SHORT COMMUNICATION

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The Safety of H1N1 Vaccine in Children in Saudi Arabia

A Cohort Study Using Modern Technology in a Developing Country

Hisham Aljadhey,[1] *Mesnad Alyabsi*,[2] *Adel Alrwisan*,[1,3] *Nasser Alqahtani*,[1,3] *Reem Almutairi*,[4] *Esraa Al Tawil*,[5] *Mansour Adam*,[1] *Saad Shakir*,[6] *Majed Aljeraisy*,[7] *Ali Al-Blowi*,[5] *Hesham Alkhashan*,[5] *Yasser Albogami*[1] and *Michael D. Murray*[8]

1 Medication Safety Research Chair, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia
2 Division of Pharmaceutical Outcomes & Policy, School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
3 Saudi Food and Drug Authority, Riyadh, Saudi Arabia
4 Princess Nora Bint Abdul Rahman University, Riyadh, Saudi Arabia
5 Riyadh Military Hospital, Riyadh, Saudi Arabia
6 Drug Safety Research Unit, Southampton, UK
7 King Abdullah International Medical Research Center, Riyadh, Saudi Arabia
8 Purdue University College of Pharmacy and Regenstrief Institute, Inc., Indianapolis, IN, USA

Abstract

Background: With its rapid introduction in 2009, concerns about the safety of the H1N1 vaccines have been raised. Data were especially limited on the pediatric safety of H1N1 vaccine in Saudi Arabia.

Objectives: The objectives of this study were to investigate the safety of the H1N1 vaccine (Pandemrix®) in children and examine the feasibility of obtaining information on possibly associated adverse reactions using mobile telephone contact with child caregivers.

Methods: A cohort study was conducted in Riyadh, Saudi Arabia. Patients were included if they were aged between 6 and 18 years and had received one dose of the H1N1 vaccine. A control group involved children from the same school system who had not received the vaccine. Six months following vaccination, a clinical pharmacist called the caregiver of the child to ask about hospitalization, emergency room visits and events related to H1N1 vaccine administration using a standardized questionnaire.

Results: Caregivers of 372 school-age children were contacted. The response rate was 97% (n = 359). A total of 169 children who received at least one dose of the H1N1 vaccine were compared with 190 children in the control group who had not received the vaccine. Controlling for age, sex, education and use of medications, the odds ratio (OR) of hospitalization or emergency room visits for children within the 6 months after vaccination relative to the unvaccinated children was 1.25 (95% CI 0.47, 3.35). The risk of influenza-like

symptoms was significantly reduced in vaccinated children compared with unvaccinated children (OR 0.63; 95% CI 0.41, 0.99).

Conclusion: School-age children in Saudi Arabia who received the H1N1 vaccine did not have an increased risk of hospitalization or emergency room visits. Larger studies are needed to confirm these results. Proactive pharmacovigilance is important in assessing the safety of vaccines and other medications. It is feasible to collect information on adverse drug reactions using mobile telephones, a method that can be of benefit in both developed and developing countries.

Background

In April 2009, the influenza A H1N1 virus was first identified in Mexico.[1,2] The virus rapidly spread to most of the world and the WHO declared a pandemic of influenza A H1N1 virus on 11 June 2009.[3] Countries deployed massive immunization programmes using a vaccine that was developed and tested to prevent H1N1 infection.[4] In Saudi Arabia, H1N1 vaccination was voluntary; however, high-risk groups such as healthcare professionals, people planning to perform pilgrimage and children of school age were strongly encouraged to be vaccinated. Besides, the recommended Pandemrix® dosing was single dose (0.5 mL) for adults and children aged 10 years and older. Half the adult dose (0.25 mL) was given to children between 6 months and 10 years of age. Worldwide, concerns about the safety of H1N1 vaccines were raised by healthcare professionals and the public because of adverse reactions such as Guillain-Barré syndrome, a serious adverse reaction associated with an influenza vaccine used previously.[5] In Saudi Arabia, any safety news relating to H1N1 vaccines was intensely followed by local newspapers in Saudi Arabia and several internet websites have raised concerns about the use of H1N1 vaccines.

