

CLAIMS

1. A hepatitis A vaccine and a unit dose of a dengue vaccine composition for use in a method of preventing hepatitis A and dengue disease in a subject or in a subject population, the method comprising simultaneously on the same day administering the hepatitis A vaccine and the unit dose of the dengue vaccine composition, wherein said unit dose comprises a tetravalent dengue virus composition including four live, attenuated dengue virus strains.
2. The hepatitis A vaccine and the unit dose for use according to claim 1, wherein the hepatitis A vaccine is an inactivated virus vaccine.
3. The hepatitis A vaccine and the unit dose for use according to claim 1 or 2, wherein the dengue vaccine composition upon reconstitution with 0.5 mL of a pharmaceutically acceptable diluent comprises
 - (i) a chimeric dengue serotype 2/1 strain in a concentration of at least 3.3 log₁₀ pfu/0.5 mL,
 - (ii) a dengue serotype 2 strain in a concentration of at least 2.7 log₁₀ pfu/0.5 mL,
 - (iii) a chimeric dengue serotype 2/3 strain in a concentration of at least 4.0 log₁₀ pfu/0.5 mL, and
 - (iv) a chimeric dengue serotype 2/4 strain in a concentration of at least 4.5 log₁₀ pfu/0.5 mL.
4. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein the subject population or subject is seronegative to all dengue serotypes.
5. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein said unit dose of the dengue vaccine composition is administered by subcutaneous injection and said hepatitis A vaccine is administered by intramuscular injection, and wherein said injections are preferably administered to the arm, more preferably to the deltoid region of the arm.
6. The hepatitis A vaccine and the unit dose for use according to claim 5, wherein said unit dose of the dengue vaccine composition and said hepatitis A vaccine are administered to different anatomical sites, such as to opposite arms.
7. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein two of said unit doses of the dengue vaccine composition are administered within 12 months or more, or within six months, or within three months.
8. The hepatitis A vaccine and the unit dose for use according to claim 7 comprising the administration of two of said unit doses of the dengue vaccine composition and one dose of said hepatitis A vaccine, in particular according to the following schedule
 - a first simultaneous administration of the first unit dose of the dengue vaccine composition and said hepatitis A vaccine on day 0, and
 - a second administration of the second unit dose of the dengue vaccine composition after said first simultaneous administration, such as about 3 months later.
9. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein the subject population or subject is of 2 to 60 years of age.

10. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein the subject population or subject is from a dengue endemic region.
- 5 11. The hepatitis A vaccine and the unit dose for use according to any one of claims 1 to 9, wherein the subject population or subject is from a dengue non-endemic region, preferably from a dengue non-endemic and hepatitis-A non-endemic region.
12. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein the hepatitis A vaccine comprises a hepatitis A virus derived from a hepatitis A virus strain HM-175.
- 10 13. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein the hepatitis A vaccine comprises an inactivated hepatitis A virus and the inactivated hepatitis A virus is derived from a hepatitis A virus strain HM-175.
- 15 14. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein the hepatitis A vaccine comprises an inactivated hepatitis A virus and wherein the inactivated hepatitis A virus is adsorbed on aluminum.
- 20 15. The hepatitis A vaccine and the unit dose for use according to claim 14, wherein the aluminum is aluminum hydroxide or aluminum hydroxyphosphate sulfate.
16. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein the hepatitis A vaccine comprises an inactivated hepatitis A virus and wherein the hepatitis A vaccine comprises a phosphate-buffered saline solution and excipients dissolved therein in the form of an amino acid and in and in the form of polysorbate.
- 25 17. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein the hepatitis A vaccine includes a hepatitis A virus expressing a viral antigen in a concentration ranging from 500 ELISA Units (EL.U.) to 2000 ELISA Units (EL.U.).
- 30 18. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein the method does not include a step of determination whether there was a previous dengue infection and/or a previous hepatitis A infection in the subject population or in the subject before the administration of the hepatitis A vaccine and before the administration of the unit dose of the dengue vaccine composition or
- 35 wherein the hepatitis A serostatus and/or the dengue serostatus of the subject population or of the subject is unknown before the administration of the hepatitis A vaccine and before the administration of the unit dose of the dengue vaccine composition.
19. The hepatitis A vaccine and the unit dose for use according to claim 18, wherein the method does not
- 40 include a step of determination whether there was a previous dengue infection and/or a previous hepatitis A infection in the subject population or in the subject at any time before, during and after the steps of administration of the hepatitis A vaccine and of the unit dose of the dengue vaccine composition or
- wherein the hepatitis A serostatus and/or the dengue serostatus of the subject population or of the subject is unknown at any time before, during or after the steps of administration of the hepatitis A vaccine and of the unit
- 45 dose of the dengue vaccine composition.

