Comparison of the Immunogenicity and Safety of the Conventional Subunit, MF59-Adjuvanted, and Intradermal Influenza Vaccines in the Elderly

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The influenza vaccination is known as the most effective method for preventing influenza infection and its complications in the elderly. Conventional subunit (Agrippal S1; Novartis), MF59-adjuvanted (Fluad; Novartis), and intradermal (IDflu15; Sanofi Pasteur) influenza vaccines are widely used throughout South Korea. However, few comparative studies evaluating the safety and immunogenicity of these vaccines are available. Prior to the beginning of the 2011-2012 influenza season, 335 healthy elderly volunteers randomly received one of three seasonal trivalent influenza vaccines, the conventional subunit, MF59-adjuvanted, or intradermal influenza vaccine. Serum hemagglutination-inhibiting antibody levels were measured at the time of vaccination and at 1 and 6 months after vaccination. Adverse events were recorded prospectively. A total of 113 conventional subunit, 111 MF59-adjuvanted, and 111 intradermal influenza vaccine volunteers were followed up during a 6-month postvaccination period. One month after vaccination, all three vaccines satisfied Committee for Medical Products for Human Use (CHMP) immunogenicity criteria for the A/H1N1 and A/H3N2 strains but not for the B strain. Compared with the subunit vaccine, the intradermal vaccine exhibited noninferiority, while the MF59-adjuvanted vaccine exhibited superiority. Furthermore, the MF59-adjuvanted vaccine was more immunogenic against the A/H3N2 strain than was the subunit vaccine up to 6 months postvaccination. The most common local and systemic reactions to the conventional subunit, MF59-adjuvanted, and intradermal influenza vaccines were pain at the injection site (7.1%, 10.8%, and 6.3%, respectively) and generalized myalgia (0.9%, 8.1%, and 5.4%, respectively). Local and systemic reactions were similar among the three vaccine groups. MF59-adjuvanted vaccine exhibited superior immunogenicity compared with a conventional subunit vaccine and had a comparable safety profile. For older adults, the MF59-adjuvanted vaccine is preferable for providing superior immunogenicity.

Seasonal influenza epidemics coincide with a significant increase in morbidity and mortality resulting from both influenza illness and associated complications (1, 2). Rates of hospitalized influenza cases increase substantially with age and increase dramatically in adults >65 years of age (3). The influenza vaccination is known as the most effective method for preventing influenza illness and its complications; however, many studies have reported that the effectiveness of the influenza vaccine is lower in elderly individuals than in young adults (4, 5).

Compared with younger individuals, antibody responses in the elderly are generally lower, and thus some elderly people may remain susceptible to infection despite having had influenza vaccination (6, 7). This observation has been explained by the gradual deterioration of the immune system with age, termed immunosenescence (8, 9). Thus, influenza vaccines that are able to overcome immunosenescence are necessary, especially for older individuals. To this end, several strategies have been proposed, including the use of adjuvants, higher doses of vaccine, and intradermal delivery (9, 10). In South Korea, MF59-adjuvanted and intradermal influenza vaccines were introduced beginning in 2009 and 2010, respectively. Although these vaccines are available for the elderly, only one head-to-head comparison study of their relative immunogenicity and safety profiles compared with those of the existing conventional trivalent vaccine has been published (11).

In order to compare the relative immunogenicity and safety profiles of the conventional subunit, MF59-adjuvanted, and intradermal vaccines, we performed a randomized noninferiority study in elderly individuals aged ≥65 years.

MATERIALS AND METHODS

Study population. This multicenter randomized controlled parallel-group study was conducted during the 2011-2012 influenza vaccination period. Individuals aged ≥65 years who were not vaccinated with influenza vaccine during the 2011-2012 season and had not been previously diagnosed with influenza infection were recruited at two centers during the first week of October 2011. All the subjects were in good health without comorbidity and were living independently in the community. Exclusion criteria were contraindications for the influenza vaccine (including egg allergy), febrile illness (a temperature of ≥37.5°C) on the day of vaccination, influenza vaccination within the previous 6 months, any other vaccinations within the previous 30 days, high-dose systemic steroid ther-
apy (i.e., ≥0.5 mg/kg of body weight prednisone daily) in the previous 30
days, treatment with immunoglobulins during the previous 3 months,
development of influenza-like illness during the vaccination study period,
and any conditions that might interfere with the study results. All subjects
provided written informed consent before enrollment.

