Jpn. J. Infect. Dis., 65, 193-197, 2012

Original Article

Comparison of the Adverse Events Associated with MF59-Adjuvanted and Non-Adjuvanted H1N1 Vaccines in Healthy Young Male Korean Soldiers

Se-Min Hwang[1], Hack-Lyoung Kim[2], Kyueng-Whan Min[3], Min Kim[3], Jae-Sung Lim[3], Jin-Man Choi[3], Byung-Chul Chun[4], Min-Jeong Kim[5], Sang-Min Lee[6], Seung-Young Kim[7], and Han-Ho Jeon[8]*

[1]*Department of Preventive Medicine, Armed Forces Medical Command, Seongnam;*
[2]*Department of Internal Medicine, Seoul National University Hospital, Seoul;*
[3]*Armed Forces Seoul Hospital, Seoul;*
[4]*Department of Preventive Medicine and Department of Epidemiology Public Health Informatics,*
[5]*Korea University School of Public Health, Seoul;*
[6]*Department of Internal Medicine, Armed Forces Capital Hospital, Seongnam;*
[7]*Department of Internal Medicine, Korea University College of Medicine, Seoul; and*
[8]*Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea.*

(Received August 24, 2011. Accepted January 31, 2012)

SUMMARY: The first large-scale outbreaks of respiratory disease in the 21st century were caused by the influenza A (H1N1) virus in 2009, which affected mostly young adults. The M59 vaccine was developed to control pandemic influenza A (H1N1). However, the complications arising from the use of the non-adjuvanted and adjuvanted vaccines in young male Korean soldiers have not previously been evaluated and compared. We conducted a prospective multicenter study of 2,864 healthy male soldiers aged 19 to 25 years to evaluate the adverse events associated with both the MF59-adjuvanted and non-adjuvanted forms of the influenza A/California/2009 (H1N1) surface-antigen vaccine. In most cases, the adverse-event symptoms were mild, and the most frequent adverse events were swelling at the injection site and myalgia, which were noted in 4.8% and 10.7% of participants, respectively. Administration of the MF59-adjuvanted vaccine was associated with an increased incidence of local (crude odds ratio [cOR], 1.56; 95% confidence interval [CI], 1.11–2.29) and systemic adverse events (cOR, 1.64; 95% CI, 1.29–2.07) after vaccination. Atopic dermatitis (adjusted OR [aOR], 2.32; 95% CI, 0.99–5.46) might be the choice risk factor for local adverse events, and adjuvant use (aOR, 1.35; 95% CI, 1.03–1.78) was a significant predictor of systemic adverse events in healthy young male Korean soldiers.

INTRODUCTION

Since the novel influenza A (H1N1) virus was recognized in Mexico and the USA in April 2009, the virus has continued to spread throughout the world. Therefore, on June 11, 2009 , the World Health Organization (WHO) raised the alert level to pandemic alert level phase 6 (1–3). The emergence of a novel influenza A (H1N1) virus of swine origin demonstrates the unpredictability of influenza (3). This virus has the potential to cause death and socioeconomic disruption (4,5). Children, young adults, and those with underlying chronic disease are known to be at high risk for complications associated with influenza A (H1N1) virus infection. Most patients who developed H1N1 infection were young adults (6). Vaccination is the most effective method to reduce morbidity and mortality during an influenza A (H1N1) pandemic. However, previous reports showed that seasonal vaccination did not result in significant protection against the H1N1 virus (7). Therefore, several vaccine products with or without adjuvants have been made available, and mass vaccination against 2009 H1N1 has begun in many countries. However, the safety of these newly developed vaccines has not been widely evaluated. The addition of adjuvant to vaccines enhances immunogenicity and induces the production of cross-reactive antibodies against antigenically drifted variants with limited antigen and inherently low immunogenicity (8,9). The WHO has suggested the use of an adjuvant in influenza A (H1N1) vaccines (10). However, data from trials comparing adjuvanted and non-adjuvanted vaccines are still pending.

