, the invention concerns isolated nucleic acid segments and recombinant vectors that include within their sequence a contiguous nucleic acid sequence from SEQ ID NO:1 (SpA domain D) or SEQ ID NO:3 (SpA) or any other nucleic acid sequences encoding coagulases or other secreted virulence factors and/or surface proteins including proteins transported by the Ess pathway, processed by sortase, or proteins incorporated herein by reference.

[00452] In certain embodiments, the present invention provides polynucleotide variants having substantial identity to the sequences disclosed herein; those comprising at least 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or higher sequence identity, including all values and ranges there between, compared to a polynucleotide sequence of this invention using the methods described herein (*e.g.*, BLAST analysis using standard parameters).

[00453] The invention also contemplates the use of polynucleotides which are complementary to all the above described polynucleotides.

A. Vectors

[00454] Polypeptides of the invention may be encoded by a nucleic acid molecule comprised in a vector. The term "vector" is used to refer to a carrier nucleic acid molecule into which a heterologous nucleic acid sequence can be inserted for introduction into a cell where it can be replicated and expressed. A nucleic acid sequence can be "heterologous," which means that it is in a context foreign to the cell in which the vector is being introduced or to the nucleic acid in which is incorporated, which includes a sequence homologous to a sequence in the cell or nucleic acid but in a position within the host cell or nucleic acid where it is ordinarily not found. Vectors include DNAs, RNAs, plasmids, cosmids, viruses (bacteriophage, animal viruses, and plant viruses), and artificial chromosomes (*e.g.*, YACs). One of skill in the art would be well equipped to construct a vector through standard recombinant techniques (for example Sambrook *et al.*, 2001; Ausubel *et al.*, 1996, both incorporated herein by reference). In addition to encoding a variant SpA polypeptide the vector can encode other polypeptide sequences such as a one or more other bacterial peptide,

a tag, or an immunogenicity enhancing peptide. Useful vectors encoding such fusion proteins include pIN vectors (Inouye *et al.*, 1985), vectors encoding a stretch of histidines, and pGEX vectors, for use in generating glutathione S-transferase (GST) soluble fusion proteins for later purification and separation or cleavage.

[00455] The term "expression vector" refers to a vector containing a nucleic acid sequence coding for at least part of a gene product capable of being transcribed. In some cases, RNA molecules are then translated into a protein, polypeptide, or peptide. Expression vectors can contain a variety of "control sequences," which refer to nucleic acid sequences necessary for the transcription and possibly translation of an operably linked coding sequence in a particular host organism. In addition to control sequences that govern transcription and translation, vectors and expression vectors may contain nucleic acid sequences that serve other functions as well and are described herein.

1. Promoters and Enhancers

[00456] A "promoter" is a control sequence. The promoter is typically a region of a nucleic acid sequence at which initiation and rate of transcription are controlled. It may contain genetic elements at which regulatory proteins and molecules may bind such as RNA polymerase and other transcription factors. The phrases "operatively positioned," "operatively linked," "under control," and "under transcriptional control" mean that a promoter is in a correct functional location and/or orientation in relation to a nucleic acid sequence to control transcriptional initiation and expression of that sequence. A promoter may or may not be used in conjunction with an "enhancer," which refers to a cis-acting regulatory sequence involved in the transcriptional activation of a nucleic acid sequence.

[00457] Naturally, it may be important to employ a promoter and/or enhancer that effectively directs the expression of the DNA segment in the cell type or organism chosen for expression. Those of skill in the art of molecular biology generally know the use of promoters, enhancers, and cell type combinations for protein expression (see Sambrook *et al.*, 2001, incorporated herein by reference). The promoters employed may be constitutive, tissue-specific, or inducible and in certain embodiments may direct high level expression of the introduced DNA segment under specified conditions, such as large-scale production of recombinant proteins or peptides.

[00458] Various elements/promoters may be employed in the context of the present invention to regulate the expression of a gene. Examples of such inducible elements, which

are regions of a nucleic acid sequence that can be activated in response to a specific stimulus, include but are not limited to Immunoglobulin Heavy Chain (Banerji *et al.*, 1983; Gilles *et al.*, 1983; Grosschedl *et al.*, 1985; Atchinson *et al.*, 1986, 1987; Imler *et al.*, 1987; Weinberger *et al.*, 1984; Kiledjian *et al.*, 1988; Porton *et al.*; 1990), Immunoglobulin Light Chain (Queen *et al.*, 1983; Picard *et al.*, 1984), T Cell Receptor (Luria *et al.*, 1987; Winoto *et al.*, 1989; Redondo *et al.*; 1990), HLA DQ α and/or DQ β (Sullivan *et al.*, 1987), β Interferon (Goodbourn *et al.*, 1986; Fujita *et al.*, 1987; Goodbourn *et al.*, 1988), Interleukin-2 (Greene *et al.*, 1989), Interleukin-2 Receptor (Greene *et al.*, 1989; Lin *et al.*, 1990), MHC Class II 5 (Koch *et al.*, 1989), MHC Class II HLA-DRα (Sherman *et al.*, 1989), β-Actin (Kawamoto *et al.*, 1988; Ng *et al.*; 1989), Muscle Creatine Kinase (MCK) (Jaynes *et al.*, 1988; Horlick *et al.*, 1989; Johnson *et al.*, 1989), Prealbumin (Transthyretin) (Costa *et al.*, 1988), Elastase I (Ornitz *et al.*, 1987), Metallothionein (MTII) (Karin *et al.*, 1987; Culotta *et al.*, 1989), Collagenase (Pinkert *et al.*, 1987; Angel *et al.*, 1987), Albumin (Pinkert *et al.*, 1987; Tronche *et al.*, 1989, 1990), α-Fetoprotein (Godbout *et al.*, 1988; Campere *et al.*, 1989), γ-Globin (Bodine *et al.*, 1987; Perez-Stable *et al.*, 1990), β-Globin (Trudel *et al.*, 1987), c-fos (Cohen *et al.*, 1987), c-Ha-Ras (Triesman, 1986; Deschamps *et al.*, 1985), Insulin (Edlund *et al.*, 1985), Neural Cell Adhesion Molecule (NCAM) (Hirsh *et al.*, 1990), α1-Antitrypain (Latimer *et al.*, 1990), H2B (TH2B) Histone (Hwang *et al.*, 1990), Mouse and/or Type I Collagen (Ripe *et al.*, 1989), Glucose-Regulated Proteins (GRP94 and GRP78) (Chang *et al.*, 1989), Rat Growth Hormone (Larsen *et al.*, 1986), Human Serum Amyloid A (SAA) (Edbrooke *et al.*, 1989), Troponin I (TN I) (Yutzey *et al.*, 1989), Platelet-Derived Growth Factor (PDGF) (Pech *et al.*, 1989), Duchenne Muscular Dystrophy (Klamut *et al.*, 1990), SV40 (Banerji *et al.*, 1981; Moreau *et al.*, 1981; Sleigh *et al.*, 1985; Firak *et al.*, 1986; Herr *et al.*, 1986; Imbra *et al.*, 1986; Kadesch *et al.*, 1986; Wang *et al.*, 1986; Ondek *et al.*, 1987; Kuhl *et al.*, 1987; Schaffner *et al.*, 1988), Polyoma (Swartzendruber *et al.*, 1975; Vasseur *et al.*, 1980; Katinka *et al.*, 1980, 1981; Tyndell *et al.*, 1981; Dandolo *et al.*, 1983; de Villiers *et al.*, 1984; Hen *et al.*, 1986; Satake *et al.*, 1988; Campbell *et al.*, 1988), Retroviruses (Kriegler *et al.*, 1982, 1983; Levinson *et al.*, 1982; Kriegler *et al.*, 1983, 1984a, b, 1988; Bosze *et al.*, 1986; Miksicek *et al.*, 1986; Celander *et al.*, 1987; Thiesen *et al.*, 1988; Celander *et al.*, 1988; Choi *et al.*, 1988; Reisman *et al.*, 1989), Papilloma Virus (Campo *et al.*, 1983; Lusky *et al.*, 1983; Spandidos and Wilkie, 1983; Spalholz *et al.*, 1985; Lusky *et al.*, 1986; Cripe *et al.*, 1987; Gloss *et al.*, 1987; Hirochika *et al.*, 1987; Stephens *et al.*, 1987), Hepatitis B Virus (Bulla *et al.*, 1986; Jameel *et al.*, 1986; Shaul *et al.*, 1987; Spandau *et al.*, 1988; Vannice *et*

al., 1988), Human Immunodeficiency Virus (Muesing *et al.*, 1987; Hauber *et al.*, 1988; Jakobovits *et al.*, 1988; Feng *et al.*, 1988; Takebe *et al.*, 1988; Rosen *et al.*, 1988; Berkhout *et al.*, 1989; Laspia *et al.*, 1989; Sharp *et al.*, 1989; Braddock *et al.*, 1989), Cytomegalovirus (CMV) IE (Weber *et al.*, 1984; Boshart *et al.*, 1985; Foecking *et al.*, 1986), Gibbon Ape Leukemia Virus (Holbrook *et al.*, 1987; Quinn *et al.*, 1989).

[00459] Inducible elements include, but are not limited to MT II - Phorbol Ester (TFA)/Heavy metals (Palmiter *et al.*, 1982; Haslinger *et al.*, 1985; Searle *et al.*, 1985; Stuart *et al.*, 1985; Imagawa *et al.*, 1987, Karin *et al.*, 1987; Angel *et al.*, 1987b; McNeall *et al.*, 1989); MMTV (mouse mammary tumor virus) – Glucocorticoids (Huang *et al.*, 1981; Lee *et al.*, 1981; Majors *et al.*, 1983; Chandler *et al.*, 1983; Lee *et al.*, 1984; Ponta *et al.*, 1985; Sakai *et al.*, 1988); β-Interferon - poly(rI)x/poly(rc) (Tavernier *et al.*, 1983); Adenovirus 5 E2 – ElA (Imperiale *et al.*, 1984); Collagenase - Phorbol Ester (TPA) (Angel *et al.*, 1987a); Stromelysin - Phorbol Ester (TPA) (Angel *et al.*, 1987b); SV40 - Phorbol Ester (TPA) (Angel *et al.*, 1987b); Murine MX Gene - Interferon, Newcastle Disease Virus (Hug *et al.*, 1988); GRP78 Gene - A23187 (Resendez *et al.*, 1988); α-2-Macroglobulin - IL-6 (Kunz *et al.*, 1989); Vimentin – Serum (Rittling *et al.*, 1989); MHC Class I Gene H-2κb – Interferon (Blanar *et al.*, 1989); HSP70 – ElA/SV40 Large T Antigen (Taylor *et al.*, 1989, 1990a, 1990b); Proliferin - Phorbol Ester/TPA (Mordacq *et al.*, 1989); Tumor Necrosis Factor – PMA (Hensel *et al.*, 1989); and Thyroid Stimulating Hormone α Gene - Thyroid Hormone (Chatterjee *et al.*, 1989).

