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**SPECIAL ISSUE**

## **Controversies and Challenges in Pediatric Vaccination Today**

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**Influenza vaccination in developing countries**

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## REVIEW ARTICLE

# Influenza vaccination in developing countries

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## Abstract:

*Influenza virus (types A, B and C) infection is one of the most common infectious diseases globally and is responsible for millions of sick-days every year, especially in younger children and those with underlying chronic systemic diseases. The infection occurs both as sporadic disease and as epidemics/ pandemics. From public health point of view type-A influenza virus is most significant as it affects other species also (in addition to humans), undergoes frequent antigenic changes thus escaping immune system and leading to epidemics/ pandemics. Vaccination is considered one of the best preventive strategies against this virus. In general, two types of influenza vaccines are available: trivalent inactivated influenza vaccine (TIV) and live-attenuated influenza vaccine (LAIV). However, there are a number of challenges in implementing vaccination programs for influenza, especially for developing countries with limited resources and many other competing health priorities. The current influenza A 2009H1N1 pandemic has shown the world how fragile today's resources in pandemic and pre-pandemic, but also seasonal, vaccines are. This article discusses, in brief, the development, immunogenicity, efficacy and safety of influenza vaccines (seasonal, pre-pandemic and pandemic 2009H1N1 vaccines) along with the rationale, current status and future prospects of influenza vaccination in infants, children and adolescents.*

**Keywords:** Influenza virus, influenza vaccines, 2009H1N1 pandemic vaccines.

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## Introduction

Influenza virus infection, one of the most common infectious diseases, is a highly contagious airborne disease that causes an acute febrile illness and results in variable degrees of systemic symptoms, ranging from mild fatigue to respiratory failure and death. Influenza viruses cause epidemic disease (influenza virus types A and B) and sporadic disease (type C) in humans. From public health point of view type A influenza virus is most significant as it affects other species also (in addition to humans) and as a result undergoes frequent antigenic changes. Emergence of an influenza virus with a major antigenic shift (major antigenic variations on the hemagglutinin surface protein) in a non-immune population along with its high degree of transmissibility sets the stage for global pandemic, like the one last year.

Although the severity of influenza epidemics varies by season, the morbidity associated with annual influenza epidemics in children is considerable from year to year. Excess pediatric outpatient clinic visits, emergency department visits, hospitalizations, and deaths occur each influenza season and are more common among younger children and those with

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conditions that increase their risk for developing influenza-related complications. Vaccination is the most effective way to prevent influenza and its complications (1). When used in an epidemic/pandemic situation, vaccination can help in decreasing severe outcomes, slowing transmission, protecting groups at increased risk of infection, complications, or death, and preventing overload of health services.

Because of constant antigenic drift in the virus, vaccination is needed on a regular basis to protect oneself from the disease. In general, two types of influenza vaccines are available: trivalent inactivated influenza vaccine (TIV) and live-attenuated influenza vaccine (LAIV). Both contain strains of influenza A subtypes H1N1 and H3N2 and influenza B, which are selected annually on the basis of the viruses anticipated for circulation during the upcoming influenza season (2). This article discusses, in brief, the development, immunogenicity, efficacy and safety of influenza vaccines (seasonal, pre-pandemic and pandemic 2009H1N1 vaccines) along with the rationale, current status and future prospects of influenza vaccination in infants, children and adolescents.

### EPIDEMIOLOGY OF INFLUENZA

Influenza viruses are RNA viruses of orthomyxovirus family. The viruses spread from person to person primarily by droplets (small particle aerosols of less than 10µm diameter) of respiratory secretions expelled by coughing or sneezing. They can also be spread by direct contact with influenza virus-contaminated surfaces. During community outbreaks of influenza, the highest attack rates occur among school-aged children. Secondary spread to adults and other children within a family/ schoolmates is common. Incidence depends in part on immunity developed by past infection or recent influenza immunization with the circulating strain or a related strain.

