Adverse Events after the Introduction of Quadrivalent Influenza Vaccine in Comparison with AH1pdm Vaccine (2009) in Japan

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(Received July 19, 2018; Accepted November 5, 2018)

Inactivated quadrivalent influenza vaccine (IIV4) has been used as seasonal influenza vaccine since 2016 in Japan. This study examined the safety of IIV4 in comparison with the AH1pdm monovalent vaccine used for novel influenza in 2009. Questionnaire surveillance associated with adverse events (AEs) was conducted at Chiba University Hospital, Japan. After being vaccinated, all health care workers (HCWs) were given a daily AEs check sheet on which they recorded solicited events, the same surveillance program used after AH1pdm vaccination in 2009. The frequency of injection site AEs with IIV4 was significantly higher than with the monovalent vaccine, but there was no significant difference with systemic AEs. Injection site and systemic AEs were reported as 83.7% and 25.5%, respectively, with IIV4. The grades of AE, mild, moderate and severe, were 67.2%, 16.4% and 0.1% with IIV4, respectively, indicating that almost all of the AEs reported with IIV4 were mild or moderate. Systemic AEs with IIV4 and monovalent vaccine were reported to be 25.5% and 23.1%, respectively, with the difference not being significant. The grade of AEs with IIV4, mild, moderate and severe, was 19.1%, 5.6% and 0.9%, respectively. The ratio of HCWs reporting AEs peaked at around 80% on day 1, then decreasing to less than 5% by day 7. AEs with IIV4 were reported more frequently compared with the AH1pdm monovalent vaccine. However, in consideration of the grade and duration of AEs, IIV4 was a well-tolerated, safe vaccine.

Key words—adverse event; quadrivalent influenza vaccine; AH1pdm vaccine

INTRODUCTION

Inactivated quadrivalent influenza vaccine (IIV4) was introduced as seasonal influenza vaccine in Japan in 2016. The former seasonal influenza vaccine was a trivalent, inactivated, split-virus, unadjuvanted one for subcutaneous injection, and both were manufactured by the same procedure. IIV4 contained two influenza strains (H3N1 and H1N1), and one strain from each influenza B lineage (Yamagata and Victoria).

Vaccination is effective for controlling seasonal influenza infections and is an important strategy for preventing possible pandemic events. Vaccines are administered to health care workers (HCWs), healthy people, and are also recommended for immunizing a considerable part of the population including elderly people and those with immunosuppressive conditions; as a result, adverse events (AEs) may affect a significant number of individuals. Compliance with high safety standard is required for influenza vaccine.

The efficacy of vaccine is affected by several factors—age, selected seed virus, prior season vaccination, individual immune response, and the degree of cross-protection of the vaccine B lineage against alternate lineage.1,2) Two distinct lineages of influenza B (Yamagata and Victoria lineages) have co-circulated worldwide since 1985; neither provided good cross-protection against the other.3) The inclusion of an influenza B strain from both Yamagata and Victoria lineages in IIV4 could improve protection against influenza B and could reduce the burden of seasonal influenza. WHO recommended B strains from both lineages for use in vaccines for the 2012–2013 season in the northern hemisphere.4) The dose of hemagglutinin contained in one injection for adults was increased from 45 μg to 60 μg, and this raised concern about an increase of AEs after the introduction of IIV4.

Chiba University Hospital (CUH) has 850 beds,
and infection control procedures during the influenza epidemic every winter are very important. For this reason we prepared the opportunity for all HCWs to be vaccinated for free. All HCWs were provided information regarding AEs before vaccination, and they were given instructions to report quickly in case they experienced AEs. Fortunately, there have been only a few severe AEs.

We conducted a questionnaire surveillance associated with AEs to determine the safety of IIV4.

**METHODS**

**Study Design**  AH1pdm vaccine was administered from October to December, 2009. IIV4 vaccine was administered from October to December, 2016. Subjects in vaccination were over 18 years old, all HCWs who worked at our hospital as hospital employee such as doctor, nurse, pharmacist, nutritionist, physical therapist, laboratory technician, clinical radiologist, clerk, researcher, etc. Vaccination was voluntary, exclusion criteria was who declined, who was judged unsuitable by doctor, who hoped to receive at other institutions. Questionnaire surveillance was conducted at a single site at CUH in Chiba, Japan. The purpose of this study was to evaluate AEs after IIV4 vaccination in HCWs.

