



ORIGINAL ARTICLE

# Evaluation of the Effectiveness of Pandemic Influenza A(H1N1) 2009 Vaccine Based on an Outbreak Investigation During the 2010–2011 Season in Korean Military Camps

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**Abstract**

**Objectives:** In December 2010, there was an outbreak of acute febrile respiratory disease in many Korean military camps that were not geographically related. A laboratory analysis confirmed a number of these cases to be infected by the pandemic influenza A(H1N1) 2009 (H1N1pdm09) virus. Because mass vaccination against H1N1pdm09 was implemented at the infected military camps eleven months ago, the outbreak areas in which both vaccinated and nonvaccinated individuals were well mixed, gave us an opportunity to evaluate the effectiveness of H1N1pdm09 vaccine through a retrospective cohort study design.

**Methods:** A self-administered questionnaire was distributed to the three military camps in which the outbreak occurred for case detection, determination of vaccination status, and characterization of other risk factors. The overall response rate was 86.8% (395/455). Case was defined as fever ( $\geq 38$  °C) with cough or sore throat, influenza-like illness (ILI), and vaccination status verified by

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vaccination registry. Crude vaccine effectiveness (VE) was calculated as “1 – attack rate in vaccinated individuals/attack rate in nonvaccinated individuals”, and adjusted VE was calculated as “1 – odds ratio” using logistic regression adjusted for potential confounding factor. A number of ILI definitions were used to test the robustness of the result.

**Results:** The attack rate of ILI was 12.8% in register-verified vaccinated individuals and 24.0% in nonvaccinated individuals. The crude VE was thus calculated to be 46.8% [95% confidence interval (CI): 14.5–66.9]. The adjusted VE rate was 46.8% (95% CI: –9.4 to 74.1). Various combinations of ILI symptoms also showed similar VE rates.

**Conclusion:** We evaluated the effectiveness of H1N1pdm09 vaccine in the 2010–2011 season in an outbreak setting. Although the result was not sensitive to any analytical method used and ILI case definition, the magnitude of effectiveness was lower than estimated in the 2009–2010 season.

## 1. Introduction

In December 2010, there was an outbreak of acute febrile respiratory disease in several Korean military camps that were not geographically related. An initial outbreak assessment showed that in each camp there were more than 10 cases with fever over 38 °C and respiratory disease for a few days. A laboratory examination confirmed influenza A(H1N1)pdm09 infection in some cases, and therefore, the authorities declared the outbreak as sporadic.

This outbreak provided an opportunity to evaluate the effectiveness of A(H1N1)pdm09 vaccine under the following conditions. First, the Korean military conducted a mass vaccination drive from January 2010 in order to protect its soldiers from H1N1pdm09 infection, and no seasonal influenza vaccination was administered except for new recruits and medical staff. Second, the medical history and vaccination history of the individuals was collected from medical records in the camps. Third, the cases lived in the same barrack, and therefore were considered to be exposed to the H1N1pdm09 virus, and were in a steady group with no huge external effect because they had restricted contacts with outside groups.

This environment and the characteristics of military camps were enough to fulfill the basic condition required to evaluate the effect of vaccination during an outbreak [1,2]. Previous research evaluating the effectiveness of H1N1pdm09 vaccine were mainly laboratory studies [3–6] or large-scale cohort studies [7–11]. Although few studies have been reported based on outbreak cases, studies on evaluating the effectiveness of vaccine 1 year after vaccination for H1N1pdm09 are rare [12,13]. This study was conducted to complement previous studies on the vaccination effect of H1N1pdm09.

Therefore, the authors aimed to evaluate the vaccination effect of H1N1pdm09 using a retrospective cohort study design on a sporadic outbreak case, based on the aforementioned conditions and potential implications.

## 2. Materials and Methods

### 2.1. Situation

The Korean military conducted a mass vaccination drive—Green Flu-S Plus vaccine that had antigen (3.25 µg) and MF-58 adjuvant—against H1N1pdm09 infection from January 2010 to March 2010. The immunogenicity of the vaccine was confirmed in a previous study [6]. Since then, with no additional vaccination of H1N1pdm09, half of the vaccinated soldiers were discharged at the end of their service term and an equal number of new recruits were placed at the camps with no history of vaccination against the virus. Each camp had recruited a number of susceptible individuals. The three camps were independent units with no geographical or administrative relation.

