Iranian Journal of Clinical Infectious Diseases
***2009;4(1):19-23***


**ORIGINAL ARTICLE**

# Surveying immunogenicity and safety of influenza vaccination in health care workers and HIV-infected individuals

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## ABSTRACT

**Background**: Influenza is a world-wide public health concern. It is one of the most important viral causes of acute respiratory illness, affecting all age groups, recurring several times during a lifetime. We assessed the antibody titers after vaccination against influenza among HIV-infected patients and health care workers (HCWs).

**Patients and methods**: During this before-after study, the antibody responses were assessed in 60 HCW and 60 HIV-infected patients vaccinated with split influenza vaccine (influvac® 2005/2006 Solvay's influenza vaccines for the influenza season 2005/2006 in the northern hemisphere).

**Results**: Although all participants had protective antibody levels against A(H1N1), A(H3N2), and B components of trivalent influenza vaccine (before vaccination), HIV-infected patients showed seroconversion against A(H1N1), A(H3N2), and B components in 75%, 45%, and 28.3% of cases, respectively. The corresponding values were 70%, 33.3%, and 53.3% among HCWs, respectively. There were no repots of any vaccine adverse reaction.

**Conclusion**: A comparable rise in antibody titers against influenza antigens without any adverse reaction supports the previous recommendations for influenza vaccination. Such programs can effectively decrease the probability of influenza infection in both HCWs and HIV-infected patients who are not seriously immune compromised.

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**Keywords**: *HIV infection, Health care worker, Influenza vaccine*.
***(Iranian Journal of Clinical Infectious Diseases 2009;4(1):19-23).***

## INTRODUCTION

Influenza is a world-wide public health problem. It is one of the most important viral causes of acute respiratory illness, occurring in people of all ages, recurring several times during a lifetime. Influenza is a highly contagious, globally spread viral disease. The high degree of viral antigenic variability is responsible for seasonal recurring epidemics and less frequent pandemics. This viral infection is usually self-limiting, but severe complications can occur, particularly in high-risk individuals, that may lead to significant increases in hospitalization and mortality (1-4) with the subsequent impact on health-care resources and costs (2).

Vaccination of people known as high-risk for developing complications (i.e. in elderly, infants, debilitated individuals, patients with respiratory disorders, cardiovascular disease, and with immunodeficiency including those infected with HIV) or vaccination of persons who can transmit the disease to high-risk individuals, is the most

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effective measure for reducing the burden of this infection (5-7).

Among people who are in greater risk of infection with influenza, those who are infected with HIV are in greater concern. Influenza has been responsible for considerable morbidity in HIV-infected individuals, including those treated with highly active antiretroviral therapy (HAART) (8,9). International guidelines recommend that HIV-infected individuals receive once-yearly vaccination (10-12). However, available evidence regarding the effectiveness of such program is not consistent (13). This study is aimed to compare the antibody (Ab) titer against A(H1N1), A(H3N2), and B antigens between health care workers (HCWs) and patients infected with HIV.

## PATIENTS and METHODS

This study was a quasi experimental clinical trial conducted at one triangular clinic (providing care and support for patients with HIV/AIDS, STDs, and those who have drug dependency) and Sina hospital in Kermanshah province, Iran. Patients with HIV/AIDS and health care workers enrolled between October 10 and November 1, 2005. Those who had received influenza vaccine of any kind were excluded. Additionally, subjects who had history of allergy to eggs or egg products and those who had history of Guillain-Barre syndrome, any acute or chronic condition that might cause the vaccination unsafe for participants or immunosuppressed individuals were excluded. Those who had history of immunoglobulin or other blood product injection within the past 3 months or a live-virus vaccine (eg, measles-mumps-rubella) during he past 4 weeks, or need to obtain a live-virus vaccine within the upcoming 4 weeks were also excluded. In addition, we excluded those HIV positive patients who had a CD4 count of <200//µl. Such patients did not receive any type of antiretroviral therapy or any type of nonspecific immunomodulator drugs like selenium, vitamin A, zinc and etc. Simultaneous administration of a live-virus vaccine was permitted (14). Data regarding the status of HBs-Ag and HCV-Ag were collected for all participants from their health records.

