

RHINOVACCINATION SYSTEM OF INFLUENZA VACCINE

Technical Field

[0001]

5 The present invention relates to a rhinovaccination system to administer an influenza vaccine composition to nasal mucosa, which is used in combination with a medical syringe.

10 Background Art

[0002]

 Influenza is an acute respiratory tract infection caused by the influenza virus, in particular, influenza becomes epidemic in winter year after year. In addition, influenza sometimes results in a pandemic, and many people become severe to result in death. For influenza, it is known that the vaccination with influenza vaccine can bring in some preventive effects, thus people are broadly vaccinated before the epidemic season.

20 [0003]

 The influenza vaccine approved in Japan is only an inactivated protein-component of an influenza viral antigen to be subcutaneously vaccinated, and currently, a split vaccine thereof is used as the seasonal influenza vaccine. Such vaccine to be subcutaneously vaccinated is highly

effective for preventing the severity in influenza infection such as pneumonia, but it has low antibody-induced activity in upper respiratory mucous membrane that is an infected area of influenza virus, which is not enough as infective protection-activity. And, such injection administration has problems, for example, a pain and side-effects such as inflammation caused by topical vaccination.

[0004]

For the above problem of influenza vaccination, a wide variety of the trials have been done until now, in which a vaccine for nasal administration has received attention as a new vaccination. However, it has been reported that it is impossible to induce a high immune response to the influenza virus even though the split vaccine which has been broadly used in current clinical practice is nasally administered to experimental animals or human beings directly.

[0005]

Under such circumstances, the world's first split influenza vaccine for nasal administration which comprises *Escherichia coli* heat labile toxin as an adjuvant was approved in Switzerland [Berna Biotech, Switzerland; Commercial name: Nasalflu], and the sale thereof started in October, 2000, but the clinical use thereof was withdrawn in February, 2004 due to the toxicity of the adjuvant. And,

Patent Reference 1 also discloses an influenza vaccine for nasal administration which comprises an adjuvant, which indicates that the immune induction can be enhanced by using the adjuvant. However, the toxicity of adjuvants is
5 an anxious matter for practical use.

[0006]

For the nasal administration, it is also necessary to consider the complicated structure of nasal cavity, and it is desirable to make influenza vaccine broadly spread,
10 attached and retained for a long time in nasal cavity. For example, the base (material) disclosed in Patent Reference 2 may be used for spray-administration.

[0007]

The pump-type spray device such as an airless-type
15 spray device used in Patent Reference 2 can achieve a good spray-suitability of a formulation (spray-dispersibility, uniformity of formulation particle size, etc.), which is expected to gain the desired enough drug efficacy, however, it is difficult to fill the spray container with only one
20 dose to make it one-shot administration system, from the point of the structure of the spray container. Thus, in order to nasally administer an influenza vaccine with such pump-type spray device, there was no other way but to fill the spray container with a large excess vaccine formulation,
25 administer it to one person, and then dispose of the rest

with the spray device or share the rest with plural subjects from the viewpoint of the cost. However, the repetitive use of such airless-type spray device's tip in nasal cavity of plural patients or subjects can make most
5 of people feel emotionally bad, and the use is unsanitary and in danger of another infection (hospital infection).

[0008]

As mentioned above, it has been desired to develop influenza vaccine for nasal administration as a next-
10 generation influenza vaccine and put it to practical use, which takes the place of a conventional influenza vaccine for subcutaneous or intramuscular administration. However, there are various problems for the practical use, for example, how the toxicity of an adjuvant used to enhance
15 the immune induction should be reduced, or how the device for administration should be devised to enhance its effect enough.

PRIOR ART

20 [0009]

[Patent Reference 1] WO 2010/114169

[Patent Reference 2] WO 2007/123193

Summary of Invention

25 [0010]

One of the purposes of the present invention is to provide a system to administer an influenza vaccine composition for spray-administration to nasal mucosa which is prepared by using an inactivated whole influenza virion as an antigen that has been already approved, but not using an adjuvant, which exhibits a high efficacy and low side effects in spite of a low antigen level, which is used in combination with a device for administration.

[0011]

10 In addition, WO 2014/103488 is an application related to the present application, which has already been published. However, the priority date of the present application is earlier than the published date of the related application, and thus it is not a prior art document for the present application.

[0012]

The present inventors have extensively studied on the above problem and then have found that a combination of (i) a gel base (material) for spray-administration to nasal mucosa comprising carboxy vinyl polymer which is treated by adding an outside shearing force to add spray-performance and (ii) an inactivated whole influenza virion, can enhance the immune induction in human beings without an adjuvant; and further have made an administration system by setting the combination into a metered-dose syringe-based squirt

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having an optimized shape/configuration of the nozzle. Based upon the new findings, the present invention has been accomplished. The present invention may provide the following embodiments.

5 [0013]

[1] A rhinovaccination system of influenza vaccine, comprising a syringe-based squirt filled with an influenza vaccine composition which comprises (i) an inactivated whole influenza virion, and (ii) a gel base material comprising carboxy vinyl polymer which is treated by adding an outside shearing force to add spray-performance, which is characterized by not comprising an adjuvant.

[0014]

[2] The rhinovaccination system of influenza vaccine according to [1], wherein the syringe-based squirt is a medical syringe having a tip opening in fluid communication with a syringe barrel, which is equipped with a rhinal spray nozzle comprising

a hollow nozzle body having a tip portion defining a nozzle orifice thereon,

a solid packing rod arranged within the nozzle body, and

a nozzle chamber defined between the packing rod and the nozzle body to allow a fluid communication between the tip opening and the nozzle orifice,

wherein the nozzle orifice has a diameter in a range between 0.25 mm and 0.30 mm.

[0015]

[3] The rhinovaccination system of influenza vaccine
5 according to [1] or [2], wherein the amount of (i) the inactivated whole influenza virion is 1 - 500 µg HA/mL per type of vaccine virus strain.

[0016]

[4] The rhinovaccination system of influenza vaccine
10 according to any one of [1] to [3], wherein the influenza vaccine composition comprises 0.1 w/v % to 1.0 w/v % carboxy vinyl polymer.

[0017]

[5] The rhinovaccination system of influenza vaccine
15 according to any one of [1] to [4], wherein the spray-performance is to control (1) the particle-size-distribution of the sprayed composition, (2) the uniformity of spray density, and/or (3) the spray angle.