20. The hepatitis A vaccine and the unit dose for use according to any of the preceding claims, wherein the method comprises a primary vaccination consisting of the steps of:
- 5 (A) selecting a subject for administration of the unit doses of the tetravalent dengue virus composition and the hepatitis A vaccine in need for protection against dengue infection and hepatitis A infection without determination whether there was a previous dengue infection and/or a previous hepatitis A infection, and
- (B) administering a first unit dose of the tetravalent dengue virus composition and a hepatitis A vaccine to the subject, and optionally
- 10 (C) administering at least one further unit dose of the tetravalent dengue virus composition to the subject within 3 to 12 months of administration of the first unit dose, and optionally
- (D) administering at least one further dose of the hepatitis A vaccine to the subject within 6 to 18 months of administration of the first unit dose.
21. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein the method comprises a primary vaccination consisting of the steps of:
- 15 (A) selecting a subject for administration of the unit doses of the tetravalent dengue virus composition and the hepatitis A vaccine in need for protection against dengue infection and hepatitis A infection, and
- (B) administering a first unit dose of the tetravalent dengue virus composition and a hepatitis A vaccine to the subject, and
- 20 (C) administering two further unit doses of the tetravalent dengue virus composition to the subject at about 6 and about 12 months of administration of the first unit dose and administering a hepatitis A vaccine to the subject at either about 6 or about 12 months of administration of the first unit dose.
22. The hepatitis A vaccine and the unit dose for use according to claim 21, wherein step (A) is carried out without determination whether there was a previous hepatitis A infection.
- 25 23. The hepatitis A vaccine and the unit dose for use according to any one of claims 3 to 22, wherein upon reconstitution of the dengue vaccine composition with a pharmaceutically acceptable diluent (i), (ii), (iii), and (iv) provide a total concentration of pfu/0.5 mL and based on said total concentration of pfu/0.5 mL the concentration of
- 30 (ii) in pfu/0.5 mL is less than 10%, and the concentration of (iv) in pfu/0.5 mL is at least 50%, and the concentration of (i) in pfu/0.5 mL is at least 1%, and the concentration of (iii) in pfu/0.5 mL is at least 6%, at least 8%, or at least 10%, or at least 12%, or at least 14%, or at least 16%, or at least 18%.
24. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein the method provides compatibility between the dengue vaccine composition and the hepatitis A vaccine.
- 35 25. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein the method provides synergy between the dengue vaccine composition and the hepatitis A vaccine.
- 40 26. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein the method provides non-inferiority in a non-inferiority clinical study including at least 60 or at least 120 healthy subjects divided into one subject population and into one control subject population, wherein the subject population receives simultaneously on the same day the hepatitis A vaccine and the unit dose of the dengue vaccine composition and the

control subject population receives simultaneously on the same day a hepatitis A vaccine and a placebo administration.

27. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein the hepatitis A vaccine provides a hepatitis A seroprotection rate of at least 95% or of at least 98% on day 30 after an administration (on day 0/1) to a subject population of at least 30 or at least 50 healthy subjects receiving simultaneously on the same day the hepatitis A vaccine and the unit dose of the dengue vaccine composition and being seronegative with respect to hepatitis A at baseline and being seronegative with respect to all dengue virus serotypes at baseline.

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28. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein the method provides a hepatitis A seroprotection rate difference with respect to a hepatitis A mono-administration, the difference being determined in a non-inferiority clinical study including at least 60 or at least 120 healthy subjects being seronegative with respect to hepatitis A at baseline and seronegative with respect to all dengue virus serotypes at baseline,

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the healthy subjects being divided into

e) a subject population of at least 30 or at least 50 healthy subjects receiving simultaneously on the same day an administration (on day 0/1) of the hepatitis A vaccine and the unit dose of the dengue vaccine composition, and

20 f) a control subject population of at least 30 or at least 50 healthy subjects receiving simultaneously on the same day an administration (on day 0/1) of a hepatitis A vaccine and a placebo,

wherein the difference is determined between the hepatitis A seroprotection rate of the control subject population on day 30 after the administration (on day 0/1) and the hepatitis A seroprotection rate of the subject population on day 30 after the administration (on day 0/1), and

25 wherein the difference has an upper bound within a two-sided 95% confidence interval which is lower than 10%.