*Vaccine:* Single lots of licensed 2005–2006 preservative free trivalent influenza vaccine provided by Solvay pharmaceuticals were used throughout the trial. The composition of influvac® 2005/2006 Solvay's influenza vaccines for the influenza season 2005/2006 in the northern hemisphere was as follows

- A/California/7/2004 (H3N2)-like strain (A/New York/55/2004 NYMC X-157 reass.)
  (15 µg haemagglutinin/dose)
- A/New Caledonia/20/99 (H1N1)-like strain (A/New Caledonia/20/99 IVR-116 reass.)
  (15 µg haemagglutinin/dose)
- B/Shanghai/361/2002-like strain (B/Jiangsu/10/2003)
  (15 µg haemagglutinin/dose)

Vaccine was prepackaged in 0.5-mL syringes and administered intramuscularly in deltoid using standard sterile technique.

Prospective self-reported side effects of influenza vaccination were obtained. The study population were requested to record their daily oral temperatures, any local reactions (pain, tenderness, redness, swelling at the site of injection of inactivated influenza vaccine), and systemic reactions (irritability, alteration in sleep behavior, emesis, changes in appetite) over next 5 days following the vaccination. In order to truly collect information regarding adverse effects of vaccination, the participants were contacted by telephone 5 days and 6 months after the vaccination.

*Titration and immunologic response:* A serum sample was collected from each subject before and 30 days after vaccination. Sera were stored at -20°C until they assayed at University of Tehran. The standard hemagglutination-inhibition (HAI) assay was conducted to determine the antibody titer

against different strains of influenza included in the vaccine. Antibody titers were determined in duplicate, running all paired specimens in the same test. Sera were treated with receptor-destroying enzyme. To inactivate the receptor-destroying enzyme, the sera were heated to 56°C for 30 minutes. Then, the sera were diluted (1:10) and subjected to two-fold serial dilutions. Twenty-five microliters of the diluted sera were incubated with an equal volume of antigen diluted to contain 4 to 8 hemoglutinin units, and 50 microliter of a 0.5% suspension of chicken red blood cells was added to the mixture. The test was achieved using 2-fold dilution of the serum in duplicate, running all paired specimens in the same test. Outcome measures were: protective antibody response defined as HAI titer ≥1:40, proportion of vaccine that showed seroconversion defined by ≥4 fold rise in HAI titer.

The geometric mean titer of each strain was calculated with the use of the log-transformed values. Finally, the antilog of the means of the transformed values was calculated. Baseline characteristics were compared using $X^2$ (for contingency tables) and two sample t-test (for continuous variables). The geometric means of antibody titers were compared before and 21 days after vaccination using paired t-test. In order to compare the proportion of people whose antibody titer reached protective level, $X^2$ was applied. The significance levels were 5% for all analyses. Data were analyzed using SPSS software (version 11.5, SPSS Inc., USA)

## RESULTS

The study population included 38 females (12 HIV-infected and 26 HCW) and 82 males (48 HIV-infected and 34 HCW). Table 1 summarized some demographic features of the subjects. Subjects in both groups were comparable in terms of age, BMI (body mass index), and the proportion of HBS-Ag positivity. However, as expected, there were higher subjects with positive antibodies against HCV among those who had a history of intravenous drug use in HIV-positive patients.

**Table 1**. Baseline characteristics of health care workers (HCW) and HIV-infected subjects

| Characteristics | HIV-infected (N=60) | HCW (N=60) | p value |
|---|---|---|---|
| Age (yrs) | 36.4±6.7 | 37.7±8.0 | 0.34 |
| Sex (female %) | 20.0 | 43.3 | 0.006 |
| BMI(kg/m$^2$) | 22.77 | 23.87 | 0.88 |
| Positive HBs-Ag (%) | 6.7 | 1.7 | 0.17 |
| Positive HCV-Ab (%) | 75 | 0 | <0.001 |
| IV drug users %) | 51.7 | 0 | <0.001 |
| CD4 count (/µl) | 520.49 | - | - |