[0018]

[6] The rhinovaccination system of influenza vaccine
20 according to any one of [1] to [3], wherein the influenza vaccine composition is prepared by treating a gel base material comprising 0.5 w/v % to 2.0 w/v % carboxy vinyl polymer by adding an outside shearing force to control (1)
25 the particle-size-distribution of the sprayed composition,

(2) the uniformity of spray density, and/or (3) the spray angle, as spray-performance, to give a gel base material, and then

5 mixing the resulting gel base material with a virus stock solution comprising an inactivated whole influenza virion homogeneously in a short time without stress.

[0019]

[7] The rhinovaccination system of influenza vaccine according to any one of [1] to [6], wherein the influenza vaccine composition is prepared with a gel base material comprising carboxy vinyl polymer that is treated by adding an outside shearing force to add spray-performance which is to control that (1) as for the particle-size-distribution of the sprayed composition, the mean particle size is in a range of 30 μm to 80 μm , and the particle distribution between 10 μm and 100 μm is 80 % or more,

(2) the spray density is uniform to form a homogeneous full-corn shape, and

(3) the spray angle is adjusted in a range of 30° to 70°.

[0020]

[8] The rhinovaccination system of influenza vaccine according to any one of [1] to [6], wherein the influenza vaccine composition is prepared with a gel base material comprising carboxy vinyl polymer that is treated by adding

an outside shearing force to add spray-performance which is to control that (1) as for the particle-size-distribution of the sprayed composition, the mean particle size is in a range of 40 μm to 70 μm , and the particle distribution
5 between 10 μm and 100 μm is 90 % or more,

(2) the spray density is uniform to form a homogeneous full-corn shape, and

(3) the spray angle is adjusted in a range of 40° to 60°.

10 [0021]

[9] The rhinovaccination system of influenza vaccine according to any one of [2] to [8], wherein the nozzle orifice includes substantially no curved portion.

[0022]

15 [10] The rhinovaccination system of influenza vaccine according to any one of [2] to [9], wherein the tip portion defining the nozzle orifice has thickness along an injection direction of the formulation which is in a range between 0.20 mm and 0.30 mm.

20 [0023]

[11] The rhinovaccination system of influenza vaccine according to any one of [2] to [10],

wherein the nozzle body includes an inner wall having at least a portion formed in a cylindrical shape and the
25 packing rod includes an outer wall at least a portion

formed in a cylindrical shape having a plurality of circumferentially spaced grooves,

wherein the nozzle chamber is defined between the at least portion of the inner wall of the nozzle body and the
5 at least portion of the outer wall of the packing rod, and

wherein the packing rod includes a vortex-flow generation member opposed to the tip portion of the nozzle body.

[0024]

10 [12] The rhinovaccination system of influenza vaccine according to [11], wherein the vortex-flow generation member is formed so that a flow direction of the formulation from the grooves of the packing rod is offset to a central axis, thereby to generate a vortex flow of the
15 formulation.

[0025]

[13] The rhinovaccination system of influenza vaccine according to [11] or [12], wherein the at least portion of the inner wall of the nozzle body is formed to have a cross
20 section substantially-perpendicular to the injection direction which is continuously or step-wisely reduced towards the injection direction.

[0026]

The present invention have made it possible to provide
25 an influenza vaccine composition comprising an inactivated

whole influenza virion as an active ingredient, but not comprising an adjuvant, which induces a high immune response in spite of a small antigen level, and low side effects because the composition does not comprise an
5 adjuvant. By using an administration system equipped with a metered-dose syringe-based squirt having an optimized-shaped rhinal spray nozzle, the influenza vaccine composition is expected to be suitably applied for the epidemic of influenza.

10 The influenza vaccine composition of the present invention can be broadly spread, attached and retained for a long time in nasal mucosa because the composition comprises a gel base material comprising carboxy vinyl polymer which is treated by adding an outside shearing
15 force to add spray-performance, thus the influenza vaccine composition of the present invention can induce a high immune response in spite of a small antigen level.

According to the process for preparing an influenza vaccine composition of the present invention, an influenza
20 vaccine composition can be provided, which well keeps the antigenicity of the inactivated whole virion because the virion is treated in a short time without stress, and induces a high immune response and low side effects.

Although the present invention comprises no adjuvant
25 as an immunopotentiating agent, the present invention can

provide an equal or more potent immune-induction for upper respiratory mucous membrane and whole body, compared with a composition comprising influenza virus vaccine and an adjuvant.

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Brief Description of Drawings

[0027]

Fig. 1 is a partially-fragmented side view of a general structure of a medical syringe comprising a rhinal spray nozzle of one embodiment according to the present invention.

Figs. 2(a) and 2(b) are partially-fragmented perspective views of the general structure of the rhinal spray nozzle of one embodiment of the present invention, showing configurations before and after the packing rod are inserted within the nozzle body, respectively.

Fig. 3(a) is a vertical cross-sectional view of the rhinal spray nozzle of Fig. 2(b), and Figs. 3(b), 3(c) and 3(d) are horizontal cross-sectional views of the rhinal spray nozzle taken along B-B line, C-C line and D-D line of Fig. 3(a), respectively.

Figs. 4(a) and 4(b) are enlarged cross-sectional views of the tip portion of the nozzle body, in which the tip portion is provided with the curved portion in Fig. 4(a) but not in Fig. 4(b).

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Fig. 5 shows a result that the particle size distribution of the formulation in Example 4 was measured with a laser diffraction particle size analyzer, which was sprayed with the syringe-based squirt of the present invention.

Fig. 6 shows a result that the spray angle of the formulation in Example 4 was measured with a high-speed microscope, which was sprayed from the tip of the nozzle in the syringe-based squirt of the present invention. The spray angle of the sprayed formulation was 52.27°.

Fig.7 shows a result that the spray behavior of the formulation in Example 4 was measured with a spray pattern test sheet, which was sprayed with the syringe-based squirt of the present invention. It was a uniform full-corn circle.

Description of Embodiments

[0028]

The present invention provides a rhinovaccination system of influenza vaccine, comprising

a medical syringe having a tip opening in fluid communication with a syringe barrel, which is equipped with a rhinal spray nozzle comprising a hollow nozzle body having a tip portion defining a nozzle orifice thereon, a solid packing rod arranged within the nozzle body, and a

nozzle chamber defined between the packing rod and the nozzle body to allow a fluid communication between the tip opening and the nozzle orifice, wherein the nozzle orifice has a diameter in a range between 0.25 mm and 0.30 mm,

5 which is filled with an influenza vaccine composition which comprises a gel base material comprising carboxy vinyl polymer which is treated by adding an outside shearing force to add spray-performance, and an inactivated whole influenza virion, which is characterized by not
10 comprising an adjuvant.