Initial epidemiologic studies demonstrated that 2009 H1N1 virus infection occurred mainly in adolescents and young adults with a median age of 20–25 years (6). This age range is similar to that of Korean soldiers who usually join the army between the ages of 20 and 22 years. Soldiers in this age group are at high risk for 2009 H1N1 influenza infection, and influenza-associated complications could have an adverse impact on military power. In addition, because of the communal boarding environment in the military, the virus could spread rapidly among soldiers, with a high chance of viral transmission within the community. Indeed, after the initial outbreak of 2009 H1N1 in Korea, rapid transmission of

*Corresponding author: Mailing address: Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, 211 Eonju-ro, Gangnam-Gu, Seoul 135-720, Republic of Korea. Tel: +82-2-2019-3298, Fax: +82-2-3463-3882, E-mail: karlfreud@naver.com

the virus was observed withiin the military. The Korean government considered soldiers a high-risk group; therefore, soldiers were preferentially vaccinated. Mass vaccination of Korean soldiers began in early November 2009.

This study evaluated the incidence of and risk factors for adverse events to MF59-adjuvanted H1N1 vaccine and a non-adjuvanted H1N1 vaccine in healthy young male Korean soldiers.

MATERIALS AND METHODS

Subjects: This study was conducted during the late pandemic H1N1 influenza season from November 2009 to January 2010 at the School of Military Medicine (SMM), the Armed Forces Medical Research Institute (AFMRI), 15 military hospitals, and 1 army division in South Korea. A total of 2,864 participants were enrolled in the original study; 944 participants received an MF59-adjuvanted vaccine in 1 army division, and 1,920 received non-adjuvanted vaccines in 17 Military Health Care Units. Participants were screened for eligibility and provided written informed consent. Eligible participants were clinically healthy male soldiers between 19 and 25 years of age at vaccination. Our main exclusion criteria were clinically confirmed influenza H1N1 infection within 3 months before the study, a history of allergy to vaccines or eggs, current febrile illness, current long-term systemic corticosteroid therapy, and/or recent (in the previous 4 weeks) vaccination or a planned vaccination within the next 4 weeks.

Study design: For this prospective study, we analyzed two parallel groups from multiple centers in Korea from November 2009 to January 2010. The H1N1 influenza vaccine was administered by intramuscular injection into the deltoid muscle of the non-dominant arm on day 0. All participants were observed for 30 min after vaccine injection. In a self-completed diary card and questionnaire, participants recorded the occurrence of symptoms at the injection site (pain, erythema, and swelling) and general symptoms (fever, headache, shivering, myalgia, and nausea) over the next 7 days. Only events that interfered with normal military activities were recorded as adverse events. All safety issues and reactogenicities were reviewed during interviews with participants at a scheduled visit (day 7). Soldiers who showed any severe or unusual adverse events were admitted to the hospital, and laboratory tests and examinations were performed, if necessary. Serious adverse events were recorded throughout the study (until day 92). The protocol and all study documents were approved by the Institutional Review Board of the Armed Forces Medical Command (Seongnam-si, Republic of Korea).

Vaccines: The influenza A (H1N1) vaccine, a monovalent, non-adjuvanted, inactivated, split-virion vaccine, was formulated and produced by the Green Cross Company (Yongin-si, Republic of Korea). The vaccine seed virus was prepared from New York Medical College X-179A, which was generated from the A/California/7/2009 strain that was distributed by National Institute for Biological Standards and Control in the United Kingdom. MF59 is a submicron oil-in-water emulsion containing 39.0 mg of squalene, 4.7 mg of polysorbate 80, and 4.7 mg of sorbitan trioleate in buffer. Each non-adjuvanted vaccine (GREEN FLU-S®) contained 15 μg of purified inactivated influenza virus antigen type A (H1N1), and each adjuvanted vaccine (GREEN FLU-S PLUS®) contained 30 μg of H1N1. For the non-adjuvanted vaccine group, 0.5 ml (15 μg) was injected as a single dose. For the adjuvanted vaccine group, the final formulation was made just prior to injection by mixing H1N1 antigen suspension and the MF59 adjuvant emulsion for a final injection volume of 0.25 ml (3.75 μg). The non-adjuvanted vaccines were prepared in single dose, prefilled syringes. The adjuvanted vaccines were prepared in multiple dose vials. All vaccines were stored at 2–8°C.

