EFFECTIVENESS OF INFLUENZA VACCINATION IN PREVENTION OF INFLUENZA-LIKE ILLNESS AMONG INHABITANTS OF OLD FOLK HOMES

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Abstract. The aims of the study were to determine the attack rate of influenza-like illness among inhabitants of five old folk homes nationwide using influenza vaccine as a probe and the effectiveness of influenza vaccination in prevention of influenza-like illness. We conducted a non-randomized, single-blind placebo control study from June 2003 to February 2004. VAXIGRIP^{R} 2003 Southern hemisphere formulation was used. Among 527 subjects, the attack rates of influenza-like illness in the influenza vaccine group were 6.4, 4.6 and 2.4% during the first, second and third 2-month periods, respectively. The attack rates of influenza-like illness in the placebo group were 17.7, 13.8 and 10.1%. Influenza vaccination reduced the risk of contracting influenza-like illness by between 14, and 45%. The vaccine effectiveness in reducing the occurrence of influenza-like illness ranged from 55 to 76%, during the 6-month study follow-up. The presence of cerebrovascular diseases significantly increased the risk of influenza-like illness ($p < 0.005$). Vaccine recipients had fewer episodes of fever, cough, muscle aches, runny nose ($p < 0.001$) and experience fewer sick days due to respiratory illness. Subjects who received influenza vaccination had clinically and statistically significant reductions in the attack rate of influenza-like illness. Our data support influenza vaccination of persons with chronic diseases and >50 year olds living in institutions.

INTRODUCTION

Influenza virus is unique among respiratory viruses in that epidemics are regularly associated with elevated patient morbidity and mortality, putting enormous pressure on health, social care and other services (Glezen, 1982). Influenza is often associated with elevated rates of pneumonia and hospitalization during epidemics. Influenza virus can cause a broad range of illnesses, from symptomless infection through various respiratory syndromes, disorders affecting the lung, heart, brain, liver, kidneys, and muscles, to fulminant primary viral and secondary bacterial pneumonia. The course is affected by the patient's age, the degree of pre-existing immunity, properties of the virus, smoking, co-morbidities, immunosuppression, and pregnancy (Nicholson *et al,* 2003). Persons age 65 years or older are particularly susceptible, experiencing more than 90% of these complications, and also exacerbations of underlying medical conditions, such as chronic heart and lung disease, even death (Glezen 1982; Mc Bean *et al,* 1993).

Annual vaccination is recommended as the mainstay in efforts to prevent influenza in the elderly. The World Health Organization has suggested that elderly individuals be targeted for immunization, but despite this recommendation, influenza vaccine is underused (Nichol

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et al, 1998). Persistent uncertainties regarding the risks of influenza and the benefits of influenza immunization may contribute to the under utilization of the influenza vaccine.

In temperate climates, influenza is characterized by occurrence of annual epidemics during the winter months. Epidemics in tropical countries are less seasonal, and influenza virus can be isolated from significant numbers of patients with respiratory symptoms throughout the year. In Malaysia, influenza virus circulates all year with peaks from June to July and December to January (Nor Shahidah *et al,* 2003). We conducted a prospective, nonrandomized, single-blind placebo controlled study to determine (1) the incidence of influenza-like illness among inhabitants of old folk homes using influenza vaccine as a probe and (2) the effectiveness of influenza vaccination in prevention of influenza-like illness.

MATERIALS AND METHODS

Setting

The study was conducted from June 2003 to February 2004 in five old folk homes in 4 states in West Malaysia. The selected homes included one each in the Malacca, Negeri Sembilan, Wilayah Persekutuan and two in Perak. These homes were administered and run by the Ministry of Social Welfare. The study was conducted in accordance with the Declaration of Helsinki Clinical Good Practice and was also approved by the Ministry of Social Affairs and the Research and Ethics Committee Boards of Universiti Kebangsaan Malaysia.

Patients

The investigators explained the study and its goals to the residents in each of the homes. Written consent was obtained from each subject who volunteered to participate. Prior to enrollment, each subject's medical history was reviewed and a physical examination was performed to ensure compliance to inclusion and exclusion criteria. Influenza vaccine was given to the treatment group and typhoid vaccine was given to the control group. Subjects were observed closely for immediate adverse reactions for a minimum of 30 minutes and adverse events were recorded throughout the study. Emergency management supplies were available for the initial treatment of allergy.

Inclusion and exclusion criteria

All residents of the old folk homes who were 50 years old or older in 2003 were eligible for the study. Those who had received influenza vaccination with the current vaccine (Southern hemisphere 2003 season), had been diagnosed with influenza within 3 months, or treated for an upper respiratory tract infection in the previous 2 weeks, or had a history of immediate hypersensitivity reaction to eggs, or a history of allergic reaction to thimerosal or who currently had a febrile illness were excluded.