Epidemiologically, two surface proteins of the virus are most important: hemagglutinin (HA) and neuraminidase (NA). The HA protein is involved in attachment and membrane fusion in the endosome of the infected cell. The receptor binding site on the virus is in a "pocket" that is not exposed to the immune system. The antigenic domains are on the surface. These can be altered and the virus can thus avoid a humoral response without affecting its ability to bind to the receptor. The NA protein digests sialic acid (neuraminic acid) - which most cells have on their surface. Since sialic acid is part of the virus receptor, when the virus binds to the cell, it will be internalized (endocytosed). By late in infection, the sialic acid will have been removed from the infected cell surface by the neuraminidase making it is easier for the progeny virions to diffuse away once they exit the cell. Neuraminidase is also involved in

penetration of the mucus layer in the respiratory tract (3).

**Antigenic drift** in the circulating strain(s) is a minor change in structure of surface proteins that occurs due to mutation(s). Both proteins (HA and NA) undergo antigenic drift (i.e. accumulate mutations) and accumulate changes such that an individual immune to the original strain is not immune to the drifted one. Antigenic drift results in sporadic outbreaks and limited epidemics. **Antigenic shift** (major changes in antigenic structure) occur due to reassortment. Since there is little immunity (particularly if both proteins change, or if new HA is present) to the "new" antigen, antigenic shift often results in widespread epidemic or pandemic (3). While antigenic drift occurs in both influenza A & B, antigenic shift occurs only in influenza A.

It is interesting to note that in infections like influenza where there is antigenic drift, vaccination is doubly beneficial. Not only does it protect the population through classical herd immunity, but the overall case reduction reduces the chance of new variants being produced; hence, subsequent epidemics may be milder as a result of this positive feedback (4)

Once influenza activity begins, community outbreaks can last 4 to 8 weeks or longer. People can spread infection 24 hours before symptoms manifest, peaking in viral shedding through nasal secretions during the first 3 days of the illness. Viral shedding is more prolonged (even lasting for weeks or months) in younger children and immunodeficient people. Because of the highly contagious nature of influenza, infected children easily spread the disease to adults and other children within a family or a community. Rates of infection are highest among school-aged children, but rates of serious illness and death are highest among people 65 years and older, children younger than 2 years, and people of any age who have medical conditions that place them at increased risk of having complications from influenza (e.g., pregnancy, hemoglobinopathies, bronchopulmonary dysplasia, asthma, cystic fibrosis, malignancy, diabetes mellitus, chronic renal disease, or congenital heart disease, certain neuromuscular conditions and immunocompromised states) (5-7). *In most of other patients, uncomplicated influenza illness typically*

*resolves in 3 to 7 days. This is especially important from perspective of developing countries with limited resources.*

In developed countries, the morbidity, absenteeism, economic burden and mortality due to influenza is well quantified and is significant. Unfortunately, in most developing countries, including India, there is scanty data on burden of influenza. This poses a major challenge in formulating the vaccination policy for these countries.

#### **PROTECTION FROM INFLUENZA**

A humoral antibody response is the main source of protection from influenza infection. IgG and IgA are important in protection against re-infection. Presence of antibodies also reduces the severity of disease if infection occurs (8). Antibody to the HA protein is most important since this can neutralize the virus and prevent the virus initiating the infection. Neutralization frequently involves blocking of the binding of the virus to host cells and may work at other steps involved in the entry and uncoating of the virus. Antibody to the NA protein has some protective effect since it seems to slow the spread of the virus. IgG persists longer than IgA and so plays a more important role in long term immunity. Antibody against one influenza virus type or subtype confers limited or no protection against another type or subtype of influenza. Furthermore, antibody to one antigenic variant of influenza virus might not completely protect against a new antigenic variant of the same type or subtype (9). Thus, it is of utmost importance that the vaccine used should incorporate the strain prevalent circulating in the population at that time. The WHO reviews that data obtained from its chain of reference laboratories from world over and recommend the composition on a biannual basis: in September/ October for the Southern Hemisphere and February/ March for the Northern Hemisphere. This gives 4-6 months to vaccine manufacturers to manufacture vaccine in time for the flu season in the respective hemisphere (10).