Clinical trials in adults 18–64 years of age showed that both vaccines elicited effective seroconversion and seroprotection on day 21 after the first dose by hemagglutination inhibition assay. The immunogenicity of the non-adjuvanted vaccine was 76.3% and 78.1% and the adjuvanted vaccine was 66.7% and 78.1% (11).

Statistical analysis: All statistical analyses were performed using SPSS 12.0 (SPSS Inc., Chicago, Ill., USA). Data are presented as percentage and mean $\pm$ SD. Differences in proportions were analyzed by the χ^2 test or Fisher's exact test. All reported P values were two-sided, and a P value ≤ 0.05 was considered statistically significant. The odds ratios (OR) of local and systemic adverse effects were tested with the χ^2 test and stratified logistic regression analysis. OR were calculated using 95% confidence intervals (CIs). The following variables were included in the analysis: body mass index (BMI), smoking, hypertension, atopic dermatitis, and asthma. Moreover, the number of hospital beds and adjuvant were included in the analysis to evaluate the differences in adverse events among the 17 hospitals and for non-adjuvanted vaccine assessment in 1 army division. The number of hospital beds was used as a variable because the Military Medical Delivery System of the Republic of Korea is categorized by the number of healthcare unit beds. The 1st medical institute category consists of hospitals that have less than 350 beds, the 2nd medical institute category consists of hospitals with 350–799 beds, and the 3rd medical institute category consists of hospitals with more than 800 beds. Disease modifiers were not changed based on their significance. Confounding factors were changed based on their significance using the stratified logistic regression of model 1 and model 2. To evaluate the adequacy of each model, we used a Hosmer-Lemeshow test, and accepted models for which the P value was >0.05.

RESULTS

Demographic characteristics: A total of 2,864 participants were enrolled in the original study; 944 participants received MF59-adjuvanted vaccines, while 1,920 received non-adjuvanted vaccines. The mean age of the two groups was similar. There were no significant differences between the groups at baseline with respect to height, weight, or BMI (Table 1). The proportion of vaccines who smoked, had asthma, and had atopic dermatitis was higher in the adjuvanted vaccine group than in the non-adjuvanted vaccine group.

Institutional characteristics: A total of 18 military

medical institutes were enrolled in the study. Eleven units and 1 army division were in the 1st medical institute category, 5 units were in the 2nd medical institute category, and 1 unit was in the 3rd medical institute category. There were no significant differences in adverse events among the three categories (Table 2).

Table 1. Clinical characteristics of the participants according to vaccine groups

Characteristic	MF59-adjuvanted vaccine (n = 944)	Non-adjuvanted vaccine (n = 1,920)
Age (y) median	22.8	20.8
Height (cm)	175.93	174.57
Weight (kg)	68.85	68.5
Body mass index	22.24	22.48
Smoker	537 (56.9)	477 (26.9)
Asthma	10 (1.1)	3 (0.2)
Hypertension	11 (1.2)	0
Atopic dermatitis	50 (5.3)	3 (0.2)

Data are presented as no. (%), unless otherwise stated.

Table 2. Difference in adverse events within 7 days after injection with H1N1 influenza vaccine among hospitals with different number of beds

Adverse event	No. of hospital beds[1)]			P[2)]
	<350 (unit = 12)	350–799 (unit = 5)	≧800 (unit = 1)	
Local reaction				
No	2,105 (94.5)	347 (95.3)	265 (97.8)	0.064
Yes	122 (5.5)	17 (4.7)	6 (2.2)	
Systemic reaction				
No	1,957 (88.0)	331 (90.9)	244 (90.0)	0.182
Yes	268 (12.0)	33 (9.1)	27 (10.0)	

Data are presented as no. (%), unless otherwise stated.
1): Military medical delivery system were consisted of the 1st medical institute (<350 beds; 11 units and 1 army division), 2nd military hospital (350–799 beds; 5 units), and 3rd military hospital (≧800 beds; 1 unit) by number of hospital beds.
2): P values were calculated using the χ^2 test.

