## Original Report

# A case–control study of influenza vaccine effectiveness among Malaysian pilgrims attending the Haj in Saudi Arabia

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**Objectives:** To determine influenza vaccine effectiveness against clinically defined influenza-like illness among Malaysian pilgrims attending the Haj in Saudi Arabia.

**Methods**: During February and March 2000, the authors conducted an unmatched case–control study. Case patients were identified at one of five hotel clinics, while controls were residents of these hotels who had not attended a clinic.

**Results**: Among 820 case patients—84% of whom had received antibiotics—and 600 controls, the adjusted vaccine effectiveness against clinic visits for influenza-like illness was 77% (95% confidence interval: 69, 83), and that against receipt of antibiotics was 66% (95% confidence interval, 54, 75). The vaccine did not prevent clinic visits for non-influenza-like upper respiratory tract illness (adjusted vaccine effectiveness, 20%; 95% confidence interval: –24, 49).

**Conclusions**: Influenza vaccine was effective in preventing clinic visits for influenza-like illness and antibiotic use. Pilgrims traveling to the Haj in Saudi Arabia should consider influenza vaccination use.

## INTRODUCTION

Each year, approximately 2 000 000 pilgrims travel to Saudi Arabia to perform the Haj, one of the five pillars of Islam. People from around the world gather in crowded conditions where the risk of disease transmission is high. Previous studies have documented that pilgrims returning from the Haj contribute to the worldwide spread of meningococcal disease[1–3] and possibly cholera.[4] Few studies, however, have examined respiratory illness among pilgrims.[5]

We conducted an unmatched retrospective case–control study to determine influenza vaccine effectiveness among Malaysian pilgrims attending the Haj. Vaccine effectiveness, rather than efficacy, was measured, since our study relied on data gathered from routine population-based influenza vaccination rather than from investigator-determined vaccine distribution. Because

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laboratory-based methods for documenting influenza illness were not available to us, we determined vaccine effectiveness against clinically defined influenza-like illness.

## MATERIALS AND METHODS

### Vaccine administration and type

During the 2000 Haj, the Malaysian Haj Authority recommended that all pilgrims receive influenza vaccine. Unlike meningococcal vaccine, however, influenza vaccine was not compulsory. Influenza vaccine was administered like other vaccines received for the Haj, and given at special Haj immunization clinics or by private health care providers.

During 1999–2000, almost all influenza vaccine sold in Malaysia was Vaxigrip, manufactured by Aventis Pasteur (Lyon, France) (formerly Pasteur Mérieux Connaught). Specific components included:

A/Sidney/5/97 ($H_3N_2$)-like strain (A/Sidney/5/97 (IVR-108)), 15 µg hemagglutinin
A/Beijing/262/95 ($H_1N_1$)-like strain (A/Beijing/262/95 (X-127)), 15 µg hemagglutinin
B/Beijing/184/93-like strain (B/Yamanashi/166/98, 15 µg hemagglutinin

The World Health Organization maintains a worldwide influenza surveillance system. Saudi Arabia did not participate in this system during the study period. During December 1999 through February 2000, 10 of

13 influenza isolates reported from Kuala Lumpur, Malaysia were type A ($H_3N_2$), none were type A ($H_1N_1$), and three were type B; similarly, the great majority of isolates reported from Asia and worldwide were type A ($H_3N_2$) (World Health Organization Flunet website: http://oms2.b3e.jussieu.fr/flunet/activity.html).

## Study subjects and study period

As in previous years, Malaysian pilgrims were assigned to one of 20 equivalent hotels in Mecca rented by the Malaysian government. Hotels housed approximately 2000 persons each. Each hotel contained a clinic, primarily for use by hotel residents, but which any Malaysian pilgrim could have attended. Pilgrims arrived by air in Mecca between 15 February and 8 March. Beginning on 15 March, pilgrims left Mecca to travel to Arafah to perform the next stage of the Haj. Consequently, cases and controls were recruited from 15 February to 14 March.

## Case patient and control definitions and selection

We arbitrarily selected five hotels in which to conduct our study. Case patients were recruited from hotel clinics. Patients who presented to the clinic with any upper or lower respiratory illness during the study period were included, regardless of whether or not they met the definition for influenza-like illness. Although persons might have attended the clinic on multiple occasions, only their first visit was used for analysis. Patients presenting for care at hotel clinics did not necessarily reside in the hotel but, since each hotel had its own clinic, this was usually the case. Influenza-like illness was the primary outcome examined. Case definitions included the following.