After being vaccinated, all HCWs were given a diary-type daily AEs check sheet on which they recorded only solicited events including pain, tenderness, redness, induration echymosis, fever, malaise, headache, myalgia, chills, nausea, vomiting for 7 d following vaccination. In this questionnaire, we didn’t set the following items, age, sex, type of work, history of medical and allergy. The intensities of AEs were graded on a four-point scale (none, mild, moderate, severe). All other AEs were recorded as unsolicited ones. The AEs grading was a simple modification of a standard scale for grading AEs, as was used by Greenberg et al. and shown in their supplementary appendix (Table 1). The grade of AEs was subjectively based.

We conducted the same questionnaire surveillance after AH1pdm monovalent influenza vaccination in 2009. In the current study, AEs were comparable between IIV4 and AH1pdm monovalent vaccine.  

**Vaccine**  IIV4 for the 2015–2016 influenza season was manufactured by The Chemo-Sero-Therapeutic Research Institute (Kumamoto), and was given once by subcutaneous injection. The seed viruses were as follows: A/California/7/2009 (X-179A) (H1N1) pdm09, A/Switzerland/9715293/2013 (NIB-88) (H3N2), B/Phuket/3073/2013 (Yamagata lineage), B/Texas/2/2013 (Victoria lineage). IIV4 was manufactured by the same procedure as used for seasonal trivalent inactivated vaccine (IIV3). Thimerosal was added as a preservative. One dose contained 15 μg of hemagglutinin antigen for every strain per 0.5 mL.  

AH1pdm vaccine in 2009 (pandemic influenza vaccine) was manufactured by The Research Foundation.
for Microbial Diseases of Osaka University (Suita), The Chemo-Sero-Therapeutic Research Institute (Kumamoto), or Kitasato Institute Research Center for Biologicals (Kitamoto), and was vaccinated once by subcutaneous injection. The seed virus was A/California/07/09 (H1N1) virus. Thimerosal was added as a preservative except for the vaccine produced by the Chemo-Sero-Therapeutic Research Institute. One dose was 15 μg of hemagglutinin antigen per 0.5 mL. AH1pdm vaccine was also produced by the same procedure as used for IIIV3.

**Statistical Analysis** The data were entered into Excel 2016 (Microsoft, Redmond) and transferred to JMP® Pro 13.0.0 (SAS Institute Inc., Cary) for statistical analysis. Chi-square test or Fisher’s exact test was applied for comparison between two or more sample proportions, with a p-value below 0.05 considered statistically significant.

**Ethical Approval** This study was approved by the Research Ethics Committee of the Graduate School of Medicine and School of Medicine, Chiba University, and was conducted in accordance with the principles of the Declaration of Helsinki and Japanese regulatory requirements.

**RESULTS**

A total of 2167 HCWs received IIIV4 in 2016. A total 1567 HCWs subjects received AH1pdm monovalent vaccine in 2009. There was no significant difference in age distributions between the recipients of the two vaccines (Table 2). The recovery of questionnaires for IIIV4 and AH1pdm was 1459 and 1066, with recovery rates of 67.3% and 68.0%, respectively (Table 2). The difference between recovery rates was insignificant. All of the HCWs who experienced systemic adverse event was alive, but some of them visited to medical institution and was absent from work.

Injection site AEs with IIIV4 and monovalent vaccine were reported in 83.7% and 43.2%, respectively (Table 2). The frequency of AEs with IIIV4 was significantly higher than with monovalent vaccine. The grades of AE, mild, moderate and severe, were 67.2%, 16.4% and 0.1% with IIIV4, respectively, indicating that almost all of the AEs reported with IIIV4 were mild or moderate. There were only a few severe cases with both IIIV4 and monovalent vaccine.

The most frequently reported injection site AEs of IIIV4 were redness, tenderness and pain. These AEs were reported by more than 60% of HCWs, being significantly more frequent than with a monovalent influenza vaccine (Table 2).

