CLAIMS:

1. A variant *Staphylococcus aureus* Leukocidin A (LukA) polypeptide of SEQ ID NO:25, said LukA variant polypeptide comprising: an amino acid substitution at each of amino acid residues corresponding to amino acid residues Lys83, Ser141, Val113, and Val193 of SEQ ID NO: 25; or an amino acid substitution at one to three amino acid residues corresponding to amino acid residues Lys83, Ser141, Val113, and Val193 of SEQ ID NO: 25.

2. The LukA variant polypeptide of claim 1, wherein said LukA variant polypeptide further comprises: an amino acid substitution at the amino acid residue corresponding to Glu323 of SEQ ID NO: 25, optionally wherein the amino acid substitution at the amino acid residue corresponding to Glu323 comprises a glutamic acid to alanine (Glu323Ala) substitution.

3. The LukA variant polypeptide of any one of claims 1 or 2, wherein the amino acid substitution at the amino acid residue corresponding to: (a) Lys83 comprises a lysine to methionine (Lys83Met) substitution; (b) Ser141 comprises a serine to alanine (Ser141Ala) substitution; (c) Val113 comprises a valine to isoleucine (Val113Ile) substitution; and/or (d) Val193 comprises a valine to isoleucine (Val193Ile) substitution.

4. The LukA variant polypeptide of any one of claims 2 or 3, wherein said LukA variant polypeptide comprises amino acid substitutions at each amino acid residue corresponding to amino acid residues Lys83, Ser141, Val113, Val193, and Glu323 of SEQ ID NO: 25, optionally wherein the amino acid substitutions comprise Lys83Met, Ser141Ala, Val113Ile, Val193Ile, and Glu323Ala.

5. The LukA variant polypeptide of claim 1, wherein said variant is:

(a) a CC8 LukA variant of SEQ ID NO: 1 comprising amino acid substitutions corresponding to Lys80Met, Ser138Ala, Val110Ile, Val190Ile, and Glu320Ala in SEQ ID NO: 1, optionally wherein said LukA variant polypeptide comprises the amino acid sequence of SEQ ID NO: 3; or

(b) a CC45 LukA variant of SEQ ID NO: 2 comprising amino acid substitutions corresponding to Lys81Met, Ser139Ala, Val111Ile, Val191Ile, and Glu321Ala in SEQ ID NO: 2; optionally wherein said LukA variant polypeptide comprises the amino acid sequence of SEQ ID NO: 4.

6. The LukA variant polypeptide of any one of claims 1–5, wherein said LukA variant polypeptide further comprises: an amino acid substitution at one or more amino acid residues corresponding to amino acid residues Tyr74, Asp140, Gly149, and Gly156 of SEQ ID NO: 25, optionally wherein:

(a) the amino acid substitution at the amino acid residue corresponding to Tyr74 comprises a tyrosine to cysteine (Tyr74Cys) substitution;

(b) the amino acid substitution at the amino acid residue corresponding to Asp140 comprises an asparagine to cysteine (Asp140Cys) substitution;

(c) the amino acid substitution at the amino acid residue corresponding to Gly149 comprises a glycine to cysteine (Gly149Cys) substitution;

(d) the amino acid substitution at the amino acid residue corresponding to Gly156 comprises a glycine to cysteine (Gly156Cys) substitution; and/or

(e) said LukA variant polypeptide comprises amino acid substitutions at each amino acid residue corresponding to amino acid residues Tyr74, Asp140, Gly149, and Gly156 of SEQ ID NO: 25, optionally where the substitutions at amino acid residues Tyr74, Asp140, Gly149, and Gly156 are as defined at (a)-(d).

7. The LukA variant polypeptide of claim 6, wherein said variant is:

(a) a CC8 LukA variant of SEQ ID NO: 1 comprising amino acid substitutions corresponding to Lys80Met, Ser138Ala, Val110Ile, Val190Ile, Glu320Ala, Tyr71Cys, Asp137Cys, Gly146Cys, and Gly153Cys of SEQ ID NO: 1, optionally wherein said LukA variant polypeptide comprises the amino acid sequence of SEQ ID NO: 5; or

(b) a CC45 LukA variant of SEQ ID NO: 2 comprising amino acid substitutions corresponding to Lys81Met, Ser139Ala, Val111Ile, Val191Ile, Glu321Ala, Tyr72Cys, Asp138Cys, Gly147Cys, and Gly154Cys of SEQ ID NO: 2, optionally wherein said LukA variant polypeptide comprises the amino acid sequence of SEQ ID NO: 6.