Although annual immunization against influenza is the preferred strategy for prevention of infection, but in certain situations the use of antiviral agents and other non-pharmacologic measures of prevention/containment are beneficial. The detailed discussion on these measures is out of scope of this article.

#### **INFLUENZA VACCINATION: HISTORICAL BACKGROUND**

The first pandemic of influenza reportedly occurred in 412 BC (11, 12), and the first attributed to influenza in 1580 (12, 13). Since then, various strategies have been tried to eradicate its cause. The etiological cause of influenza, the orthomyxoviridae was finally discovered by the Medical Research Council (MRC) of the United Kingdom in 1933. In 1940s, the US military developed the first approved inactivated vaccines against influenza for use in the Second World War. Greater advances were made in vaccinology and immunology, and vaccines became safer and mass-produced. Live attenuated, cold-adapted influenza vaccines (LAIV) were developed in the 1960s but took more than 4 decades to get licensed for general use.

#### **INFLUENZA VACCINES**

*Trivalent inactivated influenza vaccines (TIV)* are produced from virus grown in embryonated hen's eggs, and are of three types: whole virus, split-product and subunit surface-antigen formulations. Whole virus vaccines are associated with high incidence of adverse reactions, especially in children, and are currently not used. Most influenza vaccines are split-product vaccines, produced from detergent-treated, highly purified influenza virus, or surface-antigen vaccines containing purified hemagglutinin and neuraminidase. Vaccines are trivalent: containing 15µg each of the WHO recommended influenza A strains (H1N1 and H3N2) and one influenza B strain. The vaccine is licensed for use in individuals aged 6 months and older, including those who are healthy and those with chronic medical conditions. It is administered intramuscularly, the dose being 0.25 mL in children below three years and 0.5 mL in older individuals (10).

*Live-attenuated influenza vaccine (LAIV)* is a live-attenuated vaccine is composed of live-attenuated reassortants of the three WHO recommended strains and is administered as a nasal spray (0.1mL in each nostril). It has been recently licensed by the US FDA for use in healthy non-pregnant individuals of 2-49 years of age. However, unlike TIV, it has not been recommended for children younger than 2 years old, ages 2-4 old with a history of recurrent wheezing or

reactive airways disease, or older persons who have any medical condition that confers an increased risk of influenza-related complications due to lack of efficacy and safety studies (2).

Both TIV and LAIV vaccines are trivalent preparations grown in eggs and do not contain adjuvants.

**Immunogenicity:** It has been consistently shown that seroconversion rates to TIV increase with the age of the child receiving immunization, ranging from around 70% in younger children 100% in adolescence (14, 15). For immunocompromised patients, response to TIV varies depending on the degree of immunosuppression. Most HIV-infected children and adults produce increased levels of antibody after immunization with TIV, but their absolute antibody concentrations are lower than those seen in healthy, immunized individuals (16, 17). Children with cancer who are not receiving chemotherapy frequently, and children who have sickle cell disease, have also been found to achieve adequate serological response to TIV immunizations (18, 19). A recent *Cochrane review* (20) demonstrated that immune responses in children receiving chemotherapy were consistently weaker (four-fold rise of 25% to 52%) than in those children who had completed chemotherapy (50% to 86%) and in healthy children (71% to 89%). The authors concluded that patients receiving chemotherapy are able to generate an immune response to the influenza vaccine, but it remains unclear whether this immune response protects them from influenza infection or its complications.

As far as LAIV is concerned, studies have yet to determine precise humoral and cellular immunologic levels of protection by LAIV, hemagglutinin-inhibition (HAI) titer in serum, immunoglobulin A in nasal secretions, T-lymphocyte responses, and interferon production have all been correlated with LAIV protection from influenza infection (8, 21). Since it is a live-attenuated vaccine, the resulting immune response is more likely to achieve a level of immunity that would be induced by natural influenza virus infection (2).

