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Pandemic Vaccine Development in India: Case of Influenza A H1N1

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ABSTRACT

H1N1 virus emerged as the pandemic worldwide in 2009 and its reappearance was held in India in 2013. As H1N1 is a new strain of flu mutation, conventional flu vaccines and antiviral drugs are not found to be effective. Oseltamivir and zanamivir are the only one H1N1 antiviral drugs available, which are used for both prophylaxis and treatment. India has developed and launched their own vaccines (dead and living) H1N1 in 2010 after the creation of its safety and effectiveness, and with the approval of the Drug Controller General of India (DCGI). This review article focuses primarily on the influenza A H1N1 vaccines available in India; their target groups, indications, contraindications, indications for use, safety and efficiency aspects. It advises doctors to diagnose the disease not flu season and avoid prescribing these drugs (oseltamivir and zanamivir) indiscriminately routinely to prevent the emergence of resistance. Vaccines may be prescribed for prophylaxis, but the prescription should be evaluated individually.

I. INTRODUCTION

H1N1 (formerly known as swine flu in 2009) is a type of viral illness caused by a new strain of influenza virus. Due to its spread spread to many countries in 2009, H1N1A was declared as the pandemic influenza by WHO. In India, the resurgence of the H1N1 outbreak occurred in 2013 in Rajasthan exceeded in number of cases is concerned. Currently oseltamivir and zanamivir are the only drugs with proven efficacy for prophylaxis and treatment of cases. The indiscriminate use of these drugs should be avoided to prevent the emergence of resistance (CDC, 2009).

Like other flu viruses, H1N1 is transmitted from per-son to person through coughing, sneezing, runny nose and sometimes by fomites. The patient has a fever, runny nose, sore throat, sneezing, cough and myalgia. The recovery usually occurs within a week. Death can occur from H1N1 complications in susceptible patients with risk factors. Seasonal influenza virus genome expressed structural variations year to year, but they are closely related (CDC, 2009). Usually, if people had previous influenza infections have some immunity to seasonal flu viruses. In 2009 virus H1N1 flu was a new virus and different from seasonal flu viruses. Most people have little or no immunity against H1N1 (CDC, 2009; MOHFW, 2010). Because treatment options are rare and cases tends to increase in geometrical progression, great need to develop vaccines against H1N1 to control virus transmission was considered. India has developed and launched its inactivated and live attenuated vaccines in 2010, with the approval of IMCC (Controller General of India drugs).

VACCINATION GUIDELINES

Vaccines can be used as prophylaxis of influenza A H1N1. Vaccination for groups of people as suggested by CDC's Advisory Committee on Immunization Practices (ACIP) guidelines and pregnant women who are near attendees or contacts of infants under 6 months of age is recommended, health and emergency personnel, young children and adults under 50 years of age, the elderly> 65 years of age with chronic medical conditions and immune compromised patients (CDC, 2009; WHO, 2009).

INFLUENZA A H1N1 VACCINE TRIALS

In India, three pharmaceutical companies - Serum Institute of India (Pune), Bharat Biotech (Hyderabad) and Panacea Biotech (New Delhi) - have taken initiative to develop the vaccine against Influenza A H1N1. Serum Institute of India (Pune) has developed chick embryo vaccine whereas other two companies Bharat Biotech (Hyderabad) and Panacea Biotech (New Delhi) have developed cell line vaccines. Clinical trial studies were carried on healthy people in Hyderabad, Mumbai and Ahmadabad by serum institute of India and Bharat biotech. Although the trials started in adults, they were also tested in children as reported by vaccine adverse effects reporting system (VAERS). The safety

of the Influenza A H1N1 vaccine continues to be monitored by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) through reporting of vaccine related ad-verse effects to vaccine adverse effects reporting system (VAERS) (Kubavat et al, 2011; Kulkarni et al, 2012). Two types of vaccines have been developed in India commercially which are: (Kubavat et al, 2011; Kulkarni et al, 2012; http:// www.immune.org/vis).

