CLAIMS

1. An immunogenic composition comprising
    a. a clumping factor A (ClfA) antigen comprising an amino acid sequence at least 95% identical to SEQ ID NO: 32, wherein the ClfA antigen comprises a serine at a position equivalent to P116 of SEQ ID NO:2; an alanine at a position equivalent to Y118 of SEQ ID NO:2, and the sequence KDQNATK (SEQ ID NO: 31) beginning at a position equivalent to I337 of SEQ ID NO: 2;
    b. an alpha-haemolysin (Hla) antigen comprising an amino acid sequence at least 95% identical to SEQ ID NO: 12, wherein the Hla antigen comprises a leucine at a position equivalent to H35 of SEQ ID NO: 3, a cysteine at a position equivalent to H48 of SEQ ID NO: 3, a cysteine at a position equivalent to G122 of SEQ ID NO: 3, and the sequence KDQNRTK (SEQ ID NO: 30) beginning at a position equivalent to K131 of SEQ ID NO: 3; and
    c. a Staphylococcal protein A (SpA) antigen comprising an amino acid sequence at least 95% identical to SEQ ID NO: 27, wherein the SpA antigen comprises a lysine at positions equivalent to positions Q43, Q44, Q96, Q104, Q105, Q162, Q163, Q220, Q221, Q278, and Q279 of SEQ ID NO: 4; an arginine at a position equivalent to position Q97 of SEQ ID NO: 4; and an alanine at positions equivalent to positions D70, D71, D131, D132, D189, D190, D247, D248, D305, and D306;
    wherein the ClfA antigen is conjugated to a *Staphylococcus aureus* serotype 8 capsular polysaccharide, and the Hla antigen is conjugated to a *S. aureus* serotype 5 capsular polysaccharide.~~and~~
    ~~d. a staphylococcal capsular polysaccharide.~~

~~2. An immunogenic composition according to claim 1, wherein the capsular polysaccharide is conjugated to a carrier protein.~~

~~3. An immunogenic composition according to claim 1 or claim 2, wherein the capsular polysaccharide is a *S. aureus* serotype 5 and/or type 8 capsular polysaccharide.~~

~~4. An immunogenic composition according to any one of claims 1 to 3, wherein the capsular polysaccharide is conjugated to one of the antigens (a) (c) of claim 1.~~

~~5. An immunogenic composition according to any one of claims 1 to 4, wherein the composition comprises a *S. aureus* serotype 5 capsular polysaccharide and a type 8 capsular polysaccharide.~~

6. An immunogenic composition according to any one of claims 1 to 5, wherein the composition comprises a *S. aureus* serotype 5 capsular polysaccharide conjugated to a Hla antigen and/or a type 8 capsular polysaccharide conjugated to a ClfA antigen.

7. An immunogenic composition according to any one of claims 1 to 6, wherein

a. the ClfA antigen is a ClfA protein comprising the amino acid sequence of part (a) SEQ ID NO. 2 or an amino acid sequence is at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO. 3, or immunogenic fragment thereof;

b. the Hla antigen is a Hla protein having the amino acid sequence of part (b) SEQ ID NO. 3 or an amino acid sequence is at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO. 3, or immunogenic fragment thereof; and/or

c. the SpA antigen is a SpA protein having an amino acid sequence of part (c) SEQ ID NO. 13 or SEQ ID NO: 26or an amino acid sequence is at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO. 27 or SEQ ID NO: 26, or immunogenic fragment thereof.

8. A composition according to any of claims 1 to 7, wherein the ClfA antigen comprises at least one amino acid substitution selected from P116 to S and Y118 to A with reference to the amino acid sequence of SEQ ID NO. 2 (or an equivalent position in an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO. 2), optionally comprising the sequence of any of SEQ ID Nos 5-7 or 32.

9. An immunogenic composition according to claim 7 or claim 8, wherein the ClfA antigen comprises one or more PglB consensus sequence(s) selected from: D/E-X-N-Z-S/T (SEQ ID NO. 28) and K-D/E-X-N-Z-S/T-K (SEQ ID NO. 29), wherein X and Z are independently any amino acid apart from proline.

10. An immunogenic composition according to claim 9, wherein said consensus sequence has been added at, or substituted for, one or more amino acids between amino acid residues 313-342 of SEQ ID NO: 2, optionally substituted for the amino acid at position I337, or at an equivalent position within an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 2.

11. An immunogenic composition according to claim 9 or claim 10, wherein X is Q (glutamine) and Z is A (alanine) (e.g. K-D-Q-N-A-T-K, SEQ ID NO: 31.

~~12~~3. ~~An~~ The immunogenic composition according to claim ~~11~~2, wherein the ClfA antigen comprises or consists of the sequence of SEQ ID NO: 7 or SEQ ID NO: 32.