**Vaccines.** Subjects were randomized to receive one of three vaccines,
the trivalent subunit inactivated influenza vaccine Agrippal S1 (Novartis
Vaccines and Diagnostics S. R. L., Italy), the MF59-adjuvanted subunit
vaccine Flued (Novartis Vaccines and Diagnostics S. R. L.), or the
intradermal split vaccine IDflu15 (Sanofi Pasteur SA, France). All
three vaccines were formulated according to WHO recommendations
for the 2011-2012 season (Northern Hemisphere) and contained 15 μg
hemagglutinin (HA) for each of three influenza strains, A/California/
7/2009 (H1N1)-like virus, A/Perth/16/2009 (H3N2)-like virus, and
B/Brize/60/2008-like virus.

**Immunogenicity assessment.** Blood samples were collected immedi-
ately from each subject prior to the time of vaccination and then again at
1 month (28 ± 7 days) and 6 months (180 ± 7 days) after vaccination.
Hemagglutination-inhibiting (HI) antibodies against vaccine antigen
components were measured by microrotary assay (12). Sera were pre-treated
with receptor-deactivating enzyme (RDE) (1:5) (Sigma, St. Louis, MO,
USA) for 18 h at 37°C and then inactivated at 56°C for 30 min. Serum
dilutions ranging from 1:5 to 1:20,240 were then prepared in triplicate.
Serum HI antibody levels were determined using test antigens at a
concentration of 4 hemagglutinating units per 25 μl of virus per assay
in a 0.5% suspension of washed chicken erythrocytes. Microtiter plates
were maintained at room temperature until sedimentation was visible.
The serum dilution at which complete inhibition of hemagglutination
was achieved was considered the serum antibody titer. Titers of <1:10
were considered negative and arbitrarily assigned a dilution value of
1:5. The sialidase treatment procedure for serum did not include so-
dium citrate.

The geometric mean HI antibody titer (GMT), seroprotection rate
(defined as the proportion of participants with a titer level of ≥1:40
post-vaccination), seroconversion rate (defined as the proportion of partici-
pants with a ≥4-fold increase in titer from baseline or a postvaccination
titer level of ≥1:40 if the baseline titer was <1:40), and GMT fold increase
(GMT ratio of postvaccination titer to prevaccination titer) were calcu-
lated. Immunogenicity was evaluated based on the criteria of the Com-
mittee for Medical Products for Human Use (CHMP) (seroprotection
rate of ≥60%, seroconversion rate of ≥30%, and a GMT fold increase of
≥2).

**Safety assessments.** At the time of vaccination, each patient received
a thermometer, a ruler, and a clinical diary and was asked to monitor any
solicited local or systemic reactions to the vaccine for 7 days. Patients
were also asked to record their body temperature, any pain or tenderness
and redness diameter at the injection site, the severity of systemic
symptoms, such as headache, malaise, chills, muscle aches, arthralgia, and any other
adverse events. The participants reported adverse events according to the
Food and Drug Administration (FDA) toxicity grading scale for healthy
adult and adolescent volunteers enrolled in preventive vaccine clinical
trials (13).

**Statistical analysis.** The sample size guaranteed a statistical power
of 0.8 and a significance level of 0.05 and allowed for a dropout rate of
approximately 10% for the per-protocol sample. The planned number
of subjects was 118 per vaccination group. For immunogenicity analyses,
the GMT and 95% confidence intervals (CIs) were log-transformed and com-
pared by one-way analysis of variance (ANOVA) with Bonferroni tests for
multiple pairwise comparison. The seroconversion rate and the seropro-
tection rate were compared between each group with a chi-square test. An
analysis of covariance (ANCOVA) model with group and prevaccination
titers was used to compare postvaccination results adjusted according to
prevaccination levels. The study design called for testing for noninferior-
ity, which was established if the lower bound of the two-sided 95%
CI on the postvaccination ratios of GMTs (GMT_{conventional vaccine}/
GMT_{MF59-adjuvanted vaccine}) was above the noninferiority margin of 0.667 for all three strains. If noninferi-
ority was observed, superiority was established if the lower limit of the
95% CI of the difference was >1 for at least two of the three strains
(14–16). For solicited local or systemic reaction analyses, the percentages
of participants were based on the frequency and severity of the reported
responses after vaccination. A chi-square test was used to compare pro-
portions between the vaccine groups. All reported P values were two sided,
and values of ≤0.05 were considered statistically significant.

