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NOVEL DRUG DELIVERY SYSTEM OF HEMAGGLUTININ VACCINE

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Background

The influenza virus is a respiratory disease spread by coughing or sneezing from an infected person by breathing from one patient to another. The global burden of 1 billion infections and between 3 and 5 million cases of severe illness caused by influenza epidemics is projected each year. There are currently two major types of influenza vaccine available: the inactivated vaccine (monovalent and protective against the strain A (H1N1)) and the live attenuated vaccine. Then a different influenza virus was isolated (influenza B) in 1940 and the first bivalent vaccine was tested in healthy adults. Many inactive vaccines are currently being developed in embryonic chicken eggs from propagation. However, a limiting factor is the availability of embryonated chicken eggs, and global production is not expected to meet the increasing demand for doses during the pandemic season. New influenza A strains with specific HA and NA were reported in the late 1970s. Since then, in most influenza vaccines, called trivalent influenza vaccine (TIV), two influenzas A strains (H1N1 and H3N2 subtypes) and one influenza B strain have been included (l.Barberis, 2013).

Reference

The influenza virus is a member of the family Orthomyxoviridae that consists of an RNA genome with a single-stranded negative sense. Based on antigenic variations in viral nucleoprotein (NP) and matrix proteins composed of influenza A and B viruses causing seasonal epidemics, with an attack rate between 5%-10% to 20%-30% in adults and children each year, resulting in 3 to 5 million infections. It is predicted that it will take six months to produce seasonal influenza vaccines and move from obtaining the reference strain through viral dissemination, purification, inactivation, and eventually to development. An

approximate 70-90 percent of people with chronic health conditions accompanying the ineffective vaccine is safe in healthy people and 50-70 percent. This causes a higher response of mucosal IgA in live attenuated vaccines provided intranasally, and is believed to provide immunity from infection from other subtypes. However, since the vaccine contains a live virus that is adjusted only to temperatures below 25 8C, recipients are restricted to individuals between 5 and 49 years of age (Chen, J.-R, 2011).

Formulation

World Health Organization (WHO) official recommendation dor quadrivalent vaccine that use in 2019-2020 northern hemisphere influenza season. Fluquadri® contained types of virus antigens that are in accordance with the requirements of the Australian Influenza Vaccine Committee and WHO recommendations. The quadrivalent inactivated influenza vaccine contain

- A H1N1 pandemic09 (A/Brisbane/02/2018)
- A H3N2 (A/Kansas/14/2017)
- B/Colorado/06/2017 (Victoria lineage)
- B/Phuket/3073/2013 (Yamagata lineage)

The production of the Fluquadri® vaccine used conventional egg inoculation method and producing “Split Virus”. The “Split Virus” are purified and suspended in an isotonic solution of sodium chloride sodium phosphate. Viral antigens from the four strains included in the vaccine are produced separately and then combined to make quadrivalent formulation.

Pharmacodynamic

The inoculation of antigen prepared from inactivated influenza virus that stimulate specific antibody production. Influenza virus vaccine imparts immunity against the influenza virus by stimulating production of antibodies that are specific to the disease. Fluquadri® vaccine has been shown to induce antibodies to the surface glyprotein, hemagglutinin. The trimeric hemagglutinin glycoprotein acts by promoting attachment of the virus to the host cell surface resulting in fusion and thereby releasing virions into the cytoplasm. HA protein surface consists of two structural element, the head and the stalk where the head is the main target of antibodies that provide protection against influenza viruses. The quadrivalent vaccine provides active immunization against four types of influenza viruses (two subtypes A and two types B).

Protection from influenza virus infection has not been correlated with a specific level of hemagglutinin inhibition (HI) antibody titer post-vaccination but HI antibody titres have been used as a measure of vaccine activity and currently the best available surrogate marker of activity that is reasonably likely to predict clinical benefit. Annual influenza vaccination is recommended because the types circulating strains of influenza virus may change and mutate from year to year and also as immunity declines during the year after vaccination.

Pharmacokinetics

The inactivated influenza virus vaccine is administered intramuscularly or intradermal vaccines. The effectiveness of a vaccine depends on several host factors such as age (usually 70- 90% effective in healthy people under 65 years of age), underlying health status, genetic status and furthermore on antigenic matches between the vaccine and circulating viruses. The protective effect of HA vaccine usually occurs within 10 to 14 days of administration. Post-vaccine antibody titres in young adults and healthy children generally tend to be high enough to provide reistance infection by strains found in vaccines. Some studies have shown that HI titers ranging from 1:32 to 1:40 are associated with protection against disease in approximately 50% of subjects, and that protection against disease correlates with higher titers. This increased response is seen in subjects with the underlying disease (cardiovascular, respiratory, and diabetes) who are at increased risk of complications of influenza infection and in elderly subjects with low pre- immunization titre. The duration of the immune effect of influenza vaccine is generally 6 to 12 months. HA vaccine is not recommended mixed with other vaccines in the same syringe or vial.

