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Clinical insights of influenza vaccine: Efficacy and Protectiveness

Madhu Khanna[1]*; Tanusri Nandi [1]; Saugata Roy [1]; Nilanshu Manocha [2]; Prashant Kumar [2]

[1]Department of Microbiology (Virology), Vallabhbhai Patel Chest Institute, University of Delhi. India.

[2]Amity Institute of Virology and Immunology, Amity University, Uttar Pradesh, India.

***corresponding author:** **Madhu Khanna**, Department of Virology (a Unit of Dept. of Microbiology), Vallabhbhai Patel Chest Institute, University of Delhi Delhi-110007, India.

Phone: +91-11-27402432

Email: madhukhanna@hotmail.com

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Introduction

Influenza A belongs to the family of *Orthomyxoviridae*. It is an enveloped virus with a genome made up of negative sense, single-stranded, segmented RNA. Among influenza A viruses that infect humans, three major subtypes of hemagglutinins (H1, H2, and H3) and two subtypes of neuraminidases (N1 and N2) have been described. This virus has evolved a number of mechanisms that enable it to invade host cells and subvert the host cell machinery for its own purpose, that is, for the sole production of more viruses [1]. The influenza virus has caused recurrent epidemics of acute febrile syndrome every 1 to 4 years for at least the recent centuries. The first epidemic report of an influenza-like illness was noted in 1173–74 [2], but the first definitive epidemic was reported in 1694 [3]. The greatest pandemic in recorded history occurred between 1918 and 1919, when approximately 21 million deaths were recorded worldwide [4]. It was among the deadliest events in reported human history. Afterward, 3 other pandemics occurred in the 20th century: the 1957 H2N2 pandemic, the 1968 H3N2 pandemic, and the 2009 influenza A (H1N1) virus (pH1N1) pandemic. In the most recent event, an influenza strain with a combination of gene segments not previously reported in the swine or human influenza virus strains was identified firstly in Mexico and then in the United States of America [5]. After the involvement of many countries, the pandemic was declared to be over in August 2010 [6].

Epidemiology

The swine flu virus was first identified as human pathogen in 1918 when pigs and humans were infected simultaneously. The pandemic virus was transmitted from humans to pigs, and divided into two lineages; human and porcine, which exist even today. The classical swine influenza lineage has evolved continuously since 1918, while the human lineage has caused many episodes of pandemics and endemics of influenza from 1918 to 1956. Human pathogenic strain apparently disappeared entirely around 1957 and reappears in 1977, and has circulated endemically in humans. Pathogenic strain for pigs appears in 1930. A new variant of H1N1 virus appeared in 1976, which shows lethal effect on many US army soldiers, and was found to be A/New Jersey/1976/H1N1. Studies revealed that the new strain was closely related to the 1918 pandemic strain. In 1988, appearance of a new with triple reassortant swine flu HIN1virus spreads in Wisconsin infected and killed many persons. In 1994, reassorted avian–human H1N2 influenza was isolated for the first time from UK. Further, between 1997 and 2002, the emergence of new strains (H3N2 and H4N6) was reported which cause influenza among pigs in North America. Between 1958 and 2005, 37 cases of swine influenza were reported among civilians, out of these 6 people died and 16 had a history of exposure to pigs. Since then, only 12 cases of human infection with swine influenza virus have been documented [7].

Table 1: Year wise out break with specific strains of influenza A virus**.** (Table taken from Khanna *et al* 2009).

Type of strain	Year	Outbreak
H1N1 influenza A appeared in pigs	1918–19	50 million people worldwide
H1N1 from pigs	1930	--
H3N2 to swine	1970	Asia
H1N1; A/New Jersey/1976	1976	Affected soldiers at Fort Dix in the US
Reassortment between human H3N2 and avian H1N1 in swine	1984	--
H1N1 from swine	1988	--
H1N2, isolated from pigs in the UK. human–avian reassortment	1994	--
H3N2, Triple reassorted (avian–human–swine)	1998	North American population affected.
swine influenza to humans	1958–2005	37 cases
Triple reassortant swine flu virus in human	2005–2009	United States.
New strain of swine influenza H1N1	2009	Mexico and United States shows sustained human-to-human Transmission

