CLAIMS:

1. An immunogenic composition comprising:

(i) a *Staphylococcus aureus* protein A (SpA) polypeptide, and

(ii) a *S. aureus* LukA variant polypeptide, said LukA variant polypeptide comprising:

an amino acid substitution at each of the 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. A combination of two or more immunogenic compositions, together comprising:

(i) a *Staphylococcus aureus* protein A (SpA) polypeptide, and

(ii) a *S. aureus* LukA variant polypeptide, said LukA variant polypeptide comprising an amino acid substitution at one or more amino acid residues corresponding to amino acid residues Lys83, Ser141, Val113, and Val193 of SEQ ID NO: 25.

3. The immunogenic composition of claim 1 or the combination of immunogenic compositions of claim 2, wherein:

(a) the LukA variant polypeptide comprises an amino acid substitution at the amino acid residue corresponding to Glu323 of SEQ ID NO: 25; and/or

(b) 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; and/or

(c) said LukA variant polypeptide comprises an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 3 or an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 4; and/or

(d) 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 the amino acid substitutions comprise Tyr74Cys, Asp140Cys, Gly149Cys, and Gly156Cys; and/or

(e) said LukA variant polypeptide comprises an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 5 or an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 6; and/or

(f) said variant LukA protein or polypeptide further comprises:
an amino acid substitution at the amino acid residue corresponding to amino acid residue Thr249 of SEQ ID NO: 25; and/or

(g) said LukA variant polypeptide comprises an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 7 or an amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID NO: 8.

4. The immunogenic composition or the combination of immunogenic compositions of any one of claims 1–3, wherein the SpA polypeptide is a SpA variant polypeptide, optionally wherein:

(a) the SpA variant polypeptide has at least one amino acid substitution that disrupts Fc binding and at least a second amino acid substitution that disrupts VH3 binding; and/or

(b) the SpA variant polypeptide comprises a SpA D domain, said SpA D domain comprising an amino acid sequence having at least 90% identity to the amino acid sequence of SEQ ID NO: 58, optionally wherein:

(i) the SpA variant polypeptide has an amino acid substitution at one or both of amino acid positions corresponding to positions 9 and 10 of SEQ ID NO: 58; and/or

(ii) the SpA variant polypeptide further comprises a SpA E, A, B, or C domain, further optionally wherein the SpA variant polypeptide comprises SpA E, A, B, and C domains and has an amino acid

sequence having at least 90% identity to the amino acid sequence of SEQ ID NO:54, and/or wherein each SpA E, A, B, and C domain has an amino acid substitution at one or both amino acid positions corresponding to amino acid positions 9 and 10 of SEQ ID NO: 58; and/or

(iii) wherein the amino acid substitution at one or both amino acid positions corresponding to positions 9 and 10 of SEQ ID NO: 58 is a lysine residue for a glutamine residue; and/or

(c) wherein the SpA variant polypeptide comprises at least one SpA A, B, C, D, or E domain, and wherein the at least one domain has (i) a lysine substitution at the glutamine residues corresponding to positions 9 and 10 of SEQ ID NO: 58 and (ii) a glutamate substitution at the amino acid position corresponding to position 33 of SEQ ID NO: 58.

5. The immunogenic composition or the combination of immunogenic compositions of any one of claims 1–4, wherein said composition further comprises a *S. aureus* Leukocidin B (LukB) polypeptide or variant thereof, optionally wherein:

(a) the LukB polypeptide is a LukB polypeptide of SEQ ID NO: 15 or a LukB polypeptide of SEQ ID NO: 16; or

(b) the LukB polypeptide is a LukB variant polypeptide, optionally wherein the LukB variant polypeptide comprises an amino acid sequence having at least 85% sequence similarity to the amino acid sequence of SEQ ID NO:15 or an amino acid sequence having at least 85% sequence similarity to the amino acid sequence of SEQ ID NO: 16, further optionally wherein the LukB variant polypeptide comprises an amino acid substitution at the amino acid position corresponding to position 53 of SEQ ID NO: 15 and SEQ ID NO: 16, further optionally wherein the amino acid substitution is a valine to leucine substitution.

6. The immunogenic composition or the combination of immunogenic compositions of claim 5(b), wherein:

(a) said LukB variant polypeptide 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: 15; or

(b) said LukB variant polypeptide comprises an amino acid substitution at one or more amino acid residues corresponding to amino acid residues Glu45, Glu110, Thr122, and Arg155 of SEQ ID NO: 16; or

(c) the LukB variant polypeptide comprises an amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from SEQ ID NOs: 17-22.

