CLAIMS

1. Use of a dengue vaccine composition in the manufacture of a medicament for preventing dengue disease, wherein the composition is to be administered without the need to determine the occurrence of a previous dengue infection in a subject,

wherein the dengue vaccine composition is a tetravalent dengue vaccine composition including four live attenuated dengue virus strains representing serotype 1, serotype 2, serotype 3 and serotype 4,

wherein each of the four live, attenuated dengue virus strains is selected from the following:

(i) a non-chimeric dengue virus comprising all components from the same dengue serotype, and

(ii) a chimeric dengue virus having parts from two dengue serotypes,

wherein the dengue serotype 2 strain is derived from the wild type virus strain DENV-2 16681 and differs in at least three nucleotides from the wild type as follows:

a) 5'-noncoding region (NCR)-57 (nt-57 C-to-T)

b) NS1-53 Gly-to-Asp (nt-2579 G-to-A)

c) NS3-250 Glu-to-Val (nt-5270 A-to-T),

wherein the dengue serotype 1 is a chimeric dengue serotype 2/1 strain,

the dengue serotype 2 is a non-chimeric serotype 2 strain,

the dengue serotype 3 is a chimeric dengue serotype 2/3 strain,

the dengue serotype 4 is a chimeric dengue serotype 2/4 strain,

wherein the three chimeric dengue strains are derived from the serotype 2 strain by replacing the structural proteins prM and E from the serotype 2 strain with the corresponding structural proteins from the other dengue serotypes,

wherein in the chimeric dengue serotype 2/1 strain the structural proteins prM and E from serotype 2 strain are replaced with the corresponding structural proteins derived from DENV-1 16007,

wherein in the chimeric dengue serotype 2/3 strain the structural proteins prM and E from serotype 2 strain are replaced with the corresponding structural proteins derived from DENV-3 16562, and

wherein in the chimeric dengue serotype 2/4 strain the structural proteins prM and E from serotype 2 strain are replaced with the corresponding structural proteins derived from DENV-4 1036.

2. Use of a dengue vaccine composition in the manufacture of a medicament for preventing dengue disease, wherein said dengue vaccine composition is to be administered without determination whether there was a previous dengue infection in a subject,

wherein the dengue vaccine composition is a tetravalent dengue vaccine composition including four live attenuated dengue virus strains representing serotype 1, serotype 2, serotype 3 and serotype 4,

wherein each of the four live, attenuated dengue virus strains is selected from the following:

(i) a non-chimeric dengue virus comprising all components from the same dengue serotype, and

(ii) a chimeric dengue virus having parts from two dengue serotypes,

wherein the dengue serotype 2 strain is derived from the wild type virus strain DENV-2 16681 and differs in at least three nucleotides from the wild type as follows:

a) 5'-noncoding region (NCR)-57 (nt-57 C-to-T)

b) NS1-53 Gly-to-Asp (nt-2579 G-to-A)

c) NS3-250 Glu-to-Val (nt-5270 A-to-T),

wherein the dengue serotype 1 is a chimeric dengue serotype 2/1 strain,

the dengue serotype 2 is a non-chimeric serotype 2 strain,

the dengue serotype 3 is a chimeric dengue serotype 2/3 strain,

the dengue serotype 4 is a chimeric dengue serotype 2/4 strain,

wherein the three chimeric dengue strains are derived from the serotype 2 strain by replacing the structural proteins prM and E from the serotype 2 strain with the corresponding structural proteins from the other dengue serotypes,

wherein in the chimeric dengue serotype 2/1 strain the structural proteins prM and E from serotype 2 strain are replaced with the corresponding structural proteins derived from DENV-1 16007,

wherein in the chimeric dengue serotype 2/3 strain the structural proteins prM and E from serotype 2 strain are replaced with the corresponding structural proteins derived from DENV-3 16562, and

wherein in the chimeric dengue serotype 2/4 strain the structural proteins prM and E from serotype 2 strain are replaced with the corresponding structural proteins derived from DENV-4 1036.

