symptoms and fulminant hepatitis (acute liver failure), which is often fatal. Hepatitis A occurs sporadically and in epidemics worldwide, with a tendency for cyclic recurrences.

[0011] The hepatitis A virus is one of the most frequent causes of foodborne infection. Epidemics related to contaminated food or water can erupt explosively, such as the epidemic in Shanghai in 1988 that affected about 300,000 people. Hepatitis A viruses persist in the environment and can withstand food-production processes routinely used to inactivate and/or control bacterial pathogens. The disease can lead to significant economic and social consequences in communities. It can take weeks or months for people recovering from the illness to return to work, school, or daily life. The impact on food establishments identified with the virus, and local productivity in general, can be substantial. In developing countries with poor sanitary conditions and hygienic practices, most children (90%) have been infected with the hepatitis A virus before the age of 10 years.

[0012] The number of people traveling internationally has grown substantially in recent decades. According to the United Nations World Tourism Organization (UNWTO), over 1.1 billion tourists travelled abroad in 2014. The risk of becoming ill during international travel depends on many factors, such as the region of the world visited, the length of the trip, and the diversity of planned activities. Vaccine recommendations are a prominent part of health preparations before international travel. Vaccination against hepatitis A virus is commonly recommended for travelers to at-risk areas around the world including Asia, Africa, and Latin America.

[0013] For routine hepatitis A vaccination, a two-dose schedule is recommended, particularly in travelers at substantial risk of contracting hepatitis A and in immunocompromised individuals. However, in healthy individuals, comparable effectiveness has been achieved with a single dose. The vaccination schedule for children/adolescents (12 months through 18 years of age) as well as for adults (≥19 years of age) consists of a primary dose administered intramuscularly, and a further booster dose administered intramuscularly 6 to 18 months later.

[0014] Available hepatitis A vaccines include HAVRIX® and VAQTA®.

[0015] Hence, there is a need for a safe and effective method of simultaneously preventing dengue disease and hepatitis A. In particular, there is a need for hepatitis A and dengue vaccines which provide non-inferiority when administered simultaneously to a subject or subject population and a suitable administration schedule for achieving synergy.

[0016] Furthermore, there is a need of effectively and safely preventing dengue disease and hepatitis A in subjects being unaware of their hepatitis A and/or dengue serostatus, in particular in subjects from non-endemic countries which travel into dengue and hepatitis A endemic countries.

OBJECTS AND SUMMARY

[0017] It is an object of the present ~~invention~~disclosure to provide a safe and effective protection against dengue disease and hepatitis A.

[0018] It is an object of the present ~~invention~~disclosure to provide a method of administration for preventing hepatitis A and dengue disease which is useful in typical vaccination settings wherein the subjects are unaware of their serostatus for dengue and/or hepatitis A and a corresponding serotest is unavailable, unpractical or unreliable.

[0019] It is an object of the present ~~invention~~disclosure to provide a safe and effective protection against dengue disease and hepatitis A for travelers from hepatitis A and dengue non-endemic countries, in particular for travelers being

vaccinated in travel clinics. In this context it is beneficial if multiple during the same medical appointments are avoided and vaccination can be conducted simultaneously for more than one disease.

[0020] It is an object of the present ~~invention~~disclosure to provide a safe and effective vaccine for preventing hepatitis A and dengue disease in a subject or subject population and a corresponding method of preventing hepatitis A and dengue disease in a subject or a subject population from a dengue-endemic and dengue non-endemic region and for a broad range of ages, in particular for subjects between 2 to 60 years of age, preferably for subjects between 18 and 60 years of age, and independent of previous exposure to any dengue virus serotype and/or to hepatitis A virus and independent of corresponding seropositivity or seronegativity with respect to dengue and/or hepatitis A before vaccination.

[0021] It is an object of the ~~invention~~disclosure to provide vaccines and a corresponding method of preventing hepatitis A and dengue disease which avoids testing for individual dengue and/or hepatitis A serostatus before individual administration of a hepatitis A and a dengue vaccine to a subject or subject population, or analysis of seroprevalence rates of dengue and/or hepatitis A in subjects or subject populations to be vaccinated.

[0022] It is an object of the present ~~invention~~disclosure to provide a dengue vaccine and a hepatitis A vaccine which can be safely co-administered with TDV as travel vaccines before an international travel of a subject to HAV and dengue endemic countries and a method of safely administering these vaccines.

[0023] Therefore, the present ~~invention~~disclosure is directed to a method of preventing dengue disease as well as hepatitis A.

[0024] The present ~~invention~~disclosure is further directed to a method of preventing hepatitis A and dengue disease in a subject or subject population, the method comprising simultaneously on the same day administering a hepatitis A vaccine and 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.