### 2.2. Patients

The study patients were soldiers stationed at the three military camps as of December 1, 2010. The authors distributed self-administered questionnaires and reviewed the medical records of the soldiers to check their vaccination history. Informed consents were obtained from all the study participants. The questions included symptoms (fever, body temperature, cough, sore throat, running nose, chill, and muscle pain), vaccination history of seasonal influenza, vaccination history of H1N1pdm09, previous diagnosis of H1N1pdm09 infection, smoking, body mass index (BMI), frequency of hand washing, underlying diseases, and sociodemographic factors.

### 2.3. Definition of variables

Case included those individuals who reported fever ( $\geq 38$  °C) with cough or sore throat, or those who had been treated for the same symptoms in December 2010. This definition corresponded to influenza-like illness (ILI) defined by the Korea Centers for Disease Control and Prevention (KCDC). The H1N1pdm09 vaccination status was defined as follows: registry verified vaccination, self reported vaccination (non-verified), non vaccination.

## 2.4. Analysis

The epidemic curve of each camp was recorded everyday (Figure 1), and the sociodemographic characteristics of each camp were tabulated (Table 1). Among the sociodemographic characteristics and influenza-associated factors, we identified the variables related to the vaccination history by Chi-square test. The associated variables were considered to be confounding factors in evaluating the effectiveness of vaccination. Vaccination effectiveness was evaluated by crude

$VE = 1 - \text{attack rate of registry-verified vaccinated individuals} / \text{attack rate of nonvaccinated or self-reported vaccinated individuals} \times 100$

analysis, stratified analysis, and multivariate analysis. We evaluated the crude vaccine effectiveness (VE) by comparing the incidence based on the vaccination status with the following formula [1]:

We then calculated the crude VE by stratifying the sociodemographic characteristics and influenza-associated factors. In the multivariate analysis, we included age, smoking status, BMI, seasonal influenza vaccinations status, and H1N1pdm09 vaccination status.

Because we used the nonspecific clinical symptoms in the case definition, we estimated the vaccination effectiveness with various case definitions [e.g., cases with fever  $\geq 37.8$  °C or  $\geq 38$  °C in the medical record] and compared those with the VE of our case definition. This was conducted to evaluate the robustness of the results of this study, that is, a kind of sensitivity analysis.

## 2.5. Ethical considerations

Although this study does not require an Institutional Review Board (IRB) consideration, as it was conducted

as part of an epidemiological investigation of a respiratory outbreak in military camps, it contained a susceptible study group. Therefore, this study was reviewed by the Korean Military IRB. We distributed the study plan to all the study participants and received informed consents. To acknowledge their participation in the study, the participants were provided with a present.

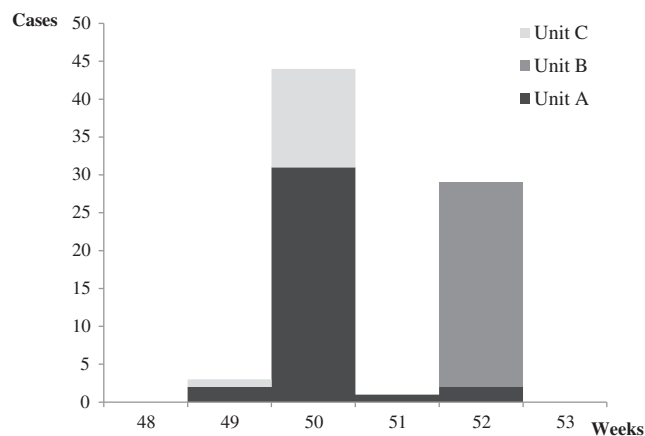
## 3. Results

As of December 1, 2010, there were a total of 455 candidates in the three military camps, and among them, 395 participated in this study (participant rate: 86.8%). A total of 50 persons rejected participation and 10 were unable to attend the interview, because they were unavailable in their respective camps during the study.

### 3.1. Outbreak situation

A total of 77 cases in three units were identified and the incidence rate was 19.5%. The incidence rate of Units A, B, and C was 14.6% (36/247), 29.0% (27/93), 25.5% (14/55), respectively. Each unit's incidence aspect is shown in Figure 1. Although the outbreak period was different, the progress of the outbreak was similar with a single peak.

