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Immune response to 2009 H1N1 vaccine in HIV-infected adults in Northern Thailand

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Background: In late 2009, the Thai Ministry of Public Health provided two million doses of the monovalent pandemic influenza H1N1 2009 vaccine (Panenza® Sanofi Pasteur), which was the only vaccine formulation available in Thailand, to persons at risk of more severe manifestations of the disease including HIV infection. Several studies have shown poorer immune responses to the 2009 H1N1 vaccines in HIV-infected individuals. There are limited data in this population in resource-limited countries.

Results: At day 28 post-vaccination, seroconversion was found in 32.0% (95% CI 24.5–40.2) of the HIV-infected group and 35.0% (95% CI 15.4- 59.2) of the healthy controls (p = 0.79). Seroprotection rate was observed in 33.3% (95% CI 25.8–41.6) and 35.0% (95% CI 15.4–59.2) of the HIV-infected group and the control group, respectively (p = 0.88). Among HIV-infected participants, the strongest factor associated with vaccine response was age 42 y or younger (p = 0.05).

Methods: We evaluated the immunogenicity of a single, 15 μg/0.5 ml dose of a monovalent, non-adjuvanted 2009 H1N1 vaccine in 150 HIV-infected Thai adults and 20 healthy controls. Immunogenicity was measured by hemagglutination inhibition assay (HI) at baseline and 28 d after vaccination. Seroconversion was defined as 1) pre-vaccination HI titer < 1:10 and post-vaccination HI titer ≥ 1:40, or 2) pre-vaccination HI titer ≥ 1:10 and a minimum of 4-fold rise in post-vaccination HI titer. Seroprotection was defined as a post-vaccination HI titer of ≥ 1:40.

Conclusions: A low seroconversion rate to the 2009 H1N1 vaccine in both study groups, corresponding with data from trials in the region, may suggest that the vaccine used in our study is not very immunogenic. Further studies on different vaccines, dosing, adjuvants, or schedule strategies may be needed to achieve effective immunization in HIV-infected population.

Introduction

Thailand was among the first countries in Southeast Asia hit hardest by the 2009 H1N1 influenza pandemic. From May 2009 to December 2010, approximately 226,000 influenza/influenza-like illnesses (ILI) with 47,000 cases of laboratory-confirmed pandemic 2009 H1N1 and 347 deaths were reported to the surveillance center at the Bureau of Epidemiology, Ministry of Public Health, Thailand (MOPH).[1] In late 2009, the MOPH purchased two million doses of the monovalent pandemic influenza H1N1 2009 vaccine (Panenza® Sanofi Pasteur), which was the only vaccine formulation available in Thailand. The MOPH provided the vaccine free of charge to persons at risk of more severe manifestations of the disease (pregnant women, persons with obesity, diabetes, cardiopulmonary dysfunction, hematological malignancy, or HIV infection) as well as healthcare personnel.

Clinical studies have been conducted to evaluate the immunogenicity and safety of different types of 2009 H1N1 vaccines in different populations. Results from five studies showed that a single dose of 2009 H1N1 vaccine induced a robust immune response in most healthy adults.[2-6] However, several studies have shown poorer immune responses to the 2009 H1N1 vaccines in HIV-infected individuals.[7-14,16,17,19-21] There are limited data in the HIV-infected population in resource-limited countries. We, therefore, evaluated the seroconversion and seroprotection rate to a 2009 H1N1 vaccine (Panenza®) in HIV-infected and healthy individuals in Thailand.

Results

One participant in the HIV-infected group developed flu-like illness one day after vaccination. A throat swab for polymerase chain reaction (PCR) performed one day later was positive for Influenza A H1N1 2009. This participant was excluded from subsequent analysis.