INACTIVATED (KILLED) VACCINE

This vaccine is prepared by Zydus Cadila, Ahmadabad, Bharat Biotech, Hyderabad and Panacea, Delhi. Inactivated (killed) vaccine is a sterile suspension of influenza virus for Intramuscular or deep subcutaneous injection. It is a purified, inactivated, split virion vaccine and is prepared with A and B Strains of influenza virus corresponding to prevailing epidemiological evidence of the year, by the procedure of inoculation into embryonated hen (chick) eggs, harvested, concentrated, purified, split, inactivated and re-purified. This vaccine is prepared by purified Influenza virus haemagglutinin antigen (HA) from each of the following 3 viruses: A/California/7/2009(H1N1)-like virus, A/ Perth/16/2009(H3N2) - like virus, B/Brisbane/60/2008. The other components include: Potassium Phosphate Dibasic, Sodium Hydrogen Phosphate, Sodium Chloride, Thiomersal, and Potassium Chloride (Kubavat et al, 2011). Dose and schedule: The vaccine is to be given single shot i/m to be followed by booster every yearly and cost is around Rs 350/- per dose. For Children from 6-35 months: one 0.25 ml dose. If the child has not been previously vaccinated against influenza, a second dose should be given after at least 4 weeks.

Children 36 months to 8 years: one 0.5 ml dose. If the child has not been previously vaccinated against influenza infection, a second dose should be given after at least 4 weeks. Adults and children aged 9 years and above: one 0.5 ml dose. The vaccine may be used during pregnancy and lactation as animal studies have shown vaccine to be safe in these conditions (Kubavat et al, 2011).

Contraindications

Individuals with a history of hypersensitivity, especially to eggs, egg proteins, acute febrile illness.

Adverse effects

Redness, Swelling and pain may occur in injection site in some patient 12-24 hours after injection. Muscle ache, headache, dizziness, sweating, unfitness, fever, shivering and other systemic reactions may occur after vaccination. Normally, no treatment is needed. The reactions will automatically disappear in one or two days (http://www.immune.org/vis).

Allergic reaction is seldom seen. Rare reactions are neuralgia, arthralgia, paraesthesia, convulsion and transient thrombocytopenia. Extremely rare reactions are serious hypersensitivity reactions may lead to anaphylactic shock, vasculitis, encephalomyelitis, neuritis and Guillain- Barre syndrome (Girard et al, 2010; Kubavat et al, 2011).

Storage Instructions

The product should be stored at 2°C to 8° C (in a refrigerator) and protected from light, not to be freezed.

Human, Live Attenuated Influenza vaccine, (LAIV)

Pandemic (Influenza A H1N1), freeze dried is a live monovalent vaccine for administration by intranasal spray. The influenza vaccine contains Influenza virus cultivated on embryonated eggs. It is prepared by Serum Institute of India, Pune and has been launched with the brand name NASOVAC. Each single dose of 0.5 ml (spray 0.25 ml per nostril) contains: A/17/California/2009/38 > 107EID50, Gelatin, Sorbitol 5%, L-Alanine 0.1%, L-Histidine 0.21%, Tricine 0.3%, L-Arginine hydrochloride 1.6%, Lactalbumin hydro-lysate 0.35%, Phosphate buffer saline Base, Reconstitute with Sterile Water for Inhalation USP. The vaccine contains no preservatives (Kulkarni et al, 2012). Needle free device and intranasal spray device are also supplied along with the vaccine.

The tip attached to the sprayer is equipped with a nozzle that produces a fine mist that is primarily deposited in the nose and nasopharynx. The vaccine complies with the WHO recommendation. Cost of vaccine is Rs 200/- per dose in India and needs single dose administration for adults. Children 2 years of age may require 2 doses. Booster dose is required every year as 100% efficacy is not expected due to high mutagenicity seen in H1N1 virus. It takes 3weeks for vaccine to develop antibody response; therefore person is vulnerable to acquire H1N1 infection before 3 weeks. Immunity acquired lasts for one year (Kulkarni et al, 2012), (http://www.immune.org/vis).