[00460] The particular promoter that is employed to control the expression of peptide or protein encoding polynucleotide of the invention is not believed to be critical, so long as it is capable of expressing the polynucleotide in a targeted cell, preferably a bacterial cell. Where a human cell is targeted, it is preferable to position the polynucleotide coding region adjacent to and under the control of a promoter that is capable of being expressed in a human cell. Generally speaking, such a promoter might include either a bacterial, human or viral promoter.

[00461] In embodiments in which a vector is administered to a subject for expression of the protein, it is contemplated that a desirable promoter for use with the vector is one that is not down-regulated by cytokines or one that is strong enough that even if down-regulated, it produces an effective amount of a variant SpA for eliciting an immune response. Non-limiting examples of these are CMV IE and RSV LTR. Tissue specific promoters can be

used, particularly if expression is in cells in which expression of an antigen is desirable, such as dendritic cells or macrophages. The mammalian MHC I and MHC II promoters are examples of such tissue-specific promoters.

2. Initiation Signals and Internal Ribosome Binding Sites (IRES)

[00462] A specific initiation signal also may be required for efficient translation of coding sequences. These signals include the ATG initiation codon or adjacent sequences. Exogenous translational control signals, including the ATG initiation codon, may need to be provided. One of ordinary skill in the art would readily be capable of determining this and providing the necessary signals.

[00463] In certain embodiments of the invention, the use of internal ribosome entry sites (IRES) elements are used to create multigene, or polycistronic, messages. IRES elements are able to bypass the ribosome scanning model of 5' methylated Cap dependent translation and begin translation at internal sites (Pelletier and Sonenberg, 1988; Macejak and Sarnow, 1991). IRES elements can be linked to heterologous open reading frames. Multiple open reading frames can be transcribed together, each separated by an IRES, creating polycistronic messages. Multiple genes can be efficiently expressed using a single promoter/enhancer to transcribe a single message (see U.S. Patents 5,925,565 and 5,935,819, herein incorporated by reference).

3. Selectable and Screenable Markers

[00464] In certain embodiments of the invention, cells containing a nucleic acid construct of the present invention may be identified *in vitro* or *in vivo* by encoding a screenable or selectable marker in the expression vector. When transcribed and translated, a marker confers an identifiable change to the cell permitting easy identification of cells containing the expression vector. Generally, a selectable marker is one that confers a property that allows for selection. A positive selectable marker is one in which the presence of the marker allows for its selection, while a negative selectable marker is one in which its presence prevents its selection. An example of a positive selectable marker is a drug resistance marker.

B. Host Cells

[00465] As used herein, the terms "cell," "cell line," and "cell culture" may be used interchangeably. All of these terms also include their progeny, which is any and all subsequent generations. It is understood that all progeny may not be identical due to deliberate or inadvertent mutations. In the context of expressing a heterologous nucleic acid

sequence, "host cell" refers to a prokaryotic or eukaryotic cell, and it includes any transformable organism that is capable of replicating a vector or expressing a heterologous gene encoded by a vector. A host cell can, and has been, used as a recipient for vectors or viruses. A host cell may be "transfected" or "transformed," which refers to a process by which exogenous nucleic acid, such as a recombinant protein-encoding sequence, is transferred or introduced into the host cell. A transformed cell includes the primary subject cell and its progeny.

[00466] Host cells may be derived from prokaryotes or eukaryotes, including bacteria, yeast cells, insect cells, and mammalian cells for replication of the vector or expression of part or all of the nucleic acid sequence(s). Numerous cell lines and cultures are available for use as a host cell, and they can be obtained through the American Type Culture Collection (ATCC), which is an organization that serves as an archive for living cultures and genetic materials (www.atcc.org).

C. Expression Systems

[00467] Numerous expression systems exist that comprise at least a part or all of the compositions discussed above. Prokaryote- and/or eukaryote-based systems can be employed for use with the present invention to produce nucleic acid sequences, or their cognate polypeptides, proteins and peptides. Many such systems are commercially and widely available.

[00468] The insect cell/baculovirus system can produce a high level of protein expression of a heterologous nucleic acid segment, such as described in U.S. Patents 5,871,986, 4,879,236, both herein incorporated by reference, and which can be bought, for example, under the name MAXBAC® 2.0 from INVITROGEN® and BACPACK™ BACULOVIRUS EXPRESSION SYSTEM FROM CLONTECH®.

[00469] In addition to the disclosed expression systems of the invention, other examples of expression systems include STRATAGENE®'s COMPLETE CONTROL™ Inducible Mammalian Expression System, which involves a synthetic ecdysone-inducible receptor, or its pET Expression System, an *E. coli* expression system. Another example of an inducible expression system is available from INVITROGEN®, which carries the T-REX™ (tetracycline-regulated expression) System, an inducible mammalian expression system that uses the full-length CMV promoter. INVITROGEN® also provides a yeast expression system called the *Pichia methanolica* Expression System, which is designed for high-level

production of recombinant proteins in the methylotrophic yeast Pichia methanolica. One of skill in the art would know how to express a vector, such as an expression construct, to produce a nucleic acid sequence or its cognate polypeptide, protein, or peptide.

III. POLYSACCHARIDES

[00470] The immunogenic compositions of the invention may further comprise capsular polysaccharides including one or more of PIA (also known as PNAG) and/or *S. aureus* Type V and/or type VIII capsular polysaccharide and/or *S. epidermidis* Type I, and/or Type II and/or Type III capsular polysaccharide.

A. PIA (PNAG)

[00471] It is now clear that the various forms of staphylococcal surface polysaccharides identified as PS/A, PIA and SAA are the same chemical entity - PNAG (Maira-Litran *et al.*, 2004). Therefore the term PIA or PNAG encompasses all these polysaccharides or oligosaccharides derived from them.

[00472] PIA is a polysaccharide intercellular adhesin and is composed of a polymer of β-(1→6)-linked glucosamine substituted with N-acetyl and O-succinyl constituents. This polysaccharide is present in both *S. aureus* and *S. epidermidis* and can be isolated from either source (Joyce *et al.*, 2003; Maira-Litran *et al.*, 2002). For example, PNAG may be isolated from *S. aureus* strain MN8m (WO04/43407). PIA isolated from *S. epidermidis* is a integral constituent of biofilm. It is responsible for mediating cell-cell adhesion and probably also functions to shield the growing colony from the host's immune response. The polysaccharide previously known as poly-N-succinyl-β-(1→6)-glucosamine (PNSG) was recently shown not to have the expected structure since the identification of N- succinylation was incorrect (Maira-Litran *et al.*, 2002). Therefore the polysaccharide formally known as PNSG and now found to be PNAG is also encompassed by the term PIA.

[00473] PIA (or PNAG) may be of different sizes varying from over 400kDa to between 75 and 400kDa to between 10 and 75kDa to oligosaccharides composed of up to 30 repeat units (of β-(1→6)-linked glucosamine substituted with N-acetyl and O-succinyl constituents). Any size of PIA polysaccharide or oligosaccharide may be use in an immunogenic composition of the invention, in one aspect the polysaccharide is over 40kDa. Sizing may be achieved by any method known in the art, for instance by microfluidization, ultrasonic irradiation or by chemical cleavage (WO 03/53462, EP497524, EP497525). In certain

aspects PIA (PNAG) is at least or at most 40-400kDa, 40-300kDa, 50-350kDa, 60-300kDa, 50-250kDa and 60-200kDa.

[00474] PIA (PNAG) can have different degree of acetylation due to substitution on the amino groups by acetate. PIA produced *in vitro* is almost fully substituted on amino groups (95- 100%). Alternatively, a deacetylated PIA (PNAG) can be used having less than 60%, 50%, 40%, 30%, 20%, 10% acetylation. Use of a deacetylated PIA (PNAG) is preferred since non-acetylated epitopes of PNAG are efficient at mediating opsonic killing of Gram positive bacteria, preferably *S. aureus* and/or *S. epidermidis*. In certain aspects, the PIA (PNAG) has a size between 40kDa and 300kDa and is deacetylated so that less than 60%, 50%, 40%, 30% or 20% of amino groups are acetylated.

[00475] The term deacetylated PNAG (dPNAG) refers to a PNAG polysaccharide or oligosaccharide in which less than 60%, 50%, 40%, 30%, 20% or 10% of the amino agroups are acetylated. In certain aspects, PNAG is deaceylated to form dPNAG by chemically treating the native polysaccharide. For example, the native PNAG is treated with a basic solution such that the pH rises to above 10. For instance the PNAG is treated with 0.1-5 M, 0.2-4 M, 0.3-3 M, 0.5-2 M, 0.75-1.5 M or 1 M NaOH , KOH or NH_4OH. Treatment is for at least 10 to 30 minutes, or 1, 2, 3, 4, 5, 10, 15 or 20 hours at a temperature of 20-100, 25-80, 30-60 or 30-50 or 35-45 °C. dPNAG may be prepared as described in WO 04/43405.

[00476] The polysaccharide(s) can be conjugated or unconjugated to a carrier protein.