[0029]

 The "gel base material comprising carboxy vinyl polymer which is treated by adding an outside shearing force to add spray-performance" used herein means, for
15 example, a "gel base material comprising a skin/mucosa-adhesive agent" disclosed in WO 2007/123193, which is a base material comprising carboxy vinyl polymer and optionally comprising gellan gum, whose viscosity is adjusted by adding an outside shearing force. The base
20 material is characterized in that the viscosity thereof can be adjusted to various ones by adding an outside shearing force, and the spray spreading-angle from a spray container and the spray density can be controlled to meet the purpose. In addition, the use of the present administration system
25 equipped with a metered-dose syringe-based squirt having an

optimized-shaped rhinal spray nozzle can achieve a good spray-suitability of a formulation (spray-dispersibility, uniformity of formulation particle size, etc.), as is the case with the pump-type spray device such as an airless-type spray device disclosed in WO 2007/123193, and thereby the use can make the spreading of an inactivated whole influenza virion in nasal mucosa in a wide spread and in a long time to enhance the immunogenicity of an antigen.

[0030]

10 Carboxy vinyl polymer which is a material ingredient of the gel base material in the present invention is a hydrophilic polymer prepared by polymerizing acrylic acid as a main ingredient, which can be chosen from pharmaceutical additives that are generally used to prepare an aqueous gel agent without any limitation.

The content of the gel base material comprising carboxy vinyl polymer which is treated by adding an outside shearing force to add spray-performance is 0.1 - 1.0 w/v %, preferably 0.3 - 0.7 w/v % as the content of carboxy vinyl polymer.

20 [0031]

The vaccine of the present invention is characterized by comprising an inactivated whole influenza virion as an antigen. The inactivated whole influenza virion used herein means a virion which is prepared by cultivating

influenza virus to give a virus suspension thereof and purifying the virus suspension while keeping its virus morphology. Thus, the influenza vaccine of the present invention means a vaccine except split vaccine (including
5 subvirion) and subunit vaccine (including purified HA or NA), and it is also referred to as whole virus vaccine.

[0032]

The above-mentioned inactivated whole influenza virion is preferably such virion that is purified from a virus
10 suspension in the absence of surfactants and ethers. The virus stock solution used herein means a virus solution comprising an inactivated whole influenza virion, which is purified or concentrated to be mixed with a gel base material in the present invention. With regard to the
15 vaccine of the present invention, the concentration of an inactivated whole influenza virion is preferably 1 - 500 μg HA/mL (in HA equivalent), more preferably 20 - 250 μg HA/mL (in HA equivalent) per type of vaccine virus strain. The above-mentioned concentration can be determined by
20 measuring the concentration of HA protein.

[0033]

The influenza virus used herein includes all types of currently-known influenza virus and all subtypes thereof, as well as all types and all subtypes of influenza virus
25 isolated or identified in future. In addition, from the

viewpoint of the necessity to also effectively prevent an infection that has not become epidemic in human beings until now, but might become epidemic in human beings in future, a combination of an influenza A virus subtype selected from the group consisting of subtypes H1 - H16 excluding subtype H1 and H3 (i.e., H2, and H4 - H16) and an influenza A virus subtype selected from the group consisting of subtypes N1 - N9 is preferable. These subtypes are also referred to as a new type influenza virus.

As the above-mentioned subtypes, a combination of a subtype selected from the group consisting of subtypes H5, H7, and H9 and a subtype selected from the group consisting of subtypes N1 - N9 is more preferable. The influenza virus may be derived from a type of strain, two or more types of strains belonging to the same subtype, or two or more types of strains belonging to different subtypes.

[0034]

The influenza virus used herein includes a strain isolated from infected animals or humans, and a recombinant virus genetically-established at cultured cells. As the method for cultivating influenza virus, the virus may be seeded in the allantoic cavity of eggs of hen and cultivated, or may be infected in cultured cells and cultivated.

[0035]

An adjuvant is a generic term of substances having the modulating-activity of the immune response such as enhancement and suppression, and is used as an immunopotentiating agent to be added to a vaccine to enhance the immunogenicity of an antigen. Until now, a lot of adjuvants have been studied. The use of an adjuvant enhances the immune effect of a vaccine, but it has disadvantages of side effects such as inflammation. Some adjuvants can be chosen as a candidate to be used in a vaccine for nasal administration, but there has not been any approved vaccine for nasal administration comprising an adjuvant because there has been no adjuvant having a pervasive safety.

[0036]

The present inventors have found that it is possible to prepare a vaccine having a high efficacy and low side effects in spite of non-adjuvant and a lower antigen level when the gel base material which has the above-mentioned useful spray-performance such as high adhesive property to nasal mucosa is used with the above-mentioned whole-virus vaccine. In addition, the present inventors have also found that using a device which can spray even a gel base material having high viscosity, an influenza vaccine composition can be sprayed to nasal mucosa, wherein the mean particle size of the sprayed composition is in a

suitable range of 30 μm to 80 μm (preferably a range of 40 μm to 70 μm), the particle-size-distribution between 10 μm and 100 μm is 80 % or more (preferably, 90 % or more), the spray angle from the device is set at a range of 30° to 70°
5 (preferably, a range of 40° to 60°) so that the composition can be administered to the desired site in nasal cavity, and the spray density is uniform to form a homogeneous full-corn shape. Further the present inventors have also found its process and a method for preventing influenza
10 using the composition. Based upon the new findings, the present invention has been accomplished.

[0037]

The vaccine of the present invention can comprise an additional pharmaceutically-acceptable carrier(s) besides
15 an inactivated whole influenza virion and a gel base material. The carrier used herein can be a carrier which is generally used in the preparation of a vaccine or a formulation for administration in nasal cavity, which includes, for example, saline, buffered saline, dextrose,
20 water, glycerin, isotonic aqueous buffer solution, and a combination thereof. And, the vaccine of the present invention may optionally include a preservative (e.g. thimerosal), an isotonic agent, a pH regulator, a surfactant, and an inactivating agent (e.g. formalin).

25 [0038]

The vaccine of the present invention is used for spray-administration into the nasal cavity.

The vaccine of the present invention can prevent influenza or relieve the symptom thereof.

5 [0039]

For the administration of the vaccine, the spray is done to one or both nares with an optimized nose-spray nozzle of the present invention, which can be used as a disposable device.