Day 28 post-vaccination follow-up was completed in 147 HIV-infected participants and all 20 healthy controls. Baseline characteristics and vaccine response rates by HIV status are

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Table 1. Baseline characteristics and vaccine response rates by HIV status

	HIV infected (n = 147)	HIV negative (n = 20)	P-value
Male gender N (%)	57 (38.8)	9 (45.0)	0.59
Mean age (SD)	42.1 (6.1)	32.4 (6.3)	< 0.05
Participant currently receiving ART N (%)	144 (98.0)	-	-
Absolute CD4 count(cells/mm^3)			
200 or less N (%)	13 (8.8)	-	-
More than 200 N (%)	134 (91.2)	20 (100)	-
Mean CD4(SD)	465.52 (206.1)	761.9 (283.4)	< 0.05
Pre-vaccination HI titer ≥ 1:40 N (%)	5(3.4)	1 (5.0)	0.72
Seroconversion rate[1] N (%) 95% CI	47 (32.0) 24.5–40.2	7 (35.0) 15.4–59.2	0.79
Seroprotection rate[2] N (%) 95% CI	49 (33.3) 25.8–41.6	7 (35.0) 15.4–59.2	0.88
Mean follow up days (SD)	26.4 (1.5)	23.1 (1.2)	

[1]Seroconversion was defined as: (1) pre-vaccination HI titer < 1:10 and post-vaccination HI titer ≥ 1:40 or (2) pre-vaccination HI titer ≥ 1:10 and a minimum of 4-fold rise in post vaccination HI titer. [2]Seroprotection was defined as a post-vaccination HI titer of ≥ 1:40.

shown in **Table 1**. 39% of HIV-infected participants were male and the mean age was 42.1 ± 6.1 y. 98% were on combination antiretroviral therapy (ART) and 91.2% of participants had CD4$^+$ cell count above 200 cells/mm^3 at time of vaccination. The mean CD4$^+$ cell count was 466 ± 206 cells/mm^3. Among the 20 healthy volunteers, 45% was male and the mean age was 32.4 ± 6.3 y. The mean CD4$^+$ cell count was 762 ± 283 cells/mm^3. At baseline, 3.4% (5/147) of HIV-infected participants and 5% (1/20) of controls had HI titers ≥ 1: 40.

Seroconversion was found in 47 of 147 (32.0%, 95% CI 24.5–40.2) HIV-infected participants and 7 of 20 (35.0%, 95% CI 15.4–59.2) healthy controls (p = 0.79). Seroprotection rate was observed in 33.3% (95% CI 25.8–41.6) and 35.0% (95% CI 15.4–59.2) of the HIV-infected group and the control group, respectively (p = 0.88).

Factors associated with vaccine response among HIV-infected participants are shown in **Table 2**. In the univariate analysis, baseline HI titer ≥ 1:40 were significantly associated with seroconversion (p < 0.05). Age 42 y or younger and baseline CD4$^+$ cell count above 200 cells/mm^3 were borderline significant. However, in multivariate analysis, the only significant variable was age 42 y or younger (p = 0.05). Since the number of healthy participants was low, we did not analyze for the factor associated with seroconversion for this group.

Discussion

Our study demonstrated low seroconversion and seroprotection rates in response to the non-adjuvanted 2009 H1N1 vaccine in both HIV-infected and healthy participants. These overall response rates were much lower than the expectation since the majority of HIV-infected participants (91%) had CD4$^+$ cell count > 200 cells/mm^3 and all the healthy participants had normal immune status. Multiple studies have shown varying but generally high seroconversion rates (from 79 to 98%) to the 2009 H1N1 vaccine in HIV-negative individuals.[2-6] While studies in HIV-infected individuals found lower seroconversion rates (**Table 3**), despite an immune recovery indicated by increase in CD4$^+$ cell count and full viral suppression indicated by an undetectable plasma HIV-1 RNA after combination antiretroviral therapy. The diversity of seroconversion rates may depend on different type of vaccines used among studies.[8] There is a trend that the ASO3 adjuvanted vaccine may elicit better immune response in HIV population than other types of vaccine.[15-18]

It is important to investigate the factors responsible for our seroconversion rate being lowest among studies conducted in HIV-infected individuals. Possible explanations include: (1) the vaccine used in our study (Panenza®) is less immunogenic than the 2009 H1N1 vaccine used in other studies, (2) imperfect effectiveness of influenza vaccine in field condition caused by factors such as breakdown of the cold chain and improper vaccine management, and (3) the laboratory method used in our study is less sensitive than that employed in other studies in detecting seroconversion.