B. Type 5 and Type 8 polysaccharides from *S. aureus*

[00477] Most strains of *S. aureus* that cause infection in man contain either Type 5 or Type 8 polysaccharides. Approximately 60% of human strains are Type 8 and approximately 30% are Type 5. The structures of Type 5 and Type 8 capsular polysaccharide antigens are described in Moreau *et al.*, (1990) and Fournier *et al.*, (1984). Both have FucNAcp in their repeat unit as well as ManNAcA which can be used to introduce a sulfhydryl group. The structures are:

[00478] Type 5

[00479] →4)-β-D-ManNAcA(3OAc)-(1→4)-α-L-FucNAc(1→3)-β-D-FucNAc-(1→

[00480] Type 8

[00481] →3)-β-D-ManNAcA(4OAc)-(1→3)-α-L-FucNAc(1→3)-β-D-FucNAc-(1→

[00482] Recently (Jones, 2005) NMR spectroscopy revised the structures to:

[00483] Type 5

[00484] →4)-β-D-ManNAcA-(1→4)-α-L-FucNAc(3OAc)-(1→3)-β-D-FucNAc-(1→

[00485] Type 8

[00486] →3)-β-D-ManNAcA(4OAc)-(1→3)-α-L-FucNAc(1→3)-α-D-FucNAc(1→

[00487] Polysaccharides may be extracted from the appropriate strain of *S. aureus* using method well known to of skill in the art, *See* U.S. Patent 6,294,177. For example, ATCC 12902 is a Type 5 *S. aureus* strain and ATCC 12605 is a Type 8 *S. aureus* strain.

[00488] Polysaccharides are of native size or alternatively may be sized, for instance by microfluidisation, ultrasonic irradiation, or by chemical treatment. The invention also covers oligosaccharides derived from the type 5 and 8 polysaccharides from *S. aureus*. The type 5 and 8 polysaccharides included in the immunogenic composition of the invention are preferably conjugated to a carrier protein as described below or are alternatively unconjugated. The immunogenic compositions of the invention alternatively contains either type 5 or type 8 polysaccharide.

C. *S. aureus* 336 antigen

[00489] In an embodiment, the immunogenic composition of the invention comprises the *S. aureus* 336 antigen described in U.S. Patent 6,294,177. The 336 antigen comprises β-linked hexosamine, contains no O-acetyl groups, and specifically binds to antibodies to *S. aureus* Type 336 deposited under ATCC 55804. In an embodiment, the 336 antigen is a polysaccharide which is of native size or alternatively may be sized, for instance by microfluidisation, ultrasonic irradiation, or by chemical treatment. The invention also covers oligosaccharides derived from the 336 antigen. The 336 antigen can be unconjugated or conjugated to a carrier protein.

D. Type I, II and III polysaccharides from *S. epidermidis*

[00490] Amongst the problems associated with the use of polysaccharides in vaccination, is the fact that polysaccharides *per se* are poor immunogens. It is preferred that the polysaccharides utilized in the invention are linked to a protein carrier which provide bystander T-cell help to improve immunogenicity. Examples of such carriers which may be conjugated to polysaccharide immunogens include the Diphtheria and Tetanus toxoids (DT, DT CRM197 and TT respectively), Keyhole Limpet Haemocyanin (KLH), and the purified protein derivative of Tuberculin (PPD), *Pseudomonas aeruginosa* exoprotein A (rEPA),

protein D from *Haemophilus influenzae*, pneumolysin or fragments of any of the above. Fragments suitable for use include fragments encompassing T-helper epitopes. In particular the protein D fragment from *H. influenza* will preferably contain the N-terminal 1/3 of the protein. Protein D is an IgD-binding protein from *Haemophilus influenzae* (EP 0 594 610 B1) and is a potential immunogen. In addition, staphylococcal proteins may be used as a carrier protein in the polysaccharide conjugates of the invention.

[00491] A carrier protein that would be particularly advantageous to use in the context of a staphylococcal vaccine is staphylococcal alpha toxoid. The native form may be conjugated to a polysaccharide since the process of conjugation reduces toxicity. Preferably genetically detoxified alpha toxins such as the His35Leu or His35Arg variants are used as carriers since residual toxicity is lower. Alternatively the alpha toxin is chemically detoxified by treatment with a cross-linking reagent, formaldehyde or glutaraldehyde. A genetically detoxified alpha toxin is optionally chemically detoxified, preferably by treatment with a cross-linking reagent, formaldehyde or glutaraldehyde to further reduce toxicity.

[00492] The polysaccharides may be linked to the carrier protein(s) by any known method (for example those methods described in U.S. Patents 4,372,945, 4,474,757, and 4,356,170). Preferably, CDAP conjugation chemistry is carried out (see WO95/08348). In CDAP, the cyanylating reagent 1-cyano-dimethylaminopyridinium tetrafluoroborate (CDAP) is preferably used for the synthesis of polysaccharide-protein conjugates. The cyanilation reaction can be performed under relatively mild conditions, which avoids hydrolysis of the alkaline sensitive polysaccharides. This synthesis allows direct coupling to a carrier protein.

[00493] Conjugation preferably involves producing a direct linkage between the carrier protein and polysaccharide. Optionally a spacer (such as adipic dihydride (ADH)) may be introduced between the carrier protein and the polysaccharide.

IV. IMMUNE RESPONSE AND ASSAYS

[00494] As discussed above, the invention concerns evoking or inducing an immune response in a subject against a variant SpA or coagulase peptide. In one embodiment, the immune response can protect against or treat a subject having, suspected of having, or at risk of developing an infection or related disease, particularly those related to staphylococci. One use of the immunogenic compositions of the invention is to prevent nosocomial infections by inoculating a subject prior to undergoing procedures in a hospital or other environment having an increased risk of infection.

A. Immunoassays

[00495] The present invention includes the implementation of serological assays to evaluate whether and to what extent an immune response is induced or evoked by compositions of the invention. There are many types of immunoassays that can be implemented. Immunoassays encompassed by the present invention include, but are not limited to, those described in U.S. Patent 4,367,110 (double monoclonal antibody sandwich assay) and U.S. Patent 4,452,901 (western blot). Other assays include immunoprecipitation of labeled ligands and immunocytochemistry, both *in vitro* and *in vivo*.

[00496] Immunoassays generally are binding assays. Certain preferred immunoassays are the various types of enzyme linked immunosorbent assays (ELISAs) and radioimmunoassays (RIA) known in the art. Immunohistochemical detection using tissue sections is also particularly useful. In one example, antibodies or antigens are immobilized on a selected surface, such as a well in a polystyrene microtiter plate, dipstick, or column support. Then, a test composition suspected of containing the desired antigen or antibody, such as a clinical sample, is added to the wells. After binding and washing to remove non specifically bound immune complexes, the bound antigen or antibody may be detected. Detection is generally achieved by the addition of another antibody, specific for the desired antigen or antibody, that is linked to a detectable label. This type of ELISA is known as a "sandwich ELISA." Detection also may be achieved by the addition of a second antibody specific for the desired antigen, followed by the addition of a third antibody that has binding affinity for the second antibody, with the third antibody being linked to a detectable label.

[00497] Competition ELISAs are also possible implementations in which test samples compete for binding with known amounts of labeled antigens or antibodies. The amount of reactive species in the unknown sample is determined by mixing the sample with the known labeled species before or during incubation with coated wells. The presence of reactive species in the sample acts to reduce the amount of labeled species available for binding to the well and thus reduces the ultimate signal. Irrespective of the format employed, ELISAs have certain features in common, such as coating, incubating or binding, washing to remove non specifically bound species, and detecting the bound immune complexes.

[00498] Antigen or antibodies may also be linked to a solid support, such as in the form of plate, beads, dipstick, membrane, or column matrix, and the sample to be analyzed is applied to the immobilized antigen or antibody. In coating a plate with either antigen or antibody,

one will generally incubate the wells of the plate with a solution of the antigen or antibody, either overnight or for a specified period. The wells of the plate will then be washed to remove incompletely-adsorbed material. Any remaining available surfaces of the wells are then "coated" with a nonspecific protein that is antigenically neutral with regard to the test antisera. These include bovine serum albumin (BSA), casein, and solutions of milk powder. The coating allows for blocking of nonspecific adsorption sites on the immobilizing surface and thus reduces the background caused by nonspecific binding of antisera onto the surface.

B. Diagnosis of Bacterial Infection

[00499] In addition to the use of proteins, polypeptides, and/or peptides, as well as antibodies binding these polypeptides, proteins, and/or peptides, to treat or prevent infection as described above, the present invention contemplates the use of these polypeptides, proteins, peptides, and/or antibodies in a variety of ways, including the detection of the presence of Staphylococci to diagnose an infection, whether in a patient or on medical equipment which may also become infected. In accordance with the invention, a preferred method of detecting the presence of infections involves the steps of obtaining a sample suspected of being infected by one or more staphylococcal bacteria species or strains, such as a sample taken from an individual, for example, from one's blood, saliva, tissues, bone, muscle, cartilage, or skin. Following isolation of the sample, diagnostic assays utilizing the polypeptides, proteins, peptides, and/or antibodies of the present invention may be carried out to detect the presence of staphylococci, and such assay techniques for determining such presence in a sample are well known to those skilled in the art and include methods such as radioimmunoassay, western blot analysis and ELISA assays. In general, in accordance with the invention, a method of diagnosing an infection is contemplated wherein a sample suspected of being infected with staphylococci has added to it the polypeptide, protein, peptide, antibody, or monoclonal antibody in accordance with the present invention, and staphylococci are indicated by antibody binding to the polypeptides, proteins, and/or peptides, or polypeptides, proteins, and/or peptides binding to the antibodies in the sample.

[00500] Accordingly, antibodies in accordance with the invention may be used for the prevention of infection from staphylococcal bacteria (*i.e.*, passive immunization), for the treatment of an ongoing infection, or for use as research tools. The term "antibodies" as used herein includes monoclonal, polyclonal, chimeric, single chain, bispecific, simianized, and humanized or primatized antibodies as well as Fab fragments, such as those fragments which maintain the binding specificity of the antibodies, including the products of an Fab

immunoglobulin expression library. Accordingly, the invention contemplates the use of single chains such as the variable heavy and light chains of the antibodies. Generation of any of these types of antibodies or antibody fragments is well known to those skilled in the art. Specific examples of the generation of an antibody to a bacterial protein can be found in U.S. Patent Application Pub. No. 20030153022, which is incorporated herein by reference in its entirety.

