A950014, 901905U, A920029, A930105, 306543X4, N218, N163, N162, N120, N107, N92, N91, D219PG, D211PG, D211PD, D204CD, D198PG, D198PD, D195PD, D195CD, D189PG, D189PD, D124PG, D124PD, D124CG, D58PG, BS433, BS432, BS430, 1714 or 1128. An amino acid sequence for PilA from *H. influenzae* strain D204CD is set forth in SEQ ID NO. 106, wherein X at position #116 is either glutamine (Q) or leucine (L); ambiguity as to the amino acid at position #116 could be cleared up by technical resolution of the second nucleotide encoding amino acid #116, clarifying the PilA sequence for strain D204CD. PilA may be PilA as set forth in any of SEQ ID NO. 58 – SEQ ID NO. 121.

[37] PilA may be a sequence with at least 95% identity, over the entire length, to any of SEQ ID NO. 58 – SEQ ID NO. 121 (as set out in Table 2).

[38] Immunogenic fragments of PilA comprise immunogenic fragments of at least 7, 10, 15, 20, 25, 30 or 50 contiguous amino acids of SEQ ID NO. 58 – SEQ ID NO. 121. The immunogenic fragments may elicit antibodies which can bind the full length sequence from which the fragment is derived.

[39] For example, immunogenic fragments of PilA comprise immunogenic fragments of at least 7, 10, 15, 20, 25, 30 or 50 contiguous amino acids of SEQ ID NO. 58. The immunogenic fragments may elicit antibodies which can bind SEQ ID NO. 58.

[40] Identity between polypeptides may be calculated by various algorithms. For example, the Needle program, from the EMBOSS package (Free software; EMBOSS: The European Molecular Biology Open Software Suite (2000). Trends in Genetics 16(6): 276—277) and the Gap program from the GCG® package (Accelrys Inc.) may be used. This Gap program is an implementation of the Needleman-Wunsch algorithm described in: Needleman, S. B. and Wunsch, C. D. (1970) J. Mol. Biol. 48, 443-453. The BLOSUM62 scoring matrix has been used, and the gap open and extension penalties were respectively 8 and 2.

[41] Looking at the computed alignment, identical residues between two compared sequences can be observed.

[42] As used herein, "adjuvant" means a compound or substance that, when administered to a subject in conjunction with a vaccine, immunotherapeutic, or other antigen- or immunogen-containing composition, increases or enhances the subject's immune response to the administered antigen or immunogen (as compared to the immune response that would be obtained in the absence of adjuvant). This is to be distinguished from "adjuvant therapy", defined by the National Cancer Institute of the United States Institutes of Health in the context of cancer treatment as additional treatment given after the primary treatment, to lower the risk that the cancer will recur.

[43] Conservative substitutions are well known and are generally set up as the default scoring matrices in sequence alignment computer programs. These programs include PAM250 (Dayhoft M.O. *et al.*, (1978), "A model of evolutionary changes in proteins", In "Atlas of Protein sequence and structure" 5(3) M.O. Dayhoft (ed.), 345-352), National Biomedical Research Foundation, Washington, and Blosum 62 (Steven Henikoft and Jorja G. Henikoft (1992), "Amino acid substitution matrices from protein blocks"), *Proc. Natl. Acad. Sci. USA* 89 (Biochemistry): 10915-10919. The invention further provides fusion proteins of formula (I) containing conservative amino acid substitutions. For example, the fusion proteins of formula (I) may contain a conservative substitution of any amino acid from PE or PilA of *H. influenzae* as described in any of the sequences set forth herein (for example, any PE sequence set forth in SEQ ID NO. 4 – SEQ ID NO. 57 and/or any PilA sequence set forth in SEQ ID NO. 58 – SEQ ID NO. 121)

[44] As used herein "signal peptide" refers to a short (less than 60 amino acids, for example, 3 to 60 amino acids) polypeptide present on precursor proteins (typically at the N terminus), and which is typically absent from the mature protein. The signal peptide (sp) is typically rich in hydrophobic amino acids. The signal peptide directs the transport and/or secretion of the translated protein through the membrane. Signal peptides may also be called targeting signals, transit peptides, localization signals, or signal sequences. For example, the signal sequence may be a co-translational or post-translational signal peptide.

