

## The Efficacy of Influenza Vaccination in Healthcare Workers in a Tropical Setting: A Prospective Investigator Blinded Observational Study

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### Abstract

**Introduction:** Influenza vaccine has been shown to be highly effective in temperate regions with well-defined seasonal influenza. Healthcare workers (HCWs) are advised to receive regular influenza vaccination to protect themselves and their patients. However, there are limited data on the efficacy of influenza vaccine in HCWs in the tropics. **Materials and Methods:** In this observational, investigator blinded cohort study, bi-monthly questionnaires recording influenza-like illness (ILI) episodes and medical leave were administered to 541 HCWs at the Singapore National University Hospital and KK Women's and Children's Hospital from 2004 to 2005. ILI was defined according to a standard symptom score. **Results:** Baseline characteristics were comparable in both the vaccinated and non-vaccinated groups. Overall, the relative risk of self-reported ILI in vaccinated HCWs was 1.13 [95% confidence interval (CI), 0.98-1.13;  $P = 0.107$ ]; medical leave taken was lower in the vaccinated group [mean  $0.26 \pm 0.6$  days per visit, compared with  $0.30 \pm 0.5$  days in the non-vaccinated group ( $P = 0.40$ )]. Because of the reported Northern Hemisphere 2003/04 vaccine mismatch, we stratified the cohort and determined that the group which received a matched vaccine had a relative risk of ILI of 0.49 (95% CI, 0.37-0.66;  $P < 0.001$ ), achieving a vaccine efficacy of 51%. Mean medical leave decreased significantly in HCWs who received the matched vaccine, compared with those who did not receive vaccination ( $0.13 \pm 0.3$  vs  $0.30 \pm 0.5$ ;  $P < 0.001$ ) and with HCWs vaccinated with mismatched strains ( $0.13 \pm 0.3$  vs  $0.39 \pm 0.9$ ;  $P = 0.01$ ). **Conclusions:** A well-matched influenza vaccine is effective in preventing ILI and reducing sickness absence in healthcare workers in tropical settings. Efforts need to be made to increase influenza vaccination rates and to improve the currently available vaccines.

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**Key words:** Efficacy, Healthcare workers, Influenza vaccination, Vaccine mismatch

### Introduction

Influenza causes significant morbidity, mortality and economic impact in Singapore. According to a recent report, there are about 4.2 million cases of influenza-like illness (ILI) annually in Singapore, leading to 3.5 million doctor visits and 2.1 million days of documented medical leave.<sup>1</sup> The authors of that report indicated that up to 15% of patients with ILI were virologically confirmed with influenza virus infection.<sup>1</sup>

The influenza vaccine has been shown to be effective in temperate regions with well-defined seasonal influenza.

However, there are limited data on the efficacy of trivalent influenza vaccine in healthcare workers (HCWs) in the tropics, where influenza is believed to be a perennial disease with occasional peaks but no regular clearly defined "season".<sup>2</sup> To our knowledge, the only published study to date reported a vaccine efficacy of 52.6% in reducing ILI, and 76% in reducing medical leave due to ILI in Malaysian dental students and staff.<sup>3</sup> In the Malaysian study, HCWs were only followed up for 4 months after vaccination. Waning immunity in the months after initial vaccination may further decrease vaccine effectiveness in a setting with

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no well-defined influenza season, because vaccination might occur too early, before the onset of any influenza activity, to produce clinical benefit.

Vaccination for seasonal influenza has been recommended for Singaporean healthcare workers to protect themselves and more importantly their patients from influenza and its complications.<sup>4</sup> In Singapore, free influenza vaccination, with both Northern and Southern Hemisphere recommended vaccines, is provided to all HCWs in restructured hospitals. Unfortunately, the uptake of influenza vaccination by Singaporean healthcare workers has not been high for a variety of reasons.<sup>5</sup> Anecdotally, many HCWs remain unconvinced of the efficacy of seasonal influenza vaccination. We therefore performed a prospective observational investigator blinded cohort study to determine the efficacy of seasonal influenza vaccination in healthcare workers.

## Materials and Methods

### Study Population

All healthcare workers at the National University Hospital (NUH) and KK Women's and Children's Hospital (KKWCH) were eligible for the study. The investigators invited all healthcare workers to participate in the study either personally at their workplaces or by email. The exclusion criteria were: declining to give consent, a history of egg protein allergy, and neurological or immunological conditions that are contraindications to the influenza vaccine.