Vaccines and definitions

The influenza vaccine used in this study was VAXIGRIP® (Aventis Pasteur, Lyon, France) having the Southern hemisphere Formulation for 2003. The strains included in the vaccine were: H3N2 A/Moscow/10/99= A/ Panama/2007/99, H1N1 A/ New Caledonia/ 20/99, and B / Hong Kong/330/2001.

The placebo used was TYPHIM VI™ which contains a polysaccharide antigen of *Salmonella typhi* (strain Ty2), 0.025 mg in each 0.5 ml dose.

Case definition

An influenza-like illness was defined as the occurrence of a respiratory illness of at least 2 days duration having at least one systemic symptom (fever >38.0ºC, chills or myalgia) and one respiratory tract symptom (rhinorrhea, sore throat, cough or hoarseness of voice).

Follow-up

The primary study outcomes were the number of episodes of influenza-like illness and symptoms. The secondary outcomes

were the number of visits to a health care clinic or hospital, antibiotic or treatment received, number of days of feeling unwell, number of days unable to perform routine activities, and number of days of hospitalization. The subjects in the treatment and control groups were interviewed by appointed medical assistance based on the Clinical Report Form (CRF) at intervals of 2 months for a period of 6 months. The interviewers recorded the primary and secondary outcomes. The questionnaires were analyzed using SPSS version 11.

Statistical analysis

Baseline demographic and health characteristics in the vaccinated and placebo persons were compared using Student's *t*-test and chi-square tests. The attack rates of influenza-like illness in the two groups were compared and computed using the Mantel-Haenszel common odds ratio.

RESULTS

The cohort was comprised of 527 per-

Table 1
Baseline characteristics of study populations.

Variable	Treatment	Control	Total	p-value
N	270	257	527	
Age mean (SD)	67.5 (±9.1)	68.2 (±9.6)	67.8	NS
Sex				
Male	60.7%	61.5%	61.1%	NS
Female	39.3%	38.5%	38.9%	
Ethnicity				
Malay	37.8%	40.5%	39.1%	NS
Chinese	33.7%	28.8%	31.3%	
Indian	27.4%	30.0%	28.7%	
Others	1.1%	0.8%	0.9%	
Highest education level				
Primary	78.0%	71.4%	74.7%	NS
Secondary and above	5.2%	7.0%	6.1%	
Others	16.8%	21.6%	19.2%	
Smoking status				
Current	42.1%	36.2%	39.3%	NS
Past	8.4%	8.1%	8.3%	
Never	49.4%	55.7%	52.5%	
Chronic medical conditions	45.7%	51.0%	48.3%	NS
Asthma	9.3%	7.8%	8.6%	NS
Diabetes	6.3%	10.1%	8.2%	NS
Hypertension	16.4%	20.6%	18.4%	NS
Cerebrovascular disease	8.6%	12.5%	10.5%	NS
Age in years				
50-59	20.6%	19.6%	20.1%	NS
60-69	32.7%	37.8%	35.3%	
70-79	35.0%	31.1%	33.0%	
80-89	10.9%	10.0%	10.4%	
≥90	0.8%	1.5%	1.1%	

Table 2
Incidence of influenza-like illness in the 6 months following the start of the study.

No. of ILI episodes	First 2 months		Second 2 months		Third 2 months	
	Treatment	Control	Treatment	Control	Treatment	Control
0	248 (93.6%)	205 (82.3%)	249 (95.4%)	213 (86.2%)	249 (97.6%)	213 (89.9%)
1	17 (6.4%)	35 (14.1%)	12 (4.6%)	32 (13.0%)	6 (2.4%)	24 (10.1%)
2	0	6 (2.4%)	0	2 (0.8%)	0	0
3	0	3 (1.2%)	0	0	0	0
Total	249	265	261	247	255	237
Pearsons Chi-square	24.888 p-value <0.001		14.363 p-value <0.001		12.964 p-value <0.001	

sons from 5 government old folk homes. The participants returned 514 completed Clinical Report Forms (97.5%) at the end of the first 2-month observation period, 508 (96.4%) at the end of the second 2-month period, and 492 (93.4%) at the end of the study. The characteristics of the study population are shown in Table 1. Overall, 48.3% suffered from at least one chronic medical problem, with hypertension (18.4%) at the top of the list, followed by cardiovascular disease (10.5%), asthma (8.6%) and diabetes (8.2%). The treatment and control groups were similar in regard to age, sex, chronic medical conditions (asthma, diabetes mellitus, hypertension and cerebrovascular disease), and smoking history.