Incidence and crude odds ratios of adverse events: Local and systemic events after vaccination are summarized in Table 3. Injection site swelling was the most common local adverse event. Generally, injection site local events occurred more frequently in the MF59-adjuvanted vaccine group (crude odds ratio [cOR], 1.56; 95% CI, 1.11–2.29). Among the local adverse events, injection site swelling (cOR, 48.11; 95% CI, 11.65–198.76) and erythema (cOR, 7.54; 95% CI, 2.10–27.10) were significantly more frequent in the MF59-adjuvanted vaccine group than in the MF59 non-adjuvanted group.

Generally, systemic events occurred more frequently in the adjuvanted vaccine group than in the non-adjuvanted vaccine group (cOR, 1.64; 95% CI, 1.29–2.07). The most commonly reported systemic event was general myalgia, which was more frequent in the MF59-adjuvanted vaccine group (cOR, 3.22; 95% CI, 2.35–4.42). Participants in the non-adjuvanted vaccine group more frequently reported fever above 38°C (cOR, 0.50; 95% CI, 0.29–0.86). These local and systemic events were mild and spontaneously disappeared within a few days. There were no severe adverse reactions, such as anaphylaxis or acute febrile illness, requiring hospitalization.

Risk factors for local and systemic adverse events: Risk factors and adjusted odds ratios (aOR) for adverse events are summarized in Table 4. Atopic dermatitis was associated with a high risk of local adverse events (aOR, 2.63; 95% CI, 1.14–6.09) without adjustment for institutional characteristics; however, atopic dermatitis was not significant in model 2, which included all risk factors (BMI, smoking, hypertension, atopic dermatitis, asthma, number of hospital beds, and adjuvant).

For systemic adverse events, smoking was associated with a high risk of systemic adverse events in model 1 (aOR, 1.35; 95% CI, 1.07–1.71), but it was not significant in model 2. Hypertension was associated with a high risk of systemic adverse events in model 1 (aOR, 4.05; 95% CI, 1.17–14.02), but it was not significant in

Table 3. Crude odds ratios of adverse events within 7 days after injection of either MF59-adjuvanted or non-adjuvanted vaccine

Adverse event[1)]	MF59-adjuvanted vaccine (n = 944)	Non-adjuvanted vaccine (n = 1,920)	cOR[2)] (95% CI)
Local event			
Any	62 (6.6)	83 (4.3)	1.56 (1.11–2.29)
Pain	21 (2.2)	80 (4.2)	0.52 (0.32–0.85)
Erythema	11 (1.2)	3 (0.2)	7.54 (2.10–27.10)
Swelling	45 (4.8)	2 (0.1)	48.11 (11.65–198.76)
Systemic event			
Any	141 (14.9)	187 (9.7)	1.64 (1.29–2.07)
Fever	17 (1.8)	68 (3.5)	0.50 (0.29–0.86)
Headache	41 (4.3)	98 (5.1)	0.85 (0.58–1.23)
Shivering	24 (2.5)	39 (2.0)	1.26 (0.75–2.11)
Myalgia	101 (10.7)	69 (3.6)	3.22 (2.35–4.42)
Nausea	6 (0.6)	4 (0.2)	3.07 (0.86–10.90)

Data are presented as no. (%), unless otherwise stated.
1): Participants used a subject scale to adverse events. Adverse events were considered if they interfered normal military activities.
2): MF59-adjuvanted vaccine adverse events for non-adjuvanted vaccine adverse events.
cOR, crude odds ratio; CI, confidence interval.