**Efficacy and effectiveness:** The efficacy (ie, prevention of illness among vaccine recipients in controlled trials) and effectiveness (ie, prevention of

illness in populations receiving vaccine) of influenza vaccines depends primarily on the age and immunocompetence of the vaccine recipient, the degree of similarity between the viruses in the vaccine and those in circulation, and the outcome being measured. Influenza vaccine efficacy and effectiveness studies typically have multiple possible outcome measures, including the prevention of medically attended acute respiratory illness, prevention of laboratory-confirmed influenza illness, prevention of influenza or pneumonia-associated hospitalizations or deaths, seroconversion to vaccine strains, or prevention of seroconversion to circulating influenza virus strains. This poses a major challenge in comparing results of various studies.

The efficacy of TIV in children has been reported to be in the range of 56%-91% in various studies (15, 22). The efficacy is lower in younger children. The live-attenuated vaccine (LAIV) is more efficacious, especially in younger children (10, 23). One study conducted with healthy children 15 to 71 months of age found that when vaccine and circulating strains were well matched, efficacy rates were 93% for participants who received 2 doses of LAIV. Even when vaccine and circulating strains were not well matched, efficacy rates remained high at 85%. LAIV was also found to be 92% efficacious in preventing culture-confirmed influenza during this two-season study (24). Thus, because of its superior efficacy and ease of administration, LAIV appears to be more cost-effective than TIV, especially in young children. There is some evidence that vaccination of pregnant women with TIV helps reducing respiratory illness visit rates among their infants (25, 26). However, some studies have failed to demonstrate this benefit (27, 28).

A recent *Cochrane review* (29) studied the efficacy and effectiveness of both types of influenza vaccines found that in children aged from two years, LAIV was better at preventing illness caused by the influenza virus (82% of illnesses were prevented) than TIV (59%). Neither type was particularly good at preventing 'flu-like illness' caused by other types of viruses (33% and 36% respectively). In children under the age of two, the efficacy of inactivated vaccine was similar to placebo.

For optimum efficacy, CDC and AAP recommend that influenza vaccine-naïve children who are 9 years

and older need only 1 dose for their first time (recommendation; evidence grade B). In contrast, any child younger than 9 years receiving TIV or LAIV for the first time should receive a second dose at least 4 weeks after the first (recommendation; evidence grade B). For the child younger than 9 years who received only 1 dose in the first year influenza vaccine was given it is recommended that the child receive 2 doses of influenza vaccine at interval of 4 weeks (30-32). Revaccination is recommended with a single annual dose (irrespective of age) and even if the vaccine antigenic composition does not change (10). It has been consistently shown that partial vaccination is of no benefit in young children (33-35), underlining the necessity to follow the guidelines strictly to benefit from influenza vaccination. Moreover, there is evidence that in case there is a major change in influenza strain (such as in a pandemic), the priming benefit of previous vaccination is reduced. In such a situation, the need for multiple doses of vaccine to produce potentially protective antibody levels in children needs to be considered, even when vaccine is in short supply (36).

**Safety:** Because viruses for both vaccines are grown in eggs, neither should be administered to anyone with known allergic reactions (ie, hives, angioedema, allergic asthma, and systemic anaphylaxis) to chicken, egg proteins, or any other component of the vaccines. Less severe or local manifestations of allergy to egg or feathers are not contraindications to administration of influenza vaccine (2).

The most common adverse effects associated with TIV administration are soreness at the injection site and fever. TIV is an inactivated vaccine that contains killed viruses and, therefore, cannot produce an active virus infection. However, hypothetically, this killed vaccine might produce mild influenza-like symptoms by inducing some of the same cytokines associated with the known symptoms of influenza disease. Fever, usually occurring 6 to 24 hours after immunization, affects approximately 10% to 35% of children younger than 2 years. Mild systemic symptoms, such as nausea, lethargy, headache, muscle aches, and chills can also occur with TIV injection.

