Pediatr Infect Vaccine. 2019 Dec;26(3):161-169
https://doi.org/10.14776/piv.2019.26.e18
pISSN 2384-1079·eISSN 2384-1087

PIV PEDIATRIC INFECTION & VACCINE

Original Article

Comparison of Split versus Subunit Seasonal Influenza Vaccine in Korean Children over 3 to under 18 Years of Age

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Received: Jun 20, 2019
Revised: Aug 29, 2019
Accepted: Sep 17, 2019

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Funding
This study was supported by the Korea Food & Drug Administration (08122KFDA336).

ABSTRACT

Purpose: This study was conducted to compare immunogenicities and reactogenicities of the trivalent inactivated subunit influenza vaccine and split influenza vaccine in Korean children and adolescents.
Methods: In total, 202 healthy children aged 36 months to <18 years were enrolled at six hospitals in Korea from October to December 2008. The subjects were vaccinated with either the split or subunit influenza vaccine. The hemagglutinin inhibition antibody titers against the H1N1, H3N2, and B virus strains were measured, and the seroconversion rates, seroprotection rates, and geometric mean titers were calculated. All subjects were observed for local and systemic reactions.
Results: Both the split and subunit vaccine groups had similar seroprotection rates against all strains (95.9%, 94.9%, 96.9% vs. 96.0%, 90.9%, and 87.9%). In children aged 36 to <72 months, the seroprotection rates were similar between the two vaccine groups. In children aged 72 months to <18 years, both vaccines showed high seroprotection rates against the H1N1, H3N2, and B strain (98.4%, 98.4%, 98.4% vs. 97.0%, 95.5%, and 91.0%), but showed relatively low seroconversion rates (39.1%, 73.4%, 35.9% vs. 34.3%, 55.2%, and 38.8%). There were more local and systemic reactions in the split vaccine group than in the subunit vaccine group; however, no serious adverse reactions were observed in both groups.
Conclusions: Both the split and subunit vaccines showed acceptable immunogenicity in all age groups. There were no serious adverse events with both vaccines.

Keywords: Influenza vaccine; Influenza; Safety; Children

INTRODUCTION

Influenza is a highly infectious disease that can cause complications leading to serious morbidity and mortality in young children. Primary viral pneumonia, secondary bacterial pneumonia, croup, myositis, toxic shock, Reye syndrome, and acute encephalopathy have been reported in children with influenza infections.[1-3] Annual vaccination is the most effective strategy for preventing influenza infections, and influenza vaccination is believed to

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: Kang S, Kim DH, Eun BW, Kim NH, Kang EK, Lee BS, Kim YK; Data curation: Kim DH, Eun BW, Kim NH, Kang EK, Lee BS, Kim YK; Formal analysis: Kang S; Funding acquisition: Kim DH; Investigation: Kim DH, Eun BW, Kim NH, Kang EK, Lee BS, Kim YK; Methodology: Kim NH, Kim YK; Project administration: Kim DH, Eun BW, Kim YK; Resources: Kim DH, Eun BW, Kim NH, Kang EK, Lee BS, Kim YK; Supervision: Kim YK; Validation: Kim YK; Writing - original draft: Kang S; Writing - review & editing: Kang S, Kim YK.

have reduced the incidence of laboratory-confirmed influenza, its associated complications, hospitalizations, and deaths.[3,4]

The inactivated trivalent influenza vaccine, which has been used consistently since 1978, contains purified and inactivated materials from 3 viral strains; that is, 2 influenza A strains and one influenza B strain.[5] The safety and tolerability of trivalent inactivated influenza vaccines have been evaluated in previous studies.[6,7]

In Korea, the current recommendation is to vaccinate children of ≥6 months of age every year. The vaccine coverage rate is much higher for young children than it is for adolescents. Although both split influenza vaccines and subunit influenza vaccines are used for children, limited data are available regarding their efficacy and safety in children in Asia, including Korea. Previous studies have compared the immunogenicity and reactogenicity of split vs. subunit influenza vaccine in Korean children of ≤35 months.[8] Therefore, the first aim of this study was to compare the immunogenicities and reactogenicities of these 2 types of influenza vaccines in children of ≥36 months. The second aim of this study was to investigate the immunogenicity and reactogenicity of the influenza vaccines commonly used in Korean children and adolescents.