Results from previous studies using non-adjuvanted 2009 H1N1 vaccine in HIV-infected individuals also showed varying seroconversion rates ranging from 31% to 71% (**Table 3**). However, the vaccine types used in those studies were different, for instances, inactivated Vero-cell-derived whole virion vaccine by Lagler et al.[7] and other non-adjuvanted recombinant vaccines produced by several pharmaceutical companies.[8-15] Therefore, comparison of differences in immunogenicity among those vaccine including that used in our study may not be possible. Nonetheless, high seroconversion rates in HIV uninfected group indicated that the immunogenicity of the vaccines employed in those studies were adequate. Conversly, our study failed to demonstrate a desire vaccine efficacy in HIV negative volunteers. This may support our hypothesis about the immunogenicity of Panenza® vaccine.

A literature review was done on the efficacy trials of the Panenza®. In the report authored by researchers affiliated with Sanofi Pasteur, two studies were conducted with single standard dose of Panenza® in 101 and 100 French healthy volunteers between August 2009 and October 2009 and between March 2010 and April 2010 respectively.[22] The seroconversion rate in the first study was 92% and that in the second study was 97%.

Table 2. Univariate and multivariate analysis for factors associated with vaccine response among HIV-infected participants

Characteristics	Number Seroconversion/total (%)	Odd Ratio (95% CI)	P-value	Adjusted Odd Ratio (95%CI)	P-value
Age in years					
≤ 42	32/83 (38.6)	**2.05**	**0.05**	**2.10**	**0.05**
> 42	15/64 (23.4)	**(0.94–4.58)**		**(0.99–4.45)**	
Gender					
Male	17/57 (29.8)	0.85	0.66	-	-
female	30/90 (33.3)	(0.39–1.84)			
Duration of HIV infection					
≤ 8 y	22/66 (33.3)	1.12	0.75	-	-
> 8 y	25/81 (30.9)	(0.53–2.38)			
Initiated Antiretroviral treatment					
Yes	46/144 (31.9)	0.94	0.96	-	-
No	1/3 (33.3)	(0.05–56.57)			
Baseline HIV RNA PCR (copies/ml)					
< 400	46/142 (32.4)	1.92	0.56	-	-
≥ 400	1/5 (20.0)	(0.18–96.40)			
Baseline CD4 count (cell/mm³)					
> 200	46/134 (34.3)	**6.27**	**0.05**	**5.86**	**0.10**
≤ 200	1/13 (7.7)	**(0.87–273.83)**		**(0.73–47.05)**	
Symptomatic or AIDs indicator conditions at baseline					
Yes	2/11 (18.2)	0.45	0.31	-	-
No	45/136 (33.1)	(0.05–2.31)			
Baseline HI titer					
≥ 1:40	4/5(80)	**9.21**	**0.02**	**8.61**	**0.06**
< 1:40	43/142(30.3)	**(0.86–457.91)**		**(0.91–81.67)**	

However, the immunologic responses to Panenza® were found to be less than that reported in French studies, involving healthy adults in Thailand and Hong Kong. First is a prospective cohort study of a single dose of Penenza® in hemodialysis patients and 149 healthy controls by Lertdumrongluk et al.[23]; the seroconversion rate was 63.1% and protective titers were obtained in 67.1% of the control group at 4 weeks post vaccination. A cross-sectional study conducted in Khon Kaen, Thailand in June 2010, 52.1% of 71 healthcare workers aged 21–75 y who had been vaccinated with Panenza® vaccine had HI titers ≥ 40.[24] A similar study conducted in 104 Hong Kong healthcare workers aged 19–64 y receiving Panenza® also showed seroprotection rate of 53.8% (95% CI 44.2%–63.2%).[25] One of the possible explanations for lower antibody response considered by the authors was imperfect effectiveness of Panenza®.