With LAIV, an increase in fever, runny nose, and nasal congestion was shown after the first dose, but

not after the second dose when administered to young children (37). Moreover, there is statistically significant increase in asthma or reactive airway disease in children 12 to 59 months of age after the first dose with LAIV (24, 38). Hence, this vaccine should preferably be avoided in children less than 5 years of age and history of reactive airway disease (10).

LAIV shedding can occur after immunization, although the amount of detectable virus is less than occurs during natural influenza infection. In the rare instance when shed vaccine virus is transmitted to a non-immunized contact, illness has not occurred. However, inactivated influenza vaccine is preferred for close contacts of very severely immunosuppressed people rather than LAIV (39).

**Guillain-Barré Syndrome:** There is some concern of association of Guillain-Barré syndrome (GBS) with influenza vaccination. Although obtaining strong epidemiologic evidence for a possible limited increase in risk for a rare condition with multiple causes is difficult, the concern is based on the fact that the incidence of GBS increased during the 1976 swine influenza vaccine program (40). Even if there is an association between seasonal influenza vaccine and, the risk is very minimal, at no more than 1 to 2 cases per million doses, based on a few studies that have found an association; other studies have found no association (41). Fortunately, the risk of influenza vaccine-associated GBS was lesser in pediatric age-group than individuals 25 years or older (42). Whether influenza immunization specifically might increase the risk of recurrence of GBS is unknown. However, avoiding immunizing people who are not at high risk of severe influenza complications and who are known to have experienced GBS within 6 weeks after a previous influenza vaccine dose is prudent (31).

**HIV:** Because past reports are conflicting, the issue of safety of TIV immunization for children and adults with HIV infection is uncertain. However, experts generally believe that the benefits of TIV influenza immunization for children with HIV infection far outweigh the risks (2).

#### RECOMMENDATIONS FOR USE

Influenza is mild, self-limiting illness in most patients. Thus, vaccination may not be cost-effective

in these individuals and, in fact, the benefit may not outweigh the risks associated with the vaccine. However, there are some individuals who are at high risk of complications and mortality because of this infection and the vaccine has been shown to be significantly beneficial and cost-effective in this group. The vaccination program in most developing countries is directed towards this high-risk group:

Children and adolescents with underlying medical conditions, including:

1. Asthma (especially those needing systemic steroids frequently)
2. Other chronic pulmonary diseases, such as cystic fibrosis
3. Hemodynamically significant cardiac disease
4. Immunosuppressive disorders or therapy
5. HIV infection (with CD4 counts above 100 cells/microl and HIV-infected children with CD4 counts >15%)
6. Sickle cell anemia and other hemoglobinopathies
7. Diseases requiring long-term aspirin therapy, such as juvenile idiopathic arthritis or Kawasaki disease (TIV only)
8. Chronic renal dysfunction
9. Chronic metabolic disease, such as diabetes mellitus
10. Any condition that can compromise respiratory function or handling of secretions or can increase the risk of aspiration, such as cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders.

In developed countries like the USA, the influenza vaccine is additionally recommended in healthy children 6 through 59 months of age, household contacts and out-of-home caregivers of healthy children younger than 5 years and all high-risk children, any female who will be pregnant during

influenza season (TIV only) and health care workers or volunteers. Thus, such recommendations cover over 80% of the total population, just short of universal immunization (43). Many developing countries, including India, do not recommend vaccination in these categories for want of data on burden of disease/ cost effectiveness and other health priorities/ financial constraints.

The influenza vaccines are given before the peak influenza season. In temperate countries, the peak influenza season is in winters and vaccination is given before the season begins. In contrast, in tropical countries the illness occurs all through the year. Thus, vaccination in these countries is recommended to be given as soon as the new vaccine is released in the market or at the time of presentation to the health care provider.