Data analyses were performed using SPSS 12.0 and GraphPad Prism 6
software. The study was approved by the ethics committee of each insti-
tution involved and was conducted in accordance with the Declaration
of Helsinki and good clinical practice.

**RESULTS**

**Study subjects.** A total of 354 participants were enrolled in our
study (conventional vaccine, n = 118; adjuvant vaccine, n = 118;
and intradermal vaccine, n = 118). Of the 354 subjects, 19 with-
drew consent during the study period for no apparent reason, so
final data were available for 335 participants (conventional vac-
cine, n = 113; adjuvant vaccine, n = 111; and intradermal vaccine,
n = 111). Table 1 shows the demographic characteristics of the
participants. The three vaccine groups were similar to each other
with respect to gender and age. There were more female (65.4%) than
male subjects in all three vaccine groups; however, the pro-
portions of female subjects were similar among the three groups.
The median age of the subjects was 71 years, and 31% of the
subjects were >75 years of age. Age distributions were similar
among the three groups.

**Immunogenicity.** Immunogenicity data for all three virus
strains are summarized in Table 2. Pre vaccination GMTs were
similar for each virus strain among the three groups (A/H1N1,
P = 0.640; A/H3N2, P = 0.053; B, P = 0.082). One month after
vaccination, the GMTs were increased in all vaccine groups for the
A/H1N1 and A/H3N2 strains but not for the B strain (Fig. 1). The
GMTs for strain A/H3N2 in the adjuvant vaccine group were
higher than those in the conventional vaccine group, although
there were no statistically significant differences between the ad-
juvant and intradermal vaccine groups (conventional versus
MF59-adjuvanted vaccine, P < 0.001; conventional versus intra-
dermal vaccine, P = 0.070; and MF59-adjuvanted versus intra-
dermal vaccine, P = 0.052). All three vaccines satisfied the CHMP
immunogenicity criteria for the A/H1N1 and A/H3N2 strains but
not for the B strain (Fig. 2). Compared with the conventional
vaccine, the intradermal vaccine exhibited noninferiority, while the
MF59-adjuvanted vaccine exhibited superiority (Fig. 3).

At 6 months postvaccination, the GMTs for the A/H1N1 and B
strains had decreased to almost prevaccination levels, while the

**TABLE 1 Demographic characteristics of study subjects**

| Characteristic          | Conventional vaccine (n = 113) | Adjuvant vaccine (n = 111) | Intradermal vaccine (n = 111) | P value |
|-------------------------|-------------------------------|---------------------------|-------------------------------|---------|
| Male (n [%])            | 44 (38.9)                     | 36 (32.4)                 | 36 (32.4)                     | 0.926   |
| Age (median [range])    | 73 (65–88)                    | 71 (65–88)                | 72 (65–86)                    | 0.775   |
| ≥65–74 yr (n [%])       | 73 (64.6)                     | 81 (73.0)                 | 76 (68.5)                     | 0.481   |
| ≥75 yr (n [%])          | 40 (35.4)                     | 30 (27.0)                 | 35 (31.5)                     | 0.401   |