Vaccine storage

Vaccines must be stored at temperatures between +2°C - +8°C at all times to maintain their potential and effectiveness. the temperature of the vaccine refrigerator should be kept tight at temperature +5°C to protect the vaccine from temperature fluctuations that can occur. before stocking the vaccine the internal refrigerator temperature must also be stabilized between +2°C - +8°C for 7 consecutive days. Refrigerator organization for vaccine are: vaccine storage in the refrigerator must be away from the walls of the refrigerator, floor and cold air vents, because it can increase the risk of increasing temperatures. Keep it in the middle shelf, never store it in the refrigerator door drawer because it can cause the vaccine to be exposed to warmer temperatures. Leave space between the vaccine packages, so that good air circulation occurs. Keep the vaccine in its original package to protect the vaccine from exposure to light.

Keep bottled water in the bottom shelf or refrigerator door to help keep the temperature stable in the refrigerator. Temperature monitoring is an important requirement for vaccine temperature monitoring. Temperature monitoring devices are calibrated to an accuracy of ± 1 ° C and must be checked for accuracy every year. Temperature monitoring devices also become less accurate if the batteries are low, so the battery must be replaced a maximum every 6 months. To facilitate the continuous temperature recording of the refrigerator, it can use a data logger equipped with a digital screen display so that the temperature can be seen visually. This device can save temperature readings that can be downloaded to a computer. but, the minimum, maximum and current temperatures still need to be recorded manually as a timely alert to any breach in the cold chain (Storage, V. 2009).

Administration

There are several routes of vaccine administration, in this case, intramuscular injection of choice. Intramuscular injection (IM) is giving the vaccine into muscle mass. Injection techniques are the most important parameter for ensuring efficient delivery of intramuscular vaccines. For all intramuscular injections, the needle must be long enough to reach muscle mass and prevent the vaccine from seeping into the subcutaneous tissue, intramuscular injections are administered at a 90-degree angle to the skin, preferably into the anterolateral aspect of the thigh or the deltoid muscle of the upper arm, depending on the age of the patient. The measuring needle for intramuscular injection is 22-25 gauge. The length of the needle and injection site for each person is based on the size of the muscle, the thickness of the adipose tissue at the injection site, the volume of material to be given, the injection technique, and the depth at which the drug material will be injected under the surface of the muscle.

For most infants **(<12 months old)**, the anterolateral aspect of the thigh is the recommended place for injection because it provides a relatively greater muscle mass than a deltoid with a 1-inch needle is enough to penetrate the thigh muscle. For toddlers **(12 Months-2 Years Old)**, anterolateral thigh muscles are preferred with a needle length of at least 1 inch. Deltoid muscles are preferred for children aged 3-10 years, with needle lengths ranging from ⅝ to 1 inch based on technique. Deltoid muscle is preferred for adolescents aged 11-18 years. Anterolateral thighs can also be used. For injection into the anterolateral thigh, most teenagers will need a 1-1.5 inch needle to ensure intramuscular administration. For adults, deltoid muscles are recommended for routine intramuscular vaccination. For men and

women weighing <130 lbs (<60 kg), a ⅝ inch needle is sufficient to ensure intramuscular injection of deltoid muscle if the injection is performed at an angle of 90 degrees and the tissue is not bound. For men and women weighing 130-152 lbs (60-70 kg), a 1-inch needle is sufficient. For women weighing 152-200 lbs (70-90 kg) and men weighing 152-260 lbs (70-118 kg), a needle of 1 to 1.5 inches is recommended. For women weighing> 200 lbs (> 90 kg) or men weighing> 260 lbs (> 118 kg), a 1.5-inch needle is recommended (Centers for Disease Control and Prevention. (2017).

Novel drug delivery system of hemagglutinin vaccine

Trade name	Presentation	Route	Vaccine Type	Age Indication	Registrant
Flubio (Bio Farma)	2.5 mL each;Multiple-dose vial 0.5 mL each; Single-dose vial	IM	Inactivated Influenza Vaccine Trivalent-Egg based	For persons >12 years	Biofarma-Indonesia
Fluquadri and Fluquadri Junior (Sanofi)	0.50 mL; Single-dose, prefilled syringe (clear plunger rod), 0.25 mL Single-dose, prefilled syringe (pink plunger rod)	IM	Inactivated Influenza Vaccine Quadrivalent - Egg based	For persons >36 months For children 6 to 35 months	Aventis pharma-Indonesia
Vaxigrip (Sanofi)	0.50 mL; Single-dose, prefilled syringe 0.25 mL; Single- dose, prefilled syringe	IM	Inactivated Influenza Vaccine Quadrivalent -Egg based	For adults and children over 36 months For children6 to 35 months	Biofarma-Indonesia
Fluarix(GlaxoSmithKl ine)	0.50 mL; Multiple-dose, prefilled syringe	IM	Inactivated Influenza Vaccine Quadrivalent -Egg based	For adults and children over 6 months	SMITH KLINE BEECHAM PHARMACEUTICAL IND.-Indonesia
INFLUVAC TETRA NH quadrivalent)-Abbott Indonesia	0.50 mL; Single- dose, prefilled syringe	IM	Inactivated Influenza Quadrivalent -Egg based	For adults and children over 3 years	ABBOTT-Indonesia

Based on the above table, all influenza vaccines registered in Indonesia in 2019 are all inactivated influenza vaccines. Influenza vaccines are developed twice a year to deal with changes in the virus. The recommended influenza vaccine for use in Indonesia in 2019 is in accordance with the table above. Annual vaccinations for people over six months and high-risk people, including (pregnant women, parents, people who have health problems or diseases) are recommended by the World Health Organization (WHO).