10 The dosage of the vaccine should be decided considering the age, sex and weight of a patient or other factors, and actually the vaccine can be administered in an amount of generally 1 μ g HA - 150 μ g HA, preferably 5 μ g HA - 50 μ g HA as an antigen per type of vaccine virus strain.

15 [0040]

With reference to attached drawings, embodiments of a rhinal spray nozzle used for a metered-dose syringe-based squirt having the rhinal spray nozzle according to the present invention will be described hereinafter. In the following description, directional terms such as "front," "rear", "proximal" and "distal" are conveniently used for better understandings, however, those terms are not intended to limit the scope of the present invention. Also, like components are denoted by like reference signs throughout the attached drawings.

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[0041]

(Medical Syringe)

Fig. 1 is a partially-fragmented side view of medical syringe 1 comprising rhinal spray nozzle 10 of an embodiment according to the present invention. As illustrated in Fig. 1, medical syringe 1 generally comprises syringe body 4 made of synthetic resin or glass having syringe barrel 3 capable of storing a pharmaceutical formulation therein, and plunger rod 5 inserted within syringe barrel 3 of syringe body 4. Medical syringe 1 also comprises piston 7 having fixing member 5a provided at the distal end of plunger rod 5 and sliding within syringe barrel 3 so as to pump the formulation in syringe barrel 3 out of distal tip opening 6 of syringe body 4, finger flange 8 provided around a proximal end of syringe body 4, and plunger end member 9 transmitting the force applied by a practitioner such as a medical doctor to plunger rod 5. Medical syringe 1 may be similar to the metered-dose syringe-based squirt disclosed in WO 2013/145789.

[0042]

It should be noted that rhinal spray nozzle 10 of the present invention may be applicable to any type of medical syringes 1 which pump the formulation in syringe barrel 3 by pushing plunger rod 5 (and piston 7), and thus, the present invention will not be limited to the known

configurations of the medical syringe. Therefore, the present disclosure will eliminate further description for the detailed structure of medical syringe (or metered-dose syringe-based squirt) 1, and discuss in more detail about the structure and the function of rhinal spray nozzle 10 used for the medical syringe. It should be noted that the disclosure of WO 2013/145789 is incorporated herein by reference into the present application.

[0043]

10 (Rhinal Spray Nozzle)

As shown in Fig. 1, medical syringes 1 further comprises rhinal spray nozzle 10 opposed to tip opening 6 of syringe body 4, and protection cap 50 for protecting sterilized tip portion 22 of rhinal spray nozzle 10 from contaminant and mechanical impact. Figs. 2(a) and 2(b) are partially-fragmented perspective views, showing the general structure of rhinal spray nozzle 10 of an embodiment of the present invention. As shown, rhinal spray nozzle 10 generally comprises hollow nozzle body 20 having tip portion 22 with nozzle orifice 21 and solid packing rod (packing bar) 30 provided within nozzle body 20. Figs. 2(a) and 2(b) show rhinal spray nozzle 10 before and after packing rod 30 is arranged or inserted within nozzle body 20, respectively. Tip portion 22 of nozzle body 20 has a circular shape and is provided with nozzle orifice 21 at

the center thereof.

[0044]

Fig. 3(a) is a vertical cross-sectional view of rhinal spray nozzle 10 of Fig. 2(b). Figs. 3(b), 3(c) and 3(d) are horizontal cross-sectional views of rhinal spray nozzle 10 taken along B-B line, C-C line and D-D line of Fig. 3(a), respectively. Hollow nozzle body 20 defines internal space 24 of a substantially cylindrical shape. As shown in Figs. 3(c) and 3(d), internal space 24 includes nozzle small-diameter portion 25 closer to nozzle orifice 21 of hollow nozzle body 20, nozzle large-diameter portion 26 opposing to tip opening 6 of syringe body 4, and nozzle shoulder 27 which is designed to have a diameter continuously or step-wisely reducing from nozzle large-diameter portion 26 towards nozzle small-diameter portion 25.

[0045]

On the other hand, solid packing rod 30 to be inserted within nozzle body 20 has outer wall 33 having a configuration substantially complementary with inner wall 23 of nozzle body 20 (internal space 24). As shown in Figs. 2(a), 3(c) and 3(d), rod small-diameter portion 35 and rod large-diameter portion 36 include rod shoulder 37 which is designed to have a diameter continuously or step-wisely reducing from rod large-diameter portion 36 towards rod small-diameter portion 35.

[0046]

Preferably, as illustrated in Fig. 3(a), inner wall 23 of nozzle body 20 is provided with protrusion 23a, while outer wall 33 of packing rod 30 is provided with recess 33a for receiving protrusion 23a. When packing rod 30 is fully inserted within internal space 24 of nozzle body 20, protrusion 23a may be closely fit in recess 33a to ensure connection between packing rod 30 and nozzle body 20.

[0047]

Also as illustrated in Figs. 2(a)-2(b) and 3(a)-3(d), packing rod 30 includes a plurality of grooves 38 and 39 circumferentially spaced from one another both on rod small-diameter portion 35 and rod large-diameter portion 36. Also, packing rod 30 is inserted within nozzle body 20 so as to define gap 40 between nozzle shoulder 27 and rod shoulder 37 (Fig. 3(a)). Thus, rhinal spray nozzle 10 assembled as illustrated in Fig. 2(b) has nozzle chamber 42 defined by grooves 38, 39 and gap 40, which allows fluid communication of formulation 2 delivered from tip opening 6 of syringe body 4 through nozzle chamber 42 to tip portion 22 of rhinal spray nozzle 10.

[0048]

Furthermore, as shown in Fig. 3(b), packing rod 30 includes vortex-flow generation member 44 opposed to tip portion 22 of rhinal spray nozzle 10. Vortex-flow

generation member 44 is configured to generate a vortex flow of formulation 2 that is delivered from each of grooves 38 of rod small-diameter portion 35 before being injected from nozzle orifice 21 of nozzle body 20. More particularly, the end portions of rod small-diameter portion 35 which define vortex-flow generation member 44 are formed so as to extend offset the vertical central axis of nozzle orifice 21. Thanks to generation of the vortex flow of formulation 2 before being injected from nozzle orifice 21, the spray angle of formulation 2 can be expanded to spray it in a more uniform manner.

