SUMMARY ~~OF THE INVENTION~~

The present ~~invention~~ disclosure relates generally to the prevention of pneumococcal disease. More specifically, the ~~invention~~ disclosure relates to compositions administered as a vaccine which include pneumococcal conjugates and a stable nanoemulsion (SNE) adjuvant formulation. The present disclosure provides, among other things, a pneumococcal conjugate composition including an SNE comprising emulsifiers and/or solubilizers and/or surfactants and/or lipids. The present disclosure provides, among other things, a pneumococcal conjugate composition including an SNE comprising surfactants and/or terpenes and/or cationic lipids or mixtures thereof. The present disclosure provides, among other things, a pneumococcal conjugate composition including an SNE comprising sorbitan esters and/or terpenes and/or cationic lipids or mixtures thereof. The present disclosure provides, among other things, a pneumococcal conjugate composition including an SNE comprising sorbitan esters, in particular polysorbate-20 or polysorbate-80 or a poloxamer and/or terpenes and/or cationic lipids or mixtures thereof. The present disclosure provides, among other things, a pneumococcal conjugate composition including an SNE comprising sorbitan esters, in particular polysorbate-20 or polysorbate-80 or a poloxamer and/or terpenes and/or cationic lipids or mixtures thereof. The present disclosure provides, among other things, a pneumococcal conjugate composition including an SNE comprising sorbitan trioleate (SPAN-85), polysorbate-20 or polysorbate-80, a terpene and an optional cationic lipid. The present disclosure provides, among other things, a pneumococcal conjugate composition including an SNE comprising sorbitan trioleate (SPAN-85), polysorbate-20 or polysorbate-80, squalene and an optional cationic lipid. The present disclosure provides, among other things, a pneumococcal conjugate composition including an SNE comprising sorbitan trioleate (SPAN-85), polysorbate-20 or polysorbate-80, squalene and a cationic lipid. The present disclosure further provides, among other things, a pneumococcal conjugate composition including an SNE adjuvant formulation comprising 1) sorbitan trioleate (SPAN-85); 2) polysorbate-20 (PS-20) or polysorbate-80 (PS-80); 3) squalene; and an optional 4) cationic lipid. A particular pneumococcal conjugate composition includes an SNE adjuvant formulation comprising 1) sorbitan trioleate (SPAN-85); 2) polysorbate-20 (PS-20) or polysorbate-80 (PS-80); 3) squalene; and 4) the cationic lipid (13Z,16Z)-N, N-dimethyl-3-nonyldocosa-13,16-dien-1-amine ("CLA" or, when the cationic lipid is included in the SNE, "CLA-SNE"). A particular pneumococcal conjugate composition includes an SNE adjuvant formulation comprising 1) sorbitan trioleate (SPAN-85); 2) polysorbate-20 (PS-20) or polysorbate-80 (PS-80); 3) squalene;

and 4) the cationic lipid (13Z,16Z)-N, N-dimethyl-3-nonyldocosa-13,16-dien-1-amine ("CLA" or, when the cationic lipid is included in the SNE, "CLA-SNE"). A particular pneumococcal conjugate composition includes an SNE adjuvant formulation comprising 1) sorbitan trioleate (SPAN-85); 2) polysorbate-20 (PS-20) or polysorbate-80 (PS-80); 3) squalene; and 4) the cationic lipid (13Z,16Z)-N, N-dimethyl-3-nonyldocosa-13,16-dien-1-amine ("CLA" or, when the cationic lipid is included in the SNE, "CLA-SNE"). A particular pneumococcal conjugate composition includes an SNE adjuvant formulation comprising 1) sorbitan trioleate (SPAN-85); 2) polysorbate-20 (PS-20); 3) squalene; and 4) the cationic lipid (13Z,16Z)-N, N-dimethyl-3-nonyldocosa-13,16-dien-1-amine ("CLA" or, when the cationic lipid is included in the SNE, "CLA-SNE"). Compared to the performance of 1) a non-adjuvanted pneumococcal conjugate composition; 2) an aluminum phosphate adjuvanted (APA) pneumococcal conjugate composition; or 3) an LNP adjuvanted pneumococcal conjugate composition; the described SNE adjuvant pneumococcal conjugate composition provided an equivalent or increased immunogenic response for the majority of pneumococcal serotypes tested.

In one aspect, there is provided a composition comprising:

a) at least one *Streptococcus pneumoniae* polysaccharide;

b) sorbitan trioleate (SPAN-85);

c) polysorbate-20 (PS-20) or polysorbate-80 (PS-80); and

d) squalene.