### Study Design

Consenting participants were asked to complete a baseline questionnaire with demographic data and risk factors that have previously been identified for influenza. Follow-up bi-monthly questionnaires, recording ILI episodes, doctor visits and medical leave taken were administered to participants at both institutions from April 2004 for a 1-year period.

Information on vaccination status and documented medical leave was independently obtained from hospital administrative records. The present investigation was a single-blinded study, as investigators were blinded to the vaccination status of participants, but the participants were fully aware of their vaccination status.

### Definitions and Outcomes

ILI was defined according to a standard symptom score that has been used in previous studies of healthy adults.<sup>6</sup> This includes a respiratory illness of at least 2 days' duration consisting of: (1) at least one of the systemic symptoms of fever, chills, or myalgia, and (2) at least one of the following respiratory tract symptoms: coryza, sore

throat, unusual cough or hoarseness of voice.

The pre-defined endpoints of this study were:

- (a) self-reported ILI in vaccinated vs non-vaccinated HCWs, and
- (b) the number of working days lost to documented medical leave.

Microsoft Office Excel 2003 (Seattle, Washington, USA) was used for data analysis. Continuous variables were compared using Student's paired *t*-test and non-continuous variables were compared with Fisher's exact test. For calculation of vaccine efficacy (VE), we used the following formula<sup>7</sup>:  $VE = (\text{Rate in non-vaccinated} - \text{Rate in vaccinated}) / \text{Rate in non-vaccinated} \times 100$ .

## Results

A total of 541 consenting HCWs participated in the study – 52% from NUH and 48% from KKWCH. The vaccination status records were maintained by the respective hospital administrations and only revealed to the investigators at the end of the study, after all the questionnaires had been completed. Overall, in both hospitals, 211 (39%) of 541 participating HCWs were vaccinated. This rate was comparable to the overall vaccination rates achieved at both hospitals in all staff. Both vaccinated and non-vaccinated HCWs were similar in terms of age, gender, the presence of young children or elderly people at home, and the proportion of smokers.

There was a slightly higher prevalence of chronic diseases, mainly diabetes and hypertension, among the individuals who did receive influenza vaccination, perhaps reflecting the role of the HCWs' own personal physicians in encouraging them to receive vaccination for their own personal protection as more vulnerable individuals. These baseline characteristics are summarised in Table 1.

Overall, 132 (63%) of 211 vaccinated HCWs reported an ILI during the study period, compared with 182 (55%) of 330 non-vaccinated HCWs. The relative risk of self-reported ILI in vaccinated HCWs was 1.13 (95% CI, 0.98-1.13; Fisher's exact test  $P = 0.107$ ) (Table 2). Vaccine efficacy was -15% for prevention of self-reported ILI. On the other hand, medical leave as documented by the hospital administration, was reduced for vaccinated HCW ( $0.26 \pm 0.6$  days in each visit) compared with non-vaccinated ( $0.3 \pm 0.5$ ) HCWs. Vaccine efficacy for prevention of all medical leave was therefore 13%, but this rate did not reach statistical significance ( $P = 0.4$ ) (Table 3).

In view of the reported mismatch of 2003-2004 vaccine (Northern Hemisphere) to circulating viruses, namely A/Fujian/411/2002,<sup>8</sup> we stratified our data to take into account the effect of the vaccine mismatch on the vaccine efficacy calculations. The group that had been vaccinated with a matched vaccine had a self-reported ILI relative risk of 0.49

Table 1. Baseline Characteristics of Study Participants

Characteristics	Vaccinated (n = 211)	Non-vaccinated (n = 330)	P
Mean age $\pm$ SD (y)	37 $\pm$ 11.3	33 $\pm$ 9.1	1.90
Gender, women:men	205:6	320:10	0.80
Occupation: Nurse:Medical/Allied Health	164:47	242:88	0.80
Mean no. of children <12 years	0.50 $\pm$ 0.92	0.45 $\pm$ 0.87	0.60
Young children at home, no. (%)	58 (27.5%)	88 (26.7%)	0.80
Older people >65 years at home, no. (%)	41 (19.4%)	45 (13.6%)	0.07
History of allergic rhinitis, no. (%)	33 (15.6%)	38 (11.5%)	0.20
Smoker, no. (%)	6 (2.8%)	5 (1.5%)	0.40
Chronic underlying illness, no. (%)	21 (9.9%)	14 (4.2%)	0.01

Table 2. Frequency of Influenza-like Illness (ILI) in Vaccinated vs Non-vaccinated Healthcare Workers

	ILI	No ILI	Relative risk (95% confidence interval)	P
No vaccine	182	148	1.13 (0.98-1.13)	0.11
Vaccinated*	132	79		
Vaccinated with matched vaccine*	36	96	0.49 (0.37-0.66)	0.0000001
Vaccinated with mismatched vaccine*	49	24	1.22 (1.01-1.47)	0.082

\* The vaccine used for 6 subjects was unclear and ILI was determined only for the year following initial vaccination; hence, the apparent discrepancy in numbers.