GMT_{conventional vaccine}/GMT_{intradermal vaccine}/GMT_{MF59-adjuvanted vaccine}
| Response measure | Strain A/H1N1 | Strain A/H3N2 | Strain B |
|------------------|--------------|--------------|---------|
| GMT (95% CI)     |              |              |         |
| Prevaccination   | 21.4 (17.2–27.0) | 21.3 (16.6–27.8) | 18.4 (14.5–23.8) |
| 1 month          | 68.1 (55.7–80.8)  | 92.7 (75.9–113.2) | 74.5 (61.0–90.8)  |
| 6 months         | 25.4 (22.2–29.0)  | 32.5 (28.4–37.1)  | 29.2 (25.6–33.3)  |
| Seroprotection rate (%) [95% CI] |              |              |         |
| 1 month          | 72.1 (63.1–80.2)  | 84.7 (78.4–91.0)  | 78.8 (71.7–86.7)  |
| 6 months         | 37.8 (28.8–46.8)  | 51.4 (42.3–61.3)  | 53.1 (44.2–61.9)  |
| Seroconversion rate (%) [95% CI] |              |              |         |
| 1 month          | 38.7 (29.7–48.6)  | 54.1 (45.0–63.1)  | 42.5 (34.5–52.2)  |
| 6 months         | 5.4 (1.8–9.9)  | 10.8 (5.4–17.1)  | 8.8 (3.5–15.0)  |
| GMT fold (95% CI) |              |              |         |
| 1 month          | 3.5 (2.2–5.7)  | 4.4 (2.7–6.3)  | 3.6 (2.3–5.6)  |
| 6 months         | 1.3 (0.8–2.1)  | 1.6 (1.0–2.6)  | 1.4 (0.9–2.2)  |
GMTs for A/H3N2 remained high in all vaccine groups (Fig. 1). In addition, the immunogenicity of MF59-adjuvanted vaccines satisfied the CHMP criteria for the A/H3N2 strain (Fig. 2). Noninferiority and superiority tests indicated that the intradermal and MF59-adjuvanted vaccines did not provide better immunogenicity than the conventional vaccine (Fig. 3).

Safety. The overall incidences of local and systemic reactions are shown in Table 3. The most frequent local reaction was pain at the injection site, which was reported by 10.8% of the participants in the MF59-adjuvanted vaccine group and by 7.1% and 6.3% in the conventional and intradermal vaccine groups, respectively. For most pain reactions, the severity was reported as mild. Other common local reactions were tenderness, redness, and swelling, all of which occurred more frequently in the intradermal vaccine group. However, the incidences of each local reaction were similar among the three vaccine groups and were without statistical significance. The most common systemic reaction was muscle ache in 0.9%, 8.1%, and 5.4% of the subjects receiving the conventional, MF59-adjuvanted, and intradermal vaccines, respectively. Reactions reported in all three vaccine groups were generally of mild-to-moderate intensity. There was a tendency toward a higher incidence of systemic reactions in participants who received the MF59-adjuvanted and intradermal vaccines; however, the differences for reactions among the three groups were statistically indistinguishable. No unsolicited signs or symptoms were reported in any of the treatment groups.

DISCUSSION

Despite the proven effectiveness of the influenza vaccine for influenza prevention, its antibody response in the elderly is generally poor. It has already been demonstrated in clinical studies that adjuvanted, intradermal, and high-dose vaccines can induce higher immunogenicity than conventional plain vaccines in the elderly. However, high-dose vaccines are not currently available in South Korea. In this study, the immunogenicities of a conventional subunit vaccine, an MF59-adjuvanted vaccine, and an intradermal vaccine were compared.

Our results showed that each of the three vaccines satisfied the CHMP criteria for persons aged ≥65 years, and thus all three vaccines are advisable for use in the elderly. The immunogenicity for the B strain was poor and conventionally lower than that measured for the A/H1N1 and A/H3N2 strains for all three vaccines (17). Indeed, it is well known that the B strain produces a low reactivity in the HI test, especially when using egg-propagated vaccine virus (18). Therefore, the immunogenicity might need to be assessed by a neutralization assay in addition to the HI test.

Intradermal vaccines are expected to improve immunogenicity through the high number of resident macrophages and dendritic cells in the skin (19). In a recent systematic review, four out of six studies indicated comparable efficacy for intradermal vaccines over the conventional subunit vaccine, while two trials showed superiority for the intradermal vaccines in healthy elderly subjects (20–22). In the present study, noninferiority of the intradermal vaccine was established in comparison to the conventional subunit vaccine. These contrasting results may be due to differences in the proportion of previous influenza vaccinations, as well as exposure to circulating influenza virus during the study period. One of the proposed mechanisms of action of the MF59-adjuvanted influenza vaccine is production of a local immunostimulatory environment at the injection site by promotion of immune mediators in muscle fibers. Indeed, the MF59-adjuvanted influenza vaccine has been shown to enhance the immune response and offer increased clinical protection in the elderly over that offered by the conventional subunit vaccine (17, 23, 24). Consistent with these studies, we also observed superior immunogenicity conferred by the MF59-adjuvanted...
vaccine over that by the conventional subunit vaccine (24, 25). To the best of our knowledge, this is one of the very few studies comparing the immunogenicity of the intradermal vaccine with that of the MF59-adjuvanted vaccine (11, 14). Previous studies, performed with adults aged ≥65 years, concluded that the intradermal vaccine exhibits noninferiority over that exhibited by the MF59-adjuvanted vaccine. If one looks at the results statistically only, our study also shows the noninferior-