In another aspect, there is provided a composition comprising:

a) at least one *Streptococcus pneumoniae* polysaccharide-carrier protein conjugate comprising a *Streptococcus pneumoniae* polysaccharide conjugated to a carrier protein;

b) sorbitan trioleate (SPAN-85);

c) polysorbate-20 (PS-20); and

d) squalene;

wherein the at least one *Streptococcus pneumoniae* polysaccharide is selected from the group consisting of serotypes:

4, 6B, 9V, 14, 18C, 19F and 23F;

1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F;

1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F;

1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F;

1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23B, 23F, 24F, 33F and 35B;

1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15A, de-O-acetylated-15B, 18C, 19A, 19F, 22F, 23B, 23F, 24F, 33F and 35B;

1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15A, 15C, 18C, 19A, 19F, 22F, 23B, 23F, 24F, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B; and

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;

and the carrier protein is CRM197.

In another aspect, there is provided a composition comprising:

a) at least one *Streptococcus pneumoniae* polysaccharide-carrier protein conjugate comprising a *Streptococcus pneumoniae* polysaccharide conjugated to a carrier protein;

b) sorbitan trioleate (SPAN-85);

c) polysorbate-20 (PS-20); and

d) squalene;

wherein the at least one *Streptococcus pneumoniae* polysaccharide is selected from the group consisting of serotypes:

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B; and

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;

and the carrier protein is CRM197.

In another aspect, there is provided a composition comprising:

a) at least one *Streptococcus pneumoniae* polysaccharide;

b) sorbitan trioleate (SPAN-85);

c) polysorbate-20 (PS-20) or polysorbate-80 (PS-80);

d) squalene; and

e) a cationic lipid.

In another aspect, there is provided a composition comprising:

a) at least one *Streptococcus pneumoniae* polysaccharide-carrier protein conjugate comprising a *Streptococcus pneumoniae* polysaccharide conjugated to a carrier protein;

b) sorbitan trioleate (SPAN-85);

c) polysorbate-20 (PS-20);

d) squalene; and

e) a cationic lipid;

wherein the at least one *Streptococcus pneumoniae* polysaccharide is selected from the group consisting of serotypes:

4, 6B, 9V, 14, 18C, 19F and 23F;

1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F;

1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F;

1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F;

1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23B, 23F, 24F, 33F and 35B;

1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15A, de-O-acetylated-15B, 18C, 19A, 19F, 22F, 23B, 23F, 24F, 33F and 35B;

1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15A, 15C, 18C, 19A, 19F, 22F, 23B, 23F, 24F, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B; and

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;

and the carrier protein is CRM197.

In another aspect, there is provided a composition comprising:

a) at least one *Streptococcus pneumoniae* polysaccharide-carrier protein conjugate comprising a *Streptococcus pneumoniae* polysaccharide conjugated to a carrier protein;

b) sorbitan trioleate (SPAN-85);

c) polysorbate-20 (PS-20);

d) squalene; and

e) a cationic lipid selected from:

(13Z,16Z)-N,N-dimethyl-3-nonyldocosa-13,16-dien-1-amine;

(6Z,9Z,26Z,29Z)-N,N-dimethylpentatriaconta-6,9,26,29-tetraen-18-amine; and

N,N-dimethyl-1-((1S,2R)-2-octylcyclopropyl)heptadecan-8-amine;

wherein the at least one *Streptococcus pneumoniae* polysaccharide is selected from the group consisting of serotypes:

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B; and

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;

and the carrier protein is CRM197.

In another aspect, there is provided a composition comprising:

a) at least one *Streptococcus pneumoniae* polysaccharide-carrier protein conjugate comprising a *Streptococcus pneumoniae* polysaccharide conjugated to a carrier protein;

b) sorbitan trioleate (SPAN-85);

c) polysorbate-20 (PS-20);

d) squalene; and

e) a cationic lipid which is (13Z,16Z)-N,N-dimethyl-3-nonyldocosa-13,16-dien-1-amine;

wherein the at least one *Streptococcus pneumoniae* polysaccharide is selected from the group consisting of serotypes:

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B; and

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;

and the carrier protein is CRM197.

In another aspect, there is provided the composition as described herein for use in treating or preventing pneumococcal diseases.