3. Use of a dengue vaccine composition in the manufacture of a medicament for preventing dengue disease, wherein the composition is to be administered to a subject whose serostatus is not determined or seropositive or seronegative for dengue virus,

wherein the dengue vaccine composition is a tetravalent dengue vaccine composition including four live attenuated dengue virus strains representing serotype 1, serotype 2, serotype 3 and serotype 4,

wherein each of the four live, attenuated dengue virus strains is selected from the following:

(i) a non-chimeric dengue virus comprising all components from the same dengue serotype, and

(ii) a chimeric dengue virus having parts from two dengue serotypes,

wherein the dengue serotype 2 strain is derived from the wild type virus strain DENV-2 16681 and differs in at least three nucleotides from the wild type as follows:

a) 5'-noncoding region (NCR)-57 (nt-57 C-to-T)

b) NS1-53 Gly-to-Asp (nt-2579 G-to-A)

c) NS3-250 Glu-to-Val (nt-5270 A-to-T),

wherein the dengue serotype 1 is a chimeric dengue serotype 2/1 strain,

the dengue serotype 2 is a non-chimeric serotype 2 strain,

the dengue serotype 3 is a chimeric dengue serotype 2/3 strain,

the dengue serotype 4 is a chimeric dengue serotype 2/4 strain,

wherein the three chimeric dengue strains are derived from the serotype 2 strain by replacing the structural proteins prM and E from the serotype 2 strain with the corresponding structural proteins from the other dengue serotypes,

wherein in the chimeric dengue serotype 2/1 strain the structural proteins prM and E from serotype 2 strain are replaced with the corresponding structural proteins derived from DENV-1 16007,

wherein in the chimeric dengue serotype 2/3 strain the structural proteins prM and E from serotype 2 strain are replaced with the corresponding structural proteins derived from DENV-3 16562, and

wherein in the chimeric dengue serotype 2/4 strain the structural proteins prM and E from serotype 2 strain are replaced with the corresponding structural proteins derived from DENV-4 1036.

4. The use according to any one of claims 1 to 3, wherein the determination of the previous dengue infection in the subject is characterized by a laboratory confirmed history of dengue or a validated serological test.

5. The use according to any one of claims 1 to 4, wherein each one of the live, attenuated dengue virus serotype 1, serotype 2, and serotype 4 strains further has:

phenylalanine at amino acid position 1308, and

alanine at amino acid position 2168,

and wherein the live, attenuated dengue virus serotype 3 strain further has:

phenylalanine at amino acid position 1306, and

alanine at amino acid position 2166.

6. The use according to any one of claims 1 to 5,

wherein the chimeric dengue serotype 2/1 strain further has:

leucine at amino acid position 1243, and

aspartic acid at amino acid position 1437,

wherein the dengue serotype 2 strain further has:

glutamic acid at amino acid position 166, and

valine at amino acid position 2903,

wherein the chimeric dengue serotype 2/3 strain has:

serine at amino acid position 503,

and

wherein the chimeric dengue serotype 2/4 strain has:

glycine at amino acid position 1193,

lysine/arginine mix at amino acid position 1226, and

valine at amino acid position 2114.

7. The use according to any one of claims 1 to 6, wherein

the dengue serotype 1 has amino acid sequence of SEQ ID NO. 2, and

the dengue serotype 2 has amino acid sequence of SEQ ID NO. 4, and

the dengue serotype 3 has amino acid sequence of SEQ ID NO. 6, and

the dengue serotype 4 has amino acid sequence of SEQ ID NO. 8.

8. The use according to any one of claims 1 to 7, wherein the dengue vaccine composition provides a reduced risk of dengue disease with hospitalization as compared to an unvaccinated subject in a subject population.

9. The use according to any one of claims 1 to 8, wherein the dengue disease is severe dengue.

10. The use according to any one of claims 1 to 9, wherein the dengue disease is dengue haemorrhagic fever (DHF) and/or dengue shock syndrome (DSS).

11. The use according to any one of claims 1 to 10 comprising that a primary vaccination is to be conducted which consists of the steps of:

(A) selecting a subject for administration of the dengue virus composition in need for protection against dengue infection without determination whether there was a previous dengue infection at times before, during and after the steps of administration or wherein the serostatus of the subject is unknown at times before, during and after the steps of administration of the dengue vaccine composition, and

(B) a first dengue virus composition being administered to the subject, and

(C) a second dengue virus composition being administered to the subject within 3 months of administration of the first dengue vaccine composition.

12. The use according to claim 11, wherein one or more booster vaccinations are to be administered at least one year, 5 years or 10 years after the primary vaccination.