[00501] Any of the above described polypeptides, proteins, peptides, and/or antibodies may be labeled directly with a detectable label for identification and quantification of staphylococcal bacteria. Labels for use in immunoassays are generally known to those skilled in the art and include enzymes, radioisotopes, and fluorescent, luminescent and chromogenic substances, including colored particles such as colloidal gold or latex beads. Suitable immunoassays include enzyme-linked immunosorbent assays (ELISA).

C. Protective Immunity

[00502] In some embodiments of the invention, proteinaceous compositions confer protective immunity to a subject. Protective immunity refers to a body's ability to mount a specific immune response that protects the subject from developing a particular disease or condition that involves the agent against which there is an immune response. An immunogenically effective amount is capable of conferring protective immunity to the subject.

[00503] As used herein in the specification and in the claims section that follows, the term polypeptide or peptide refer to a stretch of amino acids covalently linked there amongst via peptide bonds. Different polypeptides have different functionalities according to the present invention. While according to one aspect, a polypeptide is derived from an immunogen designed to induce an active immune response in a recipient, according to another aspect of the invention, a polypeptide is derived from an antibody which results following the elicitation of an active immune response in, for example, an animal, and which can serve to induce a passive immune response in the recipient. In both cases, however, the polypeptide is encoded by a polynucleotide according to any possible codon usage.

[00504] As used herein the phrase "immune response" or its equivalent "immunological response" refers to the development of a humoral (antibody mediated), cellular (mediated by antigen-specific T cells or their secretion products) or both humoral and cellular response directed against a protein, peptide, carbohydrate, or polypeptide of the invention in a recipient

patient. Such a response can be an active response induced by administration of immunogen or a passive response induced by administration of antibody, antibody containing material, or primed T-cells. A cellular immune response is elicited by the presentation of polypeptide epitopes in association with Class I or Class II MHC molecules, to activate antigen-specific CD4 (+) T helper cells and/or CD8 (+) cytotoxic T cells. The response may also involve activation of monocytes, macrophages, NK cells, basophils, dendritic cells, astrocytes, microglia cells, eosinophils or other components of innate immunity. As used herein "active immunity" refers to any immunity conferred upon a subject by administration of an antigen.

[00505] As used herein "passive immunity" refers to any immunity conferred upon a subject without administration of an antigen to the subject. "Passive immunity" therefore includes, but is not limited to, administration of activated immune effectors including cellular mediators or protein mediators (*e.g.*, monoclonal and/or polyclonal antibodies) of an immune response. A monoclonal or polyclonal antibody composition may be used in passive immunization for the prevention or treatment of infection by organisms that carry the antigen recognized by the antibody. An antibody composition may include antibodies that bind to a variety of antigens that may in turn be associated with various organisms. The antibody component can be a polyclonal antiserum. In certain aspects the antibody or antibodies are affinity purified from an animal or second subject that has been challenged with an antigen(s). Alternatively, an antibody mixture may be used, which is a mixture of monoclonal and/or polyclonal antibodies to antigens present in the same, related, or different microbes or organisms, such as gram-positive bacteria, gram-negative bacteria, including but not limited to staphylococcus bacteria.

[00506] Passive immunity may be imparted to a patient or subject by administering to the patient immunoglobulins (Ig) and/or other immune factors obtained from a donor or other non-patient source having a known immunoreactivity. In other aspects, an antigenic composition of the present invention can be administered to a subject who then acts as a source or donor for globulin, produced in response to challenge with the antigenic composition ("hyperimmune globulin"), that contains antibodies directed against Staphylococcus or other organism. A subject thus treated would donate plasma from which hyperimmune globulin would then be obtained, *via* conventional plasma-fractionation methodology, and administered to another subject in order to impart resistance against or to treat staphylococcus infection. Hyperimmune globulins according to the invention are particularly useful for immune-compromised individuals, for individuals undergoing invasive

procedures or where time does not permit the individual to produce their own antibodies in response to vaccination. See U.S. Patents 6,936,258, 6,770,278, 6,756,361, 5,548,066, 5,512,282, 4,338,298, and 4,748,018, each of which is incorporated herein by reference in its entirety, for exemplary methods and compositions related to passive immunity.

[00507] For purposes of this specification and the accompanying claims the terms "epitope" and "antigenic determinant" are used interchangeably to refer to a site on an antigen to which B and/or T cells respond or recognize. B-cell epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation. Methods of determining spatial conformation of epitopes include, for example, x-ray crystallography and 2-dimensional nuclear magnetic resonance. See, *e.g.*, Epitope Mapping Protocols (1996). Antibodies that recognize the same epitope can be identified in a simple immunoassay showing the ability of one antibody to block the binding of another antibody to a target antigen. T-cells recognize continuous epitopes of about nine amino acids for CD8 cells or about 13-15 amino acids for CD4 cells. T cells that recognize the epitope can be identified by *in vitro* assays that measure antigen-dependent proliferation, as determined by ^{3}H-thymidine incorporation by primed T cells in response to an epitope (Burke *et al.*, 1994), by antigen-dependent killing (cytotoxic T lymphocyte assay, Tigges *et al.*, 1996) or by cytokine secretion.

[00508] The presence of a cell-mediated immunological response can be determined by proliferation assays (CD4 (+) T cells) or CTL (cytotoxic T lymphocyte) assays. The relative contributions of humoral and cellular responses to the protective or therapeutic effect of an immunogen can be distinguished by separately isolating IgG and T-cells from an immunized syngeneic animal and measuring protective or therapeutic effect in a second subject.

[00509] As used herein and in the claims, the terms "antibody" or "immunoglobulin" are used interchangeably and refer to any of several classes of structurally related proteins that function as part of the immune response of an animal or recipient, which proteins include IgG, IgD, IgE, IgA, IgM and related proteins.

[00510] Under normal physiological conditions antibodies are found in plasma and other body fluids and in the membrane of certain cells and are produced by lymphocytes of the type denoted B cells or their functional equivalent. Antibodies of the IgG class are made up of four polypeptide chains linked together by disulfide bonds. The four chains of intact IgG molecules are two identical heavy chains referred to as H-chains and two identical light chains referred to as L-chains.

[00511] In order to produce polyclonal antibodies, a host, such as a rabbit or goat, is immunized with the antigen or antigen fragment, generally with an adjuvant and, if necessary, coupled to a carrier. Antibodies to the antigen are subsequently collected from the sera of the host. The polyclonal antibody can be affinity purified against the antigen rendering it monospecific.

[00512] Monoclonal antibodies can be produced by hyperimmunization of an appropriate donor with the antigen or *ex-vivo* by use of primary cultures of splenic cells or cell lines derived from spleen (Anavi, 1998; Huston *et al.*, 1991; Johnson *et al.*, 1991; Mernaugh *et al.*, 1995).

[00513] As used herein and in the claims, the phrase "an immunological portion of an antibody" includes a Fab fragment of an antibody, a Fv fragment of an antibody, a heavy chain of an antibody, a light chain of an antibody, a heterodimer consisting of a heavy chain and a light chain of an antibody, a variable fragment of a light chain of an antibody, a variable fragment of a heavy chain of an antibody, and a single chain variant of an antibody, which is also known as scFv. In addition, the term includes chimeric immunoglobulins which are the expression products of fused genes derived from different species, one of the species can be a human, in which case a chimeric immunoglobulin is said to be humanized. Typically, an immunological portion of an antibody competes with the intact antibody from which it was derived for specific binding to an antigen.

[00514] Optionally, an antibody or preferably an immunological portion of an antibody, can be chemically conjugated to, or expressed as, a fusion protein with other proteins. For purposes of this specification and the accompanying claims, all such fused proteins are included in the definition of antibodies or an immunological portion of an antibody.

[00515] As used herein the terms "immunogenic agent" or "immunogen" or "antigen" are used interchangeably to describe a molecule capable of inducing an immunological response

against itself on administration to a recipient, either alone, in conjunction with an adjuvant, or presented on a display vehicle.

D. Treatment Methods

[00516] A method of the present invention includes treatment for a disease or condition caused by a staphylococcus pathogen. An immunogenic polypeptide of the invention can be given to induce an immune response in a person infected with staphylococcus or suspected of having been exposed to staphylococcus. Methods may be employed with respect to individuals who have tested positive for exposure to staphylococcus or who are deemed to be at risk for infection based on possible exposure.

[00517] In particular, the invention encompasses a method of treatment for staphylococcal infection, particularly hospital acquired nosocomial infections. The immunogenic compositions and vaccines of the invention are particularly advantageous to use in cases of elective surgery. Such patients will know the date of surgery in advance and could be inoculated in advance. The immunogenic compositions and vaccines of the invention are also advantageous to use to inoculate health care workers.

[00518] In some embodiments, the treatment is administered in the presence of adjuvants or carriers or other staphylococcal antigens. Furthermore, in some examples, treatment comprises administration of other agents commonly used against bacterial infection, such as one or more antibiotics.

[00519] The use of peptides for vaccination can require, but not necessarily, conjugation of the peptide to an immunogenic carrier protein, such as hepatitis B surface antigen, keyhole limpet hemocyanin, or bovine serum albumin. Methods for performing this conjugation are well known in the art.

V. VACCINE AND OTHER PHARMACEUTICAL COMPOSITIONS AND ADMINISTRATION

A. Vaccines

[00520] The present invention includes methods for preventing or ameliorating staphylococcal infections, particularly hospital acquired nosocomial infections. As such, the invention contemplates vaccines for use in both active and passive immunization embodiments. Immunogenic compositions, proposed to be suitable for use as a vaccine, may be prepared from immunogenic SpA polypeptide(s), such as a SpA domain D variant, or immunogenic coagulases. In other embodiments SpA or coagulases can be used in

combination with other secreted virulence proteins, surface proteins or immunogenic fragments thereof. In certain aspects, antigenic material is extensively dialyzed to remove undesired small molecular weight molecules and/or lyophilized for more ready formulation into a desired vehicle.