In another aspect, there is provided use of the composition as described herein in the manufacture of a medicament for the treatment or prevention of pneumococcal diseases.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: Select structures of cationic lipids: (13Z,16Z)-N, N-dimethyl-3-nonyldocosa-13,16-dien-1-amine (CLA); (6Z,9Z,26Z,29Z)-N,N-dimethylpentatriaconta-6,9,26,29-tetraen-18-amine (CLX); and N,N-dimethyl-1-((1S,2R)-2-octylcyclopropyl) heptadecan-8-amine (CLY).

Figure 2: CLA-SNE components: (13Z,16Z)-N, N-dimethyl-3-nonyldocosa-13,16-dien-1-amine (CLA), SPAN-85, PS-20 and squalene.

Figure 3: Characterization of CLA-SNE adjuvant bulk preparation utilizing static light scattering (SLS). See Example 3.

Figure 4: Impact of the formulation process on the incorporation of CLA into an SNE. See Example 4.

Figure 5A: Pre-immune (pooled) and post-dose 3 (day 35) anti-6B IgG titers after immunization of mice with formulations described in Table 4. Error bars are geometric means with 95% confidence intervals. Transformed data analyzed by one-way ANOVA with Dunnett post-test *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$, NS is not significant. See Example 6.

WHAT IS CLAIMED IS:

1. A ~~pneumococcal conjugate~~ composition comprising:

a) at least one *Streptococcus pneumoniae* polysaccharide~~- carrier protein conjugates and a stable nanoemulsion (SNE), wherein the SNE comprises~~

b) sorbitan trioleate (SPAN-85);

c) polysorbate-20 (PS-20) or polysorbate-80 (PS-80); and

d) squalene.

~~2. The composition of claim 1 wherein the SNE comprises 6 µg/mL - 14 mg/mL SPAN-85, 6 µg/mL - 14 mg/mL PS-20 or PS-80 and 60 µg/mL - 34 mg/mL of squalene.~~

~~3. The composition of claim 1 or 2 wherein the SNE further comprises a cationic lipid.~~

~~4. The composition of claim 3 wherein the cationic lipid is (13Z,16Z)-N,N-dimethyl-3-nonyldocosa-13,16-dien-1-amine.~~

~~5. The composition of claim 3 or 4 comprising 30 µg/mL - 2.4 mg/mL of cationic lipid.~~

2. The composition of claim 1, wherein the at least one *Streptococcus pneumoniae* polysaccharide is conjugated to a carrier protein.

3. The composition of claim 2, wherein the carrier protein is CRM197.

~~6.~~4. The composition of any of claims ~~1-5~~1-3, wherein ~~each of the~~the at least one *Streptococcus pneumoniae* polysaccharide~~- carrier protein conjugates comprises a polysaccharide of a particular *Streptococcus pneumoniae* serotype, and wherein the *Streptococcus pneumoniae* serotypes are~~ is selected from ~~a~~ the group consisting of serotypes:

~~a)~~ 4, 6B, 9V, 14, 18C, 19F and 23F;

~~b)~~ 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F;

~~c)~~ 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F;

~~d)~~ 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F;

~~e)~~ 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23B, 23F, 24F, 33F and 35B;

f) 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15A, de-O-acetylated-15B, 18C, 19A, 19F, 22F, 23B, 23F, 24F, 33F and 35B;

g) 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15A, 15C, 18C, 19A, 19F, 22F, 23B, 23F, 24F, 33F and 35B;

h) 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B;

i) 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B;

j) 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B;

k) 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F and 35B;

l) 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F and 35B;

m) 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F and 35B;

n) 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;

o) 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B; and

p) 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B.

7. The composition of any of claims 1-6 wherein the carrier protein is CRM197.

8. The composition of claim 7, wherein the *Streptococcus pneumoniae* serotypes in the composition consist of: 4, 6B, 9V, 14, 18C, 19F and 23F.

9. The composition of claim 7, wherein the *Streptococcus pneumoniae* serotypes in the composition consist of: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F 9.

10. The composition of claim 7, wherein the *Streptococcus pneumoniae* serotypes in the composition consist of: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F.

