SUMMARY OF THE INVENTION

In one aspect, there is provided a dengue virus serotype 2 vaccine composition comprising:

(i) a dengue antigen selected from the group consisting of:

(a) a live attenuated dengue virus;

(b) an inactivated dengue virus;

(c) a live attenuated or inactivated chimeric dengue virus;

(d) a dengue virus-like particle (VLP); and

(e) a combination of two or more of (a) to (d);

or

(ii) a nucleic acid construct or viral vector which is able to express in a human cell a dengue antigen which is a dengue VLP;

wherein said dengue antigen comprises a polypeptide having at least 90% identity to SEQ ID NO: 12 and wherein said polypeptide comprises an isoleucine residue at the position within the polypeptide that corresponds to position 308 of SEQ ID NO: 12 and a valine residue at the position with the polypeptide that corresponds to position 251 of SEQ ID NO: 12.

Also disclosed is a dengue virus serotype 2 vaccine composition comprising:

(i) a dengue antigen selected from the group consisting of:

(a) a live attenuated dengue virus;

(b) an inactivated dengue virus;

(c) a live attenuated or inactivated chimeric dengue virus;

(d) a dengue virus-like particle (VLP); and

(e) a combination of two or more of (a) to (d);

or

(ii) a nucleic acid construct or viral vector which is able to express in a human cell a dengue antigen which is a dengue VLP;

wherein said dengue antigen comprises a polypeptide having at least 90% identity to SEQ ID NO: 12.

In yet another aspect, there is provided a pharmaceutical formulation comprising a vaccine composition of the present disclosure and a pharmaceutically acceptable carrier, diluent or excipient.

Also disclosed is a vaccine composition of the present disclosure for use in therapy.

Also disclosed is a vaccine composition of the present disclosure for use in a method of protecting a human subject against dengue disease caused by a dengue virus of serotype 2.

Also disclosed is a vaccine composition of the present disclosure for use in a method of generating neutralising antibodies against a dengue virus of serotype 2.

In yet another aspect, there is provided the use of a composition as defined herein for use in a method of ~~protecting a human subject against dengue disease caused by~~ generating neutralising antibodies against a dengue virus of serotype 1, serotype 2, serotype 3 or serotype 4.

Also disclosed is a vaccine composition of the present invention which comprises a dengue antigen of serotype 1, a dengue antigen of serotype 2, a dengue antigen of serotype 3 and a dengue antigen of serotype 4 for use in a method of generating neutralising antibodies against the four serotypes of dengue.

Also disclosed is the use of a vaccine composition of the present invention for the manufacture of a medicament for protecting a human subject against dengue disease caused by a dengue virus of serotype 2.

In yet another aspect there is provided the use of a composition as claimed as described herein for use in a method of ~~protecting a human subject against dengue disease caused by~~ generating neutralising antibodies against a dengue virus of serotype 2.

Also disclosed is a method of protecting a human subject against dengue disease caused by a dengue virus of serotype 2, wherein said method comprises administering to said subject an effective amount of a composition according to the present disclosure.

CLAIMS

1. A dengue virus serotype 2 vaccine composition comprising:

(i) a dengue antigen selected from the group consisting of:
   (a) a live attenuated dengue virus;
   (b) an inactivated dengue virus;
   (c) a live attenuated or inactivated chimeric dengue virus;
   (d) a dengue virus-like particle (VLP); and
   (e) a combination of two or more of (a) to (d);

or

(ii) a nucleic acid construct or viral vector which is able to express in a human cell a dengue antigen which is a dengue VLP;

wherein said dengue antigen comprises a polypeptide having at least 90% identity to SEQ ID NO: 12 and wherein said polypeptide comprises an isoleucine residue at the position within the polypeptide that corresponds to position 308 of SEQ ID NO: 12.

2. A composition as claimed in claim 1, wherein said polypeptide comprises a valine residue at the position within the polypeptide that corresponds to position 251 of SEQ ID NO: 12.

3. A composition as claimed in any preceding claim, wherein said polypeptide comprises a isoleucine residue at the position within the polypeptide that corresponds to position 129 of SEQ ID NO: 12.