Table 2 shows the incidence of influenza-like illness (ILI) in the study groups. The incidence of influenza-like illness decreased over time for both treatment and control groups. The treatment group only experienced one ILI episode during the entire 6 month follow-up period. The incidences of ILI in the influenza vaccine group were 6.4, 4.6 and 2.4% during the first, second, and third 2-month periods, respectively. During the same period, the placebo group rates of incidence were 14.1%, 13.0% and 10.1%, respectively. Subjects in the control group experienced 1-3 episodes of ILI during the same period. The Mantel-Haenszel Common Odd Ratio estimate of 0.251 for treatment versus control (95% Confidence Interval) suggested that participants who were vaccinated with influenza vaccine were less likely to have ILI. In the first 2 months, influenza vaccination reduced the risk of contracting ILI to between 14% and 45% of the risk for the placebo group.

Table 3 presents the covariates in persons with at least one episode of ILI in 6 months. ILI occurred more frequently in persons with chronic medical disease (OR 2.325, 95% Confidence Interval 1.318, 4.102). Among high-risk diseases, asthma, diabetes and hypertension did not increase the risk of ILI. Cerebrovascular diseases significantly increased the risk of ILI ($p<0.005$). Other variables, such as age, duration of stay, sex and smoking history, were not significantly different between the influenza vaccine recipients and the control groups. Cerebrovascular diseases continued to have a significant effect during the second 2-month interval ($p=0.03$) but lost their significance in the third study period. Our study results also show that influenza vaccination is significantly effective in reducing the incidence, fever, cough, runny nose, muscle aches and chills (Table 4).

Table 3
Risk factors in persons who experienced at least one episode of influenza-like illness during 6 months.

	First 2- months			Second 2-months			Third 2- months		
	At least one episode ILI n = 60	No. episode of ILI n = 448	p-value	At least one episode ILI n = 46	No. episode of ILI n = 462	p-value	At least one episode of n = 30	No. episode of ILI n = 462	p-value
Mean age	67.1	67.84	NS	67.6	67.8	NS	70.4	67.7	NS
(SD)	(10.064)	(9.209)		(7.23)	(9.53)		(10.65)	(9.36)	
Mean (SD) duration of stay in years	5.4	6.3	NS	6.5	6.2	NS	7.6	6.1	NS
	(4.84)	(5.87)		(5.78)	(5.76)		(6.69)	(5.76)	
Gender									
Male	58.3%	61.6%	NS	50.0%	62.1%	NS	30.0%	62.1%	<0.001
Female	41.7%	38.4%		50.0%	37.9%		70.0%	37.9%	
Smoking status									
Current	43.3%	39.0%	NS	38.7%	47.7%	NS	72.4%	60.7%	NS
Past/never	56.7%	61.0%		52.3%	61.3%		27.6%	39.3%	
Chronic medical conditions	66.7%	46.2%	0.003	54.3%	47.3%	NS	63.3%	46.2%	NS
Asthma	8.3%	8.6%	NS	8.7%	8.0%	NS	13.3%	7.2%	NS
Diabetes	11.7%	7.5%	NS	6.5%	8.5%	NS	6.7%	8.7%	NS
Hypertension	23.3%	17.7%	NS	15.2%	18.4%	NS	23.3%	18.0%	NS
Cerebrovascular	21.7%	9.1%	0.003	19.6%	9.3%	0.03	3.3%	10.4%	NS

Table 4
Respiratory morbidity among the study population during 6 months follow-up.

Symptoms	Treatment	Control	Vaccine effectiveness	p-value (Chi-square test)
Fever	31	74	0.601	< 0.001
Muscle aches	5	20	0.762	0.001
Sore throat	4	9	0.577	0.135
Hoarseness of voice	0	4	1.00	- (not reliable)
Chills	2	16	0.881	0.001
Runny nose	13	45	0.725	< 0.001
Cough	26	66	0.625	< 0.001

Table 5
Total number of days to get better after episodes of ILI in 6 months.

Group	1 day	2 day	3 day	4 day	5-12 day	Total
Treatment	5	9	12	1	2	29
	17.2%	31.0%	41.4%	3.4%	6.9%	100%
Control	6	12	21	10	28	77
	7.8%	15.6%	27.3%	13.0%	36.4%	100%

Pearson chi-square 14.007, p-value < 0.01

Table 6
Total number of days not able to perform routine activities due to ILI in 6 months.