Antiviral drugs for influenza therapy and prophylaxis are either of the adamantane or neuraminidase inhibitor (**NAI**) class. However, the NAIs are mainly prescribed nowadays, because of widespread adamantane resistance among influenza A viruses and ineffectiveness of adamantanes against influenza B. Emergence and spread of NAI resistance would further limit our therapeutic options [8]. Antiviral drugs should follow the category of promotes apoptotic (program cell death) pathway while influenza virus itself influences apoptosis of their host cell. Influenza virus controls apoptosis of host cell which directly influences viral pathogenesis. Reports suggested that, influenza H3N2 virus (A/Udorn/72) modulate program cell death in MDCK and HeLa cells. Also infected MDCK cells (A/Turkey/Ontario/7732/66) shows DNA fragmentation after post 16 hour of infection. Further A/Turkey/Oregon/1/71 (H7N3) also exhibits DNA fragmentation in MDCK cells. Electron microscopic examination shows potent nuclear condensation, plasma membrane blebbing in infected cells, morphological changes indicates apoptosis of host cell caused by influenza virus [9].

Vaccination is the primary strategy for prevention and control of influenza. The surface hemagglutinin (**HA**) protein of the influenza virus contains two structural elements (head and stalk) that differ in their potential utility as vaccine targets. Because of their error-prone polymerases, influenza viruses undergo genetic changes that lead to gradual antigenic changes in both HA and NA, a process known as antigenic drift that leads to the emergence of new variant strains [10].Vaccination with strain-specific pandemic vaccine is considered to be one of the most effective measures for protecting individuals in the event of a pandemic. Thus, vaccines are considered to be the best approach towards preventing spread of the swine influenza infection. The new vaccine candidate for the 2009 pandemic influenza A has been influenza A /California /7 /2009, that is being produced. The inactivated surface antigen, since the existing sequences of 2009 influenza A are similar to this strain. Vaccine development against the current virus has started with the use of adjuvant for which trials have been started with M59 adjuvant and non-adjuvant forms. In India, three pharmaceutical companies, Serum Institute of India, Bharat Biotech, Hyderabad and Panacea Biotec, New Delhi have joined in the race for development of vaccine and are working diligently on its development [11]. Antigenic shift occurs when the currently circulating influenza A virus disappears and is replaced by a new subtype with novel glycoproteins to which antibodies against the previously circulating subtype do not cross-react [12]. Due to this the influenza vaccine has to be reformulated almost every year to take into account the ever-changing virus. As per CDC's advisory committee on immunization practices (**ACIP**), people at highest risk for complications and those are in direct contact with high risk individuals who cannot afford vaccination, should receive the vaccine first. These target groups include: pregnant women, people who live with or care for children younger than 6 months of age, health care and emergency medical services personnel, anyone 6 months through 24 years of age, and people aged 25 through 64 years who are at higher risk for pandemic H1N1 (2009) virus because of certain chronic health conditions or compromised immune systems. The contradictory side for the pandemic H1N1 (2009) vaccines are: (1) persons who have a severe allergy to chicken egg protein (2) persons who have had a severe allergic reaction to an influenza vaccination, (3) people who developed Guillain–Barre syndrome (**GBS**) within 6 weeks after getting an influenza vaccine previously, (4) children younger than 6 months of age, and persons who have a moderate-to-severe illness with a fever [13]. A surveillance study based on Pandemic influenza

(2009) was co sponsored by National Institute of Allergy and Infectious Diseases (**NIAID**) and the National Heart, Lung, and Blood Institute (**NHLBI**), both part of the NIH suggest that pregnant women and person with asthma are fall in high risk group category and should provide Quick Medical Attention on Priority basis. It was monitored that mortality rate of pregnant women was higher due to pandemic influenza (2009). Post pandemic period analysis also revealed that younger's and pregnant women are repeatedly infected by H1N12009 and viral pneumonia.

Preparations to counter pandemic influenza (2009) in India

Joint venture by Centre for Disease control and prevention (**CDC**), USA and Indian Council of Medical Research (**ICMR**) have developed nine surveillance centres's to study the epidemiology and disease burden of influenza. Scientists from various institute that includes (All India Institute of Medical Sciences, New Delhi; Vallabhbhai Patel Chest Institute, Delhi; National Institute for Cholera and Enteric Diseases, Kolkata; King Institute of Preventive Medicine, Chennai; Regional Medical Research Center, Dibrugarh; Indira Gandhi Medical College, Nagpur; Christian Medical College and Hospitals, Vellore and Haffkine Institute, Mumbai) were trained by referral centre, National Institute of Virology, Pune to handle the situation [14].

Table 2: Year wise Pandemic influenza strain in association with mortality rate. (Table taken from Khanna *et al* 2012).