4. A composition as claimed in any preceding claim, wherein said polypeptide comprises an isoleucine residue at the position within the polypeptide that corresponds to position 141 of SEQ ID NO: 12.

5. A composition as claimed in any preceding claim, wherein said polypeptide comprises an isoleucine residue at the position within the polypeptide that corresponds to position 164 of SEQ ID NO: 12.

6. A composition as claimed in any preceding claim, wherein said polypeptide comprises an aspartate residue at the position within the polypeptide that corresponds to position 203 of SEQ ID NO: 12.

7. A composition as claimed in any preceding claim, wherein said polypeptide comprises a threonine residue at the position within the polypeptide that corresponds to position 226 of SEQ ID NO: 12.

8. A composition as claimed in any preceding claim, wherein said polypeptide comprises a glycine residue at the position within the polypeptide that corresponds to position 228 of SEQ ID NO: 12.

9. A composition as claimed in any preceding claim, wherein said polypeptide comprises an isoleucine residue at the position within the polypeptide that corresponds to position 484 of SEQ ID NO: 12.

10. A composition as claimed in any preceding claim, wherein said polypeptide comprises an isoleucine residue at the position within the polypeptide that corresponds to position 485 of SEQ ID NO: 12.

11. A composition as claimed in any preceding claim, wherein said polypeptide comprises an alanine residue at the position within the polypeptide that corresponds to position 491 of SEQ ID NO: 12.

12. A composition as claimed in any one of claims 1 to 11, wherein said polypeptide comprises: (i) the sequence as set forth in SEQ ID NO: 16 or a sequence having at least 1 and no more than 5 amino acid substitutions with respect to the sequence as set forth in SEQ ID NO: 16.

13. A composition as claimed in claim 1, wherein said dengue antigen comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO: 16.

14. A composition as claimed in claim 12, wherein said dengue antigen further comprises a polypeptide comprising: (i) the sequence as set forth in SEQ ID NO:

22 or a sequence having at least 1 and no more than 5 amino acid substitutions with respect to the sequence as set forth in SEQ ID NO: 22.

15. A composition as claimed in claim 13, wherein said dengue antigen further comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO: 22,.

16. A composition as claimed in claim 12, wherein said dengue antigen comprises:

i) a polypeptide having the sequence as set forth in SEQ ID NO: 16 or a polypeptide having at least 1 and no more than 5 amino acid substitutions with respect to the sequence as set forth in SEQ ID NO: 16; and
a polypeptide having the sequence as set forth in SEQ ID NO: 22 or a polypeptide having at least 1 and no more than 5 amino acid substitutions with respect to the sequence as set forth in SEQ ID NO: 22.

17. A composition as claimed in any preceding claim, wherein said dengue antigen is selected from the group consisting of: (a) a live attenuated dengue virus; (b) an inactivated dengue virus; (c) a live attenuated or inactivated chimeric dengue virus; or (d) a combination of two or more of (a) to (c); wherein said dengue antigen comprises a nucleotide sequence encoding a protein comprising a polypeptide as defined in any one of claims 1 to 16.

18. A vaccine composition comprising a dengue antigen of serotype 2 selected from the group consisting of: (a) a live attenuated dengue virus; (b) an inactivated dengue virus; (c) a live attenuated or inactivated chimeric dengue virus; or (d) a combination of two or more of (a) to (c); wherein said dengue antigen comprises a nucleotide sequence encoding a protein comprising the polypeptide or polypeptides as defined in any one of claims 1 to 16.

19. A vaccine composition comprising a dengue antigen of serotype 2 selected from the group consisting of: (a) a live attenuated dengue virus; (b) an inactivated dengue virus; (c) a live attenuated or inactivated chimeric dengue virus; or (d) a combination of two or more of (a) to (c); wherein said dengue antigen comprises a nucleotide sequence having at least 90% sequence identity to a sequence selected from the group consisting of the RNA equivalent of SEQ ID NO: 7.

20. A composition as claimed in any preceding claim, wherein said composition comprises a live attenuated chimeric dengue virus.

21. A composition as claimed in claim 20, wherein said composition comprises one or more proteins from a dengue virus and one or more proteins from a different flavivirus.