FIG 2 Comparison of seroprotection rate, seroconversion rate, and GMT fold according to influenza strain 1 and 6 months after vaccination. The seroprotection rate is the percentage of subjects with a postvaccination titer of ≥40. The seroconversion rate is a postvaccination titer of ≥40 in subjects with a prevaccination titer of <10 or a ≥4-fold increase in titer after vaccination in subjects with a prevaccination titer of ≥10. The GMT fold is the geometric mean of the ratio of the postvaccination titer to the prevaccination titer. The horizontal dashed line indicates the CHMP criteria.
ity between the intradermal and adjuvanted vaccines (data not shown). However, the intradermal vaccine showed somewhat lower immunogenicity than the adjuvanted vaccine. This trend was also found in previous studies. This might be due to a poor immune process in the dermal system in the elderly. Further studies are needed to compare the immunogenicity between intradermal and adjuvanted vaccines stratified by age group.

Contrary to previous studies, local and systemic reactions did not differ among the three vaccines in the present study. Compared with the conventional vaccine, reactions, particularly pain, erythema at the site of infection, swelling, and myalgia, were more frequent in the MF59-adjuvanted vaccine (17, 23, 25, 26). While similar findings have been observed with the intradermal vaccine (22), other studies have reported no differences in reactions between the different vaccine types (24, 27). Because pain is a very subjective symptom and objective measurements are not available, these differences may not be remarkable. On the contrary, there would be a significant difference if the groups were bigger. It is important to note that the results of our study indicated that the three vaccines were safe and generally well tolerated in elderly individuals.

This study had several limitations. First, a prevaccination history for the previous influenza season (2010-2011) was not available. Prevaccination GMTs were already high in some participants, and the prevaccination antibody titer can influence immunogenicity, leading to an underestimate. Although the use of mathematical methods to adjust for prevaccination antibody levels is not currently a standard for influenza vaccine analyses, we did so to interpret the results more precisely. To estimate the long-term immunogenicities of the vaccines, we assessed HI titers 6 months after vaccination. Interestingly, the GMTs for A/H3N2 remained higher than those before vaccination in all three vaccine groups. It cannot be excluded that the results may have been due to a boosting effect from the exposure to A/H3N2 virus circulating in the community during the study period. Finally, since the B component of the vaccine was poorly immunogenic in terms of HI titer, data from microneutralization assays might be needed to strengthen our conclusions.
In this comparative study, we observed that conventional subunit, MF59-adjuvanted, and intradermal vaccines met CHMP criteria for persons aged ≥65 years, and thus the three vaccines are advisable for use in the elderly. Intradermal vaccines exhibited immunogenicity and safety similar to those of the conventional subunit vaccine. The MF59-adjuvanted vaccine exhibited superior immunogenicity over that of the conventional subunit vaccine and comparable safety. Together, the