**Systemic AEs** with IIIV4 and monovalent vaccine were reported to be 25.5% and 23.1%, respectively (Table 2), with the difference not being significant. The grade of AEs with IIIV4, mild, moderate and severe, was 19.1%, 5.6% and 0.9%, respectively.

The most common systemic AEs in IIIV4 were malaise followed by headache, myalgia, chills, fever and nausea and/or vomiting with both vaccines (Table 2). The frequency of headache was significantly lower and myalgia was significantly higher with IIIV4.

Unsolicited AEs were reported from 25 HCWs. The most frequent one was itching at the injection site.

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Table 2. Adverse Events within 7 d after Vaccination in HCWs

<table>
<thead>
<tr>
<th></th>
<th>IIIV4 seasonal vaccine N (%)</th>
<th>Monovalent vaccine AH1pdm (2009) N (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total vaccination</td>
<td>2167</td>
<td>1567</td>
<td></td>
</tr>
<tr>
<td>20–29 year-old</td>
<td>796</td>
<td>566</td>
<td></td>
</tr>
<tr>
<td>30–39 year-old</td>
<td>724</td>
<td>517</td>
<td></td>
</tr>
<tr>
<td>40–49 year-old</td>
<td>406</td>
<td>296</td>
<td></td>
</tr>
<tr>
<td>50–59 year-old</td>
<td>196</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td>60–69 year-old</td>
<td>45</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Diary recovery (%)</td>
<td>1459 (67.3)</td>
<td>1066 (68.0)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Injection site adverse events</td>
<td>1221 (83.7)</td>
<td>461 (43.2)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Mild</td>
<td>980 (67.2)</td>
<td>418 (39.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Moderate</td>
<td>240 (16.4)</td>
<td>41 (3.8)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Severe</td>
<td>1 (0.1)</td>
<td>2 (0.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Redness</td>
<td>980 (67.2)</td>
<td>254 (23.8)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Tenderness</td>
<td>970 (66.5)</td>
<td>329 (30.9)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Pain</td>
<td>890 (61.0)</td>
<td>289 (27.1)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Indurations</td>
<td>596 (40.8)</td>
<td>137 (12.9)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>81 (5.6)</td>
<td>31 (2.9)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Systemic adverse events</td>
<td>372 (25.5)</td>
<td>246 (26.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Mild</td>
<td>278 (19.1)</td>
<td>187 (17.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Moderate</td>
<td>81 (5.6)</td>
<td>47 (4.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Severe</td>
<td>13 (0.9)</td>
<td>12 (1.1)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Malaise</td>
<td>266 (18.2)</td>
<td>180 (16.9)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Headache</td>
<td>147 (10.1)</td>
<td>136 (12.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Myalgia</td>
<td>147 (10.1)</td>
<td>56 (5.3)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Chills</td>
<td>58 (4.0)</td>
<td>48 (4.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Fever</td>
<td>52 (3.5)</td>
<td>49 (4.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Nausea and/or Vomiting</td>
<td>45 (3.1)</td>
<td>26 (2.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

IIIV4: Quadrivalent inactivated influenza vaccine, AH1pdm: pandemic influenza AH1N1 virus, HCWs: health-care workers, n.s.: not significant. Death was not reported. The number of AH1pdm-vaccinated HCWs was 1567, and 1060 adverse-event check sheets after AH1pdm vaccination were collected (recovery rate: 67.5%).
Fig. 1. Number of HCWs Reporting Initial Adverse Events and the Day after IIV4 Vaccination

The initial adverse events were reported just on the day of vaccination by most HCWs. There were a few HCWs reporting initial adverse events on day 2 or later. HCWs: health care workers, IIV4: quadrivalent inactivated influenza vaccine.

Fig. 2. Ratio of HCWs Reporting Adverse Events and the Day after IIV4 Vaccination

Adverse events were reported by around 80% of HCWs after IIV4 vaccination. The ratio peaked on day 1, and gradually fell to less than 5% by day 7. HCWs: health care workers, IIV4: quadrivalent inactivated influenza vaccine.

in 20 HCWs. Other AEs were dizziness in two HCWs, and throat pain, thumb pain, and numbness were reported from one HCW each.