[0049]

As illustrated in Figs. 3(c)-3(d), it is preferable to design grooves 38 of rod small-diameter portion 35 to be less than grooves 39 of rod large-diameter portion 36 so as to increase the pressure of formulation 2 in vortex-flow generation member 44 before being injected from nozzle orifice 21. Also, thanks to the diameters of rod large-diameter portion 36 and rod small-diameter portion 35 which are designed to continuously or step-wisely be reduced from the former to the latter, it is easier to insert rhinal spray nozzle 10 deeply into the nasal cavity and to spray the formulation towards the inferior nasal concha and even deeper portions of the patient. Thus preferably, the diameter of rod small-diameter portion 35 is smaller enough

than the nasal cavity opening of the patient without minimizing fear of the patient.

Examples

5 [0050]

According to the methods shown below, a gel base material and three kinds of virus stock solutions were prepared, and the gel base material and each virus stock solution were mixed as shown below to prepare influenza vaccine compositions as examples. Each viscosity was measured at 20°C with a viscometer type E.

[0051]

<Preparation of gel base material>

Example of gel base material (1)

Ingredients	Amount	Process of Preparation
Carboxy vinyl polymer	11.0 mg	Each ingredient shown in the left column was mixed in the ratio corresponding to each weight shown there, and stirred to become homogeneous. Then, the mixture was given an outside shearing force by a high-speed rotation with an intermittently-jet-stream-generating-type high-speed spinning-type emulsifying device. The resulting base material whose viscosity was suitably adjusted with an outside shearing force was heated at 90°C for 20 minutes to give a gel base material.
L-arginine	24.0 mg	
Concentrated glycerin	20.0 mg	
Purified water	q.s.	
Total	1.0 mL	Aspect: a clear and colorless gel base material, almost odorless. pH: 7.15 Viscosity: 4,000 mPa·s

15 [0052]

<Preparation of virus stock solution comprising inactivated whole influenza virion>

Example of virus stock solution (1)

Ingredients	Amount	Process of Preparation
Inactivated whole antigen of influenza virus A/Victoria/210/2009 (H3N2)	180 µg HA	The strain for preparing the vaccine was seeded in the allantoic cavity of embryonated eggs and cultivated, and then the virus suspension was collected. In order to clarify the virus suspension, it was centrifuged or filtrated, and ultrafiltered to be concentrated. Then, in order to purify the virus, the filtrate was ultracentrifuged by, for example, sucrose density gradient centrifugation to give a purified virus solution. The purified virus solution was inactivated with formalin to give a purified inactivated virus solution. And then, the solution was ultrafiltered to give a virus stock solution.
Sodium hydrogen phosphate hydrate	3.53 mg	
Sodium dihydrogen phosphate	0.54 mg	
Sodium chloride	8.50 mg	
Purified water	Total 1.0 mL	

[0053]

Example of virus stock solution (2)

Ingredients	Amount	Process of Preparation
Inactivated whole antigen of influenza virus A/Indonesia/5/05 (H5N1)	180 µg HA	The strain for preparing the vaccine was seeded in the allantoic cavity of embryonated eggs and cultivated, and then the virus suspension was collected. In order to clarify the virus suspension, it was centrifuged or filtrated, and ultrafiltered to be concentrated. Then, in order to purify the virus, the filtrate was ultracentrifuged by, for example, sucrose density gradient centrifugation to give a purified virus solution. The purified virus solution was inactivated with formalin to give a purified inactivated virus solution. And then, the solution was ultrafiltered to give a virus stock solution.
Sodium hydrogen phosphate hydrate	3.53 mg	
Sodium dihydrogen phosphate	0.54 mg	
Sodium chloride	8.50 mg	
Purified water	Total 1.0 mL	

[0054]

Example of virus stock solution (3)

Ingredients	Amount	Process of Preparation
Inactivated whole antigen of influenza virus A/California/7/2009 (H1N1)pdm09	60 µg HA	The strain for preparing the vaccine was seeded in the allantoic cavity of embryonated eggs and cultivated, and then the virus suspension is collected. In order to clarify the virus suspension, it was centrifuged or filtrated, and ultrafiltered to be concentrated. Then, in order to purify the virus, the filtrate was ultracentrifuged by, for example, sucrose density gradient centrifugation to give a purified virus solution. The purified virus solution was inactivated with β-propiolactone and formalin to give a purified inactivated virus solution. And then, the solution was ultrafiltered to give a virus stock solution.
Inactivated whole antigen of influenza virus A/Victoria/365/2011 (H3N2)	60 µg HA	
Inactivated whole antigen of influenza virus B/Wisconsin/01/2010	60 µg HA	
Sodium hydrogen phosphate hydrate	3.53 mg	
Sodium dihydrogen phosphate	0.54 mg	
Sodium chloride	8.50 mg	
Purified water	Total 1.0 mL	

[0055]

<Mixture of gel base material and virus stock solution>

5 Example of gel base material (1) and each of Examples of virus stock solution (1) - (3) mentioned above were mixed in the ratio of 1:1 under stirring to give each homogeneous influenza vaccine composition, Examples 1, 2, and 3, respectively. The compositions of each Example and

10 their physical properties/spray-performances obtained with a spray device or a syringe-based squirt are shown below. The mixing under stirring can be completed softly and in a short time without stressing the inactivated whole antigen of virus. The quantities of each ingredient in the

resulting influenza vaccine compositions, the physical properties thereof, and the spray-performances thereof derived by spraying the compositions with a suitable device are also shown below.

Example 1

Ingredients	Amount	Physical property/spray-performance
Inactivated whole antigen of influenza virus A/Victoria/210/2009 (H3N2)	90 µg HA	pH: 7.25 Viscosity: 500 mPa·s Spray-performance in spraying 250 µL of the solution with a spray device: ·Mean particle size of sprayed formulation: 52.7 µm ·Ratio of particle size between 10 µm and 100 µm: 91.5 % ·Spray angle from the device: 53° ·Spray density: full-corn uniformly-circle
Carboxy vinyl polymer	5.50 mg	
L-arginine	12.00 mg	
Concentrated glycerin	10.00 mg	
Sodium hydrogen phosphate hydrate	1.765 mg	
Sodium dihydrogen phosphate	0.270 mg	
Sodium chloride	4.25 mg	
Purified water	q.s.	
Total	1.0 mL	

5 [0056]