The diluents supplied with vaccine to be used for reconstituting, not of other vaccines. Using incorrect diluents may result in damage to the vaccine and/or serious reactions to those receiving the vaccine. Diluents should be kept cool and must not be frozen.

Preclinical safety data: This LAIV has undergone single- dose and repeated-dose toxicity studies in mice and rats when administered intranasally. In single-dose studies, higher than normal doses of the vaccine were given to animals and they were observed for 14 days for toxic effects. No vaccine-related untoward effects were found in animals receiving LAIV. In repeated-dose toxicity studies, three doses of higher than normal doses of the vaccine were given intranasally to animals on day 0, 7 and 14 and were subsequently sacrificed. Necropsy was done to assess adverse effects on any organs. No vaccine-related adverse effects were found in the study animals receiving LAIV (Kulkarni et al, 2012).

Contraindication to use: Individuals with a history of hypersensitivity, especially to eggs, egg proteins, gentamicin, gelatin, or arginine or with reactions to previous influenza vaccinations. Severely compromised immune systems patients like AIDS, Cancer chemotherapy, should not get live attenuated vaccine. Patients on Aspirin Therapy (risk of Reye's syndrome). Severe asthma or active wheezing (inadequate data) Guillain-Barré syndrome should not receive influenza vaccine. The vaccine can be given to people with minor illnesses (e.g., diarrhoea or mild upper respiratory tract infection with or without fever). However, if nasal congestion is present that might limit delivery of the vaccine to the nasal lining, then delaying of vaccination until the nasal congestion is reduced should be considered (Vajo Z, 2010; Kulkarni et al 2012).

Pregnancy and lactation: Data from vaccinations with unadjuvanted inter-pandemic trivalent vaccines in pregnant women do not indicate that adverse foetal and maternal outcomes were attributable to the vaccine. Animal teratogenicity studies are on-going with LAIV. Healthcare providers need to assess the benefit and potential risks of administering the vaccine to pregnant and lactating women (Kulkarni et al, 2012).

Adverse Reactions: In clinical trials a few local and systemic reaction were observed. They were mild to moderate. Local reactions are nasal discomfort, stuffy nose, sneezing, runny nose, loss of smell red eyes, lacrimation, facial swelling. The systemic reactions are: Headache, fatigue, myalgia, arthralgia, irritability, loss of ap-petite, sore throat, cough, diarrhea (Song JY, 2010; Kulkarni et al, 2012).

CONCLUSION

With the vaccine development, it is now possible to control the transmission of Influenza A H1N1. Studies conducted by Serum Institute of India have shown that live attenuated vaccine is able to provide herd immunity apart from individual immunity so as to prevent the spread of virus across the barriers in a population. Therefore close contacts of patients and vulnerable age groups must get themselves vaccinated and boosters to be given every year. The benefit risk ratio is more than 1 and vaccines (inactivated and LAIV) have been of proven safety and efficacy. Oseltamivir (Tamiflu) or Zanamivir (Relenza) can be used for prophylaxis and treatment as per the CDC Advisory Committee Guidelines.

Storage Instructions: If the vaccine is not used immediately after reconstitution then it should be stored at 2-8ºC for no longer than 6 hours. While storing the reconstituted vaccine, ensure that the administration syringe is locked on to the needle free transfer de-vice and the combined unit is stored at 2 to 8ºC to ensure that the opening created by the device is blocked and the syringe is also stored in a manner which prevents the proliferation of bio-burden. Any opened container remaining at the end of a session (within six hours of reconstitution) should be discarded (Kulkarni et al, 2012).

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