Adverse Drug Events Monitoring of Live Attenuated Pandemic Influenza Vaccine

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Introduction
On June 11, 2009 World Health Organization raised the influenza pandemic alert to the highest level.\(^1\) In India, after the first death due to pandemic influenza A (H1N1) from Pune; the Indian population panicked and at the same time there was a substantial increase in the rate of hospitalizations.

Doctors and paramedical persons and their direct contacts are at the highest risk for influenza infection, and one of the preventive strategies in pandemic control is to vaccinate this high risk group. As limited data are available on the adverse reactions to the live attenuated pandemic influenza vaccine, residents of pandemic area are faced with controversies related to choice of being vaccinated. It is therefore imperative that we should have maximum data on the adverse reactions of vaccination to allow people to make a frank informed choice regarding safety of this vaccine. This prompted us to conduct a study to monitor the adverse reactions to the live attenuated pandemic influenza vaccine.

Materials and Methods
The study was conducted at Government medical college, Miraj, Maharashtra. This was a prospective, observational, cohort study. The study was conducted from 1 June 2010 to 31 August 2010. Appropriate study protocol for monitoring the adverse events of the live attenuated pandemic influenza vaccine was developed. The doctors who were actively involved in administration of influenza vaccine like pediatricians and physicians were contacted and the details of the study protocol were explained to them. They were also asked to record the data as per protocol.

All the individuals of either sex who received live attenuated pandemic influenza vaccine voluntarily and consented to participate in the study were included in this study. In a session prior to vaccination, the vaccinating doctor explained the indications, contraindications, warning, and adverse reactions of vaccine to the each individual who requested for vaccination. The influenza vaccine was given to those individuals who wanted to be vaccinated irrespective of their age.

The vaccine used for administration was prepared by Serum Institute of India Ltd, Pune, as human, live attenuated, freeze dried, monovalent, pandemic influenza vaccine marketed under the brand *Nasovac*. The vaccine contains influenza virus cultivated on embryonated eggs. The vaccine was administered by intranasal spray; a dose of 0.5 ml was administered as 0.25 ml per nostril using a 0.5/1.0 ml syringe and a spray device. The sprayer device creates a fine spray that primarily deposits the vaccine in the nose and nasopharynx.

Information on adverse events was collected both through self reporting by individuals and through telephonic calls made by the vaccinating doctor on 7th day and on 30th day after vaccination. An adverse event to vaccination was defined as any undesirable effect or symptom recorded on the adverse event reporting form of the study protocol and that occurred within 1 month after vaccination. Total numbers of vaccinated individuals showing adverse events were noted. If a vaccinated individual reported more than one symptom as an adverse event, each adverse event was noted separately and thus total number of adverse events were noted. No remarks were made on the management of the adverse events.
Statistics
The adverse events were analyzed with respect to demographic characteristics and frequency of events reported by recipients. Chi-square test and “Z” test were used for the analysis of data.

Results
In this prospective, observational study a total 263 individuals received live attenuated influenza vaccine. The proportion of vaccinated males (55.13%) was more than that of females (44.87%). The mean age of the vaccinated individuals was 29.60 ± 13.09 years. The number of individuals vaccinated among the different age group is shown in Table 1. The incidence of adverse events in the different age group is shown in Table 2. A total 119 (45.25%) individual reported different adverse events [Table 3]. Out of these, 47.06% were males and 52.94% were females. A rare adverse event was reported by single individual as tingling numbness in right arm on the day of vaccination; the same individual reported drowsiness, palpitation and sweating.

Discussion
In this prospective, observational, cohort study, the incidence rate of adverse events after live attenuated pandemic influenza vaccination was 45.25%. This finding of our study is very similar to two other studies; in one study, (3) there were 54.9% cases of cultured-confirmed influenza in the group that received live attenuated influenza vaccine while in another study (4) live attenuated influenza vaccine recipients experienced 35–53% fewer cases of culture-confirmed influenza illness caused by antigenically matched strains.

It was observed that the incidence of adverse effect was more in younger age group (3–17 years); one of the possible reasons for this is that the younger age group might be relatively less exposed to the wild influenza virus as compared to adults. Thus after receiving live attenuated influenza vaccine, the reactogenicity against vaccine virus is seen as more number of adverse events in young age group than that of adults.

A surprising finding in our study was the incidence of adverse events in females was found significantly higher as compared to the incidence of adverse events in males. It is not clearly known why sex difference exists in adverse events to live attenuated influenza vaccine. Factors cited include differences in weight and body mass index, hormonal changes unique to females, and effect of these changes on vaccine response. (4)

The finding of frequency of adverse effect in our study is comparable to other studies; in one study, (5) the most common adverse events associated with live attenuated influenza vaccine are nasal congestion, headache, myalgia, and fever, while in other study (6) the most common adverse reactions with live attenuated influenza vaccine include runny nose/nasal congestion in all age groups, fever > 100°F in children, and sore throat in adults. In another randomized, double-blind, placebo-controlled study, (6) reactogenicity events were higher among live attenuated influenza vaccine than placebo recipients during 11 days postvaccination (P=0.042), including runny nose/nasal congestion, cough, sore throat, headache, muscle aches, tiredness, and decreased appetite.
About 1.90% individuals reported combinations of adverse events such as runny nose, throat pain, fever, body ache, fever, and/or cough; these events might be due to vaccination but not due to other viral infection as during the study period there was no viral epidemic. Individual, who reported tingling numbness in right arm on the day of vaccination recovered uneventfully on the same day and did not report any complaint on next day onward.

Based on the observations from our study, thus it can be concluded that the incidence rate of adverse events of live attenuated pandemic influenza vaccine was 45.25%. This provides initial data for large studies regarding the incidence of each adverse event and also provided data for metanalytical studies and has ascertained the importance of prospective adverse events monitoring to make a frank informed choice regarding safety of this vaccine.

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