### Influenza-like illness

This was defined as sore throat in combination with either temperature $\geq 38.0°C$ or cough. This definition was consistent with other studies using populations composed primarily of healthy working adults,[5-7] although it differs from that used by the US Centers for Disease Control and Prevention (CDC) (temperature of at least 37.8°C in combination with either sore throat or cough). For comparison purposes, we evaluated vaccine effectiveness against both outcomes during univariate analysis.

### Non-influenza-like upper respiratory tract illness

All case patients enrolled in the study who did not meet the definition of influenza-like illness were considered to have non-influenza-like upper respiratory tract illness. All case patients had one or more symptoms of upper respiratory tract illness, including sore throat, fever, cough, nasal congestion, malaise, headache, or muscle ache.

### Antibiotic and non-prescription medication use

This was defined as acquisition of medication at one of the study clinics. Approximately 18 oral and 11 injectable antibiotics were available at the clinic. Some pilgrims brought their own antibiotics and other medications from Malaysia, but this information was not collected.

Controls were defined as persons living in one of the five study hotels who had not attended any clinic. To ascertain that potential controls had not attended a clinic, we went from room to room in each of the study hotels, and interviewed people; those who reported not attending a clinic were asked to participate. To allow controls and case patients an equal time period in which to have developed illness, controls at a specific hotel were identified and interviewed during a single day, that being the day on which case enrollment ended for case patients. For example, for hotel number 1, case enrollment in the clinic ended on 9 March, and controls at the hotel were interviewed on 9 March. For hotels two to five, the dates for control enrollment were 10 March to 14 March, respectively.

We had planned to recruit approximately one unmatched control for every case patient identified, regardless of whether or not the case patient met the definition of influenza-like illness. Because of time and personnel constraints, however, only a fraction of the desired number of controls was enrolled at three of the five study hotels. We chose to control for age and gender during analysis rather than matching for these variables during enrollment, because of the considerable logistic difficulties that we would have encountered in identifying appropriate matched controls.

We did not attempt to determine whether or not controls had an upper respiratory illness that did not result in a clinic visit, since we believed that this information would be subject to substantial recall bias, and would not be comparable to the data collected from case patients. By contrast, we believed that controls could easily recall a clinic visit during approximately the previous month.

## Data collection

We collected clinical information for case patients, and background information—including influenza vaccination status, age, gender, and hotel—for both case patients and controls using a standardized reporting form. Because of the requirement for meningococcal vaccination before entry into Saudi Arabia, pilgrims generally carried vaccination cards. Persons were considered vaccinated if they had one of these cards and it documented influenza vaccination during the 3 months before the beginning of the 2000 Haj. For people who did not have a card, we accepted a verbal history.

## Analysis and power

Data were entered into two databases, one for those recruited at the clinics, and one for controls recruited in their hotel rooms. Databases were merged by linking on pilgrims' passport numbers. Vaccine effectiveness was calculated as: (1-odds ratio for vaccination) ×100.

We conducted a multiple logistic regression analysis to adjust for gender and age. Additionally, although cases and controls were recruited from the same hotels, we also included hotel in the model because of incomplete ascertainment of controls. Gender was entered as a dichotomous variable, age as a linear variable, and hotel number as a categorical variable with each of the first four hotels compared to the last hotel (arbitrarily defined). Because of the relatively small number of variables compared to the sample size, all variables were included in the final models. All analyses were conducted with SPSS statistical software, version 9.0 (SPSS Inc., 1998).

For influenza-like illness (the primary outcome of interest), we identified 820 cases. Additionally, 600 controls were identified. Given this sample size, for an alpha error of 5% and a vaccine exposure among controls of 88%, we had 80% power to detect a vaccine effectiveness of 36% or greater.

## RESULTS

### Univariate analysis

We identified 1310 persons who had a clinic visit for upper respiratory tract symptoms at the five clinics, of whom 63% had influenza-like illness, 14% had influenza by the CDC definition, 98% received an over-the-counter medication, and 78% received an antibiotic. Of the 820 persons with influenza-like illness, 99% received an over-the-counter medication, and 84% received an antibiotic. Only four patients in our study were referred to the hospital, since most seriously ill persons went directly to the hospital without first presenting to a hotel clinic. Regardless of the outcome analyzed, case patients and controls differed by gender, age, and hotel (Table 1), suggesting that these factors might be confounders.