#### **PRE-PANDEMIC INFLUENZA VACCINE**

A pre-pandemic vaccine, as the name suggests, is produced in advance of a pandemic based on the current circulating virus strain when a pandemic by a variant of the strain is likely in near future. Pre-pandemic vaccines therefore play a critical role in pandemic preparedness planning, with experts citing that immunization with such stockpiled vaccines in advance or at the onset of pandemic is the most effective strategy for protecting entire populations. However, such a strategy is debatable in developing countries where the resources are limited and there are scores of competing health priorities. Prediction of the strain that would mutate and acquire pathogenicity and transmissibility, thus leading to pandemic is extremely difficult. In 2008-09, while attention was focused on a threat of an avian influenza H5N1 pandemic emerging from Asia, a novel influenza virus of swine origin emerged in North America, and then spread worldwide. In 2007-08, European Commission granted license for H5N1 adjuvanted *Prepandrix*<sup>TM</sup> for all 27 EU member states (10, 44). Similarly, there were efforts in Russia to develop and use "tetravaccine" consisting of H5 hemagglutinin in addition to the usual three antigens of H3N2, H1N1 and B serotypes so that the population is vaccinated before the influenza pandemic caused by avian H5N1 begins (45). However, the effectiveness of these vaccines in a pandemic is not guaranteed... it was reassortant of H1N1 virus and not H5N1 that led to current pandemic!

### PANDEMIC INFLUENZA A 2009 H1N1 VACCINES

In April 2009, for the first time in 41 years, a novel type of influenza A virus acquired the capacity for human-to-human transmission and caused a pandemic that originated in Mexico and spread to all continents in just 9 weeks. This virus was derived from swine A (H1N1), which was a recombination of avian, human, and several swine influenza viruses, and named the "pandemic (H1N1) 2009 virus" (46). As of April 2010, approximately 43 million to 89 million pandemic (H1N1) 2009 infections have been estimated to have occurred (in US alone), including 14 to 28 million children/ adolescents with over 12000 deaths (including 1200 deaths in pediatric age-group) (47). Although the pandemic has currently dampened (47), there are concerns that this virus may mutate or reassort with existing influenza viruses giving rise to more transmissible or more pathogenic viruses. The 1918 Spanish flu pandemic virus was also relatively mild in its first wave and acquired more virulence when it returned in the winter. Thus preparedness on a global scale against a potential more virulent strain is highly recommended (48). Based on epidemiologic data and worldwide experiences on influenza vaccination, it is considered the best way to dampen this pandemic (49). Both seasonal and H1N1 vaccinations are recommended for anyone 6 months of age or older who is at risk of becoming ill or of transmitting the viruses to others. Overall, the rates and seriousness of a possible complication of influenza vaccination are much smaller than the risk of serious complications and mortality of influenza infection (50). It is recognized that pandemic vaccines have their greatest impact as a preventive strategy when administered before or near the peak incidence of cases in an outbreak (51). Pascua et al (52) tried to investigate whether recent seasonal human or swine H1N1 vaccines could induce cross-reactive immune responses against infection with the pandemic (H1N1) 2009 virus. It was an experimental study on animal models (mice, ferrets or mini-pigs) and suggested that neither recent human nor animal H1N1 vaccine could provide complete protectivity in all animal models. Thus, there was clearly a need for strain-specific vaccines that could yield the optimal protection desired for humans and/or animals. Acting proactively, in July-August 2009 CDC (USA)'s Advisory Committee on Immunization Practices (ACIP) reviewed epidemiologic and clinical data to determine which