~~11. The composition of claim 7, wherein the *Streptococcus pneumoniae* serotypes in the composition consist of: 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F.~~

~~12. The composition of claim 7, wherein the *Streptococcus pneumoniae* serotypes in the composition consist of: 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23B, 23F, 24F, 33F and 35B.~~

~~13. The composition of claim 7, wherein the *Streptococcus pneumoniae* serotypes in the composition consist of: 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15A, de-O-acetylated-15B, 18C, 19A, 19F, 22F, 23B, 23F, 24F, 33F and 35B.~~

~~14. The composition of claim 7, wherein the *Streptococcus pneumoniae* serotypes in the composition consist of: 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15A, 15C, 18C, 19A, 19F, 22F, 23B, 23F, 24F, 33F and 35B.~~

~~15. The composition of claim 7, wherein the *Streptococcus pneumoniae* serotypes in the composition consist of: 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F and 35B.~~

~~16. The composition of claim 7, wherein the *Streptococcus pneumoniae* serotypes in the composition consist of: 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F and 35B 6.~~

~~17. The composition of claim 7, wherein the *Streptococcus pneumoniae* serotypes in the composition consist of: 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F and 35B 7.~~

~~18. The composition of any of claims 1-17 wherein the SNE comprises PS-20.~~

~~19. The composition of any of claims 1-18 wherein the composition further comprises 5 mM - 40 mM histidine at pH 5.1 - 7.0 and 25 mM - 300 mM NaCl.~~

~~20. The composition of any of claims 1-18 wherein the composition further comprises about 20 mM histidine at about pH 5.8 and about 75 mM NaCl.~~

~~21. A method of treatment or prevention of pneumococcal diseases in a patient comprising administering an immunologically effective amount of the composition of any of claims 1 to 20 to the patient.~~

~~22. A use of the composition of any of claims 1 to 20 for the treatment or prevention of pneumococcal diseases.~~

5. The composition of any of claims 1-4, wherein the SPAN-85 concentration is 6 µg/mL - 24 mg/mL, the PS-20 or PS-80 concentration is 6 µg/mL - 24 mg/mL, and the squalene concentration is 60 µg/mL - 240 mg/mL.

6. The composition of any of claims 1-4, wherein the SPAN-85 concentration is 6 µg/mL - 2.4 mg/mL, the PS-20 or PS-80 concentration is 6 µg/mL - 2.4 mg/mL, and the squalene concentration is 60 µg/mL - 24 mg/mL.

7. A composition comprising:

a) at least one *Streptococcus pneumoniae* polysaccharide-carrier protein conjugate comprising a *Streptococcus pneumoniae* polysaccharide conjugated to a carrier protein;

b) sorbitan trioleate (SPAN-85);

c) polysorbate-20 (PS-20); and

d) squalene;

wherein the at least one *Streptococcus pneumoniae* polysaccharide is selected from the group consisting of serotypes:

4, 6B, 9V, 14, 18C, 19F and 23F;

1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F;

1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F;

1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F;

1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23B, 23F, 24F, 33F and 35B;

1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15A, de-O-acetylated-15B, 18C, 19A, 19F, 22F, 23B, 23F, 24F, 33F and 35B;

1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15A, 15C, 18C, 19A, 19F, 22F, 23B, 23F, 24F, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B; and

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;

and the carrier protein is CRM197.

8. The composition of claim 7, wherein the SPAN-85 concentration is 6 µg/mL - 24 mg/mL, the PS-20 concentration is 6 µg/mL - 24 mg/mL, and the squalene concentration is 60 µg/mL - 240 mg/mL.

9. The composition of claim 7, wherein the SPAN-85 concentration is 6 µg/mL - 2.4 mg/mL, the PS-20 concentration is 6 µg/mL - 2.4 mg/mL, and the squalene concentration is 60 µg/mL - 24 mg/mL.

10. A composition comprising:

a) at least one *Streptococcus pneumoniae* polysaccharide-carrier protein conjugate comprising a *Streptococcus pneumoniae* polysaccharide conjugated to a carrier protein;

b) sorbitan trioleate (SPAN-85);

c) polysorbate-20 (PS-20); and

d) squalene;

wherein the at least one *Streptococcus pneumoniae* polysaccharide is selected from the group consisting of serotypes:

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B; and
3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;
and the carrier protein is CRM197.

11. The composition of claim 10, wherein the SPAN-85 concentration is 6 µg/mL - 24 mg/mL, the PS-20 concentration is 6 µg/mL - 24 mg/mL, and the squalene concentration is 60 µg/mL - 240 mg/mL.

12. The composition of claim 11 wherein the composition further comprises 5 mM - 40 mM histidine at pH 5.1 - 7.0 and 25 mM - 300 mM NaCl.

13. The composition of claim 11 wherein the composition further comprises about 20 mM histidine at about pH 5.8 and about 75 mM NaCl.