29. The hepatitis A vaccine and the unit dose for use according to any one of claims 1 to 26, wherein the hepatitis A vaccine provides a hepatitis A seroprotection rate of at least 95% or of at least 98% or of at least 99% on day 30 after an administration (on day 0/1) to a subject population of at least 30 or at least 50 healthy subjects receiving simultaneously on the same day the hepatitis A vaccine and the unit dose of the dengue vaccine composition and being seronegative with respect to hepatitis A at baseline, wherein the healthy subjects include healthy subject(s) which are seropositive with respect to at least one dengue virus serotype at baseline and healthy subject(s) which are seronegative with respect to all dengue virus serotypes at baseline.

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30. The hepatitis A vaccine and the unit dose for use according to any one of claims 1 to 26, wherein the method provides a hepatitis A seroprotection rate difference with respect to a hepatitis A mono-administration, the difference being determined in a non-inferiority clinical study including at least 60 or at least 120 healthy subjects being seronegative with respect to hepatitis A at baseline, wherein the healthy subjects include healthy subject(s) which are seropositive with respect to at least one dengue virus serotype at baseline and healthy subject(s) which are seronegative with respect to all dengue virus serotypes at baseline,

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the healthy subjects being divided into

e) a subject population of at least 30 or at least 50 healthy subjects receiving simultaneously on the same day an administration (on day 0/1) of the hepatitis A vaccine and the unit dose of the dengue vaccine

- composition, wherein the subject population includes healthy subject(s) which are seropositive with respect to at least one dengue virus serotype at baseline and healthy subject(s) which are seronegative with respect to all dengue virus serotypes at baseline, and
- 5 f) a control subject population of at least 30 or at least 50 healthy subjects receiving simultaneously on the same day an administration (on day 0/1) of a hepatitis A vaccine and a placebo, wherein the control subject population includes healthy subject(s) which are seropositive with respect to at least one dengue virus serotype at baseline and healthy subject(s) which are seronegative with respect to all dengue virus serotypes at baseline,
- 10 wherein the difference is determined between the hepatitis A seroprotection rate of the control subject population on day 30 after the administration (on day 0/1) and the hepatitis A seroprotection rate of the subject population on day 30 after the administration (on day 0/1), and
- wherein the difference has an upper bound within a two-sided 95% confidence interval which is lower than 10%.
- 15 31. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein the subject or subject population is exposed to a hepatitis A virus outbreak and/or a dengue virus outbreak.
32. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein the method provides an anti-hepatitis A virus antibody Geometric Mean Concentration (GMC) of at least 70 mIU/ml or at least 80 mIU/ml or at least 90 mIU/ml on day 30 after an administration (on day 0/1) to a subject population of at least 30 or at least 50 healthy subjects receiving simultaneously on the same day the hepatitis A vaccine and the unit dose of the dengue vaccine composition and being seronegative with respect to hepatitis A at baseline and being seronegative with respect to all dengue virus serotypes at baseline.
- 20 33. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein the simultaneous on the same day administration of the hepatitis A vaccine and the unit dose of the dengue vaccine composition to the subject or the subject population is safe.
34. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein there are no serious adverse events related to the simultaneous on the same day administration.
- 30 35. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein the method provides the Geometric Mean Titer (GMT) of neutralizing antibodies measured by MNT50 of
- 35 - at least 110 or at least 140 or at least 150 for dengue serotype 1,
- at least 3000 or at least 3500 or at least 3900 for dengue serotype 2,
- at least 100 or at least 120 or at least 140 for dengue serotype 3, and/or
- at least 80 or at least 110 or at least 140 for dengue serotype 4,
- on day 30 after an administration (on day 0/1) to a subject population of at least 30 or at least 50 healthy subjects receiving simultaneously on the same day the hepatitis A vaccine and the unit dose of the dengue vaccine composition and being seronegative with respect to hepatitis A at baseline and being seronegative with respect to all dengue virus serotypes at baseline.
- 40 36. The hepatitis A vaccine and the unit dose for use according to any one of the preceding claims, wherein the subject or subject population is 18 to 60 years of age.

37. A kit against hepatitis A and dengue disease comprising
a box containing at least
- 5 (a) a first container holding a hepatitis A vaccine, and
(b) a second container holding a unit dose of a dengue vaccine composition, wherein said unit dose
comprises a tetravalent dengue virus composition including four live, attenuated dengue virus strains.