8. The LukA variant polypeptide of any one of claims 1–7, wherein said LukA variant polypeptide further comprises: an amino acid substitution at the amino acid residue corresponding to amino acid residue Thr249 of SEQ ID NO: 25, optionally wherein the amino acid substitution at the amino acid residue corresponding to Thr249 comprises a threonine to valine (Thr249Val) substitution, in particular wherein said variant LukA protein comprises the amino acid sequence of SEQ ID NO: 7 or SEQ ID NO: 8.

9. A variant *Staphylococcus aureus* Leukocidin B (LukB) protein or polypeptide of SEQ ID NO: 39, said LukB variant polypeptide comprising:

(i) an amino acid substitution at the amino acid residue corresponding to amino acid residue Val53 of SEQ ID NO: 39; or

(ii) an amino acid substitution at one or more amino acid residues corresponding to amino acid residues Glu45, Glu109, Thr121, and Arg154 of SEQ ID NO: 39.

10. The LukB variant polypeptide of option (i) of claim 9, wherein the amino acid substitution at the amino acid residue corresponding to Val53 comprises a valine to leucine (Val53Leu) substitution, optionally wherein said variant is:

(a) a CC8 LukB variant of SEQ ID NO: 15 comprising the amino acid substitution corresponding to Val53Leu of SEQ ID NO: 15, in particular wherein said LukB variant polypeptide comprises the amino acid sequence of SEQ ID NO: 17; or

(b) a CC45 LukB variant of SEQ ID NO: 16 comprising the amino acid substitution corresponding to Val53Leu of SEQ ID NO: 16, in particular wherein said LukB variant polypeptide comprises the amino acid sequence of SEQ ID NO: 18.

11. The LukB variant polypeptide of option (i) of claim 9 or claim 10, wherein said variant further comprises an amino acid substitution at one or more amino acid residues corresponding to amino acid residues Glu45, Glu109, Thr121, and Arg154 of SEQ ID NO: 39, optionally wherein:

(a) the amino acid substitution at the amino acid residue corresponding to Glu45 comprises a glutamic acid to cysteine (Glu45Cys) substitution;

(b) the amino acid substitution at the amino acid residue corresponding to Glu109 comprises a glutamic acid to cysteine (Glu109Cys) substitution;

(c) the amino acid substitution at the amino acid residue corresponding to Thr121 comprises a threonine to cysteine (Thr121Cys) substitution;

(d) the amino acid substitution at the amino acid residue corresponding to Arg154 comprises an arginine to cysteine (Arg154Cys) substitution; and/or

(e) said LukB variant polypeptide comprises amino acid substitutions at each amino acid residue corresponding to amino acid residues Glu45, Glu109, Thr121, and Arg154 of SEQ ID NO: 39, optionally where the substitutions at amino acid residues Glu45, Glu109, Thr121, and Arg154 are as defined at (a)-(d).

12. The LukB variant polypeptide of claim 11, wherein said variant is:

(a) a CC8 LukB variant of SEQ ID NO: 15 comprising the amino acid substitutions corresponding to Val53Leu, Glu45Cys, Glu109Cys, Thr121Cys, and Arg154Cys of SEQ ID NO: 15, optionally wherein said LukB variant polypeptide comprises the amino acid sequence of SEQ ID NO: 19; or

(b) a CC45 LukB variant of SEQ ID NO: 16 comprising the amino acid substitutions corresponding to Val53Leu, Glu45Cys, Glu110Cys, Thr123Cys, and Arg155Cys of SEQ ID NO: 16, optionally wherein said LukB variant polypeptide comprises the amino acid sequence of SEQ ID NO: 20.

13. The LukB variant polypeptide of option (ii) of claim 9, wherein:

(a) the amino acid substitution at the amino acid residue corresponding to Glu45 comprises a glutamic acid to cysteine (Glu45Cys) substitution and the amino acid substitution at the amino acid residue corresponding to Thr121 comprises a threonine to cysteine (Thr121Cys) substitution; and/or

(b) the amino acid substitution at the amino acid residue corresponding to Glu109 comprises a glutamic acid to cysteine (Glu109Cys) substitution and the amino acid substitution at the amino acid residue corresponding to Arg154 comprises an arginine to cysteine (Arg154Cys) substitution.

14. The LukB variant polypeptide of any one of option (ii) of claim 9 or 13, wherein said LukB variant polypeptide comprises amino acid substitutions at each amino acid residue corresponding to amino acid Glu45, Glu109, Thr121, and Arg154 of SEQ ID NO: 39, optionally wherein said variant is:

(a) a CC8 LukB variant of SEQ ID NO: 15 comprising the amino acid substitutions corresponding to Glu45Cys, Glu109Cys, Thr121Cys, and Arg154Cys of SEQ ID NO: 15,in particular wherein said LukB variant polypeptide comprises the amino acid sequence of SEQ ID NO: 21; or

(b) a CC45 LukB variant of SEQ ID NO: 16 comprising the amino acid substitutions corresponding to Glu45Cys, Glu110Cys, Thr123Cys, and Arg155Cys of SEQ ID NO: 16, in particular wherein said LukB variant polypeptide comprises the amino acid sequence of SEQ ID NO: 22.