population groups should be targeted initially for vaccination. ACIP also considered the projected vaccine supply likely to be available when vaccine is first available and the expected increase in vaccine availability during the following 6 months. The committee recommended that: 1) the five initial target groups for vaccination efforts should be pregnant women, persons who live with or provide care for infants aged <6 months, health-care and emergency medical services personnel, children and young adults aged 6 months-24 years, and persons aged 25-64 years who have medical conditions that put them at higher risk for influenza-related complications, 2) priority for a subset of persons within the initial target groups should be established in the event that initial vaccine availability is unable to meet demand, 3) the vaccine might be used in other adult population groups as vaccine availability increases and 4) Vaccination and health-care providers should be alert to announcements and additional information from state and local health departments and CDC concerning vaccination against novel influenza A (H1N1) virus infection (53). It was also recommended that, like with seasonal influenza vaccine, children aged 6 months--9 years receiving influenza A (H1N1) 2009 monovalent vaccines should receive 2 doses, with doses separated by approximately 4 weeks; persons aged  $\geq 10$  years should receive 1 dose (54). The World Health Organization (WHO), while agreeing that the development of a pandemic influenza vaccine in the fastest possible time is a global priority, brought up other major issues that also need to be taken into consideration: how long will it take to produce sufficient pandemic vaccine doses to immunize the global population at risk, including poor populations that have no resources to purchase the vaccine; and how will pandemic vaccine production affect availability of trivalent vaccine for the forthcoming 2009-2010 influenza season (55).

As early as October 2009, there were 11 available influenza A (H1N1) candidate strains provided by WHO Global Influenza Surveillance Network and ClinicalTrials.gov registered 45 phase I and II clinical trials evaluating immunogenicity and safety of influenza A (H1N1) vaccines. Preliminary results supported administration of a single dose and use of adjuvants (51). However, the first vaccines licensed for pandemic H1N1 2009 virus [live, attenuated



monovalent vaccine (LAMV) for intranasal administration and as monovalent, inactivated, split-virus or subunit vaccines for injection (MIV) containing the strain A / California / 7 / 2009 (H1N1 pdm) were non-adjuvanted (56).

In Jan 2010, results of a multicentre, double-blind, randomized, placebo-controlled trial (57) investigating safety and immunogenicity of eight formulations of 2009 pandemic influenza A H1N1 vaccine produced by ten Chinese manufacturers were published in *Lancet*. They recruited 12,691 people aged 3 years or older were recruited in ten centers in China and assessed eight formulations: split-virion formulation containing 7.5 microg, 15 microg, or 30 microg haemagglutinin per dose, with or without aluminium hydroxide adjuvant, and whole-virion formulation containing 5 microg or 10 microg haemagglutinin per dose, with adjuvant. All formulations were produced from the reassortant strain X-179A (A/California/07/2009-A/PR/8/34). They concluded that one dose of non-adjuvant split-virion vaccine containing 7.5 microg haemagglutinin could be promoted as the formulation of choice against 2009 pandemic influenza A H1N1 for people aged 12 years or older. In children (aged <12 years), two 7.5 mug doses might be needed. However, Waddington et al (57) found the AS03(B) adjuvanted split virion vaccine, while more reactogenic, was more immunogenic and, importantly, achieved high seroconversion rates in children aged less than 3 years when compared with whole virion non-adjuvanted H1N1 vaccine.

Another multicentre, randomized controlled trial (58) investigated the safety and immunogenicity of a whole-virion, inactivated, adjuvanted pandemic H1N1 vaccine in adult and elderly volunteers, given without or simultaneously with the 2009-10 seasonal trivalent influenza vaccine and concluded that vaccine is safe and immunogenic in healthy adult and elderly patients, and needs low doses and only one injection to trigger immune responses, and can be safely co-administered with the 2009-10 seasonal influenza vaccine.

Clark et al (59) tested monovalent influenza A/California/2009 (H1N1) surface-antigen vaccine, in both MF59-adjuvanted and non-adjuvanted forms in a single centre study and found adjuvanted vaccine

generates antibody responses likely to be associated with protection after a single dose is administered.

In October-November 2009, CDC reviewed vaccine safety results for the H1N1 vaccines from 3,783 reports received through the U.S. Vaccine Adverse Event Reporting System (VAERS) and electronic data from 438,376 persons vaccinated in managed-care organizations in the Vaccine Safety Datalink (VSD), a large, population-based database with administrative and diagnostic data, in the first 2 months of reporting (as of November 24). VAERS data indicated 82 adverse event reports per 1 million H1N1 vaccine doses distributed, compared with 47 reports per 1 million seasonal influenza vaccine doses distributed. However, no substantial differences between H1N1 and seasonal influenza vaccines were noted in the proportion or types of serious adverse events reported. No increase in any adverse events under surveillance was seen in VSD data (60).