Group	1 day	2 day	3 day	4 day	5-12 day	Total
Treatment	10	9	9	1	1	30
	33.3%	30.0%	30.0%	3.3%	3.3%	100%
Control	9	16	21	8	20	74
	12.2%	21.6%	28.4%	10.8%	27.0%	100%

Pearson chi-square 13.194, p-value = 0.010

Tables 5 and 6 summarize the morbidity during the 6-month study period. There was a significant difference in the number of days required for resolution of symptoms between the two study groups. Only 10.3% of subjects in the group given the influenza vaccine required 4 or more days to get better, compared to 49.4% in the control group. Table 6 shows the severity of ILI in senior citizens to the extent that those who had ILI could not perform routine activities thus requiring increased levels of care by cargivers.

DISCUSSION

The unique pattern of year round influenza activity and a biannual epidemic pattern in tropical Asian countries complicates the routine assessment of disease burden (Simonson, 1999). Consequently, the morbidity and mor-

tality from influenza are probably greatly underestimated in these regions. Most of the influenza burden and vaccine effectiveness studies have been done in temperate countries where influenza occurs in one annual epidemic during the winter months. This is the first prospective, single blind, non-randomized, placebo-controlled cohort study of influenza incidence, burden and vaccine effectiveness among institutionalized elderly in the tropics. In this cohort study we demonstrate that influenza vaccination is associated with a significantly lower attack rate of ILI over a period of 6 months in persons > 50 years old living in institutions in the tropics. The vaccine effectiveness in reducing the occurrence of ILI ranged from 55 to 76% during the 6-month study follow-up. Vaccine recipients had fewer episodes of fever, cough, muscle aches and runny nose ($p < 0.001$) and experienced fewer sick days due to respiratory illness.

The results of this study are consistent with results obtained in studies conducted in temperate climates. A typical influenza illness may result in five to six days of restricted activity in bed and three days of absenteeism from school or work (Kavet, 1977). In this study, 27.0% of the control group and only 3.3% of the vaccine group could not perform routine work for 5-12 days. In the control group, up to 36.4% felt sick for 5-12 days compared to 6.9% in the treatment group. Ideally, virological isolation of the etiological agents of respiratory illnesses improves precision of the estimated vaccine-prevented disease burden. Voordouw *et al* (2003) conducted a population-based cohort study in the Netherlands using the computerized Integrated Primary Care Information database. Subjects who were 65 years and older were eligible for the study. Influenza vaccination was associated with a significant reduction of morbidity and mortality in vaccinated elderly (Relative Risk 0.72; 95% confidence interval 0.60-0.87). Gross *et al* (1995) did a meta-analyses of 20 observational studies having a cohort design. Combined results of these studies showed that, in vaccinated patients, the risk of respiratory illness was only 44% of controls (CI, 32-61%; $p < 0.00001$); risk for hospitalization was 50% of controls (CI, 35-72%; $p=0.00023$); mortality was 32% (CI, 24-44%; $p=0.00001$). The pooled vaccine efficacy (1 minus odds ratio) was 56% (CI, 39-68%) for preventing respiratory illness, 48% (CI, 28-65%) for preventing hospitalization, and 68% (CI, 56-76%) for preventing death. Trang *et al* (2002) reported the influenza vaccine was effective in reducing ILI by 33% (CI, 27-38%), mortality following hospitalization for pneumonia and influenza by 47% (CI, 25-62%), and mortality from all causes by 50% (CI, 45-56%).

In this study, 48.3% of the study population had underlying chronic medical conditions (asthma, diabetes, hypertension, cerebrovascular diseases). Complications and death from influenza are of particular concern in those with certain “high risk” medical conditions, primarily the elderly, adults and children with cardiovascular and pulmonary conditions (Trang *et al,* 2002). The presence of such conditions significantly increases the risk of influenza related hospitalization above that associated with age alone.

The strengths of this study include the multi-center government run institutions for the elderly, availability of free medical care, use of cohort design, and having a placebo control. This study confirms that ILI occurs in the senior citizens in Malaysia, causing a substantial burden on the individuals, society and health care facilities. Influenza vaccine is known to prevent severe outcomes of influenza infections. A vaccine-probe, placebo control cohort study may provide the best burden study (Simonsen, 1999). Ready availability of medical care services in government run old folk homes overcomes the ethical issue of placebo study in the elderly.

We conclude that in this study, influenza vaccination was associated with decreased incidence of ILI in persons over 50 years living in institutions. During this period, there was an influenza outbreak in a residential secondary school in the state of Perak where 2 of the 5 old folks homes are situated (Ministry of Health). Influenza A/Fujian H3N2 was isolated from the students. Although the vaccine strains may not have fully matched the circulating strains, the vaccination significantly reduced the attack rate of ILI.

This study provides evidence of the benefits of influenza vaccination in the elderly population living in institutions. We recommend influenza vaccination for persons with chronic diseases and >50 years of age living in institutions.

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