15. The LukA variant polypeptide of any one of claims 1-8 or the LukB variant polypeptide of any one of claims 9-14 further comprising: (a) an amino-terminus signal sequence, optionally wherein the amino-terminus signal sequence comprises the amino acid sequence of SEQ ID NO: 23; or (b) an amino-terminus purification tag.

16. A nucleic acid molecule encoding:

(i) the LukA variant polypeptide of any one of claims 1–8 and 15; or

(ii) the LukB variant polypeptide of any one of claims 9-15.

17. An expression vector comprising:

(a) the nucleic acid molecule of option (i) of claim 16;

(b) the nucleic acid molecule of option (ii) of claim 16; or

(c) the nucleic acid molecule of option (i) of claim 16 operably coupled to the nucleic acid molecule of option (ii) of claim 16.

18. A host cell comprising the expression vector of claim 17.

19. A *Staphylococcus aureus* vaccine composition comprising:

(i) one or more variant LukA proteins or polypeptides of any one of claims 1–8 and 15;

(ii) one or more variant LukB proteins or polypeptides of any one of claims 9-15; or

(iii) the LukA variant polypeptide of any one of claims 1–8 and 15,

and the LukB variant polypeptide of any one of claims 9-15.

20. The vaccine composition of option (i) of claim 19, wherein the LukA variant polypeptide is a variant of SEQ ID NO: 1.

21. The vaccine composition of option (i) of claim 19 or claim 20 further comprising:

(a) a leukocidin B (LukB) protein or polypeptide, said LukB protein or polypeptide having at least 85% sequence similarity to the amino acid sequence of SEQ ID NO: 15; or

(b) a leukocidin B (LukB) protein or polypeptide, said LukB protein or polypeptide having at least 85% sequence similarity to the amino acid sequence of SEQ ID NO: 16, optionally wherein the LukA variant polypeptide comprises an amino acid substitution at one or more amino acid residues corresponding to amino acid residues Lys80, Ser138, Val110, Val190, and Glu320Ala of SEQ ID NO: 1, in particular wherein the LukA variant polypeptide comprises: (i) the amino acid sequence SEQ ID NO: 3 and the LukB polypeptide comprises the amino acid sequence of SEQ ID NO:18; (ii) the amino acid sequence of SEQ ID NO: 3 and the LukB protein or polypeptide comprises the amino

acid sequence of SEQ ID NO: 15; or (iii) the amino acid sequence of SEQ ID NO: 3 and the LukB protein or polypeptide comprises the amino acid sequence of SEQ ID NO: 17.

22. The vaccine composition of option (i) of claim 19, wherein the LukA variant polypeptide is a variant of SEQ ID NO: 2.

23. The vaccine composition of claim 22 further comprising:

(a) a leukocidin B (LukB) protein or polypeptide, said LukB protein or polypeptide having at least 85% sequence similarity to the amino acid sequence of SEQ ID NO: 16, optionally wherein the LukA variant polypeptide comprises an amino acid substitution at one or more amino acid residues corresponding to amino acid residues Lys81, Ser139, Val111, Val191, and Glu321Ala of SEQ ID NO: 2, in particular wherein the LukA variant polypeptide comprises the amino acid sequence SEQ ID NO: 4 and the LukB protein or polypeptide comprises the amino acid sequence of SEQ ID NO:16; or

(b) a leukocidin B (LukB) protein or polypeptide, said LukB protein or polypeptide having at least 85% sequence similarity to the amino acid sequence of SEQ ID NO: 15.

24. The vaccine composition of option (ii) of claim 19 further comprising: (a) a leukocidin A (LukA) protein or polypeptide, said LukA protein or polypeptide having at least 85% sequence similarity to the amino acid sequence of SEQ ID NO: 1 (CC8); or (b) a leukocidin A (LukA) protein or polypeptide, said LukA protein or polypeptide having at least 85% sequence similarity to the amino acid sequence of SEQ ID NO: 2 (CC45).

25. The vaccine composition of any one of options (i), (ii), or (iii) of claim 19 further comprising: (a) an adjuvant; or (b) one or more additional *S. aureus* antigens.

26. The vaccine composition of any one of options (i), (ii), or (iii) of claim 19 for use in a method of generating an immune response against *S. aureus* in a subject.