#### THE GREY AREAS

In most developing countries, there is gross lack of authentic epidemiological data on influenza infection in local population. This is the first step required to plan preventive strategies scientifically. We also need to answer related questions such as percentage of confirmed influenza infections responsible for "Influenza-like illness (ILI)", exacerbations of asthma, etc. Moreover, since the influenza infection is rather unique as there is marked year-to-year variation in influenza attack rates, illness severity, hospitalization costs and rates, etc, we need to update the data regularly.

Secondly, we need more and more data on efficacy and effectiveness of various types of influenza vaccines as these vaccines have been criticized for a lack of effectiveness demonstrated in controlled studies despite good immunogenicity. The effectiveness of these vaccines need to be studied in various ways including the prevention of medically attended acute respiratory illness, prevention of laboratory-confirmed influenza illness, prevention of influenza or pneumonia-associated hospitalizations or deaths, seroconversion to vaccine strains, or prevention of seroconversion to circulating influenza virus strains. In fact, authors of a recent *Cochrane review* (29) were surprised to find only one study of inactivated vaccine in children less than two years, given current recommendations to vaccinate healthy

children from six months old in the USA and Canada. We need to have more data on LAIV for immunization of infants and other high-risk groups.

Third, since influenza vaccine schedules and effectiveness depend a great deal on how well vaccine strains match circulating virus strains each year, further research is needed to further enhance the methods currently used to predict potential antigenic changes each year. Better still, vaccines that confer broad protection against heterovariant strains are needed against seasonal, epidemic and pandemic influenza. In addition to the use of vaccine adjuvants [such as alum, MF59 and the tocopherol-based oil-in-water emulsion adjuvant system family (AS03)], emerging research areas include development of a universal vaccine and the use of vaccines that exploit mechanisms of cross-protective and durable, long-term immunity (61). In fact, some of such candidate “universal” influenza vaccines are already undergoing clinical trials (62). These have utilized less variable antigens of the influenza virus such as stalk of the hemagglutinin molecule (63, 64), NP and M2e protein component of the flu virus shell (65, 66). Some *DNA vaccines* that contain DNA fragments (plasmids) are also under trial (67). Chih-Jen Wei et al (67), for example, have demonstrated increased neutralization of diverse H1N1 strains from 1934 to 2007 compared to either component alone and conferred protection against divergent H1N1 viruses in mice and ferrets using a novel prime-boost combination. They used vaccination with vaccination with plasmid DNA encoding H1N1 influenza hemagglutinin (HA) and boosting with seasonal vaccine or replication-defective adenovirus 5 (rAd5) vector encoding HA. This stimulated the production of broadly neutralizing influenza antibodies. These antibodies were directed to the conserved stem region of HA and were also elicited in nonhuman primates. Cross-neutralization of H1N1 subtypes elicited by this approach thus provides a basis for development of a universal influenza vaccine for humans.

Fourth, efforts should be explored to improve the vaccine development process so as to allow for a shorter interval between identification of vaccine strains to be included each year and vaccine production. For example, the development of a tissue culture-based vaccine (based on the mammalian cell lines Vero, MDCK and PER.C6, as well as the

baculovirus/ insect cell platform) could increase production capacity, speed and efficiency of production, eliminate the contraindication for those with known allergic reactions to egg proteins and might improve immunogenic efficacy (68, 69). However, with the recent articles in the popular press claiming that cell culture-based influenza vaccines can cause tumours raised uncertainty among physicians and the general population, rigorous safety trials would be needed before licensing these products (70).

Last but not the least, more research is needed in development of better vaccines, as current vaccines are less effective in the group of patients who need it most, e.g., young children and immunocompromised individuals.

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