22. A composition as claimed in claim 21, wherein the different flavivirus is a yellow fever virus.

23. A composition as claimed in claim 22, wherein the yellow fever virus is YF-Vax.

24. A composition as claimed in any preceding claim, wherein the composition further comprises a dengue antigen of serotype 1, a dengue antigen of serotype 3 and a dengue antigen of serotype 4.

25. A composition as claimed in claim 24, wherein said dengue antigens of serotypes 1, 3 and 4 are each independently selected from the group consisting of a live attenuated dengue virus and a live attenuated chimeric dengue virus.

26. A composition as claimed in claim 25, wherein said dengue antigens of serotypes 1, 3 and 4 are each a live attenuated chimeric dengue virus in which the genetic backbone of a recipient flavivirus has been modified by exchanging the sequences encoding the prM and E proteins of the recipient flavivirus with the corresponding sequences of a dengue virus.

27. A composition as claimed in claim 26, wherein the recipient flavivirus is a yellow fever virus.

28. A pharmaceutical formulation comprising a composition as claimed in any preceding claim and a pharmaceutically acceptable carrier, diluent or excipient.

29. A composition as claimed in any one of claims 1 to 42 for use in therapy.

30. A composition as claimed in any one of claims 1 to 42 for use in a method of protecting a human subject against dengue disease caused by a dengue virus of serotype 2.

31. A composition as claimed in any one of claims 38 to 42 for use in a method of protecting a human subject against dengue disease caused by a dengue virus of serotype 1, serotype 2, serotype 3 or serotype 4.

CLAIMS

1. A dengue virus serotype 2 vaccine composition comprising:

   (i) a dengue antigen selected from the group consisting of:
   - (a) a live attenuated dengue virus;
   - (b) an inactivated dengue virus;
   - (c) a live attenuated or inactivated chimeric dengue virus;
   - (d) a dengue virus-like particle (VLP); and
   - (e) a combination of two or more of (a) to (d);

   or

   (ii) a nucleic acid construct or viral vector which is able to express in a human cell a dengue antigen which is a dengue VLP;

   wherein said dengue antigen comprises a polypeptide having at least 90% identity to SEQ ID NO: 12 and wherein said polypeptide comprises an isoleucine residue at the position within the polypeptide that corresponds to position 308 of SEQ ID NO: 12 and a valine residue at the position with the polypeptide that corresponds to position 251 of SEQ ID NO: 12.

2. A composition as claimed in any preceding claim, wherein said polypeptide comprises an isoleucine residue at the position within the polypeptide that corresponds to position 129 of SEQ ID NO: 12.

3. A composition as claimed in any preceding claim, wherein said polypeptide comprises an isoleucine residue at the position within the polypeptide that corresponds to position 141 of SEQ ID NO: 12.

4. A composition as claimed in any preceding claim, wherein said polypeptide comprises an isoleucine residue at the position within the polypeptide that corresponds to position 164 of SEQ ID NO: 12.

5. A composition as claimed in any preceding claim, wherein said polypeptide comprises an aspartate residue at the position within the polypeptide that corresponds to position 203 of SEQ ID NO: 12.

6. A composition as claimed in any preceding claim, wherein said polypeptide comprises a threonine residue at the position within the polypeptide that corresponds to position 226 of SEQ ID NO: 12.

7. A composition as claimed in any preceding claim, wherein said polypeptide comprises a glycine residue at the position within the polypeptide that corresponds to position 228 of SEQ ID NO: 12.

8. A composition as claimed in any preceding claim, wherein said polypeptide comprises an isoleucine residue at the position within the polypeptide that corresponds to position 484 of SEQ ID NO: 12.

9. A composition as claimed in any preceding claim, wherein said polypeptide comprises an isoleucine residue at the position within the polypeptide that corresponds to position 485 of SEQ ID NO: 12.

10. A composition as claimed in any preceding claim, wherein said polypeptide comprises an alanine residue at the position within the polypeptide that corresponds to position 491 of SEQ ID NO: 12.

11. A composition as claimed in any one of claims 1 to 10, wherein said polypeptide comprises: (i) the sequence as set forth in SEQ ID NO: 16 or a sequence having at least 1 and no more than 5 amino acid substitutions with respect to the sequence as set forth in SEQ ID NO: 16.