Example 2

Ingredients	Amount	Physical property/spray-performance
Inactivated whole antigen of influenza virus A/Indonesia/5/05 (H5N1)	90 µg HA	pH: 7.10 Viscosity: 430 mPa·s Osmotic pressure: 293 mOsm Spray-performance in spraying 250 µL of the solution with a spray device: ·Mean particle size of sprayed formulation: 55.2 µm ·Ratio of particle size between 10 µm and 100 µm: 95.0 % ·Spray angle from the device: 51° ·Spray density: full-corn uniformly-circle
Carboxy vinyl polymer	5.50 mg	
L-arginine	12.00 mg	
Concentrated glycerin	10.00 mg	
Sodium hydrogen phosphate hydrate	1.765 mg	
Sodium dihydrogen phosphate	0.270 mg	
Sodium chloride	4.25 mg	
Purified water	q.s.	
Total	1.0 mL	

[0057]

Example 3

Ingredients	Amount	Physical property/spray-performance
Inactivated whole antigen of influenza virus A/California/7/2009(H1N1)pdm09	30 µg HA	pH: 7.15 Viscosity: 520 mPa·s Osmotic pressure: 295 mOsm Spray-performance in spraying 250 µL of the solution with a spray device: ·Mean particle size of sprayed formulation: 57.4 µm ·Ratio of particle size between 10 µm and 100 µm: 95.0 % ·Spray angle from the device: 52° ·Spray density: full-corn uniformly-circle Spray-performance in spraying 250 µL of the solution with a syringe-based squirt ·Mean particle size of sprayed formulation: 56.5 µm ·Ratio of particle size between 10 µm and 100 µm: 88.2% ·Spray angle from the device: 51.48° ·Spray density: full-corn uniformly-circle
Inactivated whole antigen of influenza virus A/Victoria/365/2011 (H3N2)	30 µg HA	
Inactivated whole antigen of influenza virus B/Wisconsin/01/2010	30 µg HA	
Carboxy vinyl polymer	5.50 mg	
L-arginine	12.00 mg	
Concentrated glycerin	10.00 mg	
Sodium hydrogen phosphate hydrate	1.765 mg	
Sodium dihydrogen phosphate	0.270 mg	
Sodium chloride	4.25 mg	
Purified water	q.s.	
Total	1.0 mL	

[0058]

Example 4

Ingredients	Amount	Physical property/spray-performance
Inactivated whole antigen of influenza virus A/California/7/2009(H1N1)pdm09	30 µg HA	pH: 7.17 Viscosity: 525 mPa·s Osmotic pressure: 291 mOsm Spray-performance in spraying 250 µL of the solution with a syringe-based squirt: ·Mean particle size of sprayed formulation: 59.6 µm (see, Fig. 5) ·Ratio of particle size between 10 µm and 100 µm: 85.6 % (see, Fig. 5) ·Spray angle from the device: 52.27° (see, Fig. 6) ·Spray density: full-corn uniformly-circle (see, Fig. 7)
Inactivated whole antigen of influenza virus A/Victoria/365/2011 (H3N2)	30 µg HA	
Inactivated whole antigen of influenza virus B/Brisbane/60/2008	60 µg HA	
Carboxy vinyl polymer	5.50 mg	
L-arginine	12.00 mg	
Concentrated glycerin	10.00 mg	
Sodium hydrogen phosphate hydrate	1.765 mg	
Sodium dihydrogen phosphate	0.270 mg	
Sodium chloride	4.25 mg	
Purified water	q.s.	
Total	1.0 mL	

[0059]

As an influenza vaccine composition without a gel base material, Comparative examples 1 - 4 were prepared according to the compositions shown in the following tables by optionally using the inactivated whole antigen used in the above examples.

Comparative example 1

Ingredients	Amount
Inactivated split antigen of influenza virus A/Uruguay/716/2007(H3N2)	90 µg HA
Sodium hydrogen phosphate hydrate	3.53 mg
Sodium dihydrogen phosphate	0.54 mg
Sodium chloride	8.50 mg
Purified water	q.s.
Total	1.0 mL

[0060]

Comparative example 2

Ingredients	Amount
Inactivated whole antigen of influenza virus A/Indonesia/5/05 (H5N1)	90 µg HA
Sodium hydrogen phosphate hydrate	3.53 mg
Sodium dihydrogen phosphate	0.54 mg
Sodium chloride	8.50 mg
Purified water	q.s.
Total	1.0 mL

[0061]

Comparative example 3

Ingredients	Amount
Inactivated whole antigen of influenza virus A/California/7/2009 (H1N1)pdm09	30 µg HA
Inactivated whole antigen of influenza virus A/Victoria/365/2011 (H3N2)	30 µg HA
Inactivated whole antigen of influenza virus B/Wisconsin/01/2010	30 µg HA
Sodium hydrogen phosphate hydrate	3.53 mg
Sodium dihydrogen phosphate	0.54 mg
Sodium chloride	8.50 mg
Purified water	q.s.
Total	1.0 mL

[0062]

Comparative example 4

Ingredients	Amount
Inactivated split antigen of influenza virus A/California/7/2009 (H1N1)pdm09	30 µg HA
Inactivated split antigen of influenza virus A/Victoria/365/2011 (H3N2)	30 µg HA
Inactivated split antigen of influenza virus B/Wisconsin/01/2010	30 µg HA
Sodium hydrogen phosphate hydrate	3.53 mg
Sodium dihydrogen phosphate	0.54 mg
Sodium chloride	8.50 mg
Purified water	q.s.
Total	1.0 mL

[0063]

5 Test for Evaluating Immune Response (1)

With each influenza vaccine composition prepared in

Example 1 and Comparative example 1, two groups composed of 4 adult volunteers in each group were vaccinated by nasal spray-administration with an appropriate disposable device, in an amount of 0.25 mL for one nostril (equivalent of 45
5 μ g HA for both nostrils), twice at an interval of 3 weeks.

The blood and the washings of nasal cavity were consecutively collected, and the neutralizing antibody titer thereof for vaccine strain was measured and analyzed. The results are shown in Table 1 for Example 1, and Table 2
10 for Comparative example 1.