Pandemic Name	Year	Strain type	Mortality rate
Asiatic (Russian) Flu	1889–1890	H2N2	1 million
Spanish Flu	1918–1920	H1N1	50 million
Asian Flu	1957–1958	H2N2	1.5–2 million
Hong Kong Flu	1968–1969	H3N2	1 million
Pandemic H1N1-2009 Flu	2009–2010	H1N1	Over 18,209

Influenza Vaccines

Seasonal influenza vaccine is formulated to contain the viruses (or their HA proteins) representing the influenza A (H3N2), A (H1N1), and influenza B strains considered to be the most likely to circulate in the influenza season. Vaccine candidates can be developed by cloning HA into vector viruses, resulting in recombinant vaccines expressing the HA protein that induce protective cellular and antibody responses against the vaccine virus [15]. Adjuvants have been used to augment the immune response to vaccine antigens since the 1920s. Both their benefits and their side effects are associated with activation of certain components of the innate immune system [16]. A universal influenza vaccine has the capacity to protect against most varieties of influenza strains and subtypes. Many strategies for developing a universal influenza vaccine are based on raising an immune response against influenza proteins that are highly conserved across all strains [17,18]. Other approaches have focused on using conserved epitopes of the viral proteins, including the extracellular domain of matrix 2 ion channel protein (M2) and NP as protective antigens. Based on H5N1 challenges in ferrets, immunization with DNA vaccines encoding for HA induces higher neutralizing antibody titer than NP and M2 DNA immunization, suggesting that NP and M2 may require combinatorial vaccination with HA to be suitable candidates for universal influenza vaccines [19]. Epitop based DNA vaccines may be considered as universal vaccine, which have cross-reactivity neutralizing antibodies targeted against highly conserved stalk of influenza HA. Functional parameters of the vaccine are invertionally proportional to strains of influenza virus. This type of vector based DNA vaccines can be delivered intranasal or intramuscularly and in the antigen presenting cell of the host body. The host itself able to synthesize and induce both humoral and cellular immunogenic responses [20] Clinical manifestation of Pandemic and seasonal influenza are quite similar, that makes difficulty in diagnosis process from Pandemic influenza to seasonal flu.

Vaccination is one of the prime approaches to fight against influenza virus. There are two types of flu vaccine available:

- Trivalent
- Quadrivalent.

Trivalent vaccines protect against two influenza A viruses (H1N1 and H3N2) and influenza B virus. Trivalent vaccines

are available in:

- Standard-dose trivalent shots (IIV3), approved for people six months and older.
- High dose trivalent shot approved for people 65 years or older.
- Recombinant trivalent shot that is egg-free, approved for people 18 years or older.
- A trivalent flu shot made with adjuvant approved for people 65 years of age and older.

Quadivalent vaccines protect against two influenza A viruses and two influenza B viruses. Quadrivalent vaccines are approved for different age groups which include:

- Intradermal quadrivalent flu shot:

This can be injecting into the skin instead of the muscle. It is approved for people 18 through 64 years of age.

- Quadrivalent flu shot:

Containing virus grown in cell culture, which is approved for people 4 years of age and older [21].

Food and Drug Administration (**FDA**) urging health care organizations to ensure influenza vaccination programs are available for health care personnel (**HCP**). Because unvaccinated HCP can be a primary cause of outbreaks in health care, annual immunization programs may decrease the likelihood of contracting influenza and the chance of infecting others. Studies have shown, some of the primary deterrents to immunization are concerns about the safety and efficacy of the influenza vaccine. But, each year the vaccine undergoes a review by FDA to assure its safety and potency before it is approved for immunization of the public. The misconception that the vaccine causes influenza, and they are not at risk is also another reason why many HCP don't get vaccinated. The healthy adults also can pass influenza virus to someone else one day before symptoms begin, and they can continue to infect others up to five days after getting sick. Therefore, it is possible for a healthy adult to unknowingly spread the virus to patients at high risk for serious complications from influenza [22].

Types of Available Vaccines:

FLUAD

Influenza Vaccine, Adjuvant. Indicated for active immunization of persons 65 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

Influenza Virus Vaccine, Trivalent, Types A and B

Seasonal Influenza Vaccine

Intranasal Vaccine

FluMist® Quadrivalent vaccine

Influenza Vaccine Live, Intranasal. For active immunization of individuals 2 through 49 years of age for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.

Injectable Vaccine

AFLURIA Quadrivalent vaccine.

For active immunization of persons ages 5 years and older against influenza disease caused by influenza virus subtypes A and type B present in the vaccine.

Fluarix Quadrivalent vaccine.

For active immunization of persons 3 years of age and older for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.

Fluzone Quadrivalent vaccine.

Fluzone Quadrivalent: For active immunization of persons 6 months of age and older for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.