[45] A heterologous signal peptide may be cleaved from a fusion protein construct by signal peptide peptidases during or after protein transportation or secretion. For example, the signal

Claims:

1. Use of a fusion protein of formula I in the manufacture of a medicament for the treatment or prevention of a medical condition in a subject in need thereof,

wherein formula I is:

$$(X)_m - (R_1)_n - A - (Y)_o - B - (Z)_p \text{ (formula I)}$$

wherein:

X is a signal peptide or MHHHHHH (SEQ ID NO. 2);

m is 0 or 1;

R_1 is an amino acid;

n is 0, 1, 2, 3, 4, 5 or 6;

A is an immunogenic fragment of Protein E selected from SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 179 or SEQ ID NO. 180 or a sequence having at least 95% sequence identity to any one of SEQ ID NO. 122, SEQ ID NO. 123, SEQ ID NO. 124, SEQ ID NO. 125, SEQ ID NO. 126, SEQ ID NO. 179 or SEQ ID NO. 180;

Y is selected from the group consisting of GG, SG, SS, GGG and $(G)_h$ wherein h is 4, 5, 6, 7, 8, 9, or 10;

o is 0 or 1;

B is an immunogenic fragment of PilA, at least 95% identical to amino acids 40-149 of any of SEQ ID NO. 58 to SEQ ID NO. 121;

Z is GGHHHHHH (SEQ ID NO. 3); and

p is 0 or 1, and

wherein the medical condition is selected from the group consisting of otitis media, acute exacerbations of chronic obstructive pulmonary disease (AECOPD), pneumonia, *H. influenzae* infection or disease, and NTHi infection or disease.

2. The use according to claim 1 wherein X is selected from the group consisting of FlgI, NadA and pelB.

3. The use according to claim 1 wherein m is 0.

4. The use according to any one of claims 1-3 wherein n is 0.

5. The use according to any one of claims 1-4 wherein A is an immunogenic fragment of Protein E from *H. influenzae* selected from the group consisting of amino acids 17-160 of SEQ ID NO. 4 (SEQ ID NO. 122), amino acids 18-160 of SEQ ID NO. 4 (SEQ ID NO. 123), amino acids 19-160 of SEQ ID NO. 4 (SEQ ID NO. 124), amino acids 20-160 of SEQ ID NO. 4 (SEQ ID NO. 125), amino acids 22-160 of SEQ ID NO. 4 (SEQ ID NO. 126), amino acids 23-160 of SEQ ID NO. 4 (SEQ ID NO. 179) and amino acids 24-160 of SEQ ID NO. 4 (SEQ ID NO. 180).

6. The use according to any one of claims 1-5 wherein A is the immunogenic fragment of Protein E from *H. influenzae* as set forth in SEQ ID NO: 124.

7. The use according to any of claims 1-5 wherein A is the immunogenic fragment of Protein E from *H. influenzae* as set forth in SEQ ID NO: 125.

8. The use according to any one of claims 1-7 wherein Y is GG.

9. The use according to any one of claims 1-8 wherein B is an immunogenic fragment of PilA, consisting of amino acids 40-149 from any of SEQ ID NO. 58 -SEQ ID NO. 121.

10. The use according to any one of claims 1-9 wherein B is the immunogenic fragment of PilA from *H. influenzae* as set forth in SEQ ID NO. 127.

11. The use according to any one of claims 1-5 wherein B is the fragment of PilA as set forth in SEQ ID NO. 127 and A is an immunogenic fragment of Protein E selected from the group consisting of SEQ ID NO. 122, SEQ ID NO. 124, SEQ ID NO. 125 and SEQ ID NO. 126.

12. Use of a fusion protein selected from the group consisting of SEQ ID NO. 138, SEQ ID NO. 140, SEQ ID NO. 142, SEQ ID NO. 144, SEQ ID NO. 146, SEQ ID NO. 148, SEQ ID NO. 150, SEQ ID NO.182, SEQ ID NO.184, SEQ ID NO.186, SEQ ID NO.188, SEQ ID NO. 190, SEQ ID NO.192, SEQ ID NO.194, SEQ ID NO.196, SEQ ID NO.198, SEQ ID NO.200, SEQ ID NO.202 and SEQ ID NO.204, in the manufacture of a medicament for the treatment or prevention of a medical condition in a subject in need thereof,

wherein the medical condition is selected from the group consisting of otitis media, acute exacerbations of chronic obstructive pulmonary disease (AECOPD), pneumonia, *H. influenzae* infection or disease, and NTHi infection or disease.

13. Use of a fusion protein 95% identical to any of SEQ ID NO. 138, SEQ ID NO. 140, SEQ ID NO. 142, SEQ ID NO. 144, SEQ ID NO. 146, SEQ ID NO. 148, SEQ ID NO. 150, SEQ ID NO. 182, SEQ ID NO. 184, SEQ ID NO. 186, SEQ ID NO. 188, SEQ ID NO. 190, SEQ ID NO. 192, SEQ ID NO. 194, SEQ ID NO. 196, SEQ ID NO. 198, SEQ ID NO. 200, SEQ ID NO. 202 or SEQ ID NO. 204, in the manufacture of a medicament for the treatment or prevention of a medical condition in a subject in need thereof,

wherein the medical condition is selected from the group consisting of otitis media, acute exacerbations of chronic obstructive pulmonary disease (AECOPD), pneumonia, *H. influenzae* infection or disease, and NTHi infection or disease.