The only study of Panenza® in HIV-infected individuals in Thailand was done at Siriraj Hospital in Bangkok and Chiang Mai University Hospital in Chiang Mai, Thailand.[26] 119 children with a median age of 10.4 y (IQR 7.2–13.7) were given 2 doses of Panenza® 28 d apart. The seroconversion rates were 54.2% and 67.8% after the first and second doses, respectively. Our study is the first report of this particular vaccine in HIV-infected adults.

To answer the question of improper vaccine management, the vaccines used in our study were delivered from the Department of Disease Control, MOPH to our institute on January 14, 2010. Vaccine expiration date was September 30, 2010. Vaccinations were started from January 21, 2010 to March 2010. To ensure vaccine quality, all vaccines were stored and delivered under temperature controlled conditions in accordance with the Pharmacy guidelines and Instruction s for DAIDS Clinical Trials Networks Division of AIDS pharmaceutical Affairs Branch, July 2008 and the vaccine package insert. Each vaccine vial was only used within a day of first opening. After reviewing the vaccine management records, we did not find any errors that could explain the result of this study. It was also unlikely that cold chain breakdown and improper vaccine management had occurred concurrently in Hong Kong, Khon Kaen, Bangkok and Chiang Mai.

Lastly, considerable variability can be introduced into the laboratory assay used to measure HI antibodies including differences in viral strains and red blood cell types, and the presence of non-specific inhibitors in the assay medium.[27] In our study, the HI test was performed according to standard method,[28] the only exception is the use of goose erythrocyte instead of turkey erythrocyte. However, a study by Lerdsamran et al.[29] has demonstrated that goose and turkey erythrocytes yielded comparable HI antibody titers. A study by Miraglia et al.[11] also used the standard HI assay and demonstrated the low seroconversion rate (55%) to Sanofi-Pasteur non-adjuvanted H1N1 vaccine in HIV infected

Table 3. Summary of studies of a single dose H1N1 vaccination.

No. of HIV-infected/control	Age of HIV-infected vaccinees	CD4 count of HIV-infected vaccinees	Seroprotectionrate at baseline HIV/ Control	Seroprotection rate post vaccination HIV/Control	Seroconversion rate HIV/ Control	Author/Country/ Reference number
Non-adjuvanted 15 μg						
79/0	40 (37–42)[a]	502 (449–556)[a]	70/0	92/0	31/0	Lagler et al./Austria/7
182/42	47 (13)[b]	411 (178)[b]	13/12	50/86	39/ 86	Yanagisawa et al./Japan/8
CD4 < 200: 35/0 CD4 ≥ 200: 60/0	46 (9)[b] 46 (10)[b]	156 (97)[b] 610 (269)[b]	21/0 18/0	47/0 64/0	41/0 52/0	El Sahly et al./USA/9
104/0	43 (34 -53)[c]	373 (256–520)[c]	12/0	56/0	50/0	Hatakeyama et al./Japan/10
256/0	45 (22–75)[c]	Not evaluated	9/0	59/0	55/0	Miraglia et al./Brazil/11
120/0	46 (40–53)[c]	502 (307–640)[c]	25/0	69/0	56/0	Tebas et al./USA/12
65/66	36 (26–45)[c]	581 (476–814)[c]	20/33	65/85	68/83	Crum-Cianflone et al./ USA/13
126/0	44 (37–51)[c]	530 (400–685)[c]	39/0	87/0	67/0	Maruszak et al./Australia/14
150/0	47 (40–54)[c]	551 (428–702)[c]	10/0	76/0	71/0	Launay et al./France/15
ASO3 adjuvanted 3.75 μg						
155/0	47(39–54)[c]	522 (387–752)[c]	8/0	93/0	89/0	Launay et al./France/15
84/0	48 (11)[b]	427 (178)[b]	8/0	45/0	44/0	Tremblay et al./Canada/16
160/0	46 (11)[b]	514 (246)[b]	14/0	75/0	69/0	Bickel et al./Germany/17
252/0	47 (10)[b]	570 (266)[b]	26/0	92/0	83/0	Orlando et al./Italy/18
MF59 adjuvanted 7.5 μg						
44/148	45 (no SD)[b]	563 (505–621)[d]	80/35	98/97	36/79	Kajaste-Rudnitski et al./ Italy/19
57/44	52 (11)[b]	507 (349–697)[c]	44/23	88/93	53/73	Soonawala et al./ Netherlands/20
41/0	46(41–55)[c]	528(406–736)[c]	24/0	78/0	61/0	Fabbiani et al./Italy/21