~~13. An immunogenic composition according to any one of claims 1 to 12, wherein the Hla antigen comprises an amino acid substitution at position H35 of SEQ ID NO. 3 or at an equivalent position within an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO. 3, wherein said amino acid substitution is optionally H to L.~~

~~14. An immunogenic composition according to any one of claims 1 to 13, wherein the Hla antigen comprises one or more PglB consensus sequence(s) selected from: D/E-X-N-Z-S/T (SEQ ID NO. 28) and K-D/E-X-N-Z-S/T-K (SEQ ID NO. 29), wherein X and Z are independently any amino acid apart from proline.~~

~~15. An immunogenic composition according to claim 14, wherein said consensus sequence has been added at, or substituted for, one or more amino acids of the amino acid sequence of SEQ ID NO. 3 or an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO. 3.~~

~~16. An immunogenic composition according to claim 14, wherein said consensus sequence has been substituted for the amino acid at position K131 of SEQ ID NO. 3 of SEQ ID NO: 3, or at an equivalent position within an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 3.~~

~~17. An immunogenic composition according to any one of claims 14 to 16, wherein X is Q (glutamine) and Z is R (arginine) (e.g. K-D-Q-N-R-T-K (SEQ ID NO 30)~~

~~18~~4. ~~An~~ The immunogenic composition according to claim ~~17~~2, wherein the Hla antigen comprises or consists of the sequence of SEQ ID NO: 11 or SEQ ID NO 12.

~~19. .The immunogenic composition according to any one of claims 1 to 18, wherein the SpA antigen comprises (a) one or more amino acid substitutions in a V_H3-binding sub-domain of domain E, D, A, B or C that disrupts or decreases binding to V_H3, and (b) one or more amino acid substitutions in an IgG Fc binding sub-domain of domain E, D, A, B or C that disrupts or decreases binding to IgG Fc.~~

~~20. An immunogenic composition according to any one of claims 1 to 19, wherein the SpA antigen comprises comprises (i) a domain E with an amino acid substitution at the amino acid positions 34 and 35 of SEQ ID NO: 14 or at an equivalent position within an amino acid sequence at least 80%,~~

85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 14; a domain D with an amino acid substitution at amino acid positions 39 and 40 of SEQ ID NO: 15 or at an equivalent position within an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 15; a domain A with an amino acid substitution at positions 36 and 37 of SEQ ID NO: 16 or at an equivalent position within an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 16; a domain B with an amino acid substitution at positions amino acid positions 36 and 37 of SEQ ID NO: 17 or at an equivalent position within an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 17, and/or a domain C with an amino acid substitution at positions amino acid positions 36 and 37 of SEQ ID NO: 18 or at an equivalent position within an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 18; and/or (ii) comprises a domain E with an amino acid substitution at amino acid positions 7 and 8 of SEQ ID NO: 14 or at an equivalent position within an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 14; a domain D with an amino acid substitution at amino acid positions 12 and 13 of SEQ ID NO: 15 or at an equivalent position within an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 15; a domain A with an amino acid substitution at positions 9 and 10 of SEQ ID NO: 16 or at an equivalent position within an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 16; a domain B with an amino acid substitution at positions amino acid positions 9 and 10 of SEQ ID NO: 17 or at an equivalent position within an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 17, and/or a domain C with an amino acid substitution at positions amino acid positions 9 and 10 of SEQ ID NO: 18 or at an equivalent position within an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 18.

21. An immunogenic composition according to claim 20, wherein said amino acid substitutions are substitution of lysine for glutamine and/or substitution of alanine for aspartic acid.

22. An immunogenic composition of any one of claims 1 to 21, wherein the SpA antigen comprises a domain D with an amino acid substitution at amino acid positions 4 and 5 of SEQ ID NO: 15. or at an equivalent position within an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NO: 15.

23. An immunogenic composition according to claim 22, wherein said amino acid substitution is glutamine to lysine and/or glutamine to arginine, e.g. QQ to KR.

~~24~~5. ~~An~~ The immunogenic composition according to ~~any one of~~ claim~~s 1 to 23~~2, wherein ~~said~~ the SpA antigen comprises or consists of the ~~an amino acid~~ sequence of SEQ ID NO~~s~~: ~~19-23,~~ 26 or SEQ ID NO: 27~~, or an amino acid sequence at least 80%, 85%, 90%, 92%, 95%, 96%, 97%, 98% or 99% identical to SEQ ID NOs: 19-23, 26 or 27~~.

~~25~~6. ~~An~~ The immunogenic composition according to ~~any one of~~ claim~~s 1 to 24~~2, wherein ~~the immunogenic composition comprises~~ (i) ~~a~~ the ClfA antigen ~~comprising~~ comprises the amino acid sequence of SEQ ID NO: 7 or SEQ ID NO: 32; (ii) ~~a~~ the Hla antigen ~~comprising~~ comprises the amino acid sequence ~~sequence~~ of SEQ ID NO: 11 or SEQ ID NO: 12; and (iii) ~~an~~ the SpA antigen ~~comprising~~ comprises the amino acid sequence of SEQ ID NO: 26 or SEQ ID NO: 27~~; (iii) a *S. aureus* serotype 5 capsular polysaccharide, and (iii) a *S. aureus* serotype type 8 capsular polysaccharide~~.