Table 3. Documented Medical Leave Taken Vaccinated vs Non-Vaccinated Healthcare Workers

	Mean medical leave taken for each visit $\pm$ SD	P
Unvaccinated	0.299 $\pm$ 0.449	
Vaccinated	0.260 $\pm$ 0.595	0.406
Matched vaccine	0.134 $\pm$ 0.280	<0.001* 0.014†
Mismatched vaccine	0.392 $\pm$ 0.925	0.419

\* Compared with unvaccinated

† Compared with mismatched vaccine

(95% CI, 0.37-0.66;  $P < 0.001$ ), producing a vaccine efficacy rate of 51%. In contrast, in the group that had been vaccinated with a mismatched vaccine, the ILI relative risk was 1.22 (95% CI, 1.01-1.47;  $P = 0.08$ ), with a vaccine efficacy of -22%. Mean documented medical leave taken at each bi-monthly survey visit was significantly reduced in those who received the matched vaccine compared to those who did not receive vaccination (0.13  $\pm$  0.28 vs 0.30  $\pm$  0.5,  $P < 0.001$ ) and those vaccinated with mismatched strains (0.13  $\pm$  0.28 vs 0.39  $\pm$  0.9,  $P = 0.01$ ). The vaccine efficacy of the matched vaccine for reduction of medical leave was 55%.

## Discussion

The efficacy of influenza vaccines in reducing morbidity

and mortality in the young, elderly, and in people with underlying conditions is well established.<sup>9,10</sup> However, almost all of these data, with a few notable exceptions,<sup>11</sup> come from temperate settings with well-defined influenza seasons. In previous studies, vaccine effectiveness in reducing ILI in healthy working adults was reported at 25%, and reduction in all illness medical leave at 36%.<sup>7</sup> A study conducted in Malaysian petrochemical workers reported a vaccine effectiveness of 79% in decreasing medical leave due to all causes.<sup>12</sup> In healthcare workers, vaccine effectiveness has been reported as being even higher,<sup>11</sup> possibly because of the younger age of the healthcare worker cohort compared to the general population or the population whom they serve. However, most studies reported a lower effectiveness in reducing clinically suggestive ILI. This pattern suggests that while ILI might be a convenient surrogate for laboratory confirmed influenza, it is not sufficiently accurate, and more objective measures such as seroconversion rate, positive molecular diagnostic tests, or official medical leave records are needed. Our experience supports this inference.

The difficulty in quantifying influenza-related morbidity on a large scale lies in the low specificity of clinical diagnosis, despite the widespread use of clinical definitions similar to the one we used. A low specificity is due to other pathogens causing similar symptoms. The confounding pathogens include rhinoviruses, parainfluenza, corona-

viruses,<sup>13</sup> *Mycoplasma pneumoniae*, and respiratory syncytial viruses.<sup>14</sup> The sensitivity of symptoms is high, with fever commonly being the most sensitive (>97%).<sup>15</sup> However, positive predictive values for clinical case definitions of influenza vary between 27% and 40%; whereas negative predictive values are between 80% and 91%.<sup>13</sup> In our study, we used an internationally accepted definition of ILI symptoms as a surrogate to determine the effectiveness of influenza vaccines as has been done in other settings.<sup>3</sup> In addition, we used medical leave data from administrative databases, independent of subject responses. However, we found discordance between the medical leave data and the subjects' responses. For the mismatched vaccine, there was a small though not statistically significant benefit from influenza vaccination in terms of overall medical leave reduction, despite the fact that the vaccinated HCWs had a higher prevalence of underlying chronic medical conditions. On the other hand, self reported ILI did not decrease, perhaps because the ongoing lack of confidence of Singapore HCWs in the seasonal influenza vaccines might have produced a recall bias in completing our questionnaires. It may be argued that the medical leave data are more robust, coming from administrative sources, in particular in countries such as Singapore, in which medical leave is rigorously documented.