The vaccination rate among case patients was 63%, compared to 88% among controls. The observed vaccine effectiveness was 78% against clinic visits for influenza-like illness and 66% against clinic visits for influenza using the CDC definition (Table 2). By contrast, the observed vaccine effectiveness was –14% against clinic visits for non-influenza-like upper respiratory tract illness.

Vaccine was also effective in preventing receipt of antibiotics and over-the-counter medications from the clinics (Table 2), an expected finding, since most case patients received both categories of medication. Observed vaccine effectiveness was greater than 65% for four of the study hotels but was –18% (95% confidence interval: –116, 36) at the fifth; the proportion of upper respiratory illness due to influenza-like illness was 84–100% at the first four hotels, compared to 58% at the fifth. Persons at the fifth hotel did not differ from those at the other hotels with respect to age, gender, or vaccine receipt.

**Table 1.** Potential confounding factors in a study of influenza vaccine effectiveness among Malaysian pilgrims attending the 2000 Haj in Saudi Arabia

| Risk factor[a] | Controls | Influenza-like illness[b] | Non-influenza-like upper respiratory tract illness[c] | Influenza by CDC definition[d] |
|---|---|---|---|---|
| **Gender** | | | | |
| Male | 198 | 367 | 199 | 78 |
| Female | 399 | 425 | 269 | 96 |
| Odds ratio | – | 1.7 | 1.5 | 1.6 |
| 95% CI | | 1.4, 2.2 | 1.2, 1.9 | 1.2, 2.3 |
| **Age <60 years** | | | | |
| Yes | 387 | 575 | 313 | 126 |
| No | 210 | 231 | 160 | 50 |
| Odds ratio | – | 1.4 | 1.1 | 1.4 |
| 95% CI | | 1.1, 1.7 | 0.82, 1.4 | 0.95, 2.0 |
| **Hotel[e]** | | | | |
| 1 | 102 | 295 | 57 | 83 |
| 2 | 127 | 108 | 11 | 22 |
| 3 | 63 | 114 | 21 | 107 |
| 4 | 91 | 179 | 0 | 165 |
| 5 | 217 | 124 | 90 | 113 |

[a] In rare instances, gender and age were not filled in on the questionnaire for case patients or controls.
[b] Influenza-like illness: sore throat in combination with either temperature ≥38.0°C or cough.
[c] Non-influenza-like upper respiratory tract illness: case patients who did not meet the definition of influenza-like illness and had sore throat, fever, cough, nasal congestion, malaise, headache, or muscle ache.
[d] Influenza according to US Centers for Disease Control and Prevention definition: temperature of at least 37.8°C in combination with either sore throat or cough.
[e] For case patients, hotel refers to the hotel at which they attended a clinic, while for controls, hotel refers to the hotel of residence during the Haj.

**Table 2.** Influenza vaccine effectiveness from a case–control study among Malaysian pilgrims attending the 2000 Haj in Saudi Arabia

| | Controls[a] | Influenza-like illness[b] | Non-influenza-like upper respiratory tract illness[c] | Influenza by CDC definition[d] | Received antibiotics at the clinic | Received over the counter medications at the clinic |
|---|---|---|---|---|---|---|
| N (% vaccinated) | 600 (88) | 820 (63) | 490 (90) | 179 (72) | 1016 (71) | 1286 (72) |
| Observed vaccine effectiveness[e] (95% confidence interval) | – | 78% (71, 83) | –14% (–67, 22) | 66% (49, 87) | 67% (57, 75) | 65% (54, 74) |
| Adjusted vaccine effectiveness[f] (95% confidence interval) | – | 77% (69, 83) | 20% (–24, 49) | 71% (53, 82) | 66% (54, 75) | 64% (52, 74) |

[a] Each of the five dichotomous outcome variables was compared to the same group of controls.
[b] Influenza-like illness: sore throat in combination with either temperature $\geq 38.0°C$ or cough.
[c] Non-influenza-like upper respiratory tract illness: case patients who did not meet the definition of influenza-like illness and had sore throat, fever, cough, nasal congestion, malaise, headache, or muscle ache.
[d] Influenza according to US Centers for Disease Control and Prevention definition: temperature of at least 37.8°C in combination with either sore throat or cough.
[e] Vaccine effectiveness = (1–odds ratio).
[f] Adjusted for age, gender, and hotel.