Table 4. Multiple logistic regression showing odds ratios (95% confidence interval) of local and systemic adverse events after H1N1 influenza vaccination

	Local adverse events		Systemic adverse events	
	Model 1[1)]	Model 2[1)]	Model 1[2)]	Model 2[2)]
Individual characteristics				
Body mass index				
<25	1	1	1	1
25–29	1.10 (0.64–1.88)	1.13 (0.66–1.94)	0.97 (0.66–1.43)	1.01 (0.68–1.48)
≧30	2.48 (0.56–11.00)	2.75 (0.61–12.33)	2.20 (0.71–6.85)	2.47 (0.79–7.72)
Smoking				
No	1	1	1	1
Yes	1.35 (0.96–1.89)	1.27 (0.89–1.81)	1.35 (1.07–1.71)	1.24 (0.97–1.59)
Hypertension				
No	1	1	1	1
Yes	1.54 (0.19–12.47)	1.35 (0.17–10.98)	4.05 (1.17–14.02)	3.40 (0.98–11.83)
Atopic dermatitis				
No	1	1	1	1
Yes	2.63 (1.14–6.09)	2.32 (0.99–5.46)	1.48 (0.72–3.06)	1.28 (0.62–2.66)
Asthma				
No	1	1	1	1
Yes	0.82 (0.10–6.83)	0.78 (0.09–6.47)	1.67 (0.44–6.41)	1.60 (0.42–6.11)
Institutional characteristics				
No. of hospital beds				
<350 (11 units + 1 army)		1		1
350–799 (5 units)		0.99 (0.57–1.73)		0.90 (0.60–1.35)
≧800 (1 unit)		0.51 (0.22–1.20)		0.73 (0.73–1.77)
Adjuvant				
No (17 units)		1		1
Yes (1 army)		1.20 (0.81–1.78)		1.35 (1.03–1.78)
Hosmer-Lemeshow test, χ^2 (P value)	0.77 (0.86)	2.99 (0.81)	0.50 (0.78)	1.12 (0.98)

[1)]: Model 1: Odds ratio (95% CI) estimated by logistic regression controlling for individual characteristics (body mass index, smoking, hypertension, atopic dermatitis, asthma).
[2)]: Model 2: Odds ratio (95% CI) estimated by logistic regression controlling for Model 1 + institutional characteristics (number of hospital beds, adjuvant).

model 2. Adjuvant use was associated with a high risk of systemic adverse events in model 2 (aOR, 1.35; 95% CI, 1.03–1.78) by forward selection and backward selection of all risk factors.

DISCUSSION

Clinical data from studies of both the adjuvanted and non-adjuvanted forms of the 2009 H1N1 influenza vaccine are slowly becoming available (12–15). In this prospective study, we evaluated the adverse events associated with both non-adjuvanted and MF59-adjuvanted H1N1 vaccines produced by a Korean manufacturer in healthy young male soldiers. Similar to the results of previous studies, no severe adverse events were observed (12–15).

Administration of the MF59-adjuvanted vaccine was associated with an increased incidence of local and systemic events after vaccination; however, these were generally mild and transient. A greater frequency of local and systemic events is expected with the use of an adjuvant, and these results are consistent with previous studies of other MF59-adjuvanted vaccines (16–20). In our study, MF59-adjuvanted vaccination was associated with a significantly increased risk of adverse systemic events. Adjuvanted vaccine use had a higher risk of systemic events (aOR, 1.35; 95% CI, 1.03–1.78) than non-adjuvanted vaccine use. According to the aOR obtained by stratified logistic regression analysis, atopic dermatitis was a confounder. However, since the CI range of OR narrowly includes 1.00 (aOR, 2.32; 95% CI, 0.99–5.46), if we enlarge the sample size for atopic dermatitis, it may be a risk factor for local adverse events. A recent study showed that virus-specific IgE, which cross-links the high affinity IgE receptor on lung dendritic cells, triggered the development and exacerbation of asthma (21). In addition, the postvaccination-specific IgE responses to tetanus and diphtheria toxoids have been previously reported, and another study reported that high rates of local side effects were found (22,23). We presume that a similar mechanism could occur in the cutaneous dendritic cells of patients with atopic dermatitis in our study.