[00521] Other options for a protein/peptide-based vaccine involve introducing nucleic acids encoding the antigen(s) as DNA vaccines. In this regard, recent reports described construction of recombinant vaccinia viruses expressing either 10 contiguous minimal CTL epitopes (Thomson, 1996) or a combination of B cell, cytotoxic T-lymphocyte (CTL), and T-helper (Th) epitopes from several microbes (An, 1997), and successful use of such constructs to immunize mice for priming protective immune responses. Thus, there is ample evidence in the literature for successful utilization of peptides, peptide-pulsed antigen presenting cells (APCs), and peptide-encoding constructs for efficient *in vivo* priming of protective immune responses. The use of nucleic acid sequences as vaccines is exemplified in U.S. Patents 5,958,895 and 5,620,896.

[00522] The preparation of vaccines that contain polypeptide or peptide sequence(s) as active ingredients is generally well understood in the art, as exemplified by U.S. Patents 4,608,251; 4,601,903; 4,599,231; 4,599,230; 4,596,792; and 4,578,770, all of which are incorporated herein by reference. Typically, such vaccines are prepared as injectables either as liquid solutions or suspensions: solid forms suitable for solution in or suspension in liquid prior to injection may also be prepared. The preparation may also be emulsified. The active immunogenic ingredient is often mixed with excipients that are pharmaceutically acceptable and compatible with the active ingredient. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol, or the like and combinations thereof. In addition, if desired, the vaccine may contain amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents, or adjuvants that enhance the effectiveness of the vaccines. In specific embodiments, vaccines are formulated with a combination of substances, as described in U.S. Patents 6,793,923 and 6,733,754, which are incorporated herein by reference.

[00523] Vaccines may be conventionally administered parenterally, by injection, for example, either subcutaneously or intramuscularly. Additional formulations which are suitable for other modes of administration include suppositories and, in some cases, oral formulations. For suppositories, traditional binders and carriers may include, for example, polyalkalene glycols or triglycerides: such suppositories may be formed from mixtures containing the active ingredient in the range of about 0.5% to about 10%, preferably about

1% to about 2%. Oral formulations include such normally employed excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate and the like. These compositions take the form of solutions, suspensions, tablets, pills, capsules, sustained release formulations or powders and contain about 10% to about 95% of active ingredient, preferably about 25% to about 70%.

[00524] The polypeptides and polypeptide-encoding DNA constructs may be formulated into a vaccine as neutral or salt forms. Pharmaceutically-acceptable salts include the acid addition salts (formed with the free amino groups of the peptide) and those that are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like.

[00525] Typically, vaccines are administered in a manner compatible with the dosage formulation, and in such amount as will be therapeutically effective and immunogenic. The quantity to be administered depends on the subject to be treated, including the capacity of the individual's immune system to synthesize antibodies and the degree of protection desired. Precise amounts of active ingredient required to be administered depend on the judgment of the practitioner. However, suitable dosage ranges are of the order of several hundred micrograms of active ingredient per vaccination. Suitable regimes for initial administration and booster shots are also variable, but are typified by an initial administration followed by subsequent inoculations or other administrations.

[00526] The manner of application may be varied widely. Any of the conventional methods for administration of a vaccine are applicable. These are believed to include oral application within a solid physiologically acceptable base or in a physiologically acceptable dispersion, parenterally, by injection and the like. The dosage of the vaccine will depend on the route of administration and will vary according to the size and health of the subject.

[00527] In certain instances, it will be desirable to have multiple administrations of the vaccine, *e.g.*, 2, 3, 4, 5, 6 or more administrations. The vaccinations can be at 1, 2, 3, 4, 5, 6, 7, 8, to 5, 6, 7, 8, 9 , 10, 11, 12 twelve week intervals, including all ranges there between. Periodic boosters at intervals of 1-5 years will be desirable to maintain protective levels of the antibodies. The course of the immunization may be followed by assays for antibodies against the antigens, as described in U.S. Patents 3,791,932; 4,174,384 and 3,949,064.

1. Carriers

[00528] A given composition may vary in its immunogenicity. It is often necessary therefore to boost the host immune system, as may be achieved by coupling a peptide or polypeptide to a carrier. Exemplary and preferred carriers are keyhole limpet hemocyanin (KLH) and bovine serum albumin (BSA). Other albumins such as ovalbumin, mouse serum albumin, or rabbit serum albumin can also be used as carriers. Means for conjugating a polypeptide to a carrier protein are well known in the art and include glutaraldehyde, m-maleimidobencoyl-N-hydroxysuccinimide ester, carbodiimyde, and bis-biazotized benzidine.

2. Adjuvants

[00529] The immunogenicity of polypeptide or peptide compositions can be enhanced by the use of non-specific stimulators of the immune response, known as adjuvants. Suitable adjuvants include all acceptable immunostimulatory compounds, such as cytokines, toxins, or synthetic compositions. A number of adjuvants can be used to enhance an antibody response against a variant SpA polypeptide or coagulase, or any other bacterial protein or combination contemplated herein. Adjuvants can (1) trap the antigen in the body to cause a slow release; (2) attract cells involved in the immune response to the site of administration; (3) induce proliferation or activation of immune system cells; or (4) improve the spread of the antigen throughout the subject's body.

[00530] Adjuvants include, but are not limited to, oil-in-water emulsions, water-in-oil emulsions, mineral salts, polynucleotides, and natural substances. Specific adjuvants that may be used include IL-1, IL-2, IL-4, IL-7, IL-12, γ-interferon, GMCSP, BCG, aluminum salts, such as aluminum hydroxide or other aluminum compound, MDP compounds, such as thur-MDP and nor-MDP, CGP (MTP-PE), lipid A, and monophosphoryl lipid A (MPL). RIBI, which contains three components extracted from bacteria, MPL, trehalose dimycolate (TDM), and cell wall skeleton (CWS) in a 2% squalene/Tween 80 emulsion. MHC antigens may even be used. Others adjuvants or methods are exemplified in U.S. Patents 6,814,971, 5,084,269, 6,656,462, each of which is incorporated herein by reference).

[00531] Various methods of achieving adjuvant affect for the vaccine includes use of agents such as aluminum hydroxide or phosphate (alum), commonly used as about 0.05 to about 0.1% solution in phosphate buffered saline, admixture with synthetic polymers of sugars (Carbopol®) used as an about 0.25% solution, aggregation of the protein in the vaccine by heat treatment with temperatures ranging between about 70° to about 101°C for a

30-second to 2-minute period, respectively. Aggregation by reactivating with pepsin-treated (Fab) antibodies to albumin; mixture with bacterial cells (*e.g.*, *C. parvum*), endotoxins or lipopolysaccharide components of Gram-negative bacteria; emulsion in physiologically acceptable oil vehicles (*e.g.*, mannide mono-oleate (Aracel A)); or emulsion with a 20% solution of a perfluorocarbon (Fluosol-DA®) used as a block substitute may also be employed to produce an adjuvant effect.

[00532] Examples of and often preferred adjuvants include complete Freund's adjuvant (a non-specific stimulator of the immune response containing killed *Mycobacterium tuberculosis*), incomplete Freund's adjuvants, and aluminum hydroxide.

[00533] In some aspects, it is preferred that the adjuvant be selected to be a preferential inducer of either a Th1 or a Th2 type of response. High levels of Th1-type cytokines tend to favor the induction of cell mediated immune responses to a given antigen, while high levels of Th2-type cytokines tend to favor the induction of humoral immune responses to the antigen.

[00534] The distinction of Th1 and Th2-type immune response is not absolute. In reality an individual will support an immune response which is described as being predominantly Th1 or predominantly Th2. However, it is often convenient to consider the families of cytokines in terms of that described in murine CD4+ T cell clones by Mosmann and Coffman (Mosmann, and Coffman, 1989). Traditionally, Th1-type responses are associated with the production of the INF-γ and IL-2 cytokines by T-lymphocytes. Other cytokines often directly associated with the induction of Th1-type immune responses are not produced by T-cells, such as IL-12. In contrast, Th2-type responses are associated with the secretion of IL- 4, IL-5, IL-6, IL-10.

[00535] In addition to adjuvants, it may be desirable to co-administer biologic response modifiers (BRM) to enhance immune responses. BRMs have been shown to upregulate T cell immunity or downregulate suppresser cell activity. Such BRMs include, but are not limited to, Cimetidine (CIM; 1200 mg/d) (Smith/Kline, PA); or low-dose Cyclophosphamide (CYP; 300 mg/m^2) (Johnson/ Mead, NJ) and cytokines such as γ-interferon, IL-2, or IL-12 or genes encoding proteins involved in immune helper functions, such as B-7.

B. Lipid Components and Moieties

[00536] In certain embodiments, the present invention concerns compositions comprising one or more lipids associated with a nucleic acid or a polypeptide/peptide. A lipid is a

substance that is insoluble in water and extractable with an organic solvent. Compounds other than those specifically described herein are understood by one of skill in the art as lipids, and are encompassed by the compositions and methods of the present invention. A lipid component and a non-lipid may be attached to one another, either covalently or non-covalently.

[00537] A lipid may be a naturally occurring lipid or a synthetic lipid. However, a lipid is usually a biological substance. Biological lipids are well known in the art, and include for example, neutral fats, phospholipids, phosphoglycerides, steroids, terpenes, lysolipids, glycosphingolipids, glucolipids, sulphatides, lipids with ether and ester-linked fatty acids and polymerizable lipids, and combinations thereof.

[00538] A nucleic acid molecule or a polypeptide/peptide, associated with a lipid may be dispersed in a solution containing a lipid, dissolved with a lipid, emulsified with a lipid, mixed with a lipid, combined with a lipid, covalently bonded to a lipid, contained as a suspension in a lipid or otherwise associated with a lipid. A lipid or lipid-poxvirus-associated composition of the present invention is not limited to any particular structure. For example, they may also simply be interspersed in a solution, possibly forming aggregates which are not uniform in either size or shape. In another example, they may be present in a bilayer structure, as micelles, or with a "collapsed" structure. In another non-limiting example, a lipofectamine(Gibco BRL)-poxvirus or Superfect (Qiagen)-poxvirus complex is also contemplated.