## Multivariate analysis

For the two definitions of influenza analyzed, we created a multiple logistic regression model, entering simultaneously vaccine status, gender, age, and hotel. The adjusted vaccine effectiveness was 77% (95% confidence interval: 69, 83) against influenza-like illness and 71% (95% confidence interval: 53, 82) against influenza according to the CDC definition (Table 2). Similar to the results obtained from univariate analysis, vaccination did not prevent non-influenza-like upper respiratory tract illness.

## DISCUSSION

We found that vaccine was effective in preventing clinic visits for influenza-like illness among Malaysian pilgrims attending the 2000 Haj in Saudi Arabia. These results support an earlier study reporting similar findings among Pakistani pilgrims attending the 1999 Haj,[5] and add to the relatively sparse data on influenza vaccine efficacy or effectiveness among populations composed largely of healthy working adults.[6,7] In addition to preventing clinic visits for influenza, vaccine was also effective in preventing the dispensing of over-the-counter medications and antibiotics, since almost all persons who presented to a clinic with influenza-like illness received both of these categories of drugs.

To the extent that influenza vaccine can decrease clinic visits, it may result in substantial savings to the health care system. These savings could accrue to the pilgrims and their governments in instances where the pilgrims' countries provide direct medical care in Saudi Arabia, such as with Malaysia. Alternatively, for pilgrims who depend on locally financed medical care, influenza vaccine may result in substantial savings to the Saudi Arabian government. Studies in industrialized countries have found that influenza vaccine is one of the most cost-effective public health measures known.[8,9]

If influenza vaccine decreases the inappropriate use of antibiotics at the Haj, it may lead to a decrease in the worldwide distribution of antibiotic-resistant organisms. Although no studies have examined the contribution of Haj pilgrims to the transmission of antibiotic-resistant organisms, some studies have documented the ease with which antibiotic-resistant pneumococcal clones can spread.[10,11] Additional studies, including some performed during the 2000 Haj, have documented the initiation of meningococcal outbreaks following the return of pilgrims to their home countries.[1–3]

Influenza vaccine effectiveness in our study was higher than that reported previously.[5–7,12] The reasons for this are unclear. An influenza outbreak may have occurred among Malaysian pilgrims during the 2000 Haj if a large proportion of pilgrims had inadequate immunity to circulating strains. Alternatively, the lack of outbreaks from other causes of upper respiratory infection could also have increased vaccine effectiveness. Either explanation is consistent with our finding that the only hotel in which vaccine was not effective had a high proportion of non-influenza-like respiratory illness. Additionally, our relatively high reported effectiveness may have resulted from the biases inherent in the case–control design,[13] since previous studies have tended to use the cohort method.

The major limitation of the current study was that it was non-randomized and non-blinded. Consequently, it is possible that persons who reported receiving vaccine were less likely than unvaccinated persons to present to a clinic and more likely to take measures to prevent illness. If this were a major factor, however, it is probable that vaccine would have shown effectiveness against both influenza-like and non-influenza-like illness. In this context, it is somewhat reassuring that vaccine was not effective against non-influenza-like upper respiratory tract illness. Our study was also limited by our inability

to calculate attack rates and by a limited questionnaire, which did not allow us to evaluate potential confounding factors such as pre-existing illness and smoking history. Finally, we estimated vaccine effectiveness against clinic visits for influenza-like illness but not against all influenza-like illnesses. The former may represent much of the cost and relatively severe illness associated with influenza but does not reflect the overall disease burden.

Approximately 2 000 000 pilgrims a year travel to Saudi Arabia to attend the Haj. Because of the close contact that pilgrims have with each other, widespread antibiotic use, and the international nature of the Haj, ample opportunity exists for disease transmission, development of antibiotic resistance, and worldwide dissemination of disease-causing organisms. The current study suggests that influenza vaccine may partially address these concerns. As with a previous study among Haj pilgrims,[5] we recommend that governments with substantial numbers of Haj attendees support influenza immunization programs for pilgrims, and that the Saudi government consider requiring influenza vaccination for all pilgrims before entrance into Mecca or Medina.

## ACKNOWLEDGEMENTS

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