MATERIALS AND METHODS

1. Study design

Our study was carried out in 2 non-randomized cohorts of children in an open-label trial at 6 hospitals from October 2008 to December 2008, after a protocol was approved by the Institutional Review Board (IRB) of each hospital (Korea University Ansan Hospital IRB No. AS0219). Written informed consent was obtained from all parents and from the participants of >7 years of age at the time of enrollment.

Subjects enrolled in the study were 36 months to <18 years of age. Children who were allergic to influenza vaccines or egg protein, had developed acute febrile illness within 24 hours of vaccination, were on immune-suppressant medication (including corticosteroids), had a history of transfusion within 6 months, and had any condition that might interfere with the evaluation were excluded. All subjects were divided into 2 age groups (36 to <72 months and 72 months to <18 years) to compare the immunogenicity according to age as it has been reported in previous studies that children under 6 years have lower seroprevalence rates.[9-11]

All subjects were observed for 30 minutes following vaccine administration to check for immediate local and/or systemic reactions. Each subject (or their guardian) filled out a diary card and recorded any local (pain, redness, swelling, petechiae, ecchymosis, edema, abscess) and/or systemic reaction (axillary temperature of ≥37.5°C, fever, shivering, headache, myalgia, arthralgia, fatigue, malaise) that occurred during 7 days following the vaccination. Any serious adverse event that occurred between the vaccination day and 30th day post-vaccination and any medication taken during the study period were recorded. Venous blood samples were obtained from all subjects on days 0 and 30.

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2. Vaccines

The 2 vaccines used in the study were Vaxigrip® (a split influenza vaccine; Aventis Pasteur MSD, Lyon, France) and SK Influenza Trivaccine® (a subunit influenza vaccine, Agripal S1; Chiron Vaccines, Siena, Italy). Both vaccines contained A/Brisbane/59/2007 (H1N1) strain (IVR-148), A/Uruguay/716/2007 (H3N2) strain (NYMCX-175C), and B/Florida/4/2006 strain. The vaccines were injected intramuscularly into the deltoid muscle at a single dose of 0.5 mL.

3. Antibody studies

The antibody titers of the H1N1, H3N2, and B virus strains were determined using the hemagglutination inhibition (HI) test. The HI test is based on the ability of specific anti-influenza antibodies to inhibit the hemagglutination of chicken red blood cells by influenza virus hemagglutinin. The sera to be tested were previously treated in order to eliminate nonspecific inhibitors and the anti-species hemagglutinin. The titer was expressed as the reciprocal of the highest dilution of serum that completely inhibited hemagglutination. For evaluation purposes, a titer of 40 was considered to be protective.[12,13]

The HI titers to strains H1N1, H3N2, and B were measured using A/Brisbane/59/2007 IVR-148 (H1N1), A/Uruguay/716/2007 NYMCX-175C (H3N2), and B/Florida/4/2006, respectively. The immunogenicities of the 2 studied vaccines were assessed on the bases of the frequency of seroconversion on day 30, the proportion of subjects seroprotected on days 0 and 30, and the increase in geometric mean titer of anti-HI antibodies between days 0 and 30, defined as the geometric mean titer ratio. Seroconversion was defined as a change from a pre-vaccination titer of <10 to a post-vaccination titer of ≥40, or a ≥4-fold rise in titer in those with an initial anti-HI antibody titer of ≥10. Seroprotection was defined as a titer of ≥40.[12]

The following serological assessments were considered for each strain in the subjects: 1) the number of seroconversions, or a significant increase in the anti-hemagglutinin antibody titer of >40%; 2) a mean geometric increase of >2.5; and 3) the proportion of subjects achieving an anti-HI antibody titer of 1:40 to be >70%.[14]

4. Statistical analysis

All analyses were performed using IBM SPSS Statistics ver. 20.0 (IBM Corp., Armonk, NY, USA). The χ^2 test and Mann-Whitney test were used for comparisons between the 2 vaccine groups.