Serious adverse reactions were not found in clinical trials that were conducted to evaluate the immunogenicity and safety of the H1N1 vaccine.[1,6-10] However, because of the small sample size and the short follow-up time, the usefulness of these studies was considered limited. In Italy and China, no pattern of adverse reactions after H1N1 vaccination was observed using passive surveillance.[11,12] However, the most commonly reported adverse events in the UK were injection site reactions, flu-like symptoms and muscle pain. Febrile convulsion cases were less frequently reported.[13] To our knowledge, no observational studies have used active surveillance to report the safety of H1N1 vaccines in a developing country. In developing countries, researchers are faced with many obstacles to carry out observational studies. These obstacles include a lack of clinical or administrative databases and difficulties with patient follow-up. Using technology, such as an interactive voice response system, to actively detect adverse drug reactions toward medications is promising in countries where the use of such method of communications is possible.[14] However, the feasibility of using these technologies must be investigated.

The objectives of the current study were (i) to explore the feasibility of conducting a pharmacoepidemiological study using mobile telephone calls as the primary means for data collection; and (ii) to assess the safety of the H1N1 vaccine in children. The study focused on children because they have had no prior exposure to H1N1 influenza yet they were among the groups targeted in H1N1 vaccination campaigns.

Methods

Design and Subjects

We conducted a cohort study of children aged between 6 and 18 years who had received one dose of the H1N1 vaccine in Riyadh, Saudi Arabia. A team from school health visited schools to offer

the H1N1 vaccine (Pandemrix®), and immunization records and contacts were collected by nurses from caregivers during their clinic visit. All children who received one dose of the H1N1 vaccine were included in the study. The control group included those children from the same schools in a similar age group but where the guardians had not approved the immunization to their children. The index date was defined as the date of the first dose of the H1N1 vaccine. Six months following vaccination, a follow-up telephone call to the child's caregiver was made by a pharmacist. The local ethical and research committee at the Riyadh Military Hospital approved the study. The approval included calling caregivers of children included in the study.

Call Procedure

The questions and information to be gathered from caregivers were developed and written by the investigators. A pharmacist was trained by one of the study investigators with expertise in structured telephone interviews. Mock phone interviews were made between the pharmacist and the study investigators to ensure completeness and appropriateness of ascertaining the information. We used mobile phones as the only method for interviewing guardians as they are widely used by the Saudi population and may represent the preferred means of communication. The pharmacist then made calls between 11:00am and 9:00pm. If there was no response to the first attempt, a second call was made at another time. If there was still no response, a brief text message was sent to explain the goal of the study and the purpose of the call. After sending the text message, a third and final call was made. We planned to have a maximum of three attempted phone calls to the caregiver's mobile phone over 2 days.

During the call, the pharmacists introduced themself, described the importance of the study and obtained oral consent to participate in the study. Information collected included subjects' demographic characteristics and educational level (elementary school, middle school or high school). Information regarding relevant medical history was obtained (history of asthma, diabetes mellitus, heart disease, renal disease, liver disease, blood disorder or immunosuppression). Each caregiver was asked if his or her child was currently using any medications (figure 1).

Endpoints

Study outcomes included hospitalization or emergency room visits for the child within 6 months after the index date. If caregivers reported a hospitalization or emergency room visit, we obtained from the guardians the hospital name, time and duration of hospitalization, reason(s) for hospitalization and whether any treatment was provided. Caregivers were also asked if their children had had influenza-like symptoms within the previous 6 months; such symptoms included fever, cough, headache, vomiting, diarrhoea and sore throat.

Analyses

Descriptive statistics were performed for demographic variables. Chi-squared tests and t-tests were used to compare categorical and continuous variables, respectively. Data analysis was conducted using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA). We used logistic regression (PROC GENMOD) and coded the outcome as a dichotomous variable (hospitalization/emergency room visit or not). Odds ratios (ORs) were calculated for the risk of hospitalization and emergency room visits while controlling for age, sex, education level and the use of medications.