[0024a] In one aspect, the present disclosure provides a use of a hepatitis A vaccine and a unit dose of a dengue vaccine composition in the manufacture of a medicament for combination therapy to prevent hepatitis A and dengue disease in a subject or in a subject population, the use comprising that the hepatitis A vaccine and the unit dose of the dengue vaccine composition are to be administered simultaneously on the same day, wherein said unit dose comprises a tetravalent dengue virus composition including four live, attenuated dengue virus strains.

[0024b] In another aspect, the present disclosure provides a use of a hepatitis A vaccine in the manufacture of a first medicament and use of a unit dose of a dengue vaccine composition in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to prevent hepatitis A and dengue disease in a subject or in a subject population, the use comprising that the hepatitis A vaccine and the unit dose of the dengue vaccine composition are to be administered simultaneously on the same day, wherein said unit dose comprises a tetravalent dengue virus composition including four live, attenuated dengue virus strain.

[0024c] In a further aspect, the present disclosure provides a use of a unit dose of a dengue vaccine composition in the manufacture of a medicament for use in combinatorial therapy for preventing dengue disease and hepatitis A in a subject or in a subject population, wherein said medicament is to be administered in combination with a hepatitis A vaccine, the use comprising that the unit dose of the dengue vaccine composition and the hepatitis A

vaccine are to be administered simultaneously on the same day, wherein said unit dose comprises a tetravalent dengue virus composition including four live, attenuated dengue virus strains.

[0024d] In yet another aspect, the present disclosure provides a kit against hepatitis A and dengue disease comprising

(a) a first container holding a hepatitis A vaccine, and

(b) a second container holding a unit dose of a dengue vaccine composition as a combined pharmaceutical formulation for use in preventing hepatitis A and dengue disease in a subject or in a subject population, wherein said unit dose comprises a tetravalent dengue virus composition including four live, attenuated dengue virus strains.

DEFINITIONS

[0025] In describing the present invention, the following terms are to be used as indicated below. As used herein, the singular forms "a," "an," and "the" include plural references unless the context clearly indicates otherwise.

[0026] As used herein, the terms "unit dose of a dengue vaccine composition", "unit dose" and "unit dose of the invention as described herein" refer to the amount of a dengue vaccine which is administered to a subject in a single dose. In one embodiment, one unit dose is present in a vial and this unit dose is administered to a subject, e.g. optionally after reconstitution. In one embodiment, more than one unit dose of the dengue vaccine composition may be present in a vial so that with the content of one vial more than one subject can be vaccinated.

[0027] A "lyophilized unit dose" or "unit dose in lyophilized form" refers to the unit dose that is obtained by subjecting a given volume of the liquid dengue vaccine composition, such as 0.5 mL, to lyophilization. Thus, the aqueous formulations of the dengue vaccine composition being produced by combining the pharmaceutically acceptable excipients and the dengue virus composition comprising the four dengue virus strains, preferably TDV-1 to TDV-4, is subjected to lyophilization to obtain the lyophilized unit dose.

[0028] A "reconstituted unit dose" or "unit dose in reconstituted form" is obtained from the lyophilized dose by reconstitution with a pharmaceutically acceptable diluent. The diluent does not contain dengue virus. The

CLAIMS

1. Use of a~~A~~ hepatitis A vaccine and a unit dose of a dengue vaccine composition ~~for use~~ in the manufacture of a medicament for combination therapy to ~~a method of~~ prevent~~ing~~ hepatitis A and dengue disease in a subject or in a subject population, the ~~method~~ use comprising ~~simultaneously on the same day administering~~ that the hepatitis A vaccine and the unit dose of the dengue vaccine composition are to be administered simultaneously on the same day, wherein said unit dose comprises a tetravalent dengue virus composition including four live, attenuated dengue virus strains.

2. Use of a hepatitis A vaccine in the manufacture of a first medicament and use of a unit dose of a dengue vaccine composition in the manufacture of a second medicament, wherein the first and second medicaments are to be used in combination therapy to prevent hepatitis A and dengue disease in a subject or in a subject population, the use comprising that the hepatitis A vaccine and the unit dose of the dengue vaccine composition are to be administered simultaneously on the same day, wherein said unit dose comprises a tetravalent dengue virus composition including four live, attenuated dengue virus strains.

3. Use of a unit dose of a dengue vaccine composition in the manufacture of a medicament for use in combinatorial therapy for preventing dengue disease and hepatitis A in a subject or in a subject population, wherein said medicament is to be administered in combination with a hepatitis A vaccine, the use comprising that the unit dose of the dengue vaccine composition and the hepatitis A vaccine are to be administered simultaneously on the same day, wherein said unit dose comprises a tetravalent dengue virus composition including four live, attenuated dengue virus strains.

~~2~~4. The ~~hepatitis A vaccine and the unit dose for~~ use according to any one of the preceding claims ~~1~~, wherein the hepatitis A vaccine is an inactivated virus vaccine.