[00539] In certain embodiments, a composition may comprise about 1%, about 2%, about 3%, about 4% about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, about 91%, about 92%, about 93%, about

94%, about 95%, about 96%, about 97%, about 98%, about 99%, or any range therebetween, of a particular lipid, lipid type, or non-lipid component such as an adjuvant, antigen, peptide, polypeptide, sugar, nucleic acid or other material disclosed herein or as would be known to one of skill in the art. In a non-limiting example, a composition may comprise about 10% to about 20% neutral lipids, and about 33% to about 34% of a cerebroside, and about 1% cholesterol. In another non-limiting example, a liposome may comprise about 4% to about 12% terpenes, wherein about 1% of the micelle is specifically lycopene, leaving about 3% to about 11% of the liposome as comprising other terpenes; and about 10% to about 35% phosphatidyl choline, and about 1% of a non-lipid component. Thus, it is contemplated that compositions of the present invention may comprise any of the lipids, lipid types or other components in any combination or percentage range.

C. Combination Therapy

[00540] The compositions and related methods of the present invention, particularly administration of a secreted virulence factor or surface protein, including a variant SpA polypeptide or peptide, and/or other bacterial peptides or proteins to a patient/subject, may also be used in combination with the administration of traditional therapies. These include, but are not limited to, the administration of antibiotics such as streptomycin, ciprofloxacin, doxycycline, gentamycin, chloramphenicol, trimethoprim, sulfamethoxazole, ampicillin, tetracycline or various combinations of antibiotics.

[00541] In one aspect, it is contemplated that a polypeptide vaccine and/or therapy is used in conjunction with antibacterial treatment. Alternatively, the therapy may precede or follow the other agent treatment by intervals ranging from minutes to weeks. In embodiments where the other agents and/or a proteins or polynucleotides are administered separately, one would generally ensure that a significant period of time did not expire between the time of each delivery, such that the agent and antigenic composition would still be able to exert an advantageously combined effect on the subject. In such instances, it is contemplated that one may administer both modalities within about 12-24 h of each other or within about 6-12 h of each other. In some situations, it may be desirable to extend the time period for administration significantly, where several days (2, 3, 4, 5, 6 or 7) to several weeks (1, 2, 3, 4, 5, 6, 7 or 8) lapse between the respective administrations.

[00542] Various combinations may be employed, for example antibiotic therapy is "A" and the immunogenic molecule given as part of an immune therapy regime, such as an antigen, is "B":

[00543] A/B/A B/A/B B/B/A A/A/B A/B/B B/A/A A/B/B/B B/A/B/B

[00544] B/B/B/A B/B/A/B A/A/B/B A/B/A/B A/B/B/A B/B/A/A

[00545] B/A/B/A B/A/A/B A/A/A/B B/A/A/A A/B/A/A A/A/B/A

[00546] Administration of the immunogenic compositions of the present invention to a patient/subject will follow general protocols for the administration of such compounds, taking into account the toxicity, if any, of the SpA composition, or other compositions described herein. It is expected that the treatment cycles would be repeated as necessary. It also is contemplated that various standard therapies, such as hydration, may be applied in combination with the described therapy.

D. General Pharmaceutical Compositions

[00547] In some embodiments, pharmaceutical compositions are administered to a subject. Different aspects of the present invention involve administering an effective amount of a composition to a subject. In some embodiments of the present invention, staphylococcal antigens, members of the Ess pathway, including polypeptides or peptides of the Esa or Esx class, and/or members of sortase substrates may be administered to the patient to protect against infection by one or more staphylococcus pathogens. Alternatively, an expression vector encoding one or more such polypeptides or peptides may be given to a patient as a preventative treatment. Additionally, such compounds can be administered in combination with an antibiotic or an antibacterial. Such compositions will generally be dissolved or dispersed in a pharmaceutically acceptable carrier or aqueous medium.

[00548] In addition to the compounds formulated for parenteral administration, such as those for intravenous or intramuscular injection, other pharmaceutically acceptable forms include, *e.g.*, tablets or other solids for oral administration; time release capsules; and any other form currently used, including creams, lotions, mouthwashes, inhalants and the like.

[00549] The active compounds of the present invention can be formulated for parenteral administration, *e.g.*, formulated for injection via the intravenous, intramuscular, sub-cutaneous, or even intraperitoneal routes. The preparation of an aqueous composition that contains a compound or compounds that increase the expression of an MHC class I molecule

will be known to those of skill in the art in light of the present disclosure. Typically, such compositions can be prepared as injectables, either as liquid solutions or suspensions; solid forms suitable for use to prepare solutions or suspensions upon the addition of a liquid prior to injection can also be prepared; and, the preparations can also be emulsified.

[00550] Solutions of the active compounds as free base or pharmacologically acceptable salts can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

[00551] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions; formulations including sesame oil, peanut oil, or aqueous propylene glycol; and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that it may be easily injected. It also should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms, such as bacteria and fungi.

[00552] The proteinaceous compositions may be formulated into a neutral or salt form. Pharmaceutically acceptable salts, include the acid addition salts (formed with the free amino groups of the protein) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, oxalic, tartaric, mandelic, and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, histidine, procaine and the like.

[00553] The carrier also can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion, and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the

use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

[00554] Sterile injectable solutions are prepared by incorporating the active compounds in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum-drying and freeze-drying techniques, which yield a powder of the active ingredient, plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00555] Administration of the compositions according to the present invention will typically be via any common route. This includes, but is not limited to oral, nasal, or buccal administration. Alternatively, administration may be by orthotopic, intradermal, subcutaneous, intramuscular, intraperitoneal, intranasal, or intravenous injection. In certain embodiments, a vaccine composition may be inhaled (*e.g.*, U.S. Patent 6,651,655, which is specifically incorporated by reference). Such compositions would normally be administered as pharmaceutically acceptable compositions that include physiologically acceptable carriers, buffers or other excipients. As used herein, the term "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem complications commensurate with a reasonable benefit/risk ratio. The term "pharmaceutically acceptable carrier," means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a chemical agent.

[00556] For parenteral administration in an aqueous solution, for example, the solution should be suitably buffered, if necessary, and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous, and intraperitoneal administration. In this connection, sterile aqueous media which can be employed will be known to those of skill in the art in light of the present disclosure. For example, one dosage could be dissolved in isotonic NaCl solution and either added to hypodermoclysis fluid or injected at the proposed

site of infusion, (see for example, Remington's Pharmaceutical Sciences, 1990). Some variation in dosage will necessarily occur depending on the condition of the subject. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

[00557] An effective amount of therapeutic or prophylactic composition is determined based on the intended goal. The term "unit dose" or "dosage" refers to physically discrete units suitable for use in a subject, each unit containing a predetermined quantity of the composition calculated to produce the desired responses discussed above in association with its administration, *i.e.*, the appropriate route and regimen. The quantity to be administered, both according to number of treatments and unit dose, depends on the protection desired. It is contemplated that in compositions of the invention, there is between about 0.001 mg and about 10 mg of total antigen, antibody, polypeptide, peptide, and/or protein per ml. The concentration of protein in a composition can be about, at least about or at most about 0.001, 0.010, 0.050, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0 mg/ml or more (or any range derivable therein). Of this, about, at least about, or at most about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100% may be an SpA variant or an antibody that specifically binds SpA. In certain embodiments a dose of about, at least about or at most about 0.001, 0.010, 0.050, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0 mg/kg or more, including all values and ranges there between are administered to a subject.

[00558] Precise amounts of the composition also depend on the judgment of the practitioner and are peculiar to each individual. Factors affecting dose include physical and clinical state of the subject, route of administration, intended goal of treatment (alleviation of symptoms versus cure), and potency, stability, and toxicity of the particular composition.

[00559] Upon formulation, solutions will be administered in a manner compatible with the dosage formulation and in such amount as is therapeutically or prophylactically effective. The formulations are easily administered in a variety of dosage forms, such as the type of injectable solutions described above.

E. In Vitro, Ex Vivo, or *In Vivo* Administration

[00560] As used herein, the term *in vitro* administration refers to manipulations performed on cells removed from or outside of a subject, including, but not limited to cells in culture. The term *ex vivo* administration refers to cells which have been manipulated *in vitro*, and are subsequently administered to a subject. The term *in vivo* administration includes all manipulations performed within a subject.

[00561] In certain aspects of the present invention, the compositions may be administered either *in vitro*, *ex vivo*, or *in vivo*. In certain *in vitro* embodiments, autologous B-lymphocyte cell lines are incubated with a virus vector of the instant invention for 24 to 48 hours or with a variant SpA and/or cogaulase and/or any other composition described herein for two hours. The transduced cells can then be used for *in vitro* analysis, or alternatively for *ex vivo* administration. U.S. Patents 4,690,915 and 5,199,942, both incorporated herein by reference, disclose methods for *ex vivo* manipulation of blood mononuclear cells and bone marrow cells for use in therapeutic applications.

F. Antibodies And Passive Immunization

[00562] Another aspect of the invention is a method of preparing an immunoglobulin for use in prevention or treatment of staphylococcal infection comprising the steps of immunizing a recipient or donor with the vaccine of the invention and isolating immunoglobulin from the recipient or donor. An immunoglobulin prepared by this method is a further aspect of the invention. A pharmaceutical composition comprising the immunoglobulin of the invention and a pharmaceutically acceptable carrier is a further aspect of the invention which could be used in the manufacture of a medicament for the treatment or prevention of staphylococcal disease. A method for treatment or prevention of staphylococcal infection comprising a step of administering to a patient an effective amount of the pharmaceutical preparation of the invention is a further aspect of the invention.

[00563] Inocula for polyclonal antibody production are typically prepared by dispersing the antigenic composition in a physiologically tolerable diluent such as saline or other adjuvants suitable for human use to form an aqueous composition. An immunostimulatory amount of inoculum is administered to a mammal and the inoculated mammal is then maintained for a time sufficient for the antigenic composition to induce protective antibodies.

[00564] The antibodies can be isolated to the extent desired by well known techniques such as affinity chromatography (Harlow and Lane, 1988). Antibodies can include antiserum

preparations from a variety of commonly used animals; *e.g.* goats, primates, donkeys, swine, horses, guinea pigs, rats or man.