Hypertension and smoking were confounders of systemic adverse events. We also used stratified logistic regression analysis to analyze the data. Although the underlying reason for a potential relationship between adjuvant and systemic events remains to be elucidated, the MF59 adjuvant may have an effect on immunity and inflammation (24,25).

Our study had some limitations. First, the subject population was comprised of only healthy young male

adults; therefore, the generalizability of our results is unclear. Second, although both groups were fairly well matched in terms of patient characteristics, the proportions of soldiers who smoked, had asthma, had hypertension, and had atopic dermatitis was higher in the MF59-adjuvanted vaccine group. Since our study was not a phase III clinical trial using random allocation, such differences in risk factor allocation were expected. Finally, our adverse event results seemed to be lower than in previous reports (11,12). The reason for this difference is that the male soldiers aged 20–25 years were specifically selected as subjects. This group had a lower risk of adverse events associated with H1N1 vaccination (26). Also, this group of soldiers has above average mental toughness and pain threshold (27,28). In addition, only events that interfered with normal military activities were recorded as adverse events. However, we hoped to find a strong association with the adverse events of H1N1 vaccination, because the bias is toward the null (29).

In conclusion, our results indicate that adjuvant was a risk factor for systemic events, which were generally mild and transient in healthy young male adults. However, atopic dermatitis might be the choice risk factor for local adverse events. Large, prospective, multicenter studies are needed to confirm our findings of adjuvanted and non-adjuvanted forms of the influenza H1N1 vaccine.

Acknowledgments We are grateful to Ho Kim, Ph.D, School of Public Health, Seoul National University, Chang-Hoon, Kim, Office of Public Healthcare Services, and Myung Ki, Department of Preventive Medicine, School of Medicine, Eulji University, for their help with the statistical analyses.

Conflict of interest None to declare.