~~26. An immunogenic composition according to claim 25, wherein the ClfA antigen is conjugated to the *S. aureus* serotype type 8 capsular polysaccharide, and the Hla antigen is conjugated to the *S. aureus* serotype 5 capsular polysaccharide.~~

~~27~~7. ~~An~~ The immunogenic composition according to claim ~~26~~1, wherein said ClfA-CP8 and Hla-CP5 conjugates are bioconjugates.

~~28~~8. ~~An~~ The immunogenic composition according to ~~any one of~~ claim~~s 1 to 27~~2, ~~which composition comprises~~further comprising an adjuvant.

~~29. An immunogenic composition according to claim 28, wherein the adjuvant comprises a saponin and a lipopolysaccharide.~~

~~30. An immunogenic composition according to claim 29, wherein the adjuvant comprises a saponin, a lipopolysaccharide in a liposomal formation.~~

~~31. An immunogenic composition according to claim 29 or claim 30, further comprising a sterol.~~

~~32. An immunogenic composition according to claim any one of claims 29 to 31, wherein the saponin is an immunologically active saponin fraction derived from the bark of Quillaja Saponaria Molina.~~

~~33. An immunogenic composition according to claim 32, wherein the saponin is QS21.~~

~~34. An immunogenic composition according to any one of claims 29 to 33, wherein the lipopolysaccharide is a lipid A derivative.~~

~~35. An immunogenic composition according to claim 34, wherein the lipopolysaccharide is 3D- MPL.~~

~~36. An immunogenic composition according to any one of claims 31 to 35, wherein the sterol is cholesterol.~~

~~37. An immunogenic composition according to any one of claims 29 to 36, wherein the immunogenic composition comprises QS21 at a level of 25 µg per human dose.~~

~~38. An immunogenic composition according to any one of claims 29 to 37, wherein the immunogenic composition comprises 3D-MPL at a level of 25 µg per human dose.~~

~~39. A vaccine comprising an immunogenic composition according to any one of claims 1 to 27 and a pharmaceutically acceptable excipient or carrier.~~

~~40. A vaccine comprising an immunogenic composition according to any one of claims 28 to 38 and a pharmaceutically acceptable excipient or carrier.~~

~~41. An immunogenic composition according to any one of claims 1 to 27, or a vaccine according to claim 39, for use in a method of prevention or treatment of staphylococcal infection, wherein said composition is administered in combination with an adjuvant.~~

~~42. An immunogenic composition or vaccine for use according to claim 41, wherein the immunogenic composition is mixed with the adjuvant before administration to a subject.~~

~~43. An immunogenic composition or vaccine for use according to claim 41 or claim 42, wherein the adjuvant is as defined in any one of claims 29 to 36.~~

~~44. An immunogenic composition or vaccine for use according to claim 43, wherein the adjuvant comprises 3D-MPL at a level of 25 µg per human dose and QS21 at a level of 25 µg per human dose.~~

~~45~~9. A kit comprising (i) a first container comprising ~~an~~ the immunogenic composition of ~~any one of~~ claim~~s 1 to 27~~2; ~~or a vaccine according to claim 39;~~ and (ii) a second container comprising an adjuvant.

~~46. A kit according to claim 45, wherein the adjuvant is as defined in any one of claims 29 to 36.~~

~~47. A kit according to claim 46, wherein the adjuvant comprises 3D-MPL at a level of 25 µg per human dose and QS21 at a level of 25 µg per human dose.~~

~~48. A method of prevention or treatment of staphylococcal infection, comprising administering to a subject in need thereof an immunogenic composition according to any one of claims 1 to 27 or a vaccine according to claim 39.~~

~~49. A method according to claim 48, further comprising administering an adjuvant to said subject.~~

~~50. A method according to claim 49, wherein said adjuvant is administered concomitantly with the immunogenic composition.~~

~~51. A method according to claim 49 or claim 50, wherein the adjuvant is as defined in any one of claims 29 to 36.~~

~~52. A method of prevention or treatment of staphylococcal infection, comprising administering to a subject in need thereof an immunogenic composition according to any one of claims 28 to 38 or a vaccine according to claim 40.~~

~~53. A method of making an immunogenic composition or vaccine according to any one of claims 1-40, comprising the steps of mixing antigens, and optionally an adjuvant, with a pharmaceutically acceptable excipient.~~

10. The immunogenic composition of claim 8, wherein the adjuvant comprises a saponin and a Toll Like Receptor 4 (TLR4) agonist.

11. The immunogenic composition of claim 10, wherein the TLR4 agonist is a lipopolysaccharide.

12. The immunogenic composition of claim 11, wherein the lipopolysaccharide is 3-de-O-acylated monophosphoryl lipid A (3D-MPL).

13. The immunogenic composition of claim 10, wherein the saponin comprises an active fraction of the saponin derived from the bark of Quillaja Saponaria Molina.

14. The immunogenic composition of claim 13, wherein the active fraction of the saponin derived from the bark of Quillaja Saponaria Molina is QS21.

15. The immunogenic composition of claim 8, wherein the adjuvant comprises 3D-MPL and QS21 in a liposome.

16. The immunogenic composition of claim 8, wherein the adjuvant comprises a Toll Like Receptor 7 (TLR7) agonist adsorbed to aluminum hydroxide (AlOH).