7. The immunogenic composition or the combination of immunogenic compositions of claim 5, wherein:

(a) said composition comprises a LukA variant polypeptide comprising the amino acid sequence SEQ ID NO: 4 or an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 4 and a LukB polypeptide comprising the amino acid sequence of SEQ ID NO: 16, or an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 16; or

(b) said composition comprises a LukA variant polypeptide comprising the amino acid sequence SEQ ID NO: 3 or an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 3 and a LukB polypeptide comprising the amino acid sequence of SEQ ID NO: 15, or an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 15; or

(c) said composition comprises a LukA variant polypeptide comprising the amino acid sequence SEQ ID NO: 3 or an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 3 and a LukB polypeptide comprising the amino acid sequence of SEQ ID NO: 18, or an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 18; and/or

(d) the SpA polypeptide is a SpA variant polypeptide, optionally wherein the SpA variant polypeptide comprises at least one SpA A, B, C, D, or E domain, and wherein the at least one domain has (i) a lysine substitution at the glutamine residues

corresponding to positions 9 and 10 of SEQ ID NO: 58 and (ii) a glutamate substitution at the amino acid position corresponding to position 33 of SEQ ID NO: 58.

8. The immunogenic composition or the combination of immunogenic compositions of claim 5, wherein (i) the SpA variant polypeptide comprises at least one SpA A, B, C, D, or E domain, and wherein the at least one domain has lysine substitutions at the amino acid positions corresponding to positions 9 and 10 of SEQ ID NO: 58 and a glutamate substitution at the amino acid position corresponding to position 33 of SEQ ID NO: 58; (ii) the LukA variant polypeptide comprises a CC8 LukA variant polypeptide comprising a methionine substitution at the amino acid position corresponding to position 80 of SEQ ID NO: 1, an alanine substitution at the amino acid position corresponding to position 138 of SEQ ID NO: 1, an isoleucine substitutions at the amino acid positions corresponding to positions 110 and 190 of SEQ ID NO:1, and an alanine substitution at the amino acid position corresponding to position 320 of SEQ ID NO: 1; and (iii) the LukB polypeptide is a CC45 LukB variant polypeptide comprising a leucine substitution at the amino acid position corresponding to position 53 of SEQ ID NO: 16, optionally wherein the SpA variant polypeptide comprises consecutively SpA E, D, A, B, and C domains, each domain having the lysine substitutions at the amino acid positions corresponding to positions 9 and 10 of SEQ ID NO: 58 and a glutamate substitution at the amino acid position corresponding to position 33 of SEQ ID NO: 58.

9. The immunogenic composition or the combination of immunogenic compositions of any one of claims 1 to 7, further comprising an adjuvant, optionally wherein:

(a) the adjuvant is a stable oil-in-water emulsion; or

(b) the adjuvant comprises a saponin, optionally wherein the saponin is QS21; or

(c) the adjuvant comprises a TLR4 agonist, optionally wherein:

(i) the TLR4 agonist is lipid A or an analog or derivative thereof; or

(ii) the TLR4 agonist is glycopyranosyl lipid adjuvant (GLA), optionally wherein the adjuvant comprises GLA-SE or GLA-LSQ; or

(iii) the adjuvant comprises a TLR-4 agonist in combination with a stable oil-in-water emulsion; or

(iv) the adjuvant comprises a TLR-4 agonist in combination with a saponin.

10. An immunogenic composition or a combination of immunogenic compositions, wherein said compositions comprise one or more nucleic acid molecules encoding the *Staphylococcus aureus* protein A (SpA) polypeptide or variant thereof, the LukA variant polypeptide, and the LukB polypeptide or variant thereof of the immunogenic compositions of any one of claims 1–8, optionally wherein:

(a) the one or more nucleic acid molecules are contained in one or more vectors; and/or

(b) said compositions comprise a host cell, wherein said host cell comprises said one or more nucleic acid molecules or said one or more vectors.

11. The immunogenic composition or the combination of immunogenic compositions of any one of claims 1 to 10 for use in a method for treating or preventing a Staphylococcus infection in a subject in need thereof, the method comprising:

an effective amount of the immunogenic composition or the combination of immunogenic compositions of any one of claims 1 to 10 to be administered to the subject.

12. The immunogenic composition or the combination of immunogenic compositions of any one of claims 1 to 10 for use in a method for eliciting an immune response to a Staphylococcus bacterium in a subject in need thereof, the method comprising:

an effective amount of the immunogenic composition or the combination of immunogenic compositions of any one of claims 1 to 10 to be administered to the subject.

13. The immunogenic composition or the combination of immunogenic compositions of any one of claims 1 to 10 for use in a method for decolonization or preventing colonization or recolonization of a Staphylococcus bacterium in a subject in need thereof, the method comprising:

an effective amount of the immunogenic composition or the combination of immunogenic compositions of any one of claims 1 to 10 to be administered to the subject.

14. The immunogenic composition or the combination of immunogenic compositions of any one of claims 1–10 for use in a method of generating an immune response against *S. aureus* in a subject.

15. The immunogenic composition or the combination of immunogenic compositions of any one of claims 1–10 for use as a medicament.