13. The use according to any one of claims 1 to 12, providing a combined vaccine efficacy in preventing dengue with hospitalization against all four serotypes and irrespective of serostatus of the subject at baseline of more than 82%, or of more than 85%, or of more than 88%.

14. The use according to any one of claims 1 to 13, providing a combined vaccine efficacy in preventing dengue disease against all four serotypes and irrespective of serostatus of the subject at baseline of more than 70%.

15. The use according to any one of claims 1 to 14 providing a vaccine efficacy against serotype 1 in preventing dengue disease irrespective of the serostatus of the subject at baseline of more than 60% or more than 65%.

16. The use according to any one of claims 1 to 15, providing a vaccine efficacy against serotype 2 in preventing dengue disease irrespective of the serostatus of the subject at baseline of more than 60%, or more than 70%, or more than 80%, or more than 85%.

17. The use according to any one of claims 1 to 16, providing a combined vaccine efficacy against all four serotypes, in preventing dengue disease and/or hospitalization of more than 80 % or of more than 85% in subjects seronegative against all serotypes at baseline.

18. The use according to any one of claims 1 to 17, providing a vaccine efficacy against serotype 1 in preventing dengue disease of more than 35 % in subjects seronegative against all serotypes at baseline.

19. The use according to any one of claims 1 to 18, providing a vaccine efficacy against serotype 2 in preventing dengue disease of more than 60% in subjects seronegative against all serotypes at baseline.

20. The use according to any one of claims 1 to 19, providing a combined vaccine efficacy in preventing dengue disease with hospitalization against all four serotypes irrespective of serostatus of the subject at baseline with a 2-sided 95% confidence interval, wherein the lower bound is more than 65%.

21. The use according to any one of claims 1 to 20, providing a combined vaccine efficacy in preventing dengue disease against all four serotypes irrespective of serostatus of the subject at baseline with a 2-sided 95% confidence interval, wherein the lower bound is more than 60%.

22. The use according to any one of claims 1 to 21 providing a vaccine efficacy against serotype 1 in preventing dengue disease irrespective of the serostatus of the subject at baseline with a 2-sided 95% confidence interval, wherein the lower bound is more than 45% or more than 50%.

23. The use according to any one of claims 1 to 22, providing a vaccine efficacy against serotype 2 in preventing dengue disease irrespective of the serostatus of the subject at baseline with a 2-sided 95% confidence interval, wherein the lower bound is more than 60%, or more than 70%, or more than 80%, or more than 85%.

24. The use according to any one of claims 1 to 23, providing a combined vaccine efficacy against all four serotypes, in preventing dengue disease and/or hospitalization in subjects seronegative against all serotypes at baseline with a 2-sided 95% confidence interval, wherein the lower bound is more than 45 %.

25. The use according to any one of claims 1 to 24, providing a vaccine efficacy against serotype 1 in preventing dengue disease in subjects seronegative against all serotypes at baseline, with a 2-sided 95% confidence interval, wherein the lower bound is more than 35 %.

26. The use according to any one of claims 1 to 25, providing a vaccine efficacy against serotype 2 in preventing dengue disease, in subjects seronegative against all serotypes at baseline, with a 2-sided 95% confidence interval, wherein the lower bound is more than 60%.

27. The use according to any one of claims 1 to 26, wherein the vaccine is to be administered by subcutaneous injection.

28. The use according to any one of claims 1 to 27, wherein the subject is from a dengue endemic region.

29. The use according to any one of claims 1 to 27, wherein the subject is from a dengue non-endemic region.

30. The use according to any one of claims 1 to 27, wherein the subject is from a region wherein the seroprevalence rate is unknown, and/or
wherein the seroprevalence is below 80%, or below 70%, or below 60%.

31. The use according to any one of claims 1 to 30, wherein the subject is exposed to dengue serotype 1 and/or dengue disease is due to a dengue serotype 1.

32. The use according to any one of claims 1 to 31, wherein the subject is exposed to dengue serotype 2 and/or dengue disease is due to a dengue serotype 2.

33. The use according to any one of claims 1 to 32, wherein the subject is under 9 years of age, or 4 to 5 years of age, or 6 to 11 years of age or 12 to 16 years of age, or 6 to 16 years of age, or 4 to 16 years of age, or 2 to 17 years of age, or 9 years of age, or over 9 years of age, or 9 to 19 years of age, or 18 to 60 years of age, or 18 to 45 years of age, or 46 to 60 years of age.