RESULTS

1. Subjects

Among the 202 children enrolled in the study, half received the split vaccine and the other half received the subunit vaccine. Five subjects were excluded from the immunogenicity study owing to a failure to obtain paired blood samples from them. Therefore, in total, 197 (98 in split vaccine group and 99 in subunit vaccine group) paired blood specimens (days 0 and 30) were obtained for antibody assessment (**Table 1**).

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Table 1. Demographic characteristics

Characteristic	Split vaccine group (n=98)	Subunit vaccine group (n=99)
Age		
36 to <72 mon	34 (34.7)	32 (32.3)
72 mon to <18 yr	64 (65.3)	67 (67.7)
Sex		
Female	55 (56.1)	40 (40.4)
Male	43 (43.9)	59 (59.6)
Pre-vaccination status		
Unprimed	-	-
For H1N1	17 (17.3)	21 (21.2)
For H3N2	3 (3.1)	2 (2.0)
For B	33 (33.7)	25 (25.3)

Values are presented as number (%). Unprimed: children with an initial hemagglutination inhibition titer <1:10 were regarded as unprimed subjects due to the unavailability of previous vaccination history.

2. Immunogenicity

The seroprotection and seroconversion rates were compared between the 98 children in the split vaccine group and 99 children in the subunit vaccine group. Both vaccines induced increases in these rates in a large proportion of the subjects (**Table 2**).

In both the split and subunit vaccine group, similar seroprotection rates (anti-HI antibody titers ≥40) were achieved against the H1N1, H3N2, and B strain (95.9%, 94.9%, 96.9% vs. 96.0%, 90.9%, 87.9%). The seroconversion rates in both the split and subunit vaccine groups showed no significant differences (32.7%, 75.5%, 52.0% vs. 40.4%, 61.6%, 49.5%).

3. Immunogenicity according to age group

The seroprotection and seroconversion rates for the 2 vaccines were also separately assessed in 2 age groups (36 to <72 months and 72 months to <18 years). Both rates for the split vaccine and subunit vaccine were similar in both age groups.

Table 2. Comparison of immunogenicity between split and subunit influenza vaccine

End point	Split vaccine group (n=98)		Subunit vaccine group (n=99)		*P*-value*	
	Pre	Post	Pre	Post	Pre	Post
HAI Ab ≥1:40						
H1N1	74 (75.5)	94 (95.9)	60 (60.6)	95 (96.0)	0.037	1.000
H3N2	55 (56.1)	93 (94.9)	49 (49.5)	90 (90.9)	0.430	0.417
B	63 (64.3)	95 (96.9)	59 (59.6)	87 (87.9)	0.595	0.033
HAI Ab ≥1:330						
H1N1	12 (12.2)	27 (27.6)	4 (4.0)	16 (16.2)	0.065	0.078
H3N2	0 (0.0)	36 (36.7)	7 (7.1)	24 (24.2)	0.014	0.080
B	7 (7.1)	29 (29.6)	3 (3.0)	18 (18.2)	0.322	0.087
GMT						
H1N1	210.9 (154.7–267.1)	423.5 (296.4–550.7)	95.0 (69.1–120.9)	270.7 (198.9–342.4)	0.003	0.001
H3N2	89.8 (67.0–112.6)	668.9 (485.0–852.9)	96.4 (63.5–129.2)	483.0 (335.7–630.2)	0.709	0.056
B	122.9 (91.1–154.6)	445.4 (362.0–528.9)	79.1 (55.9–102.3)	261.9 (216.7–307.1)	0.180	0.001
Seroconversion						
H1N1	32 (32.7)		40 (40.4)		0.326	
H3N2	74 (75.5)		61 (61.6)		0.052	
B	51 (52.0)		49 (49.5)		0.830	

Values are presented as number (%) or 95% confidence interval.
Abbreviations: GMT, geometric mean titer; HAI Ab, hemagglutination inhibiting antibody.
*P<0.05, compared by vaccine groups for HAI Ab and GMT; P<0.05, compared for pre to post change by vaccine groups for seroconversion number.

https://doi.org/10.14776/piv.2019.26.e18

In the age group of 36 to <72 months, the seroprotection rates against the H1N1, H3N2, and B strains were not very different between the 2 vaccine groups. However, the H1N1 seroconversion rate was higher in the subunit vaccine group than in the split vaccine group (53.1% vs. 20.6%) (**Table 3**).