Fluzone Intradermal Quadrivalent: For active immunization of persons 18 through 64 years of age for the prevention of influenza disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.

FluLaval.

For active immunization of persons 6 months of age and older for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine.

Flucelvax Quadrivalent vaccine.

For active immunization of children and adolescents 4 years of age and older for the prevention of disease caused by influenza A subtype viruses and type B viruses contained in the vaccine [23].

Killed and live attenuated influenza virus vaccines are effective in preventing and curbing the spread of influenza epidemics when the strains present in the vaccines are closely matched with the predicted epidemic strains. These vaccines are primarily targeted to induce immunity to the variable major target antigen, hemagglutinin (HA) of influenza virus [24]. Infection with seasonal influenza A viruses induces immunity to potentially pandemic influenza A viruses of other subtypes (hetero subtypic immunity). Reports suggested, vaccination against seasonal influenza prevented the induction of hetero subtypic immunity against influenza A/H5N1 virus induced by infection with seasonal influenza in animal models [25]. Genetic vaccine technology has been developed within the last two decades. This cost effective and promising strategy can be applied for therapy of cancers and for curing allergy, chronic and infectious diseases, such as a seasonal and pandemic influenza. Efficient delivery of DNA vaccines into the host cells might significantly decrease the cellular immune response and fight against diseases [26].

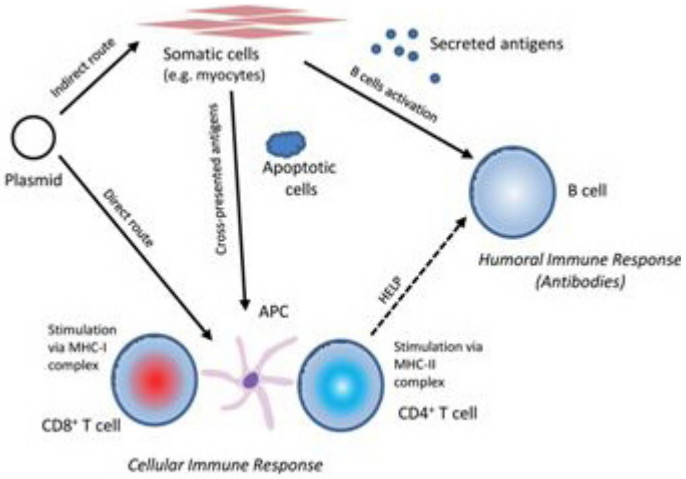

Figure1: Over view of DNA Vaccine

Flu is more likely to cause severe illness in pregnant women than in healthy women who are not pregnant. Changes in the immune system, heart, and lungs during pregnancy make pregnant women more susceptible to flu, which in results of hospitalizations and even death. There is some evidence to suggest that getting flu during pregnancy also raises the risks of certain pregnancy complications, including premature labour pain and delivery, and in such conditions flu vaccine can reduce the risk. In addition, studies have shown that vaccinating a pregnant woman also can protect a baby after birth from flu. CDC recommended that pregnant women should get flu shot during any trimester of their pregnancy to protect

themselves and their newborn babies from flu [27].

Conclusion

Current influenza virus vaccines are effective when well matched to the circulating strains. Unfortunately, antigenic drift and the high diversity of potential emerging zoonotic and pandemic viruses make it difficult to select the right strains for vaccine production. This problem causes vaccine mismatches, which lead to sharp drops in vaccine effectiveness and long response times to manufacture matched vaccines in case of novel pandemic viruses. Novel vaccine candidates face significant challenges including the regulatory and economic hurdles at the transition between preclinical and clinical development, the costs of clinical trials, the absence of established correlates of protection and—specific for universal influenza virus vaccines—the presence of a seasonal vaccine with moderate efficacy on the market. However, these novel vaccines have potentially vast advantages compared to the current standard of care. They have the potential to be a disruptive technology that could abolish the need for annual re-formulation and re-administration of influenza virus vaccines completely, thereby changing the practice of influenza virus prophylaxis. Furthermore, universal influenza virus vaccines would significantly enhance pandemic preparedness. In addition to these vaccines, therapeutic mAbs that have the same conserved targets are developed in the clinic and show great promise as a future tool to combat influenza virus infections. The universal vaccine might be a chance to raise awareness and popularity for influenza virus vaccines. Furthermore, the burden for receiving a universal influenza vaccine that should be given only two or three times in a lifetime is lower than the current approach of annual re-vaccination. In addition, it might also make it easier for low- and middle-income countries to implement an influenza virus vaccine programme. Vaccine that needs to be re-administered every year this is almost impossible due to economic and logistic challenges.

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