[00565] An immunoglobulin produced in accordance with the present invention can include whole antibodies, antibody fragments or subfragments. Antibodies can be whole immunoglobulins of any class (*e.g.,* IgG, IgM, IgA, IgD or IgE), chimeric antibodies or hybrid antibodies with dual specificity to two or more antigens of the invention. They may also be fragments (*e.g.*, F(ab')2, Fab', Fab, Fv and the like) including hybrid fragments. An immunoglobulin also includes natural, synthetic, or genetically engineered proteins that act like an antibody by binding to specific antigens to form a complex.

[00566] A vaccine of the present invention can be administered to a recipient who then acts as a source of immunoglobulin, produced in response to challenge from the specific vaccine. A subject thus treated would donate plasma from which hyperimmune globulin would be obtained via conventional plasma fractionation methodology. The hyperimmune globulin would be administered to another subject in order to impart resistance against or treat staphylococcal infection. Hyperimmune globulins of the invention are particularly useful for treatment or prevention of staphylococcal disease in infants, immune compromised individuals, or where treatment is required and there is no time for the individual to produce antibodies in response to vaccination.

[00567] An additional aspect of the invention is a pharmaceutical composition comprising two of more monoclonal antibodies (or fragments thereof; preferably human or humanised) reactive against at least two constituents of the immunogenic composition of the invention, which could be used to treat or prevent infection by Gram positive bacteria, preferably staphylococci, more preferably *S. aureus* or *S. epidermidis*. Such pharmaceutical compositions comprise monoclonal antibodies that can be whole immunoglobulins of any class, chimeric antibodies, or hybrid antibodies with specificity to two or more antigens of the invention. They may also be fragments (*e.g.*, F(ab')2, Fab', Fab, Fv and the like) including hybrid fragments.

[00568] Methods of making monoclonal antibodies are well known in the art and can include the fusion of splenocytes with myeloma cells (Kohler and Milstein, 1975; Harlow and Lane, 1988). Alternatively, monoclonal Fv fragments can be obtained by screening a suitable phage display library (Vaughan *et al.*, 1998). Monoclonal antibodies may be humanized or part humanized by known methods.

VI. EXAMPLES

[00569] The following examples are given for the purpose of illustrating various embodiments of the invention and are not meant to limit the present invention in any fashion. One skilled in the art will appreciate readily that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those objects, ends and advantages inherent herein. The present examples, along with the methods described herein are presently representative of preferred embodiments, are exemplary, and are not intended as limitations on the scope of the invention. Changes therein and other uses which are encompassed within the spirit of the invention as defined by the scope of the claims will occur to those skilled in the art.

EXAMPLE 1

Immunization with SpA_{KKAA} modifies host immune responses to staphylococcal infection

[00570] The model of immune evasion during *S. aureus* infections includes the initial activation of B cells via IgM receptor crosslinking by cell wall anchored or secreted protein A - up to 20% of peptidoglycan with attached surface protein is released during each bacterial division event (Ton-That et al., 1999). In the absence of specific antigen stimuli, activated B cells undergo apoptotic collapse, thereby diminishing host antibody production against antigens that are presented during staphylococcal infection. If so, neutralizing SpA-specific antibodies may enable animals to develop humoral immune responses against many different staphylococcal antigens. This possibility was investigated by immunizing BALB/c mice with SpA_{KKAA} or an adjuvant (aluminum hydroxide) control followed by intravenous challenge with a sublethal dose of MRSA strain USA300. Serum samples were withdrawn thirty days after MRSA challenge and then analyzed by immunoblotting with 27 staphylococcal antigens immobilized on a membrane filter (FIG. 1). Naïve mice, which had not been infected with the MRSA strain USA300 LAC, did not harbor antibodies against ClfA, ClfB, Coa, Eap, Ebh, Emp, EsxA, EsxB, FnbpA, FnbpB, Hla, IsdA, IsdB, LukD, LukE, LukF, SdrC, SdrD, SdrE, SasA, SasD, SasF, SasG, SasI, SasK, SpA_{KKAA} or vWbp (data not shown). Mock immunized mice that had been subjected to USA300 infection developed high-titer antibodies against the Eap protein as well as low-titer antibodies against IsdA, IsdB, Hla, LukD, LukE and LukF (FIG. 1). Animals that been immunized and that elaborated SpA_{KKAA}-specific antibodies [IgG titer 2,907 (±357); $P<0.001$ SpA_{KKAA} vs. mock] mounted humoral immune responses

against every one of the 27 antigens in response to a challenge with the MRSA strain USA300 (FIG. 1). With the exception of Eap, IsdA and IsdB antibodies, the serum of SpA_{KKAA}-immunized animals harbored higher antibody titers against each staphylococcal antigen when compared to mice that had been naïve at the time of challenge (FIG. 1).

5

REFERENCES

The following references, to the extent that they provide exemplary procedural or other details supplementary to those set forth herein, are specifically incorporated herein by reference.

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U.S. Patent 4,338,298
U.S. Patent 4,356,170
U.S. Patent 4,367,110
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U.S. Patent 4,608,251
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U.S. Patent 4,684,611
U.S. Patent 4,690,915
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U.S. Patent 4,748,018
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WHAT IS CLAIMED IS:

1. An immunogenic composition comprising an isolated Protein A (SpA) specific antibody and a bacterial antigen, wherein the Protein A specific antibody enhances an immune response to the bacterial antigen.

2. The composition of claim 1, wherein the antibody is a polyclonal antibody, a monoclonal antibody, or an antibody fragment.

3. The composition of claim 1, wherein the bacterial antigen is comprised in or on a bacteria.

4. The composition of claim 3, wherein the bacteria is an attenuated bacteria.

5. The composition of claim 1, wherein the bacterial antigen is a staphylococcal antigen.

6. The composition of claim 5, wherein the staphylococcal antigen is selected from the group consisting of: FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh and immunogenic fragments thereof.

7. A vaccine comprising the composition of any one of claims 1-6 and a pharmaceutically acceptable excipient.

8. A method of making a vaccine comprising the steps of mixing antibody and antigens to make the composition of any one of claims 1-7.

9. A method of preventing or treating staphylococcal infection comprising the step of administering the vaccine of claim 7 to a patient in need thereof.

10. A use of the composition of any one of claims 1-7 in the manufacture of a vaccine for treatment or prevention of staphylococcal infection.

11. A method for treating a bacterial infection in a subject comprising providing to a subject having, suspected of having or at risk of developing a bacterial infection effective amounts of an isolated Protein A (SpA) specific antibody and one or more bacterial antigens.

12. The method of claim 11, wherein the one or more bacterial antigens are comprised in or on a bacteria.

13. The method of claim 12, wherein the bacteria is an attenuated bacteria.

14. The method of claim 13, wherein the attenuated bacteria is a staphylococcal bacteria.

15. The method of claim 11, wherein the subject is diagnosed with a staphylococcal infection.

16. The method of claims 11, 12, 13, or 15, wherein the bacterial antigen is a staphylococcal antigen.

17. The method of claim 16, wherein the staphylococcal antigen is selected from the group consisting of: FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, vWh and immunogenic fragments thereof.

18. The method of claim 11, wherein two or more bacterial antigens are provided to the subject.

19. The method of claim 11, wherein the Protein A (SpA) specific antibody is provided concurrently with the bacterial antigen.

20. The method of claim 11, wherein the Protein A (SpA) specific antibody is provided before providing the one or more bacterial antigens.

21. The method of claim 11, wherein the Protein A (SpA) specific antibody and the one or more bacterial antigens are provided in the same composition.

22. The method of claim 11, wherein the subject is a mammal.

23. The method of claim 11, wherein the subject is human.

24. A method for enhancing an immune response against a bacterium in a subject comprising providing to the subject effective amounts of an isolated Protein A (SpA) specific antibody and one or more antigens from the bacterium.

25. The method of claim 24, wherein the one or more antigens are comprised in or on a bacteria.

26. The method of claim 25, wherein the bacteria is an attenuated bacteria.

27. The method of claim 26, wherein the attenuated bacteria is a staphylococcal bacteria.

28. The method of claim 24, wherein the bacterium is a staphylococcal bacterium.

29. The method of claim 28, wherein the staphylococcus bacterium is a *S. aureus* bacterium.

30. The method of claim 28, wherein the staphylococcus bacterium is resistant to one or more treatments.

31. The method of claim 30, wherein the bacterium is methicillin resistant.

32. The method of claim 24, further comprising administering the composition more than one time to the subject.

33. The method of claim 24, wherein the antigen is a staphylococcal antigen.

34. The method of claim 33, wherein the staphylococcal antigen is one or more of FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, or vWh.

35. A method of eliciting an immune response in a subject comprising administering a SpA variant polypeptide to the subject before or after administering one or more bacterial antigens to the subject.

36. The method of claim 35, wherein the SpA polypeptide variant is administered at least 24 hours before or 24 hours after administration of one or more bacterial antigens.

37. The method of claim 35, wherein the SpA variant comprises a variant A domain having an amino acid substitution at position(s) 7, 8, 34, and/or 35 of SEQ ID NO:4; a variant B domain having an amino acid substitution at position(s) 7, 8, 34, and/or 35 of SEQ ID NO:6; a variant C domain having an amino acid substitution at position(s) 7, 8, 34, and/or 35 of SEQ ID NO:5; a variant D domain having an amino acid substitution at position(s) 9, 10, 36, and/or 37 of SEQ ID NO:2; and/or a variant E domain having an amino acid substitution at position(s) 6, 7, 33, and/or 34 of SEQ ID NO:3.

38. The method of claim 35, wherein the one or more bacterial antigens are one or more staphylococcal antigens.

39. The method of claim 38, wherein the one or more staphylococcal antigens are selected from FnBpA, FnBpB, LukD, LukE, LukF, SasA, SasD, SasG, SasI, SasK, SpA (and variants thereof), Eap, Ebh, Emp, EsaB, EsaC, EsxA, EsxB, SdrC, SdrD, SdrE, IsdA, IsdB, ClfA, ClfB, Coa, Hla (*e.g.*, H35 mutants), IsdC, SasF, vWbp, or vWh antigens.