In the age group of 72 months to <18 years, the split vaccine and subunit vaccine did not show differences in both the seroprotection rate and seroconversion rate for the 3 strains. Both vaccines showed high seroprotection rates against the H1N1, H3N2, and B strains, but relatively low seroconversion rates for all 3 (**Table 4**).

Table 3. Comparison of immunogenicity between split and subunit influenza vaccine according to age group: 36 to <72 months

End point	Split vaccine group (n=34)		Subunit vaccine group (n=32)		*P*-value*	
	Pre	Post	Pre	Post	Pre	Post
HAI Ab ≥1:40						
H1N1	24 (70.6)	31 (91.2)	12 (37.5)	30 (93.8)	0.014	1.000
H3N2	14 (41.2)	30 (88.2)	12 (37.5)	26 (81.3)	0.957	0.505
B	13 (38.2)	32 (94.1)	10 (31.3)	26 (81.3)	0.736	0.143
HAI Ab ≥1:330						
H1N1	5 (14.7)	8 (23.5)	0 (0.0)	4 (12.5)	0.054	0.400
H3N2	0 (0.0)	15 (44.1)	3 (9.4)	10 (31.3)	0.108	0.410
B	1 (2.9)	11 (32.4)	0 (0.0)	8 (25.0)	1.000	0.698
GMT						
H1N1	229.0 (119.6–338.3)	370.0 (200.2–539.8)	75.5 (35.8–115.1)	223.4 (130.3–316.5)	0.016	0.164
H3N2	97.4 (47.6–147.1)	791.2 (432.8–1,149.6)	107.7 (39.2–176.1)	625.7 (282.2–1,023.1)	0.541	0.289
B	60.7 (19.0–102.5)	483.8 (308.1–659.6)	44.1 (15.2–72.9)	269.4 (185.4–353.3)	0.579	0.070
Seroconversion						
H1N1	7 (20.6)		17 (53.1)		0.013	
H3N2	27 (79.4)		22 (68.8)		0.479	
B	28 (82.4)		23 (71.9)		0.471	

Values are presented as number (%) or 95% confidence interval.
Abbreviations: GMT, geometric mean titer; HAI Ab, hemagglutination inhibiting antibody.
*P<0.05, compared by vaccine groups for HAI Ab and GMT in ages 36 to <72 months; P<0.05, compared for pre to post change by vaccine groups for seroconversion number in ages 36 to <72 months.

Table 4. Comparison of immunogenicity between split and subunit influenza vaccine according to age group: 72 months to <18 years

End point	Split vaccine group (n=64)		Subunit vaccine group (n=67)		*P*-value*	
	Pre	Post	Pre	Post	Pre	Post
HAI Ab ≥1:40						
H1N1	50 (78.1)	63 (98.4)	48 (71.6)	65 (97.0)	0.514	1.000
H3N2	41 (64.1)	63 (98.4)	37 (55.2)	64 (95.5)	0.394	0.620
B	50 (78.1)	63 (98.4)	49 (73.1)	61 (91.0)	0.645	0.116
HAI Ab ≥1:330						
H1N1	7 (10.9)	19 (29.7)	4 (6.0)	12 (18.0)	0.478	0.168
H3N2	0 (0.0)	21 (32.8)	4 (6.0)	14 (20.9)	0.120	0.179
B	6 (9.4)	18 (28.1)	3 (4.5)	10 (14.9)	0.317	0.103
GMT						
H1N1	192.8 (130.0–255.6)	477.0 (292.4–661.5)	114.5 (77.9–151.0)	317.9 (201.0–434.8)	0.051	0.002
H3N2	82.1 (60.0–104.2)	546.6 (344.5–748.8)	85.1 (49.4–120.7)	313.2 (233.1–393.3)	0.718	0.140
B	185.1 (129.8–240.4)	407.0 (319.1–494.8)	114.1 (79.3–148.9)	254.3 (200.2–308.5)	0.071	0.006
Seroconversion						
H1N1	25 (39.1)		23 (34.3)		0.703	
H3N2	47 (73.4)		39 (55.2)		0.099	
B	23 (35.9)		26 (38.8)		0.874	