Approximately 85% of the study participants were  $\leq 25$  years, and all were men except one. The number of recruits admitted prior to January 1, 2010, who were supposed to have H1N1pdm09 vaccination in the camp, was 224 (56.7%). A total of 16 soldiers (4%) were treated for H1N1pdm09 infection prior to joining the military camp, and 27 (6.8%) had seasonal



**Figure 1.** Epidemic curves of influenza-like illness by military units (A, B, C).

**Table 1.** Details for pandemic influenza A(H1N1) ILI cases and controls

	Case <i>N</i> = 77 (100%)	Control <i>N</i> = 318 (100%)	<i>p</i>
Unit			
A (247)	36 (47)	211 (66)	0.005
B (93)	27 (35)	66 (21)	
C (55)	14 (18)	41 (13)	
Age (y)			
≤19	13 (17)	37 (12)	0.263
20–24	56 (72)	230 (73)	
25–53	8 (10)	51 (16)	
Day of military recruitment			
Prior to 2010	34 (44)	190 (60)	0.013
After 2010	43 (56)	128 (40)	
Smoking history			
Current smoker	26 (34)	166 (52)	0.004
Nonsmoker/ex-smoker (≥1 mo)	51 (66)	152 (48)	
Body mass index			
<23	53 (69)	173 (54)	0.066
23–24.9	13 (17)	86 (27)	
≥25	11 (14)	59 (19)	
Past history of dx on influenza A(H1N1)pdm09			
Yes	3 (4)	13 (4)	0.939
No	74 (96)	305 (96)	
Past history of seasonal influenza vaccination (recent 1 y)			
Yes	5 (6)	22 (7)	0.895
No	72 (94)	296 (93)	
Past history of influenza A(H1N1)pdm09 vaccination			
Yes	Registry-verified 19 (25)	130 (41)	0.031
	Self-report 29 (38)	96 (30)	
No	29 (38)	92 (29)	

Data are presented as *n* (%). ILI = influenza-like illness; dx = diagnosis for influenza A(H1N1)pdm09 infection.

influenza vaccination in the past 1 year. The vaccination rate of H1N1pdm09 as verified by the registry was 37.7% (149/395). However, it will increase up to 69.3% (274/395) if the soldiers who checked the vaccination history in the questionnaires were also included (Table 1).

### 3.2. Effectiveness of influenza vaccine

Crude VE was 45.9% [95% confidence interval (CI): 12.9–66.4], and the risk to get infected with ILI in the

vaccinated group decreased by about half. If adjusted by age, smoking history, BMI, seasonal influenza vaccination history, H1N1pdm09 infection, the crude VE was 47.3% (95% CI: 4.1–71.0), and the risk to get ILI in the vaccinated group decreased similarly. A similar result (46.8%) was obtained if we exclude the unconfirmed H1N1pdm09 vaccination with no confirmation in the registry (Table 2). If various ILI definitions were applied, we had various incidence rates, but the values of vaccination effectiveness were relatively consistent.

**Table 2.** Number of pandemic influenza A(H1N1) ILI cases according to vaccination status and vaccine effectiveness (crude and adjusted) estimates\*

Vaccination status	Case/control [ <i>n</i> (%)]	Crude VE (%) (95% CI)	Adjusted VE <sup>†</sup> (%) (95% CI)
Vaccination 1	No + self-reported	58/188 (23.6/76.4)	45.9
	Registry verified	19/130 (12.8/87.2)	(12.9–66.4)
Vaccination 2	No	29/92 (24.0/76.0)	46.8
	Registry verified	19/130 (12.8/87.2)	(9.9–68.6)

\*Case included patients who had influenza-like illness (≥38 °C and cough/sore throat), which is either self-reported or medically attended; <sup>†</sup>Adjusted for age group, smoking history, BMI, seasonal influenza vaccination history (past 1 year), past influenza A(H1N1)pdm09 diagnosis history. BMI = body mass index; CI = confidence interval; ILI = influenza-like illness; VE = vaccine effectiveness.

**Table 3.** Sensitivity analysis of vaccine effectiveness according to case definition

Case definition	Crude VE % (95% CI)	
	Vaccination 1*	Vaccination 2 <sup>†</sup>
ILI	45.9 (12.9–66.4)	46.8 (9.9–68.6)
ILI MA	46.2 (5.2–69.5)	45.9 (–1.9–71.2)
ILI SR	49.2 (14.4–69.9)	50.0 (11.2–71.9)
Fever $\geq 38.0$ °C	43.1 (9.3–64.3)	44.0 (6.1–66.6)
Cough	46.9 (27.2–61.3)	51.3 (31.8–65.2)

\*Comparing “no” or “self-reported” vaccination with “registry-verified” vaccination; <sup>†</sup>Comparing “no” vaccination with “registry-verified” vaccination. CI = confidence interval; ILI = all influenza-like illnesses ( $\geq 38$  °C and cough/sore throat), which are self-reported cases or medically attended cases; ILI MA = influenza-like illness ( $\geq 38$  °C and cough/sore throat), which is a medically attended case only; ILI SR = influenza-like illness ( $\geq 38$  °C and cough/sore throat), which is a self-reported case only; VE = vaccine effectiveness.