12. A composition as claimed in claim 1, wherein said dengue antigen comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO: 16.

13. A composition as claimed in claim 11, wherein said dengue antigen further comprises a polypeptide comprising: (i) the sequence as set forth in SEQ ID NO: 22 or a sequence having at least 1 and no more than 5 amino acid substitutions with respect to the sequence as set forth in SEQ ID NO: 22.

14. A composition as claimed in claim 12, wherein said dengue antigen further comprises a polypeptide comprising a sequence selected from the group consisting of SEQ ID NO: 22,.

15. A composition as claimed in claim 11, wherein said dengue antigen comprises:

    i) a polypeptide having the sequence as set forth in SEQ ID NO: 16 or a polypeptide having at least 1 and no more than 5 amino acid substitutions with respect to the sequence as set forth in SEQ ID NO: 16; and
    a polypeptide having the sequence as set forth in SEQ ID NO: 22 or a polypeptide having at least 1 and no more than 5 amino acid substitutions with respect to the sequence as set forth in SEQ ID NO: 22.

16. A composition as claimed in any preceding claim, wherein said dengue antigen is selected from the group consisting of: (a) a live attenuated dengue virus; (b) an inactivated dengue virus; (c) a live attenuated or inactivated chimeric dengue virus; or (d) a combination of two or more of (a) to (c); wherein said dengue antigen comprises a nucleotide sequence encoding a protein comprising a polypeptide as defined in any one of claims 1 to 15.

17. A vaccine composition comprising a dengue antigen of serotype 2 selected from the group consisting of: (a) a live attenuated dengue virus; (b) an inactivated dengue virus; (c) a live attenuated or inactivated chimeric dengue virus; or (d) a combination of two or more of (a) to (c); wherein said dengue antigen comprises a nucleotide sequence encoding a protein comprising the polypeptide or polypeptides as defined in any one of claims 1 to 15.

18. A vaccine composition comprising a dengue antigen of serotype 2 selected from the group consisting of: (a) a live attenuated dengue virus; (b) an inactivated dengue virus; (c) a live attenuated or inactivated chimeric dengue virus; or (d) a combination of two or more of (a) to (c); wherein said dengue antigen comprises a nucleotide sequence having at least 90% sequence identity to a sequence selected from the group consisting of the RNA equivalent of SEQ ID NO: 7.

19. A composition as claimed in any preceding claim, wherein said composition comprises a live attenuated chimeric dengue virus.

20. A composition as claimed in claim 19, wherein said composition comprises one or more proteins from a dengue virus and one or more proteins from a different flavivirus.

21. A composition as claimed in claim 20, wherein the different flavivirus is a yellow fever virus.

22. A composition as claimed in claim 21, wherein the yellow fever virus is YF-Vax.

23. A composition as claimed in any preceding claim, wherein the composition further comprises a dengue antigen of serotype 1, a dengue antigen of serotype 3 and a dengue antigen of serotype 4.

24. A composition as claimed in claim 23, wherein said dengue antigens of serotypes 1, 3 and 4 are each independently selected from the group consisting of a live attenuated dengue virus and a live attenuated chimeric dengue virus.

25. A composition as claimed in claim 24, wherein said dengue antigens of serotypes 1, 3 and 4 are each a live attenuated chimeric dengue virus in which the genetic backbone of a recipient flavivirus has been modified by exchanging the sequences encoding the prM and E proteins of the recipient flavivirus with the corresponding sequences of a dengue virus.

26. A composition as claimed in claim 25, wherein the recipient flavivirus is a yellow fever virus.

27. A pharmaceutical formulation comprising a composition as claimed in any preceding claim and a pharmaceutically acceptable carrier, diluent or excipient.

28. Use of a composition as claimed in any one of claims 1 to 26 for the manufacture of a medicament for use in a method of generating neutralising antibodies against a dengue virus of serotype 2.

29. Use of a composition as claimed in any one of claims 23 to 25 for the manufacture of a medicament for use in a method of generating neutralising antibodies against a dengue virus of serotype 1, serotype 2, serotype 3 or serotype 4.