Values are presented as number (%) or 95% confidence interval.
Abbreviations: GMT, geometric mean titer; HAI Ab, hemagglutination inhibiting antibody.
*P<0.05, compared by vaccine groups for HAI Ab and GMT in ages 72 months to <18 years; P<0.05, compared for pre to post change by vaccine groups for seroconversion number in ages 72 months to <18 years.

https://doi.org/10.14776/piv.2019.26.e18

Table 5. Local and systemic reactions by vaccine type and age group

Characteristic	Split vaccine			Subunit vaccine			*P*-value*		
	36 to <72 mon (n=34)	72 mon to <18 yr (n=64)	Total (n=98)	36 to <72 mon (n=32)	72 mon to <18 yr (n=67)	Total (n=99)	Split vaccine	Subunit vaccine	Total
Local ADEs	19 (55.9)	43 (67.2)	62 (63.3)	12 (37.5)	30 (44.8)	42 (42.4)	0.376	0.640	0.312
Systemic ADEs	8 (23.5)	34 (53.1)	42 (42.9)	8 (25.0)	21 (31.3)	29 (29.3)	0.009	0.680	0.022
Subjects experiencing ADEs	27 (79.4)	53 (82.8)	81 (82.7)	14 (43.8)	37 (55.2)	51 (51.5)	1.000	0.393	0.580

Values are presented as number (%).
Abbreviations: ADE, adverse drug events.
*P<0.05, compared by age groups for split and subunit vaccine; P<0.05, compared by vaccine group for total.

4. Reactogenicity

The 197 vaccinated subjects were evaluated for local and systemic reactions. The overall proportion of local reactions (occurring 30 minutes to 7 days after vaccine administration) was higher in the split vaccine group than in the subunit vaccine group (n=62 vs. 42; 63.3% vs. 42.4%). The local reactions consisted mainly of pain, erythema, induration, and petechiae, but were not serious in both groups. Systemic reactions (occurring 30 minutes to 7 days after vaccine administration) were also more prevalent in the split vaccine group than in the subunit vaccine group (n=42 vs. 29; 42.9% vs. 29.3%). The intensity of most systemic reactions was also mild for both vaccines. With regard to the reactogenicity difference between the 2 age groups, children of 72 months to <18 years had more frequent elicitations of systemic reactions with both vaccines (**Table 5**).

DISCUSSION

Influenza is a cause of morbidity and mortality in children, and vaccination has proven to be an effective method for preventing this disease and its complications. In the results obtained from this study, we found that both the split and subunit influenza vaccines showed effective immunogenicity and safety in Korean children and adolescents. Furthermore, by age group, children of 72 months to <18 years showed higher rates of systemic side effects and lower seroconversion rates. Both types of vaccines meet all 3 criteria set by the Committee for Medicinal Products for Human Use for all 3-virus strains in the vaccine.[14]

For both the split and subunit vaccines, the seroconversion rate was relatively low compared with the high seroprotection rate. The probable reason for the lower seroconversion rate is a high pre-vaccination antibody titer, since a high titer of preexisting homologous antibodies may mask the antibody fold increase. Such high pre-vaccination antibody titer probably resulted from either the high vaccination coverage of Korean children compared with that in other countries or the high morbidity of influenza in Korea.[15] This correlated with the lower seroconversion rates seen in the children of older age.

The immunogenicity of the split vaccine in children has already been confirmed in previous studies.[16] However, there is limited comparative data on the clinical effects of split and subunit vaccines in children. In previous adult studies, split vaccines showed greater clinical effectiveness in younger adults than in adults aged >50 years,[17] but in other studies in Europe,[18,19] there was no difference in effectiveness in the elderly. In a study by Kim et al.,[8] the immunogenicity of the split vaccine was found to be superior to that of the subunit vaccine in children <3 years of age in a given flu season. In our present study, we confirmed that the split vaccine also exhibited better immunogenicity in children and adolescents

https://doi.org/10.14776/piv.2019.26.e18

of 36 months to <18 years of age. This difference in immunogenicity might be due to the manufacturing process. Differences in the influenza antigen variety may affect its efficacy.