Table 1

No.	Sex	Neutralizing antibody titer in serum			Neutralizing antibody titer in washings of nasal cavity		
		Initial (pre)	3 weeks later	6 weeks later	Initial (pre)	3 weeks later	6 weeks later
01	M	80	≥ 1280	≥ 1280	40	640	640
02	M	5	5	40	<20	<20	40
03	F	20	160	320	<20	40	40
04	F	640	≥ 1280	≥ 1280	40	40	160

Table 2

No.	Sex	Neutralizing antibody titer in serum			Neutralizing antibody titer in washings of nasal cavity		
		Initial (pre)	3 weeks later	6 weeks later	Initial (pre)	3 weeks later	6 weeks later
01	M	40	160	160	20	80	160
02	M	<10	<10	10	20	20	80
03	M	20	20	20	40	80	320
04	M	<10	<10	<10	20	20	80

Comparing the results of the vaccine of Example 1 (the virus stock solution + the gel base material) and the

vaccine of Comparative example 1 (a composition comprising the inactivated split antigen of influenza virus without the gel base material), the neutralizing antibody titer in serum of 3/4 subjects vaccinated with the vaccine of Comparative example 1 did not increase, while the neutralizing antibody titer in serum of 4/4 subjects vaccinated with the vaccine of Example 1 increased, and that significantly increased. The neutralizing antibody titer in washings of nasal cavity increased in all cases about both the vaccines of Example 1 and Comparative example 1, but the vaccine of Example 1 showed greater increase.

[0064]

Test for Evaluating Immune Response (2)

With each influenza vaccine composition prepared in Example 2 and Comparative example 2, two groups composed of 25 adult volunteers for Example 2 and 24 adult volunteers for Comparative example 2 were vaccinated by nasal spray-administration with an appropriate disposable device, in an amount of 0.25 mL for one nostril (equivalent of 45 µg HA for both nostrils), twice at an interval of 3 weeks, and one more time about a half year later, totally three times.

The blood and the washings of nasal cavity were collected 3 weeks after the third vaccination, and the neutralizing antibody titer thereof to vaccine strain was

measured and analyzed. The results are shown in Table 3.

Table 3

	Variation of neutralizing antibody titer to A/Indonesia/5/05 (H5N1)							
	Serum				Washings of nasal cavity			
	Example 2		Comparative example 2		Example 2		Comparative example 2	
	pre	post	pre	post	pre	post	pre	post
Geometric mean titer* (GMT)	5.0 (<10)	164.5	5.0 (<10)	84.8	10.0 (<20)	105.6	10.0 (<20)	46.2
GMT percentage of rise		32.9		17.0		10.5		4.6

Comparing the results of the vaccine of Example 2 (the virus stock solution + the gel base material) and the vaccine of Comparative example 2 (only the virus stock solution), it was shown that the vaccine of Example 2 comprising the gel base material increased the immune response more greatly than that of Comparative example 2.

It is known that a human in a naive state who has never contacted influenza virus antigen (such as babies and children) induces less immune response. It is thought that the immune response in such susceptible individuals to influenza vaccine can be estimated by evaluating the immune response in healthy adults to the vaccine of highly pathogenic avian influenza virus (H5N1 stain) because almost all healthy adults have never contacted the avian influenza virus (i.e., in a naive state).

As shown in the above results, it has been found that even for susceptible individuals, the neutralizing antibody

titer in serum and washings of nasal cavity can be induced in high level by nasally-vaccinating the vaccine of Example 2 (the virus stock solution + the gel base material) three times.

5 [0065]

Analytical Test of Immune Response (3)

With each influenza vaccine composition prepared in Example 3, Comparative example 3 and Comparative example 4, two groups composed of 47 adult volunteers for Example 3
10 and 47 adult volunteers for Comparative example 3 were vaccinated by nasal administration with a syringe-based squirt, in an amount of 0.25 mL for one nostril (in total, 15 µg HA/strain/0.5 mL for both nostrils), twice at an interval of 3 weeks. And, with the influenza vaccine
15 composition prepared in Comparative example 4 (currently-used vaccine), a group composed of 38 adult volunteers was subcutaneously vaccinated once in an amount of 0.5 mL (15 µg HA/strain/0.5 mL).

The blood and the washings of nasal cavity were
20 collected 3 weeks after the final vaccination (2nd or 1st), and the neutralizing antibody titer thereof to vaccine strain was measured and analyzed. Tables 4 and 5 show each result about the different kinds of influenza vaccine.

Table 4

	Variation of neutralizing antibody titer to A/California/7/2009 (H1N1)pdm09					
	Neutralizing antibody titer in serum					
	Example 3		Comparative example 3		Comparative example 4	
	nasal		nasal		subcutaneous	
	pre	post	pre	post	pre	post
Geometric mean titer* (GMT)	64.12	160.00	80.00	119.13	110.00	285.98
GMT percentage of rise		2.50		1.49		2.60

	Variation of neutralizing antibody titer to A/California/7/2009 (H1N1)pdm09					
	Neutralizing antibody titer in washings of nasal cavity					
	Example 3		Comparative example 3		Comparative example 4	
	nasal		nasal		subcutaneous	
	pre	post	pre	post	pre	post
Geometric mean titer* (GMT)	20.90	56.99	21.85	46.36	25.35	25.82
GMT percentage of rise		2.73		2.12		1.02

Table 5

	Variation of neutralizing antibody titer to A/Victoria/365/2011 (H3N2)					
	Neutralizing antibody titer in serum					
	Example 3		Comparative example 3		Comparative example 4	
	nasal		nasal		subcutaneous	
	pre	post	pre	post	pre	post
Geometric mean titer* (GMT)	88.7	245.39	86.12	169.72	148.45	332.22
GMT percentage of rise		2.77		1.97		2.24

	Variation of neutralizing antibody titer to A/Victoria/365/2011(H3N2)					
	Neutralizing antibody titer in washings of nasal cavity					
	Example 3		Comparative example 3		Comparative example 4	
	nasal		nasal		subcutaneous	
	pre	post	pre	post	pre	post
Geometric mean titer* (GMT)	24.95	80.00	28.49	77.67	28.80	29.88
GMT percentage of rise		3.21		2.73		1.04

Comparing the results of the nasally-administered vaccine of Example 3 (the virus stock solution + the gel base material), the nasally-administered vaccine of Comparative example 3 (only the virus stock solution), and the subcutaneously-administered vaccine of Comparative example 4 (currently-used vaccine for subcutaneous-administration), it was shown that the nasally-administered vaccine of Example 3 comprising the gel base material increased the immune response more greatly than that of the nasally-administered vaccine of Comparative example 3. In addition, from the results in the washings of nasal cavity, the nasally-administered vaccine group of Example 3 showed the elicitation of neutralizing antibody on the nasal mucosa, but the subcutaneously-administered vaccine (currently-used vaccine) group of Comparative example 4 did not show the elicitation.

