NOTES

A Heterologous MF59-Adjuvanted H5N1 Preparandemic Influenza Booster Vaccine Induces a Robust, Cross-Reactive Immune Response in Adults and the Elderly

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Immunogenicity and safety of a booster dose of an MF59-adjuvanted H5N1 vaccine containing 7.5 µg A/turkey/Turkey/1/2005-like (clade 2.2) H5N1 hemagglutinin, given approximately 18 months after primary vaccination with a heterologous strain, were evaluated. The booster vaccine was well tolerated and induced a robust, cross-reactive immune response.

Immunization against pandemic virus strains, such as H5N1, is a keystone of pandemic preparedness plans (5, 7, 12). In addition, due to the need to rapidly produce many doses, vaccine hemagglutinin (HA) content may be a limiting factor, which may be countered by the inclusion of an adjuvant, such as MF59. Considering the unpredictable emergence and rapid spread of pandemic influenza together with the time needed to produce and distribute a pandemic influenza vaccine, proactive prepandemic vaccination presents a valuable opportunity to reduce the impact of pandemic influenza disease. In addition to having an excellent safety profile, a prepandemic vaccine should offer broad, robust immunity that can be easily boosted with a flexible dosing schedule (5).

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An H5N1 vaccine containing the MF59 adjuvant (Aflunov; Novartis Vaccines and Diagnostics) was developed and administered to healthy volunteers in a clinical trial setting. The present study was an extension of a trial (NCT00311480) in which 486 subjects over 18 years of age received two primary doses of the MF59-adjuvanted H5N1 vaccine, formulated with 7.5 µg or 15 µg HA per dose of the A/Vietnam/1194/2004 (clade 1), at an interval of 3 weeks; a subset of 223 subjects received a homologous booster dose at 6 months (2). Those who did not receive the booster dose at 6 months were eligible for inclusion in this extension study (NCT 00561184), which evaluated the safety and immunogenicity of one 0.5-ml dose of MF59-adjuvanted H5N1 vaccine, containing 7.5 µg of HA from the A/turkey/Turkey/1/2005-like strain (clade 2), approximately 18 months after primary vaccination. The inclusion and exclusion criteria and laboratory and safety surveillance methods used in this extension study were similar to those of the initial study (2). There was no statistical null hypothesis for the immunogenicity assessments, which were based on European Committee for Medicinal Products for Human Use (CHMP) criteria (4), and the calculations of all statistical parameters and confidence intervals are descriptive.

Following completion of the primary vaccination course in the initial study using the MF59-adjuvanted H5N1 vaccine formulated with A/Vietnam/1194/2004 (clade 1), all CHMP criteria were met (2). Following the primary course, hemagglutination inhibition (HI) antibody for the priming strain, A/Vietnam/1194/2004 (clade 1), declined to low levels by the time of the booster dose (Table 1). Antibody levels increased 1 week following the booster vaccination for both the booster (A/turkey/Turkey/1/2005-like [clade 2.2]) and heterologous priming (A/Vietnam/1194/2004 [clade 1]) strains and remained high 3 weeks postbooster (Table 1). The CHMP criterion for the seroprotection rate by HI was met 3 weeks following the booster vaccination for the A/turkey/Turkey/1/2005-like (clade 2.2) and A/Vietnam/1194/2004 (clade 1) strains in elderly subjects and for the A/Vietnam/1194/2004 (clade 1) strain in nonelderly subjects. The seroprotection rates 3 weeks after booster vaccination were comparable to those reached after completion of the primary vaccination course (2). The CHMP criterion for the seroconversion rate by HI was met for both strains 1 week after the booster dose in the nonelderly subjects.

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trials, with similar immune responses after primary vaccination and booster doses (6, 9). These results suggest that subjects were effectively primed, which facilitated a rapid immune response to the heterologous A/turkey/Turkey/1/2005-like (clade 2.2) strain after a single dose.