40. A method of eliciting an immune response in a subject comprising administering a SpA variant polypeptide to the subject before or after administering one or more bacterial antigensselected from sta001, sta002, sta003, sta004, sta005, sta006, sta007, sta008, sta009, sta010, sta011, sta012, sta013, sta014, sta015, sta016, sta017, sta018, sta019, sta020, sta021, sta022, sta023, sta024, sta025, sta026, sta027, sta028, sta029, sta030, sta031, sta032, sta033, sta034, sta035, sta036, sta037, sta038, sta039, sta040, sta041, sta042, sta043, sta044, sta045, sta046, sta047, sta048, sta049, sta050, sta051, sta052, sta053, sta054, sta055, sta056, sta057, sta058, sta059, sta060, sta061, sta062, sta063, sta064, sta065, sta066, sta067, sta068, sta069, sta070, sta071, sta072, sta073, sta074, sta075, sta076, sta077, sta078, sta079, sta080, sta081, sta082, sta083, sta084, sta085, sta086, sta087, sta088, sta089, sta090, sta091, sta092, sta093,

sta094, sta095, sta096, sta097, sta098, sta099, sta100, sta101, sta102, sta103, sta104, sta105, sta106, sta107, sta108, sta109, sta110, sta111, sta112, sta113, sta114, sta115, sta116, sta117, sta118, sta119, sta120, or EsxAB hybrid polypeptide or immunogenic fragment thereof to the subject.

41. A method for manufacturing a composition comprising preparing the composition of claim 1.

42. The method of claim 41, wherein the method comprises isolating the Protein A specific antibody from a cell.

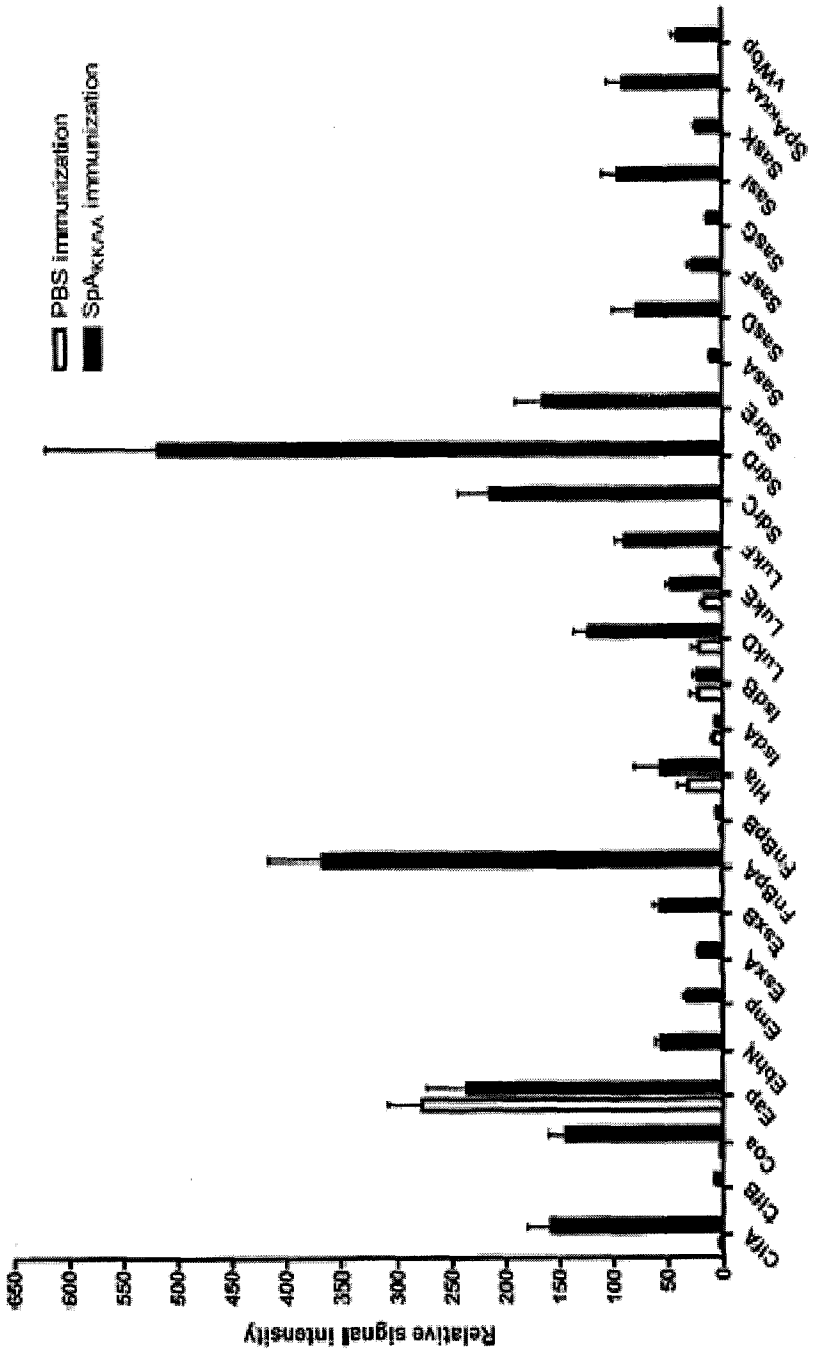
PBS immunization
SpAKKAA immunization
Relative signal intensity
650
600
550
500
450
400
350
300
250
200
150
100
50
0
ClfA
ClfB
Cna
Esp
EbhN
Emp
EsxA
EsxB
FnbpA
FnbpB
Hla
IsdA
IsdB
LukD
LukE
LukF
SdrC
SdrD
SdrE
SasA
SasD
SasF
SasG
SasI
SraX
SpAKKAA
WtbP
Staphylococcal antigen matrix

FIG. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/31213

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/085 (2011.01)
USPC - 424/243.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - A61K 39/085 (2011.01)
IPC(8) - 424/243.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 424/184.1 (Text Search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB, USPT, USOC, EPAB, JPAB); Google Scholar; PubMed: protein A, SpA, vaccine, immune, immunolog$, staphylococc$, immunity, antibody, mAb, antigen, attenuat$, FnBpA, immune response, protect, protect$, adminis$, resist, resis$.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2006/0263792 A1 (MOHAMED et al.) 23 November 2006 (23.11.2006) para [0013], [0016]-[0017], [0054], [0067], [0106], [0104], [0152], [0181], [0191], [0194], [0196]-[0197], [0213]-[0215], [0224]-[0231]	1-5, 7/(1-5), 11-16, 18-30, 32-33 and 41-42 --- 6, 7/6, 17, 31 and 34
Y	US 2005/0123552 A1 (HOOK et al.) 09 June 2005 (09.06.2005) para [0014], [0013]-[0014], [0138], [0299], [0316]	6, 7/6, 17 and 34
Y	GOMEZ, et al. Staphylococcus aureus Protein A Activates TNFR1 Signaling through Conserved IgG Binding Domains. JBC 2006, 281(29):20190-20196; abstract	31
A, P	KIM, et al. Nontoxigenic Protein A Vaccine for Methicillin-Resistant Staphylococcus Aureus Infections in Mice. JEM. 16 August 2010, 207(9):1863-1870.	1-6, 7/(1-6), 11-34 and 41-42

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 July 2011 (27.07.2011)	03 AUG 2011
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/31213

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 8-10
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I+: claims 1-7, 11-42, drawn to an immunogenic composition comprising an isolated Protein A (SpA) specific antibody and a bacterial antigen, wherein the Protein A specific antibody enhances an immune response to the bacterial antigen. The first invention is restricted to a FnBpA staphylococcal antigen. Should an additional fee(s) be paid, Applicant is invited to elect an additional specific antigen(s) and/or SEQ ID NO(s) to be searched. The exact claims searched will depend on Applicant's election.
[NOTE: Claims 35-40 were excluded from the search, because they are drawn to a non-elected subject matter.]

**********Continued in Supplemental Box**********

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Claims 1-7, 11-34 and 41-42, restricted to a FnBpA antigen

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/31213

********** Supplemental Box **********

Continuation of: Box No. III - Observations where unity of invention is lacking:

The inventions listed as Group I+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The inventions of Group I+ share the technical feature of an immunogenic composition comprising an isolated Protein A (SpA) specific antibody and a bacterial antigen, wherein the Protein A specific antibody enhances an immune response to the bacterial antigen. However, this shared technical feature does not represent a contribution over the prior art of as being obvious over US 2005/0118190 A1 to Pavliak et al. (hereinafter "PAVLIAK") in view of the article titled "Staphylococcal Protein A Deletes B-1a and Marginal Zone B Lymphocytes Expressing Human Immunoglobulins: An Immune Evasion Mechanism" by Viau, et al. (hereinafter "VIAU") (J Immunol 2005, 175:7719-7727) as follows:

PAVLIAK discloses an immunogenic composition comprising a bacterial antigen (para [0005]-[0007]).
PAVLIAK does not expressly disclose said composition further comprises an isolated Protein A (SpA) specific antibody, wherein the Protein A specific antibody enhances an immune response to the bacterial antigen. However, PAVLIAK discloses that said bacterial antigen is a staphylococcal antigen (para [0005]-[0007]).
Further VIAU discloses that Protein A (SpA) of staphylococcus cripples host immune response and leads to immune evasion of said staphylococcus (abstract). Based on this disclosure, one of ordinary skill in the art would have been able to deduce and confirm without undue experimentation that a composition comprising a neutralizing antibody specific for staphylococcal Protein A could inhibit said immune response crippling effect of said Protein A and as a result could enhance overall host immune response to staphylococcal antigen(s); further one of ordinary skill in the art would have been able to produce without undue experimentation a Protein A specific neutralizing antibody using standard protocols and techniques.
One of ordinary skill in the art would have been motivated to modify the immunogenic composition comprising a bacterial antigen, wherein the bacterial antigen is a staphylococcal antigen disclosed by PAVLIAK based on the immune response crippling effect of staphylococcal Protein A disclosed by VIAN to manufacture a more effective vaccine by including in said vaccine a neutralizing antibody specific for staphylococcal Protein A to inhibit its immune response crippling effect and enhance an immune response to the staphylococcal antigen used in the vaccine. As said immunogenic composition would have been obvious toone of ordinary skill in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

The special technical feature of the inventions listed as Group I+ is the specific bacterial antigen recited therein. As no significant structural similarities can readily be ascertained among the antigens, the inventions do not share a special technical feature. Without a shared special technical feature, the inventions lack unity with one another.

Group I+ therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.