[a]Median with 95% CI. [b]Mean with Standard deviation. [c]Median with Interquartile range. [d]Mean with 95% CI. Figures are rounded to the nearest whole number: rounded up for half or greater (≥ 0.5), rounded down for less than half (< 0.5).

individuals. Therefore, the method used may not be a potential factor to the low response rate. The fact that the strain used in HI assay in our study, is not identical to the strain included in the vaccine could be a reason for a lower immunogenicity. The A/Thailand/104/2009(H1N1) strain which was also used to evaluate the vaccine response in the other two Thai studies[23,26] was isolated from a confirmed case of pandemic H1N1 2009 who had recently traveled back from Mexico. The strain was submitted to the GenBank database on June 13, 2009 where full genomic sequence of A/Thailand/104/2009(H1N1) can be retrieved. Its HA gene is 99.7% identical to that of A/California/7/2009 pandemic virus.[29] The author's unpublished data (PP and HL) have shown that the antibody titers against these two viruses were comparable as assayed in 100 individuals without immune deficiency (patients and non-patients). Therefore, the strain used in the HI assay would probably not have a significant influence on

the vaccine response rate. To avoid the intra-laboratory variability of the test, we selected the HI assay instead of the viral neutralization assay that may have higher variability in results.[30] In addition, we performed the tests for all sera in a batch process using the same reagents and by the same lab personnel.

In conclusion, the unexpected low immune response to the single dose of non-adjuvanted 2009 H1N1 vaccine in our study together with similar results in the three other studies[23-25] suggest that the vaccine formulation Panenza® bought by the Hong Kong and Thai government in late 2009 may be the cause of this suboptimal response. Alternatively, there might be problems with cold chain, vaccine management, or the sensitivity of laboratory method. However, these are unlikely to happen in Hong Kong, Bangkok, Chiang Mai, and Khon Kaen concurrently. Further reports from countries that employed Panenza® and/or investigation by Sanofi Pasteur of the lot of Panenza® marketed in late 2009 are needed. Further studies on different vaccines, dosing, adjuvants, or schedule strategies may be needed to achieve effective immunization in HIV-infected population.

Limitations. Limitations of our study were a small number of HIV-negative controls which may have insufficient power to determine vaccine response in this population and lack of different type of vaccine to compare with Panenza® vaccine.

Methods

Participants. Our study was conducted after the first wave of pandemic influenza H1N1 2009 outbreak in Thailand. Between January 2010 and March 2010, we invited and enrolled, on a first-come-first-served basis, a total of 150 HIV-infected individuals aged 18–60 y from the Infectious Disease Clinic, Chiang Mai University Hospital, a 1,500-beds tertiary care facility in Chiang Mai, Thailand, where a treatment-cohort of approximately 1,300 HIV-infected patients was under active follow-up. Exclusion criteria were an allergy to eggs or a history of Guillain-Barré Syndrome or family history of Guillain- Barré Syndrome. A total of 20 healthy volunteers were enrolled under the same protocol.