14. The use according to claim 12 or claim 13 wherein the signal peptide of the fusion protein has been removed.

15. Use of a fusion protein of SEQ ID NO. 148, wherein the signal peptide has been removed, SEQ ID NO. 177 (QIQKAEQN DVKLAPPTDV RSGYIRLVKN VNYYIDSESI WVDNQEPQIV HFDAVVNLDK GLYVYPEPKR YARSVRQYKI LNCANYHLTQ VRTDFYDEFW GQGLRAAPKK QKKHTLSLTP DTTLYNAAQI ICANYGEAFS VDKKGGTKKA AVSELLQASA PYKADVELCV YSTNETTNCT GGKNGIAADI TTAKGYVKSV TTSNGAITVK GDGTLANMEY ILQATGNAAT GVTWTTTCKG TDASLFPANF CGSVTQ), in the manufacture of a medicament for the treatment or prevention of a medical condition in a subject in need thereof, wherein the medical condition is selected from the group consisting of otitis media, acute exacerbations of chronic obstructive pulmonary disease (AECOPD), pneumonia, *H. influenzae* infection or disease, and NTHi infection or disease.

16. Use of a fusion protein of SEQ ID NO. 194, wherein the signal peptide has been removed, SEQ ID NO. 219 (IQKAEQND VKLAPPTDVR SGYIRLVKNV NYYIDSESIW VDNQEPQIVH FDAVVNLDKG LYVYPEPKRY ARSVRQYKIL NCANYHLTQV RTDFYDEFWG QGLRAAPKKQ KKHTLSLTPD TTLYNAAQII CANYGEAFSV DKKGGTKKAA VSELLQASAP YKADVELCVY STNETTNCTG GKNGIAADIT TAKGYVKSVT TSNGAITVKG DGTLANMEYI LQATGNAATG VTWTTTCKGT DASLFPANFC GSVTQ), in the manufacture of a medicament for the treatment or prevention of a medical condition in a subject in need thereof,

wherein the medical condition is selected from the group consisting of otitis media, acute exacerbations of chronic obstructive pulmonary disease (AECOPD), pneumonia, *H. influenzae* infection or disease, and NTHi infection or disease.

17. Use of an immunogenic composition comprising isolated Protein E from *H. influenzae and* isolated PilA from *H. influenzae*, in the manufacture of a medicament for the treatment or prevention of a medical condition in a subject in need thereof,

wherein the medical condition is selected from the group consisting of otitis media, acute exacerbations of chronic obstructive pulmonary disease (AECOPD), pneumonia, *H. influenzae* infection or disease, and NTHi infection or disease,

wherein the Protein E from *H. influenzae* and the PilA from *H. influenzae* are comprised as the fusion protein of any one of claims 1-16.

18. The use of claim 17, wherein the immunogenic composition further comprises Protein D from H. influenzae.

19. The use of claims 17 or 18, wherein the immunogenic composition further comprises an adjuvant, optionally wherein the adjuvant is AS01, for instance, AS01B or AS01E.

20. Use of an immunogenic composition comprising the fusion protein of SEQ ID NO. 177 (QIQKAEQN DVKLAPPTDV RSGYIRLVKN VNYYIDSESI WVDNQEPQIV HFDAVVNLDK GLYVYPEPKR YARSVRQYKI LNCANYHLTQ VRTDFYDEFW GQGLRAAPKK QKKHTLSLTP

DTTLYNAAQI ICANYGEAFS VDKKGGTKKA AVSELLQASA PYKADVELCV YSTNETTNCT GGKNGIAADI TTAKGYVKSV TTSNGAITVK GDGTLANMEY ILQATGNAAT GVTWTTTCKG TDASLFPANF CGSVTQ), in the manufacture of a medicament for the treatment or prevention of a medical condition in a subject in need thereof,

wherein the medical condition is selected from the group consisting of otitis media, acute exacerbations of chronic obstructive pulmonary disease (AECOPD), pneumonia, *H. influenzae* infection or disease, and NTHi infection or disease.

21. Use of an immunogenic composition comprising the fusion protein of SEQ ID NO. 219 (IQKAEQND VKLAPPTDVR SGYIRLVKNV NYYIDSESIW VDNQEPQIVH FDAVVNLDKG LYVYPEPKRY ARSVRQYKIL NCANYHLTQV RTDFYDEFWG QGLRAAPKKQ KKHTLSLTPD TTLYNAAQII CANYGEAFSV DKKGGTKKAA VSELLQASAP YKADVELCVY STNETTNCTG GKNGIAADIT TAKGYVKSVT TSNGAITVKG DGTLANMEYI LQATGNAATG VTWTTTCKGT DASLFPANFC GSVTQ), in the manufacture of a medicament for the treatment or prevention of a medical condition in a subject in need thereof,

wherein the medical condition is selected from the group consisting of otitis media, acute exacerbations of chronic obstructive pulmonary disease (AECOPD), pneumonia, *H. influenzae* infection or disease, and NTHi infection or disease.

22. The use according to any one of claims 1 to 21, wherein the medical condition is acute exacerbations of chronic obstructive pulmonary disease (AECOPD).