The incidence of solicited reactions reported within 7 days of booster administration was 72% (22/29) in nonelderly subjects and 39% (7/18) in elderly subjects. The most frequently reported local reactions for all subjects were pain and induration (Fig. 1). The most frequently reported solicited systemic reactions were myalgia and headache for nonelderly subjects and myalgia and fatigue for elderly subjects (Fig. 1). No subject reported fever. All reactions were transient (<2 days) and were considered mild to moderate in intensity. No unsolicited AEs and SAEs were considered to be vaccine related. The incidence of AEs compares favorably with the results from the initial study (2). Overall, the safety assessments confirmed that the A/turkey/Turkey/1/2005-like (clade 2.2) booster was well tolerated when administered after primary vaccination with A/Vietnam/1194/2004 (clade 1), supporting the safety profile of MF59-adjuvanted vaccines (8, 10).

Several studies have demonstrated that the inclusion of MF59 in a seasonal or pandemic influenza vaccine increases both the homologous and heterologous immune responses (1, 3, 9–11) even at low antigen doses. The findings from this extension study provide further support for both the immunopotentiating capabilities of MF59 and the potential for adoption of antigen-sparing strategies in a prepandemic context. This study further illustrates how prepandemic vaccination may prime a population, providing initial protection against an influenza pandemic that can be boosted with a different strain. This prime-boost strategy is likely to be the most effective way to protect populations against future influenza pandemics.

A. Banzhoff had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. R. Gasparini was the principal investigator. All authors participated in the analysis and interpretation of the data and/or were involved in drafting and revising the manuscript for important intellectual content.

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### TABLE 1. Hemagglutination inhibition response by MF59-adjuvanted H5N1 subunit influenza vaccine formulation and age cohort

<table>
<thead>
<tr>
<th>Time after Booster</th>
<th>Strain H5N1 A/turkey/Turkey (clade 2.2)</th>
<th>Strain H5N1 A/Vietnam (clade 1)</th>
<th>Strain H5N1 A/turkey/Turkey (clade 2.2)</th>
<th>Strain H5N1 A/Vietnam (clade 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GMT</td>
<td>Seroprotection rate, %</td>
<td>GMT</td>
<td>Seroprotection rate, %</td>
</tr>
<tr>
<td>Prebooster</td>
<td>5 (5–5)</td>
<td>0 (0–12)</td>
<td>14 (5.79–33)</td>
<td>20 (6.75–59)</td>
</tr>
<tr>
<td></td>
<td>(4.78–8.44)</td>
<td>(7–123)</td>
<td>(5.79–33)</td>
<td>(6.75–59)</td>
</tr>
<tr>
<td>1 week after booster</td>
<td>37 (19–70)</td>
<td>16 (8.17–32)</td>
<td>35 (13–95)</td>
<td>59 (20–173)</td>
</tr>
<tr>
<td></td>
<td>(16–32)</td>
<td>(49–85)</td>
<td>(28–77)</td>
<td>(38–86)</td>
</tr>
<tr>
<td>3 weeks after booster</td>
<td>72 (34–151)</td>
<td>156 (73–336)</td>
<td>102 (38–277)</td>
<td>181 (67–490)</td>
</tr>
<tr>
<td></td>
<td>(11–53)</td>
<td>(56–90)</td>
<td>(2.74–20)</td>
<td>(2.97–28)</td>
</tr>
</tbody>
</table>

*Primary vaccination with H5N1 A/Vietnam, 7.5 or 15 μg on study days 1 and 22; booster with H5N1 A/turkey/Turkey, 7.5 or 15 μg on study day 382. GMT, geometric mean titer; GMR, geometric mean ratio. Two-sided 95% confidence intervals are shown in parentheses. CHMP criteria: nonelderly, GMR > 2.5; seroprotection ≥ 70%; seroconversion ≥ 40%; elderly, GMR > 2.0; seroprotection ≥ 60%; seroconversion ≥ 30%.

a Nonelderly cohort (n = 29), 18 to 60 years of age; elderly cohort (n = 17), >60 years of age.
analysis; F. Laghi-Pasini has received a travel grant from Novartis Vaccines and Diagnostics.

REFERENCES