~~3~~5. The ~~hepatitis A vaccine and the unit dose for~~ use according to any one of the preceding claims ~~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~~6. 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~~7. 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 to be administered by subcutaneous injection and said hepatitis A vaccine is to be administered by intramuscular injection, and wherein said injections are to be preferably administered to the arm, more preferably to the deltoid region of the arm.

~~6~~8. The ~~hepatitis A vaccine and the unit dose for~~ use according to claim ~~5~~7, wherein said unit dose of the dengue vaccine composition and said hepatitis A vaccine are to be administered to different anatomical sites, such as to opposite arms.

~~7~~9. 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 to be administered within 12 months or more, or within six months, or within three months.

~~8~~10. The ~~hepatitis A vaccine and the unit dose for~~ use according to claim ~~7~~9 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~~11. 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~~12. 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.

~~11~~13. The ~~hepatitis A vaccine and the unit dose for~~ use according to any one of claims 1 to ~~9~~11, 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~~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 a hepatitis A virus derived from a hepatitis A virus strain HM-175.

~~13~~15. 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.

~~14~~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 inactivated hepatitis A virus is adsorbed on aluminum.

~~15~~17. The ~~hepatitis A vaccine and the unit dose for~~ use according to claim ~~14~~16, wherein the aluminum is aluminum hydroxide or aluminum hydroxyphosphate sulfate.

~~16~~18. 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.

~~17~~19. 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.).

~~18~~20. The ~~hepatitis A vaccine and the unit dose for~~ use according to any one of the preceding claims, wherein the ~~method~~ use 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
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~~21. The ~~hepatitis A vaccine and the unit dose for~~ use according to claim ~~18~~20, wherein the ~~method~~ use 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 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 dose of the dengue vaccine composition.

~~20~~22. The ~~hepatitis A vaccine and the unit dose for~~ use according to any of the preceding claims, wherein the ~~method~~ use comprises a primary vaccination consisting of the steps of:
(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~~ administration of a first unit dose of the tetravalent dengue virus composition and a hepatitis A vaccine to the subject, and optionally
(C) administration of~~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) administration of~~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~~23. The ~~hepatitis A vaccine and the unit dose for~~ use according to any one of the preceding claims, wherein the ~~method~~ use comprises a primary vaccination consisting of the steps of:
(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) administration of ~~administering~~ a first unit dose of the tetravalent dengue virus composition and a hepatitis A vaccine to the subject, and
(C) administration of~~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~~ administration of a hepatitis A vaccine to the subject at either about 6 or about 12 months of administration of the first unit dose.

~~22~~24. The ~~hepatitis A vaccine and the unit dose for~~ use according to claim ~~21~~23, wherein step (A) is carried out without determination whether there was a previous hepatitis A infection.

~~23~~25. The ~~hepatitis A vaccine and the unit dose for~~ use according to any one of claims ~~3~~5 to ~~22~~24, 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 (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~~26. The ~~hepatitis A vaccine and the unit dose for~~ use according to any one of the preceding claims, wherein the use~~method~~ provides compatibility between the dengue vaccine composition and the hepatitis A vaccine.

~~25~~27. The ~~hepatitis A vaccine and the unit dose for~~ use according to any one of the preceding claims, wherein the ~~method~~ use provides synergy between the dengue vaccine composition and the hepatitis A vaccine.

~~26~~28. The ~~hepatitis A vaccine and the unit dose for~~ use according to any one of the preceding claims, wherein the ~~method~~ use 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~~29. 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.

~~28~~30. The ~~hepatitis A vaccine and the unit dose for~~ use according to any one of the preceding claims, wherein the ~~method~~ use 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,

the healthy subjects being divided into

a) 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

b) 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

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

~~29~~31. The ~~hepatitis A vaccine and the unit dose for~~ use according to any one of claims 1 to ~~26~~28, 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.

~~30~~32. The ~~hepatitis A vaccine and the unit dose for~~ use according to any one of claims 1 to ~~26~~28, wherein the use ~~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,

the healthy subjects being divided into

a) 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

b) 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,

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%.

~~31~~33. 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~~34. The ~~hepatitis A vaccine and the unit dose for~~ use according to any of the preceding claims, wherein the use~~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.

~~33~~35. 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~~36. 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.

~~35~~37. The ~~hepatitis A vaccine and the unit dose for~~ use according to any one of the preceding claims, wherein the use~~method~~ provides the Geometric Mean Titer (GMT) of neutralizing antibodies measured by MNT50 of

- 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.

~~36~~38. 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~~39. A kit against hepatitis A and dengue disease comprising

~~a box containing at least~~

(a) a first container holding a hepatitis A vaccine, and

(b) a second container holding a unit dose of a dengue vaccine composition as a combined pharmaceutical formulation for use in preventing hepatitis A and dengue disease in a subject or in a subject population, wherein said unit dose comprises a tetravalent dengue virus composition including four live, attenuated dengue virus strains.