If loose case definition was applied (lowering the fever temperature or containing nonspecific symptoms only), the incidence rates were increasing, but the values of vaccination effectiveness were consistent. By contrast, if strict case definition was applied, the incidence rates decreased, but the vaccination effectiveness was not much different with that of the original setting (Table 3).

#### 4. Discussion

The H1N1pdm09 vaccine administered in January 2010 has about 50% effectiveness on the H1N1pdm09 outbreak that occurred in December 2010. The magnitude of vaccination effectiveness was robust with no huge difference, even when multivariate analysis was applied and various ILI definitions were adopted.

The magnitude of VE in this study was lower than the 2009–2010 H1N1pdm09 season in the previous studies, which reported a 70% magnitude. However, the magnitude in this study was similar to that calculated for the next season (2010–2011) in the previous studies. Studies to evaluate the vaccination effectiveness 1 year after vaccination had suggested the hypothesis that the vaccination effectiveness was not persistent because no statistically significant results were available [12,13]. However, this study showed that statistically significant vaccination effectiveness does exist even 1 year after vaccination. The study result was immunologically consistent with a previous antigenicity study in which the vaccination effectiveness was noted even 1 year after seasonal influenza vaccination, but with decreased antibody titer [14].

This study was designed and conducted to evaluate the vaccination effectiveness of H1N1pdm09 and methodologically makes up for the previous studies with case-control designs. In case-control study, exposure to a pathogen in the two groups is put artificially similar or is assumed to be similar. In this study, the study participants shared living space and contacted frequently, and therefore, we could assume that they were all similarly exposed to the pathogen regardless of vaccination status, which is the major explanatory variable.

Using various combinations of case definition based on various body symptoms, respiratory symptoms, treatment status, and ILI confirmation status, the incidence rates of the vaccinated group were found to be lower than those of the nonvaccinated group. Although some CIs include the null value, no combination was statistically significant in the direction of effectiveness. This implied that the results of this study were not by chance, but were rather very robust. While interpreting the results of this study, the following should be considered. First, the case definition in this study was not that of a laboratory test but was a nonspecific one based on ILI symptoms, and so it could underestimate the vaccination effectiveness as in general studies with information misclassification [15,16]. However, the magnitude was considered minimum for the following reasons: First, a laboratory analysis confirmed all the cases to be H1N1pdm09 infected. Second, considering the aspect of outbreak, a single pathogen was suspected. Third, according to the KCDC influenza laboratory surveillance report, 95% of respiratory infection was due to H1N1pdm09 infection [17]. Fourth, the vaccination effectiveness under various case definitions was relatively consistent. Although the case definition was not based on the confirmative result of laboratory test, the aforementioned situations strongly suggested that the vaccination effectiveness in this study was not for ILI but for H1N1pdm09.

Next, we needed to evaluate the intergroup heterogeneity (study participants, type of exposure, method to measure the result) in order to review the validity of pooled analysis. The study participants from the three groups were all men in their early 20s, shared camp lives, and were vaccinated with the same vaccine during the H1N1pdm09 mass vaccination drive. In addition, the aspect of outbreak was similar. The results were measured with the same questionnaire. Therefore, we thought that this study evaded any critical fault to suspect the results of pooled analysis.

Finally, with regard to the external validity, the results of this study could not be applied to other age groups as well, especially to the elderly individuals who

have low vaccination effectiveness. In this study, all the participants were young adult men. As for the internal validity, the study participants were homogeneous, a factor which enhanced the internal validity.

Although there were some limitations, this study complemented the previous studies in study design and duration of effectiveness by evaluating the effectiveness of H1N1pdm09 vaccine 1 year after vaccination in military camps during an outbreak. The strength of this study was that the vaccination effectiveness was robust regardless of case definitions and analytical models, and that we considered other factors that could possibly affect influenza outbreak in our analysis.

In conclusion, the effectiveness of H1N1pdm09 vaccine 1 year after vaccination was approximately 47%, and this study confirmed the results of previous studies, which showed that vaccination effectiveness decreased as time passed.

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