REFERENCES

1. Centers for Disease Control and Prevention (2009): Swine influenza A (H1N1) infections—California and Texas, April 2009. Morbid. Mortal. Wkly. Rep., 58, 435–437.
2. Centers for Disease Control and Prevention (2009): Swine influenza A (H1N1) infection in two children—Southern California, March–April 2009. Morbid. Mortal. Wkly. Rep., 58, 400–402.
3. World Health Organization (2009): New influenza A (H1N1) virus: global epidemiological situation, June 2009. Wkly. Epidemiol. Rec., 84, 249–257.
4. Dawood, F.S., Jain, S., Finelli, L., et al. (2009): Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N. Engl. J. Med., 360, 2605–2615.
5. Perez, P.R., Rosa, D.Z., de Leon, S.P., et al. (2009): Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. N. Engl. J. Med., 361, 680–689.
6. Kelly, H.A., Grant, K.A., Williams, S., et al. (2009): Epidemiological characteristics of pandemic influenza H1N1 2009 and seasonal influenza infection. Med. J. Australia, 191, 146–149.
7. Hancock, K., Veguilla, V., Lu, X., et al. (2009): Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. N. Engl. J. Med., 361, 1945–1952.
8. Atmar, R.L., Keitel, W.A., Patel, S.M., et al. (2006): Safety and immunogenicity of nonadjuvanted and MF59-adjuvanted influenza A/H9N2 vaccine preparations. Clin. Infect. Dis., 43, 1135–1142.
9. Galli, G., Hancock, K., Hoschler, K., et al. (2009): Fast rise of broadly cross-reactive antibodies after boosting long-lived human memory B cells primed by an MF59 adjuvanted prepandemic vaccine. Proc. Natl. Acad. Sci. USA, 106, 7962–7967.
10. World Health Organization (2009): Global Alert and Response: WHO Recommendations on Pandemic (H1N1) 2009 Vaccines. Geneva.
11. Cheong, H.J., Song, J.Y., Heo, J.Y., et al. (2011): Immunogenicity and safety of the influenza A/H1N1 2009 inactivated split-virus vaccine in young and older adults: MF59-adjuvanted vaccine versus nonadjuvanted vaccine. Clin. Vaccine Immunol., 18, 1358–1364.
12. Clark, T.W., Pareek, M., Hoschler, K., et al. (2009): Trial of 2009 influenza A (H1N1) monovalent MF59-adjuvanted vaccine. N. Engl. J. Med., 361, 2424–2435.
13. Greenberg, M.E., Lai, M.H., Hartel, G.F., et al. (2009): Response to a monovalent 2009 influenza A (H1N1) vaccine. N. Engl. J. Med., 361, 2405–2413.
14. Zhu, F., Wang, H., Fang, H., et al. (2009): A novel influenza A (H1N1) vaccine in various age groups. N. Engl. J. Med., 361, 2414–2423.
15. Liang, X., Wang, H., Wang, J., et al. (2009): Safety and immunogenicity of 2009 pandemic influenza A H1N1 vaccines in China: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet, 375, 56–66.
16. Treanor, J., Campbell, J.D., Zangwill, K.M., et al. (2006): Safety and immunogenicity of an inactivated subvirion influenza A (H5N1) vaccine. N. Engl. J. Med., 354, 1343–1351.
17. Podda, A. (2001): The adjuvanted influenza vaccines with novel adjuvants: experience with the MF59-adjuvanted vaccine. Vaccine, 19, 2673–2680.
18. Gasparini, R., Pozzi, T., Montomoli, E., et al. (2001): Increased immunogenicity of the MF59-adjuvanted influenza vaccine compared to a conventional subunit vaccine in elderly subjects. Eur. J. Epidemiol., 17, 135–140.
19. Donato, D.S., Granoff, D., Minutello, M., et al. (1999): Safety and immunogenicity of MF59-adjuvanted influenza vaccine in the elderly. Vaccine, 17, 3094–3101.
20. Minutello, M., Senatore, F., Cecchinelli, G., et al. (1999): Safety and immunogenicity of an inactivated subunit influenza virus vaccine combined with MF59 adjuvant emulsion in elderly subjects, immunized for three consecutive influenza seasons. Vaccine, 17, 99–104.
21. Kumar, A. and Grayson, M.H. (2009): The role of viruses in the development and exacerbation of atopic disease. Ann. Allergy Asthma Immunol., 103, 181–186.
22. Nagel, J.E., White, C. and Lin, M.S. (1979): IgE synthesis in man, II: comparison of tetanus and diphtheria IgE antibody in allergic and nonallergic children. J. Allergy Clin. Immunol., 63, 308–314.
23. Mark, A., Bjorksten, B. and Granstrom, M. (1995): Immunoglobulin IgE response to diphtheria and tetanus toxoid after booster with aluminium-adsorbed and fluid DT-vaccine. Vaccine, 13, 669–673.
24. Schultze, V., D'Agosto, V., Wack, A., et al. (2008): Safety of MF59 adjuvant. Vaccine, 26, 3209–3222.
25. O'Hagan, D.T. (2007): MF59 is a safe and potent vaccine adjuvant that enhances protection against influenza virus infection. Expert. Rev. Vaccines, 6, 699–710.
26. Hwang, S.M., Choe, K.W., Cho, S.H., et al. (2011): The adverse events of influenza A (H1N1) vaccination and its risk factors in healthcare personnel in 18 military healthcare units in Korea. Jpn. J. Infect. Dis., 64, 183–189.
27. Walker, T.B., Lennemann, L.M., McGregor, J.N., et al. (2011): Physiological and psychological characteristics of successful combat controller trainees. J. Spec. Oper. Med., 11, 39–47.
28. Dar, R., Ariely, D. and Frenk, H., (1995): The effect of past-injury on pain threshold and tolerance. Pain, 60, 189–193.
29. Kleinbaum, D.G., Kupper, L.L. and Morgenstern, H. (1982): Epidemiologic Research: Principles and Quantitative Methods. John Wiley and Sons, New York.