Clinical and laboratory Procedures. The vaccine, Panenza®, is a monovalent, non-adjuvanted vaccine formulated to contain 15 μg/0.5 mL of hemagglutinin (HA) of influenza A/California/07/2009 (H1N1) v-like virus produced by Sanofi Pasteur. A single 0.5 mL intramuscular dose of the vaccine was administered to all 170 participants. Clinical assessment was performed in HIV-infected individuals prior to vaccination for classification of CDC clinical category.[31] Baseline Laboratory evaluation included $CD4^+$ cell count and hemagglutination inhibition (HI) antibody titer against 2009 H1N1 virus for both groups and plasma HIV-1 RNA measurement for HIV-infected group. The $CD4^+$ cell count was performed using flow cytometry techniques and plasma HIV-1 RNA was measured by the COBAS Amplicor. Analyzer, ROCHE Diagnostic System at the Research Institute for Health Sciences, Chiang Mai University.

The HI assay was performed at the Department of Microbiology, Faculty of Medicine Siriraj Hospital, Mahidol University. The methodology was described previously.[29] Briefly, 50 μl of the test serum were mixed with 150 μl of receptor destroying enzyme (RDE, Denka Seiken) and incubated overnight in water bath at 37°C. This step was followed by heat inactivation at 56°C for 30 min, and removal of nonspecific agglutinator by absorbing with goose erythrocytes for 1 h at 4°C. The replicating virus, A/Thailand/104/2009, at final concentration of 4 HA units/25 μl was used as the test antigen; and goose erythrocytes were used as the indicator. The treated serum was 2-fold serially diluted in duplicate wells of a microtiter V shaped plate at an initial dilution of 1:10; and 25 μl of the diluted serum were incubated with 25 μl of the test antigen for 30 min at room temperature. Thereafter, the reaction wells were added with 50 μl of 0.5% goose erythrocyte suspension and further incubated for 30 min at 4 C before the HI antibody titers were determined. HI antibody titer is defined as the reciprocal of the highest serum dilution that completely inhibits hemagglutination reaction. Reference/positive control serum with known HI titer, the serum control and back titration of virus antigen were included in each run. The reference human serum was obtained from the National Institute for Biological Standards and Control (NIBSC). The full genomic sequence of the virus, A/Thailand/104/2009, has been deposited with GenBank. Its HA gene is 99.7% identical to that of A/California/7/2009 pandemic virus.[29] This virus was the second strain isolated in Thailand in May 2009 from a case who traveled back from Mexico (PP, personal communication).

Evaluations and endpoints. Any participant who developed influenza-like illness was asked to come to the clinic within 72 h for respiratory specimen collection to confirm the diagnosis of 2009 H1N1 infection. The immunogenicity endpoint was the proportion of participants who had seroconversion and seroprotection from vaccination. Seroconversion was defined in accordance with the US FDA guidance[27] as 1) pre–vaccination HI titer < 1:10 and post-vaccination HI titer ≥ 1:40, or 2) pre-vaccination HI titer ≥ 1:10 and a minimum of 4–fold rise in post-vaccination HI titer. Seroprotection was defined as a post-vaccination HI titer of ≥ 1:40.

Ethics. The study protocol was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University.

Statistical methods. For baseline characteristics, continuous variables such as age and absolute $CD4^+$ cell count are presented as mean ± standard deviation. Seroconversion rate and seroprotection rate with the corresponding 95% confidence interval (CI) were calculated. Univariate analyses and multivariate analysis by logistic regression were used to determine factors associated with seroconversion in HIV-infected group. Results were reported by presenting odds ratios and adjusted odds ratios with 95% confidence interval. Level of significance was defined as a p-value of < 0.05.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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