14. The composition of claim 10, wherein the SPAN-85 concentration is 6 µg/mL - 2.4 mg/mL, the PS-20 concentration is 6 µg/mL - 2.4 mg/mL, and the squalene concentration is 60 µg/mL - 24 mg/mL.

15. The composition of claim 14 wherein the composition further comprises 5 mM - 40 mM histidine at pH 5.1 - 7.0 and 25 mM - 300 mM NaCl.

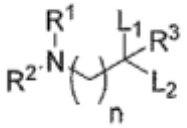
16. The composition of claim 14 wherein the composition further comprises about 20 mM histidine at about pH 5.8 and about 75 mM NaCl.

17. A composition comprising:
a) at least one *Streptococcus pneumoniae* polysaccharide;
b) sorbitan trioleate (SPAN-85);
c) polysorbate-20 (PS-20) or polysorbate-80 (PS-80);
d) squalene; and
e) a cationic lipid.

18. The composition of claim 17, wherein the at least one *Streptococcus pneumoniae* polysaccharide is conjugated to a carrier protein.

19. The composition of claim 18, wherein the carrier protein is CRM197.

20. The composition of any of claims 17-19, wherein the cationic lipid is selected from Formula 1:



Formula 1

wherein:

R^1 and R^2 are each methyl;

R^3 is H;

n is 1 or 2;

L_1 is selected from C_8-C_{24} alkyl and C_8-C_{24} alkenyl; and

L_2 is selected from C_4-C_9 alkyl and C_4-C_9 alkenyl;

or any pharmaceutically acceptable salt or stereoisomer thereof.

21. The composition of any of claims 17-19, wherein the cationic lipid is selected from:

(13Z,16Z)-N,N-dimethyl-3-nonyldocosa-13,16-dien-1-amine;

(6Z,9Z,26Z,29Z)-N,N-dimethylpentatriaconta-6,9,26,29-tetraen-18-amine; and

N,N-dimethyl-1-((1S,2R)-2-octylcyclopropyl)heptadecan-8-amine.

22. The composition of any of claims 17-19 wherein the cationic lipid is (13Z,16Z)-N,N-dimethyl-3-nonyldocosa-13,16-dien-1-amine.

23. The composition of any of claims 17-22, wherein the at least one *Streptococcus pneumoniae* polysaccharide is selected from the group consisting of serotypes: 4, 6B, 9V, 14, 18C, 19F and 23F;

1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F;

1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F;

1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F;

1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23B, 23F, 24F, 33F and 35B;

1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15A, de-O-acetylated-15B, 18C, 19A, 19F, 22F, 23B, 23F, 24F, 33F and 35B;

1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15A, 15C, 18C, 19A, 19F, 22F, 23B, 23F, 24F, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B; and

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B.

24. The composition of any of claims 17-23, wherein the SPAN-85 concentration is 6 µg/mL - 14 mg/mL, the PS-20 or PS-80 concentration is 6 µg/mL - 14 mg/mL, the squalene concentration is 60 µg/mL - 34 mg/mL and the cationic lipid concentration is 30 µg/mL - 2.4 mg/mL.

25. The composition of any of claims 17-23, wherein the SPAN-85 concentration is 6 µg/mL - 14 mg/mL, the PS-20 or PS-80 concentration is 6 µg/mL - 14 mg/mL, the squalene concentration is 60 µg/mL - 34 mg/mL and the cationic lipid concentration is 60 µg/mL - 2.4 mg/mL.

26. A composition comprising:

a) at least one *Streptococcus pneumoniae* polysaccharide-carrier protein conjugate comprising a *Streptococcus pneumoniae* polysaccharide conjugated to a carrier protein;

b) sorbitan trioleate (SPAN-85);

c) polysorbate-20 (PS-20);

d) squalene; and

e) a cationic lipid;

wherein the at least one *Streptococcus pneumoniae* polysaccharide is selected from the group consisting of serotypes:

4, 6B, 9V, 14, 18C, 19F and 23F;

1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F;

1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F and 33F;

1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F and 33F;

1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15A, 15B, 18C, 19A, 19F, 22F, 23B, 23F, 24F, 33F and 35B;

1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15A, de-O-acetylated-15B, 18C, 19A, 19F, 22F, 23B, 23F, 24F, 33F and 35B;

1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15A, 15C, 18C, 19A, 19F, 22F, 23B, 23F, 24F, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B; and

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;

and the carrier protein is CRM197.