| TABLE 3 Solicited local and systemic adverse effects within 7 days after receipt of subunit, adjuvant, or intradermal influenza vaccine according to vaccine group |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Reaction type and severity       | Subunit vaccine (n = 113)        | Adjuvant vaccine (n = 111)       | Intradermal vaccine (n = 111)    | P value                         |
| Local                           |                                 |                                 |                                 |                                 |
| Pain                            | None                            | 105 (92.9)                      | 99 (89.2)                       | 104 (93.7)                      | 0.527                           |
|                                | Mild                             | 11 (9.9)                        | 9 (8.1)                         | 1 (0.9)                         |                                 |
|                                | Moderate                         | 7 (6.3)                         | 1 (0.9)                         | 0 (0)                           |                                 |
|                                | Severe                           | 0 (0)                           | 0 (0)                           | 0 (0)                           |                                 |
| Tenderness                      | None                            | 110 (97.3)                      | 100 (90.1)                      | 100 (90.1)                      | 0.119                           |
|                                | Mild                             | 3 (2.7)                         | 10 (9.0)                        | 11 (9.9)                        |                                 |
|                                | Moderate                         | 0 (0)                           | 1 (0.9)                         | 0 (0)                           |                                 |
|                                | Severe                           | 0 (0)                           | 0 (0)                           | 0 (0)                           |                                 |
| Redness diam (mm)               | 0                               | 109 (96.5)                      | 105 (94.6)                      | 100 (90.1)                      | 0.130                           |
|                                | 1–4                             | 1 (0.8)                         | 0 (0)                           | 0 (0)                           |                                 |
|                                | ≥5                               | 3 (2.7)                         | 6 (5.4)                         | 11 (9.9)                        |                                 |
| Swelling diam (mm)              | 0                               | 109 (96.5)                      | 108 (97.3)                      | 104 (93.7)                      | 0.373                           |
|                                | 1–4                             | 1 (0.8)                         | 0 (0)                           | 0 (0)                           |                                 |
|                                | ≥5                               | 3 (2.7)                         | 3 (2.7)                         | 7 (6.3)                         |                                 |
| Systemic                       | Fever, temp ≥ 38°C               | 0 (0)                           | 0 (0)                           | 1 (0.9)                         | 0.363                           |
|                                | Headache                         |                                 |                                 |                                 |                                 |
|                                | None                            | 112 (99.1)                      | 108 (97.3)                      | 106 (95.5)                      | 0.406                           |
|                                | Mild                             | 1 (0.9)                         | 2 (1.8)                         | 4 (3.6)                         |                                 |
|                                | Moderate                         | 0 (0)                           | 1 (0.9)                         | 0 (0)                           |                                 |
|                                | Severe                           | 0 (0)                           | 0 (0)                           | 1 (0.9)                         |                                 |
|                                | Malaise                          |                                 |                                 |                                 | 0.121                           |
|                                | None                            | 113 (100)                       | 105 (94.6)                      | 106 (95.5)                      |                                 |
|                                | Mild                             | 0 (0)                           | 5 (4.5)                         | 4 (4.5)                         |                                 |
|                                | Moderate                         | 0 (0)                           | 1 (0.9)                         | 0 (0)                           |                                 |
|                                | Severe                           | 0 (0)                           | 0 (0)                           | 0 (0)                           |                                 |
|                                | Chills                           |                                 |                                 |                                 | 0.241                           |
|                                | None                            | 111 (98.2)                      | 108 (97.3)                      | 111 (100)                       |                                 |
|                                | Mild                             | 2 (1.8)                         | 3 (2.7)                         | 0 (0)                           |                                 |
|                                | Moderate                         | 0 (0)                           | 0 (0)                           | 0 (0)                           |                                 |
|                                | Severe                           | 0 (0)                           | 0 (0)                           | 0 (0)                           |                                 |
|                                | Fatigue                          |                                 |                                 |                                 | 0.169                           |
|                                | None                            | 112 (99.1)                      | 105 (94.6)                      | 105 (94.6)                      |                                 |
|                                | Mild                             | 1 (0.9)                         | 3 (2.7)                         | 5 (4.5)                         |                                 |
|                                | Moderate                         | 0 (0)                           | 3 (2.7)                         | 1 (0.9)                         |                                 |
|                                | Severe                           | 0 (0)                           | 0 (0)                           | 0 (0)                           |                                 |
|                                | Muscle aches                     |                                 |                                 |                                 | 0.176                           |
|                                | None                            | 112 (99.1)                      | 102 (91.9)                      | 105 (94.6)                      |                                 |
|                                | Mild                             | 1 (0.9)                         | 7 (6.3)                         | 4 (3.6)                         |                                 |
|                                | Moderate                         | 0 (0)                           | 1 (0.9)                         | 2 (1.8)                         |                                 |
|                                | Severe                           | 0 (0)                           | 1 (0.9)                         | 0 (0)                           |                                 |
|                                | Arthralgia                       |                                 |                                 |                                 | 0.148                           |
|                                | None                            | 112 (99.1)                      | 105 (94.6)                      | 108 (97.3)                      |                                 |
|                                | Mild                             | 1 (0.9)                         | 5 (4.5)                         | 1 (0.9)                         |                                 |
|                                | Moderate                         | 0 (0)                           | 1 (0.9)                         | 2 (1.8)                         |                                 |
|                                | Severe                           | 0 (0)                           | 0 (0)                           | 0 (0)                           |                                 |
results of our study suggest that for healthy older adults, the MF59-adjuvanted vaccine is preferable for providing superior immunogenicity.

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