Influenza has a significant impact on the young adult population,<sup>16</sup> with important economic consequences. Cross protection provided by mismatched strains of the vaccine has been reported previously for laboratory-confirmed influenza in a general practice network,<sup>17</sup> although obviously the degree of protection was much lower than for matched strains. In our subjects, the relative risk of ILI in vaccinated HCWs decreased (from 1.13 to 0.49) when the vaccine mismatch was accounted for. A matched vaccine in our study gave an efficacy of 51% for the prevention of ILI, comparable to those reported in Malaysian HCWs<sup>3</sup> and in temperate countries.<sup>18</sup> The Southern Hemisphere 2004 and Northern Hemisphere 2004-2005 vaccines were relatively well matched.<sup>19,20</sup> The Northern hemisphere 2003-2004 vaccine,<sup>21</sup> however, was poorly matched because it did not include the A/Fujian/411/2002 strain. A majority of the influenza circulating were caused by H3N2 viruses, which are closely related to A/Fujian/411/2002, antigenically different from the vaccine strain A/Moscow/10/99. The influenza B strain was also poorly matched, with few reportedly closely related to the prototype vaccine strain, B/Hong Kong/330/2001.<sup>21</sup>

The protective effect of an influenza vaccine is largely dependent on how closely related the chosen vaccine strains are to those that circulate 9 months later, when the vaccines become available. This is a result of viral antigenic drift, which occurs regularly with both influenza A and

influenza B. Our observational study has shown that the mismatched Northern Hemisphere 03/04 vaccine was not protective against ILI. Similar data have been reported by a retrospective cohort study involving healthcare workers in Denver.<sup>8</sup> Another study on children showed that the mismatched inactivated influenza vaccine was not associated with a significant reduction in culture-positive influenza illness during the 03/04 influenza season although the live attenuated influenza vaccine had some benefit.<sup>22</sup>

The lack of effectiveness of reducing ILI in adults by a poorly matched vaccine has been reported in previous influenza seasons. Bridges et al's double-blind, randomised trial in the 1997-1998 mismatch season showed that the vaccine did not reduce ILI, physician visits, or lost workdays; the net societal cost was \$65.59 per person compared with no vaccination.<sup>23</sup>

In contrast, in our subjects, when the matched vaccine was used, significant benefits were noted in both ILI, with vaccine effectiveness of 51%, and in medical leave lost, with an effectiveness of 55%. These data support the current recommendations for Singapore HCWs to receive employer sponsored annual influenza vaccination with the appropriate vaccine. Simply in reducing sickness absence, the vaccine is likely to be cost effective. We did not estimate the reduction in nosocomial transmission of influenza from sick healthcare workers to their patients, but given the vulnerability of Singapore's elderly population to seasonal influenza, which results in several hundred deaths a year,<sup>2</sup> it is likely that vaccinating all staff working in hospitals and long-term care facilities will have a significant effect on morbidity and mortality. This should be studied in a well-designed randomised controlled trial because it has profound implications for the health of our citizens.

In our study, a selection bias due to the observational nature of the study with lack of blinding of participants, and its non-randomised nature might limit our conclusions. We attempted to reduce this potential bias by blinding the investigators to the vaccination status of the participants. We also did not obtain serological or virological confirmation of infection. In addition, it was difficult to account for the different occupational exposures in the various work settings.

In conclusion, our investigator-blinded non-randomised observational study has shown that influenza vaccine efficacy in a tropical setting is comparable to that in temperate countries, in particular when a matched vaccine is used. Healthcare workers in Singapore should be encouraged to go for annual influenza vaccination to reduce the morbidity associated with these infections. The recent SARS epidemic has highlighted the role of hospitals and healthcare workers in the transmission of viral respiratory pathogens. Fears have also arisen about

pandemic influenza and the role of HCWs with sick children in bringing a novel virus into hospitals or nursing homes containing vulnerable patients. If Singapore HCWs are all routinely vaccinated against seasonal influenza, it is likely that the logistics and psycho-social hurdles to pandemic or pre-pandemic vaccination are going to be more easily overcome.

Our study also highlights the problems with vaccine mismatches. The World Health Organisation (WHO) has a worldwide network of national influenza centres located in developing as well as developed countries which provide viruses to the WHO influenza coordinating centres. Complex mathematical models are then used to predict which strains are most likely to cause disease in the following influenza season. Seed stock is then given to large pharmaceutical companies who sell the vaccine mainly to wealthy countries. This system has been in place for more than 50 years and is being challenged in recent years. While that is a public policy issue, if science could come up with a novel vaccine that provides long lasting immunity against a variety of strains and subtypes, then the issue of strain mismatch would be irrelevant.<sup>24</sup> Until then, large randomised controlled studies are needed in tropical settings to determine the ideal vaccination regime for HCWs in countries without a well defined influenza season.

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