Results

We were able to reach 169 out of 179 caregivers for subjects who received one dose of vaccination, and 190 out of 193 caregivers for subjects in the control group (response rate of 97%). A total of 318 caregivers answered the first call, 25 answered the second and 16 were called three times (figure 2). Demographic characteristics were similar between the two groups (table I), with the exception of fewer male subjects in the vaccinated group. Prescribed medications were mainly for asthma and included albuterol inhaler and fluticasone/salmeterol diskus. There were nine and eight cases

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A. Participant Details

Patient Name: Date of birth: Age: Sex: ☐ M ☐ F
Health Institution : Region:
Parents' contact of participant aged <16 years old:

B. Contact details

Caller Name: Method of contact: Date and time:
Subject number:

C. Educational level

Educational Level:
☐ Elementary. ☐ Intermediate. ☐ High School. ☐ Graduate degree. ☐ Post-graduate degree (M.Sc., Ph.D)

D. Follow-up outcome

The patient responded: ☐ First attempt ☐ Second attempt ☐ Third attempt ☐ No response
Respondent to the call: ☐ Patient him/herself ☐ Subject proxy
Number of swine flu vaccination till date ☐ One ☐ Two, date of the second vaccine:

E. Event(s) description

Any hospitalization or ER visits during the last six months	☐ No	☐ yes	If yes…
			Date:
			Hospital name:
			Cause of hospitalization:
			Duration:
			Type of reaction, if any:
			Treatment:

F. Medical conditions

Do you have any of the following underlying medical conditions?

☐ Asthma	☐ Diabetes	☐ Heart diseases	☐ Renal diseases	☐ Liver diseases
☐ Blood disorders	☐ Immunosuppression	☐ Other, specify:		
Marital status ☐ single ☐ married	Pregnancy ☐ Yes ☐ No	If yes, expected date of delivery: / /		
☐ Flu-like symptoms during the past six months		☐ No	☐ Yes	

G. Medications used

Do you take any prescribed medications?	☐ No	☐ Yes	If yes, please list:	
Medication	*Indication*		*Dosing*	*Frequency*

Fig. 1. Questionnaire-follow-up form. Monitoring the safety of influenza A H1N1 vaccine. **ER** = emergency room.

of hospitalization or emergency room visits during the 6 months following the index date among the vaccinated and unvaccinated children, respectively. Table II shows the causes of hospital admissions and emergency room visits. Controlling for age, sex, education level and use of medications, the OR

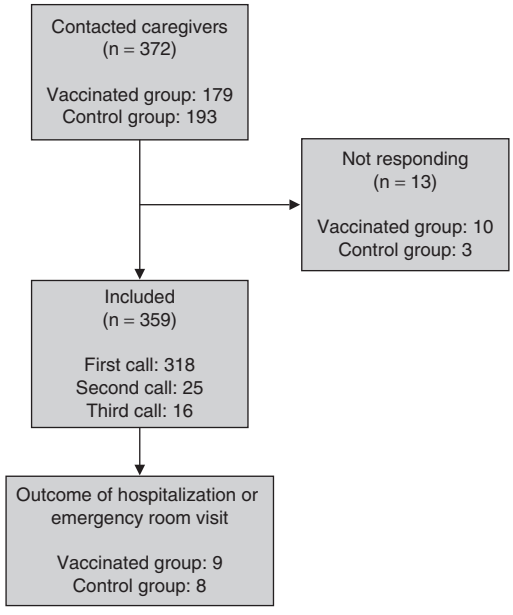

Fig. 2. Study flowchart.

of hospitalization or an emergency room visit in the vaccinated children relative to the unvaccinated children was 1.25 (95% CI 0.47, 3.35). The risk of flu-like symptoms was significantly lower among vaccinated children than among unvaccinated children (OR 0.63; 95% CI 0.41, 0.99).

Discussion

This cohort study determined events associated with H1N1 vaccine (Pandemrix®) administered to children and explored the feasibility of active pharmacovigilance by contacting caregivers on their mobile phone. The response rate to our phone calls was excellent (97%). This was the first observational study to assess the safety of the H1N1 vaccine in school-age children using guardian-reported outcomes for the child by mobile telephone. The risk of hospitalization or emergency room visits within 6 months after the H1N1 vaccine was administered was not statistically significant.