27. The composition of claim 26, wherein the SPAN-85 concentration is 6 µg/mL - 14 mg/mL, the PS-20 or PS-80 concentration is 6 µg/mL - 14 mg/mL, the squalene concentration is 60 µg/mL - 34 mg/mL and the cationic lipid concentration is 30 µg/mL - 2.4 mg/mL.

28. The composition of claim 26, wherein the SPAN-85 concentration is 6 µg/mL - 14 mg/mL, the PS-20 or PS-80 concentration is 6 µg/mL - 14 mg/mL, the squalene concentration is 60 µg/mL - 34 mg/mL and the cationic lipid concentration is 60 µg/mL - 2.4 mg/mL.

29. A composition comprising:

a) at least one *Streptococcus pneumoniae* polysaccharide-carrier protein conjugate comprising a *Streptococcus pneumoniae* polysaccharide conjugated to a carrier protein;

b) sorbitan trioleate (SPAN-85);

c) polysorbate-20 (PS-20);

d) squalene; and

e) a cationic lipid selected from:

(13Z,16Z)-N,N-dimethyl-3-nonyldocosa-13,16-dien-1-amine;

(6Z,9Z,26Z,29Z)-N,N-dimethylpentatriaconta-6,9,26,29-tetraen-18-amine; and

N,N-dimethyl-1-((1S,2R)-2-octylcyclopropyl)heptadecan-8-amine;

wherein the at least one *Streptococcus pneumoniae* polysaccharide is selected from the group consisting of serotypes:

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B; and

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;

and the carrier protein is CRM197.

30. The composition of claim 29, wherein the SPAN-85 concentration is 6 µg/mL - 14 mg/mL, the PS-20 or PS-80 concentration is 6 µg/mL - 14 mg/mL, the squalene concentration is 60 µg/mL - 34 mg/mL and the cationic lipid concentration is 30 µg/mL - 2.4 mg/mL.

31. The composition of claim 29, wherein the SPAN-85 concentration is 6 µg/mL - 14 mg/mL, the PS-20 or PS-80 concentration is 6 µg/mL - 14 mg/mL, the squalene concentration is 60 µg/mL - 34 mg/mL and the cationic lipid concentration is 60 µg/mL - 2.4 mg/mL.

32. A composition comprising:

a) at least one *Streptococcus pneumoniae* polysaccharide-carrier protein conjugate comprising a *Streptococcus pneumoniae* polysaccharide conjugated to a carrier protein;

b) sorbitan trioleate (SPAN-85);

c) polysorbate-20 (PS-20);

d) squalene; and

e) a cationic lipid which is (13Z,16Z)-N,N-dimethyl-3-nonyldocosa-13,16-dien-1-amine;

wherein the at least one *Streptococcus pneumoniae* polysaccharide is selected from the group consisting of serotypes:

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, de-O-acetylated-15B, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B; and

3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20B, 22F, 23A, 23B, 24F, 31, 33F and 35B;
and the carrier protein is CRM197.

33. The composition of claim 32, wherein the SPAN-85 concentration is 6 µg/mL - 14 mg/mL, the PS-20 or PS-80 concentration is 6 µg/mL - 14 mg/mL, the squalene concentration is 60 µg/mL - 34 mg/mL and the cationic lipid concentration is 30 µg/mL - 2.4 mg/mL.

34. The composition of claim 33 wherein the composition further comprises 5 mM - 40 mM histidine at pH 5.1 - 7.0 and 25 mM - 300 mM NaCl.

35. The composition of claim 33 wherein the composition further comprises about 20 mM histidine at about pH 5.8 and about 75 mM NaCl.

36. The composition of claim 32, wherein the SPAN-85 concentration is 6 µg/mL - 14 mg/mL, the PS-20 or PS-80 concentration is 6 µg/mL - 14 mg/mL, the squalene concentration is 60 µg/mL - 34 mg/mL and the cationic lipid concentration is 60 µg/mL - 2.4 mg/mL.

37. The composition of claim 36 wherein the composition further comprises 5 mM - 40 mM histidine at pH 5.1 - 7.0 and 25 mM - 300 mM NaCl.

38. The composition of claim 36 wherein the composition further comprises about 20 mM histidine at about pH 5.8 and about 75 mM NaCl.

39. The composition of any of claims 1 to 38 for use in therapy.

40. Use of the composition of any of claims 1 to 38 in the manufacture of a medicament for the treatment or prevention of pneumococcal diseases.