34. The use according to any one of claims 1 to 32, wherein the subject belongs to the elderly population of more than 60 years of age.

35. The use according to any one of claims 1 to 32, wherein the subject belongs to the paediatric population.

36. The use according to claim 35, wherein the subject is less than 4 years of age, less than 2 years of age, or 2 months to 2 years of age or 2 months to 1.5 years of age or 2 months to 1 year of age.

37. The use according to any one of claims 1 to 36, wherein the dengue vaccine composition is to be administered concomitantly, simultaneously, or sequentially with another vaccine.

38. The use according to claim 37, wherein the other vaccine is to be administered by subcutaneous injection or intramuscular injection.

39. The use according to claim 37 or 38, wherein the dengue vaccine composition and the other vaccine are to be administered to different anatomical sites.

40. The use according to any one of claims 37 to 39, wherein the dengue vaccine composition is to be administered concomitantly, simultaneously, or sequentially, with a yellow fever vaccine for preventing yellow fever, a hepatitis A vaccine for preventing hepatitis A, an HPV vaccine for preventing HPV-associated cancers or genital warts, an MMR vaccine for preventing measles, mumps and rubella, a tetanus, diphtheria, and pertussis (Tdap) vaccine for preventing tetanus, diphtheria, and pertussis, a DTaP/IPV/Hib vaccine for preventing diphtheria, tetanus, pertussis, poliomyelitis and diseases caused by Haemophilus influenzae type b, or wherein the dengue

vaccine composition is to be administered concomitantly, simultaneously, or sequentially with cholera vaccine, hepatitis E vaccine, Japanese encephalitis vaccine, meningococcal disease vaccine, rabies vaccine, thick-borne encephalitis vaccine, typhoid fever vaccine, or a combination thereof.

41. The use according to any one of claims 37 to 40, wherein the dengue vaccine composition is to be administered concomitantly, simultaneously, or sequentially, with a yellow fever vaccine for preventing yellow fever.

42. The use according to claim 41, wherein the dengue vaccine composition is to be administered concomitantly, simultaneously, or sequentially, with a yellow fever vaccine for preventing yellow fever wherein

- a first yellow fever vaccine is to be administered on day 0,
- the first dengue vaccine composition is to be administered after said administration of the first yellow fever vaccine, and
- the second dengue vaccine composition is to be administered after said first dengue vaccine composition administration,

  or
- the first dengue vaccine composition is to be administered on day 0,
- the second dengue vaccine composition is to be administered after said administration of the first dengue vaccine composition, and
- a first yellow fever vaccine is to be administered after said administration of the second dengue vaccine composition,

  or
- the first dengue vaccine composition and a first yellow fever vaccine are to be simultaneously administered on day 0,

- the second dengue vaccine composition is to be administered after said simultaneous administration of the first dengue vaccine composition and the first yellow fever vaccine.

43. The use according to claim 42, wherein said second dengue vaccine composition is to be administered 3 months after the administration of said first dengue vaccine composition.

44. The use according to any one of claims 37 to 40, wherein the dengue vaccine composition is to be administered concomitantly, simultaneously, or sequentially, with a hepatitis A vaccine for preventing hepatitis A.

45. The use according to claim 44, wherein the dengue vaccine composition is to be administered concomitantly, simultaneously, or sequentially, with a hepatitis A vaccine for preventing hepatitis A, wherein

- the first dengue vaccine composition and a first dose of the hepatitis A vaccine are to be simultaneously administered on day 0,
- the second dengue vaccine composition is to be administered after said simultaneous administration of the first dengue vaccine composition and the first dose of the hepatitis A vaccine.

46. The use according to claim 45, wherein said second dengue vaccine composition is to be administered 3 months after the administration of said first dengue vaccine composition.

47. The use according to any one of claims 37 to 40, wherein the dengue vaccine composition is to be administered concomitantly, simultaneously, or sequentially, with an HPV vaccine for preventing HPV-associated cancers or genital warts.