Usually, the hemagglutinin titer of 1:40 has been known to correlate with a 50% reduction in contracting influenza. However, this is based on adult studies, and previous studies have shown that this might not effectively reflect the protective level for children.[12,13] Black et al.[20] reported that a cutoff value of 1:330 would predict an 80% rate of protection. On the basis of this criterion, we compared the seroprotection rates of the split and subunit vaccines, whereupon no significant difference between the 2 vaccine groups and the 2 age groups were found.

With regard to the local adverse effects, the subunit vaccine elicited less side effects than the split vaccine. The differences in the concentrations of nonviral compounds (e.g., ovalbumin and endotoxin) may lead to different post-vaccination reactogenicity profiles. The contents of total protein and matrix protein are lower in the subunit vaccines than in the split vaccines.[21] In previously reported studies, Korean children tended to show higher rates of local side effects than the children in European and US studies, for which the incidence was commonly reported as 20–30%.[22] In our study, 37.5–67.2% of the vaccinated children reported at least one of the local reactions indicated on the diary card, and 23.5–53.1% reported systemic signs/symptoms. However, no serious reactions were reported in our study. The Fluarix® clinical study showed a high frequency of local reactions (15–52.6%) in subjects of 3 to <18 years of age. These results are in accord with the findings of our study.[23]

The limitation of our study is that it was open and non-randomized. Most of the clinical studies conducted so far have used inactivated split vaccines and enrolled children ≥3 years old. More comparative studies like the present one are needed to demonstrate the efficacy and safety of trivalent inactivated subunit influenza vaccines in children.

In conclusion, both the split and subunit influenza vaccines that are commonly used in Korean children and adolescent were immunogenic and well tolerated. However, each of the vaccines showed different immune responses and side effects depending on the child's age. Children in the older age group showed lower seroconversion rates and elicited local and systemic adverse events more frequently. Whether these observations are true in other ethnicities and with other vaccines needs confirmation through further clinical experience and a well-designed randomized prospective study.

ACKNOWLEDGEMENT

The authors would like to thank the staff members at each of the participating institutions, as well as the participants who provided samples and data for this work.

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요약

목적: 본 연구는 국내 소아청소년에서 인플루엔자 분할백신 접종군과 인플루엔자 아단위백신 접종군 간 면역원성 및 안전성을 파악하기 위해 시행하였다.
방법: 2008년 10월부터 12월까지 서울과 경기도 지역의 여섯 개의 병원에 방문한 202명의 건강한 만 36개월에서 18세 미만의 소아청소년을 대상으로 하였으며 이들은 인플루엔자 분할백신 또는 아단위백신을 접종받았다. H1N1, H3N2, 그리고 B형의 인플루엔자 바이러스 항원의 면역원성을 평가하기 위해 접종 후 혈구응집억제 항체가가 1:40 이상인 피험자의 비율, 항체 양전률, 그리고 geometric mean titer를 계산하였다. 모든 접종자들에서 국소 그리고 전신 이상반응을 관찰하였다.
결과: 분할백신 접종군과 아단위백신 접종군에서 H1N1, H3N2, B형 항원에 대하여 항체가가 1:40 이상으로 나타난 피험자의 비율은 유사하였다(95.9%, 94.9%, 96.9% vs. 96.0%, 90.9%, 87.9%). 36개월 이상 72개월 미만의 소아에서 두 접종군 간 항체가가 1:40 이상으로 나타난 피험자의 비율은 유사하게 나타났다. 72개월 이상 18세 미만의 소아에서는 H1N1, H3N2, 그리고 B에 대해 항체가가 1:40 이상으로 나타난 피험자의 비율은 모두 높게 나타났으나 (98.4%, 98.4%, 98.4% vs. 97.0%, 95.5%, 91.0%), 항체 양전율은 상대적으로 낮았다 (39.1%, 73.4%, 35.9% vs. 34.3%, 55.2%, 38.8%). 또한 분할백신 접종군에서 아단위백신 접종군에서보다 국소 및 전신 이상반응의 비율이 더 높았으나 두 접종군 모두에서 중대한 이상반응은 나타나지 않았다.
결론: 인플루엔자 분할백신 접종군과 아단위백신 접종군 모두에서 3세 이상 18세 미만의 연령군에서 적절한 면역원성을 보였다. 또한 두 접종군에서 모두 중대한 이상반응은 발생하지 않았다.