There are several different type of vaccines such as live-attenuated vaccines, inactivated vaccines, and (subunit, recombinant, polysaccharide, and conjugate vaccines). All of them also have some limitations, for example live-attenuated vaccines because they contain a small amount of the weakened live virus, peope with weakened immune systems, long-term health problems, or people who've had an organ transplant, must be careful and should talk to the doctor before receiving the vaccines. Inactivated vaccines is a type of vaccine that is very widely used and registered in Indonesia today, its also has some limitations inactivated vaccines usually don't provide immunity (protection) that's as strong as live vaccines. So its may need several doses over time in order to get ongoing immunity against diseases. And type vaccines is subunit, recombinant, polysaccharide, and conjugate vaccines, one limitation of these vaccines is need booster shots to get ongoing protection against diseases. Based on the limitations of the vaccines type we chose to use virosome.

A virosome is a virus-like particle but does not contain or have the genetic makeup of the virus. Made like the original virus consisting of a newly formed influenza virus envelope. Virosomes are produced from influenza virus through a detergent solubilization and removal procedure. Properly reconstituted virosomes retain the cell binding and membrane fusion properties of the native virus, mediated by the viral envelope glycoprotein haemagglutinin. These functional characteristics of virosomes form the basis for their enhanced immunogenicity. First, virosomes represent an antigen presentation system that activates both the humoral and the cellular arm of the immune system, such that not only solid antibody responses but also cell- mediated immunity is induced. Second, virosomes provide the opportunity to incorporate lipophilic or amphiphilic adjuvants in the vaccine for specific boosting of the antibody response against the viral haemagglutinin.

Most of the routes for administering vaccines are by injection, which has several disadvantages, namely causing injury and causing pain. Therefore, we devised a new method for administering vaccines through nasal spray. this has the advantage of not using needles so

they do not cause pain, and this route can be local and more targeted which has easy access to important parts of the immune system.

This nasal spray method is not recommended for children under 2 years old, pregnant women, people who have a history of allergies to influenza vaccines, as well as people aged 50 years and over. This administartions method is also contraindicated for patients using aspirin or salicylic acid (for ages 2-17 years), asthma patients who have a history of wheezing in the last 12 months.

REFERENCE

1. Andrew J. Broadbent, Kanta Subbarao, in Mucosal Immunology (Fourth Edition), 2015.
2. Australian Public Assessment Report for Influenza Virus Haemagglutinin H1N1, H3N2, B Victoria lineage, B Yamagata lineage, Therapeutic goods Administration, 2015.
3. Barberis., M.Martini., F.Iavarone., & A. Orsi. Available influenza vaccines: immunization strategies, history and new tools for fighting the disease. Journal of Preventive Medicine and Hygine, 2013; 57(1): E41–E46. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4910442/#
4. Centers for Disease Control and Prevention. Vaccine recommendations and guidelines of the ACIP: contraindications and precautions, 2017.
5. Chen, J.-R., Ma, C., & Wong, C.-H. Vaccine design of hemagglutinin glycoprotein against influenza. *Trends in Biotechnology*, 2011; *29(9): 426–434.* doi:10.1016/j.tibtech.2011.04.007
6. De Bruijn, I. A., Nauta, J., Gerez, L., & Palache, A. M. *The virosomal influenza vaccine Invivac®: Immunogenicity and tolerability compared to an adjuvanted influenza vaccine (Fluad®) in elderly subjects. Vaccine*, 2006; *24(44-46): 6629–6631.* doi:10.1016/j.vaccine.2006.05.035
7. Huckriede, A., Bungener, L., Stegmann, T., Daemen, T., Medema, J., Palache, A. M., & Wilschut, J. *The virosome concept for influenza vaccines. Vaccine*, 2005; *23: S26– S38.* doi:10.1016/j.vaccine.2005.04.026
8. N. Marasini, I. Toth, in Micro and Nanotechnology in Vaccine Development, 2017.
9. Peter C.Soema, Ronald Kompier et al. *Current and Next Generation Influenza Vaccines: Formulation and Production Strategies.* European Journal of Pharmaceuticals and Biopharmaceutical, 2015; 94(2015): 251-263.
10. Storage, V. Handling Guidelines. *Perth district health unit Ontario-Canada*, 2009.

11. WHO Inflfluenza. (Seasonal), 2014.
12. Yusuf, H., & Kett, V. *Current prospects and future challenges for nasal vaccine delivery. Human Vaccines & Immunotherapeutics,* 2016; *13(1): 34–45.* doi:10.1080/21645515.2016.1239668