Geometrical mean titers (GMT) of antibodies before and after influenza vaccination against A(H1N1), A(H3N2), and B antigens in both groups are presented in table 2. The antibody levels against A(H1N1), A(H3N2), and B antigens increased four times in HIV-infected patients as found in 75%, 45%, and 28.3% of participants, respectively. The relevant values in HCWs were 70%, 33.3%, and 53.3%, respectively. Except for antibodies against B antigen (p=0.005), the proportion of candidates showed seroconversion were comparable in both groups. Furthermore, within each group, higher proportion of seroconversion was demonstrated against A(H1N1) (all p values<0.05). There were no adverse reactions to influenza vaccine either in health care workers or HIV-positive patients.

**Table 2**. The comparison of antibody level* within and between two groups of health care workers (HCW) and HIV-infected individuals

| | HCW | | | HIV infected patients | | | |
|---|---|---|---|---|---|---|---|
| Antigen | before | after | p | before | after | p | p† |
| **A(H1N1)** | 96 | 432 | 0.05 | 102 | 446 | 0.03 | 0.34 |
| **A(H3N2)** | 48.17 | 100.67 | 0.24 | 70 | 198.67 | 0.009 | 0.13 |
| **B** | 244.2 | 618.67 | 0.59 | 101.5 | 254.67 | 0.001 | 0.005 |

* The values show geometric mean of antibody titer

† The values show the results of testing the proportion of people whose antibody titer reached to protective level between two groups

## DISCUSSION

Our results revealed that all HIV-infected patients had a good antibody response to the antigenic constituents of inactivated influenza vaccine. Increase in geometric means of antibodies against A(H1N1) either among HIV-infected patients or HCWs were significantly more than other antigenic constituents. The presence of protective antibody (even before vaccination) against influenza in all HIV-infected patients and HCWs was unexpectedly occurred. This incidental finding implies that all participants have had previous exposure to influenza viruses with the same strains or with the same antigenic components. Our intervention in vaccinating the HIV-infected patients and HCWs increased the titer of antibody that already exists.

An acceptable antibody response against all antigenic components of inactivated influenza vaccine might be in part explained by good immune status of both HIV-infected patients and HCWs. In fact, none of the HIV-infected patients were in advance stages of HIV infection. Antibody response against influenza vaccination may be weaker in advanced HIV-infected subjects with CD4+ count less than 200 cells per microliter (14). Even a second dose of vaccine does not improve the immune response in HIV-infected patients who are in advance stages of the disease (15). Moreover, despite the recommendation of the US Center for Disease Control and Prevention (CDC) regarding vaccination of all patients infected with HIV, whether such vaccination in such patients is as safe as others, it is still needed to be further investigated. Although there are frequent reports about non significant changes in CD4 and viral load of such patients after vaccination against influenza (16-23), we excluded those with CD4 less than 200/μl.

Influenza vaccine has been demonstrated to produce substantial antibody titers against influenza virus among vaccinated HIV-infected subjects who have minimal acquired immunodeficiency syndrome-related symptoms and high CD4 cell counts (14). A randomized, placebo-controlled trial determined that influenza vaccine was highly effective in preventing symptomatic, laboratory-confirmed influenza infection among HIV-infected persons with a mean 400 CD4 count of 400cells/$mm^3$ (13). Although, a protective level of antibody titer does not guarantee the clinical protection against influenza, in our study the rise in antibody titer among the participants of two groups were comparable. In fact, a follow-up study is required to show whether such rise in titer of antibody can effectively decrease the episode of influenza.

As it is recommended in other studies (15-18) vaccination against influenza should be performed in HCWs and HIV-infected patients annually, because it is highly immunogenic and safe. Although the use of vaccine in high risk groups such as HIV-infected patients and HCWs is highly recommended, with respect to the differences in health priorities and limitations in resources even in developed countries, such groups are not completely covered, yet. It is predictable that the situation in developing countries with more serious restrictions in health budget is even worse. A cost-benefit analysis of a vaccination program can provide essential information for health policy makers in order to decide whether to expand such programs to the larger population or not.

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