48. The use according to claim 47, wherein the dengue vaccine composition is to be administered concomitantly, simultaneously, or sequentially, with an HPV vaccine for preventing HPV-associated cancers or genital warts, wherein

- the first dengue vaccine composition and a first dose of HPV vaccine are to be simultaneously administered on day 0,
- the second dengue vaccine composition is to be administered after said simultaneous administration of the first dengue vaccine composition and the first dose of the HPV vaccine,
- a second dose of the HPV vaccine is to be administered after said administration of the second dengue vaccine composition.

49. The use according to claim 48, wherein said second dengue vaccine composition is to be administered 3 months after the administration of said first dengue vaccine composition.

50. The use according to any one of claims 37 to 40, wherein the dengue vaccine composition is to be administered concomitantly, simultaneously, or sequentially, with an MMR vaccine for preventing measles, mumps and rubella.

51. The use according to claim 50, wherein the dengue vaccine composition is to be administered concomitantly, simultaneously, or sequentially, with an MMR vaccine for preventing measles, mumps and rubella, wherein

- the first dengue vaccine composition and a first dose of the MMR vaccine are to be simultaneously administered on day 0,
- the second dengue vaccine composition is to be administered after said simultaneous administration of the first dengue vaccine composition and the first dose of the MMR vaccine,
- a second dose of the MMR vaccine is to be administered after said administration of the second dengue vaccine composition.

52. The use according to claim 51, wherein said second dengue vaccine composition is to be administered 3 months after the administration of said first dengue vaccine composition.

53. The use according to any one of claims 37 to 40, wherein the dengue vaccine composition is to be administered concomitantly, simultaneously, or sequentially, with a tetanus, diphtheria, and pertussis (Tdap) vaccine for preventing tetanus, diphtheria, and pertussis.

54. The use according to claim 53, wherein the dengue vaccine composition is to be administered concomitantly, simultaneously, or sequentially, with a tetanus, diphtheria, and pertussis (Tdap) vaccine for preventing tetanus, diphtheria, and pertussis, wherein

- the first dengue vaccine composition and a first dose of the Tdap vaccine are to be simultaneously administered on day 0, and
- the second dengue vaccine composition is to be administered after said simultaneous administration of the first dengue vaccine composition and the first dose of the Tdap vaccine.

55. The use according to claim 54, wherein said second dengue vaccine composition is to be administered 3 months after the administration of said first dengue vaccine composition.

56. The use according to any one of claims 37 to 40, wherein the dengue vaccine composition is to be administered concomitantly, simultaneously, or sequentially, with a DTaP/IPV/Hib vaccine for preventing diphtheria, tetanus, pertussis, poliomyelitis and diseases caused by Haemophilus influenzae type b.

57. The use according to claim 56, wherein the dengue vaccine composition is to be administered concomitantly, simultaneously, or sequentially, with a DTaP/IPV/Hib vaccine for preventing diphtheria, tetanus, pertussis, poliomyelitis and diseases caused by Haemophilus influenzae type b, wherein

- the first dengue vaccine composition and a first dose of the DTaP/IPV/Hib vaccine are to be simultaneously administered on day 0,

- a second dose of the DTaP/IPV/Hib vaccine is to be administered after said simultaneous administration of the first dengue vaccine composition and the first dose of the DTaP/IPV/Hib vaccine,
- the second dengue vaccine composition is to be administered after said second dose of the DTaP/IPV/Hib vaccine,
- a third dose of the DTaP/IPV/Hib vaccine is to be administered after said administration of the second dengue vaccine composition,
- a fourth dose of the DTaP/IPV/Hib vaccine is to be administered after said administration of the third dose of the DTaP/IPV/Hib vaccine,

  or

- a first dose of the DTaP/IPV/Hib vaccine is to be administered on day 0,
- a second dose of the DTaP/IPV/Hib vaccine is to be administered after said administration of the first dose of the DTaP/IPV/Hib vaccine,
- a third dose of the DTaP/IPV/Hib vaccine is to be administered after said administration of the second dose of the DTaP/IPV/Hib vaccine,
- the first dengue vaccine composition and a fourth dose of the DTaP/IPV/Hib vaccine are to be simultaneously administered after said administration of the third dose of the DTaP/IPV/Hib vaccine,
- the second dengue vaccine composition is to be administered after said simultaneous administration of the first dengue vaccine composition and the fourth dose of the DTaP/IPV/Hib vaccine.

58. The use according to claim 57, wherein said second dengue vaccine composition is to be administered 3 months after the administration of said first dengue vaccine composition.