[0066]

Thus, by filling a medical syringe having a tip

opening in fluid communication with a syringe barrel, which is equipped with a rhinal spray nozzle comprising a hollow nozzle body having a tip portion defining a nozzle orifice thereon, a solid packing rod arranged within the nozzle
5 body, and a nozzle chamber defined between the packing rod and the nozzle body to allow a fluid communication between the tip opening and the nozzle orifice, wherein the nozzle orifice has a diameter in a range between 0.25 mm and 0.30 mm

10 with the formulation for nasally-administering influenza vaccine of Example 4 which was prepared with a gel base material prepared by adding an outside shearing force,

a rhinovaccination system of influenza vaccine having
15 spray-performance which is to control that (1) as for the particle-size-distribution of the sprayed composition, the mean particle size is in a range of 30 μm to 80 μm [59.6 μm], and the particle distribution between 10 μm and 100 μm is 80 % or more [85.6%], (2) the spray density is uniform
20 to form a homogeneous full-corn shape, and (3) the spray angle is adjusted in a range of 30° to 70° [52.27°] was able to be prepared.

Denotation of Reference Numerals

25 [0067]

1: medical syringe, 2: pharmaceutical formulation, 3:
syringe barrel, 4: syringe body, 5: plunger rod, 5a: fixing
member, 6: opening, 7: piston, 8: finger flange, 9: plunger
end member, 10: rhinal spray nozzle, 20: nozzle body, 21:
5 nozzle orifice, 22: tip portion, 23: inner wall, 23a:
protrusion, 24: internal space, 25: nozzle small-diameter
portion, 26: nozzle large-diameter portion, 27: nozzle
shoulder, 30: packing rod, 33: outer wall, 33a: recess, 35:
rod small-diameter portion, 36: rod large-diameter portion,
10 37: rod shoulder, 38, 39: groove, 40: gap, 42: nozzle
chamber, 44: vortex-flow generation member, 46: curved
portion, 50: protection cap.

CLAIMS

1. A rhinovaccination system of influenza vaccine, comprising a syringe-based squirt filled with an influenza vaccine composition which comprises (i) an inactivated whole influenza virion, and (ii) a gel base material comprising carboxy vinyl polymer which is treated by adding an outside shearing force to add spray-performance, which is characterized by not comprising an adjuvant.
2. The rhinovaccination system of influenza vaccine according to claim 1, wherein the syringe-based squirt is a medical syringe having a tip opening in fluid communication with a syringe barrel, which is equipped with a rhinal spray nozzle comprising
- a hollow nozzle body having a tip portion defining a nozzle orifice thereon,
- a solid packing rod arranged within the nozzle body, and
- a nozzle chamber defined between the packing rod and the nozzle body to allow a fluid communication between the tip opening and the nozzle orifice,
- wherein the nozzle orifice has a diameter in a range between 0.25 mm and 0.30 mm.
3. The rhinovaccination system of influenza vaccine

according to claim 1 or 2, wherein the amount of (i) the inactivated whole influenza virion is 1 - 500 µg HA/mL per type of vaccine virus strain.

5 4. The rhinovaccination system of influenza vaccine according to any one of claims 1 to 3, wherein the influenza vaccine composition comprises 0.1 w/v % to 1.0 w/v % carboxy vinyl polymer.

10 5. The rhinovaccination system of influenza vaccine according to any one of claims 1 to 4, wherein the spray-performance is to control (1) the particle-size-distribution of the sprayed composition, (2) the uniformity of spray density, and/or (3) the spray angle.

15

6. The rhinovaccination system of influenza vaccine according to any one of claims 1 to 3, wherein the influenza vaccine composition is prepared by treating a gel base material comprising 0.5 w/v % to 2.0 w/v % carboxy vinyl polymer by adding an outside shearing force to control (1) the particle-size-distribution of the sprayed composition, (2) the uniformity of spray density, and/or (3) the spray angle, as spray-performance, to give a gel base material, and then

25 mixing the resulting gel base material with a virus

stock solution comprising an inactivated whole influenza virion homogeneously in a short time without stress.

7. The rhinovaccination system of influenza vaccine
5 according to any one of claims 1 to 6, wherein the influenza vaccine composition is prepared with a gel base material comprising carboxy vinyl polymer that is treated by adding an outside shearing force to add spray-performance which is to control that (1) as for the
10 particle-size-distribution of the sprayed composition, the mean particle size is in a range of 30 μm to 80 μm ; and the particle distribution between 10 μm and 100 μm is 80 % or more,
(2) the spray density is uniform to form a homogeneous
15 full-corn shape, and
(3) the spray angle is adjusted in a range of 30° to 70°.

8. The rhinovaccination system of influenza vaccine
20 according to any one of claims 1 to 6, wherein the influenza vaccine composition is prepared with a gel base material comprising carboxy vinyl polymer that is treated by adding an outside shearing force to add spray-performance which is to control that (1) as for the
25 particle-size-distribution of the sprayed composition, the

mean particle size is in a range of 40 μm to 70 μm , and the particle distribution between 10 μm and 100 μm is 90 % or more,

(2) the spray density is uniform to form a homogeneous
5 full-corn shape, and

(3) the spray angle is adjusted in a range of 40° to 60°.

9. The rhinovaccination system of influenza vaccine
10 according to any one of claims 2 to 8, wherein the nozzle orifice includes substantially no curved portion.

10. The rhinovaccination system of influenza vaccine
according to any one of claims 2 to 9, wherein the tip
15 portion defining the nozzle orifice has thickness along an injection direction of the formulation which is in a range between 0.20 mm and 0.30 mm.

11. The rhinovaccination system of influenza vaccine
20 according to any one of claims 2 to 10,

wherein the nozzle body includes an inner wall having at least a portion formed in a cylindrical shape and the packing rod includes an outer wall at least a portion formed in a cylindrical shape having a plurality of
25 circumferentially spaced grooves,

wherein the nozzle chamber is defined between the at least portion of the inner wall of the nozzle body and the at least portion of the outer wall of the packing rod, and

5 wherein the packing rod includes a vortex-flow generation member opposed to the tip portion of the nozzle body.

12. The rhinovaccination system of influenza vaccine according to claim 11, wherein the vortex-flow generation
10 member is formed so that a flow direction of the formulation from the grooves of the packing rod is offset to a central axis, thereby to generate a vortex flow of the formulation.

15 13. The rhinovaccination system of influenza vaccine according to claim 11 or 12, wherein the at least portion of the inner wall of the nozzle body is formed to have a cross section substantially-perpendicular to the injection direction which is continuously or step-wisely reduced
20 towards the injection direction.