Two pediatric studies evaluated the safety and immunogenicity of the H1N1 vaccine in a total of 556 children aged 6 months to 12 years.[15,16] The most frequent adverse events were fever, decreased feeding and irritability.[15,16] Studies in adult populations did not report significant adverse effects with the H1N1 vaccine.[17,18] Similar to our findings, the vast majority of adverse reactions reported to the Saudi National Pharmacovigilance Center that were associated with the H1N1 vaccine administration were deemed mild. These reactions were mild and ranged from redness or pain at the injection site to arthralgia, nausea and diarrhoea.[19] However, the usefulness of investigating the safety of medications using only voluntary reports of suspected adverse drug reactions is limited by underreporting, lack of an accurate denominator to estimate incidence and the inability to compare risk with non-users.

The current study was the first to use mobile phones for pharmacovigilance in Saudi Arabia. The use of mobile phones has significant advantages compared with a postal questionnaire in follow-up studies evaluating the safety of medications, including ready access to respondents and a higher response rate. Using such new methods for detecting adverse drug reactions is promising.[20] In other areas, use of an interactive voice response system to monitor symptoms experienced by ambulatory patients resulted in a response rate of 43% of participants contacted by the system.[14]

Table I. Demographics and medical history of study population

Variable	Vaccinated	Non-vaccinated
Number of subjects	169	190
Age (y)	10 ± 2.3	11 ± 3.8
Gender, male [n (%)]	83 (49.1)*	137 (72.1)
Level of education [n (%)]		
Elementary	137 (81)	120 (63.1)
Intermediate	30 (17.7)	25 (13.1)
High School	2 (1.3)	45 (23.8)
Use of prescribed medications [n (%)]	12 (7.1)	7 (3.7)
Medical conditions		
Heart disease	0	0
Renal disease	0	0
Liver disease	0	0
Blood disorder	1	0
Immunosuppressant	0	0
Asthma [n (%)]	9 (5.3)	5 (2.6)

* $p < 0.01$.

Table II. Cause of hospitalization or emergency room visits

Cause	Vaccinated [n (%)]	Non-vaccinated [n (%)]	Total
Fever	3 (33)	4 (50)	7
Headache	1 (11)	0	1
Cough	1 (11)	0	1
Diarrhoea	2 (22)	3 (37.5)	5
Tonsillitis	1 (11)	1 (12.5)	2
Asthma symptoms	1 (11)	0	1
Total	**9**	**8**	**17**

The current study has several limitations. First, even though we included all patients who received the vaccine from the clinics, sample size was small because of the low vaccination rate that occurred in Saudi Arabia and was observed in most countries.[11] As such, there was insufficient statistical power to detect differences in the outcomes of hospitalization and emergency room visits between vaccinated and unvaccinated groups or investigate rare outcomes such as Guillain-Barré syndrome. Second, some confounders were not adequately controlled in the analysis. Although we included factors that we thought would be related to vaccine administration or the outcomes of the study, other confounders, such as health status of the children and education level of caregivers, may have differed between comparison groups. A selection bias could occur if patients who received the vaccine were healthier or their caregivers more conscious about the child's health compared with the unvaccinated group. Third, recall bias could affect the study since caregivers were asked about symptoms 6 months after the vaccination date. However, recall bias is unlikely to affect the results when we used hospitalization or emergency room visits as the primary outcome. Lastly, since the study was retrospective, we did not have information on the exact timing of the adverse events.

Conclusions

We found no increase in the risk of hospitalization or emergency room visits associated with the H1N1 vaccine in a Saudi pediatric population. This result provides some assurance of the public safety of this important vaccine. Notwithstanding these findings, larger studies are needed to confirm our results. Finally, we determined that contacting caregivers by mobile telephone is a feasible approach to assess the safety of medications in Saudi Arabia and can be a useful tool for obtaining safety outcomes in other countries.

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Correspondence: Dr *Hisham Aljadhey*, Director of Medication Safety Research Chair, Vice Dean for Academic Affairs, College of Pharmacy, King Saud University, P.O. Box 2475, Riyadh 11451, Saudi Arabia.
E-mail: haljadhey@ksu.edu.sa