The timing of the appearance of initial AEs was also analyzed (Fig. 1). Most AEs appeared on the day of vaccination (day 0). The number of HCWs reporting initial AEs decreased after day 2. The daily change of the ratio of HCWs reporting AEs with IIV4 vaccination was analyzed (Fig. 2). The ratio of HCWs reporting AEs peaked at around 80% on day 1, then the ratio gradually decreased to less than 5% on day 7. AEs resolved within 7 d of vaccination in most HCWs.

**DISCUSSION**

We conducted questionnaire surveillance to assess the safety of the newly introduced IIV4 for seasonal influenza vaccine 2015/2016 in Japan. This study showed that IIV4 caused injection site AEs in around 80% of HCWs; however, the grade of AEs was mild to moderate, and few HCWs reported severe AEs.

When a new strain was added to a vaccine, several studies demonstrated that the new antigen did not interfere with the immune response to the existing vaccine antigens.\(^7\) IIV4 contained 60 \(\mu\)g of hemagglutinin (15 \(\mu\)g of each antigen), while IIV3 contained 45 \(\mu\)g of hemagglutinin. In addition, AH1pdm monovalent influenza vaccine in 2009 contained 15 \(\mu\)g of hemagglutinin. The higher dose of antigenic content in IIV4 could have led to severer reaction and greater frequency of AEs. The AEs profiles of both IIV4 and IIV3 were found to be similar in several studies.\(^7\) A meta-analysis revealed no significant differences in the frequencies of injection sites.
or systemic adverse events when comparing IIV4 with IIV3.\textsuperscript{8} However, there was a higher incidence of injection site pain with IIV4.\textsuperscript{8} This difference might be due to the higher dose of hemagglutinin (60\(\mu\)g versus 45\(\mu\)g). Our study demonstrated that the frequency of AEs especially in injection site events was significantly higher with IIV4 compared to AH1pdm monovalent vaccine. The grade of AEs with IIV4 was mild to moderate in most cases, and AEs appeared within 2 d after vaccination according to the report, resolving within 7 d. Our results demonstrated that IIV4 is tolerated as a safe vaccine.

For immunogenicity outcomes, IIV4 revealed similar efficacy for the three common strains—A/H1N1, A/H3N2, and the B lineage included in IIV3. IIV4 also showed superior efficacy for the B lineage not included in the trivalent influenza vaccine.\textsuperscript{8} Although the introduction of IIV4 caused slightly increased AEs at the injection site, the results suggest that the addition of the fourth strain to IIV4 did not compromise the safety as compared to IIV3.

The frequency of every AE was also analyzed. As for injection AEs, redness, pain and indurations were 67.2\%, 61.0\% and 40.8\% in this study, respectively, which were higher compared to other studies.\textsuperscript{9,11} The rate of pain was relatively high, and our result of 61.0\% was the highest. Redness (including erythema) occurred in 67.2\%. The nearest figure of 60\% was seen in another Japanese facility.\textsuperscript{10} Induration was also observed in 40.8\% in this study, and in 26.4\% in another Japanese facility.\textsuperscript{10} However, AEs of redness and induration were less than 10\% in other studies.\textsuperscript{7,9,11-15} Redness and induration might be observed frequently in Japanese, or Japanese might possibly claim redness and induration more often. It is reported that the frequency of injection site AEs have been varied from 10\% to 60\%,\textsuperscript{11,13,16,18} These studies were conducted in north American, Europe, Australia and Philippine. The frequency of AEs varied among researches. One of the reasons is the method of subjective AEs estimation. Other reason might be attributed to the difference of the contents in the vaccine, and the difference of the productive process among manufactures. In this study, we compared two vaccines, IIV4 and monovalent AH1pdm. Our result revealed that the dose of antigens would boost the frequency of AEs. Unfortunately, we cannot found the articles associated with AEs in other Asian countries.

The frequency of systemic AEs was also analyzed. The frequency of 25.5\% with IIV in the present study was lower than in other studies.\textsuperscript{10,11,13} Malaise, headache and myalgia were 18.2\%, 10.1\% and 10.1\%, respectively. Malaise was more frequent, and headache and myalgia were less frequent in this study in comparison with other studies.\textsuperscript{7,9,10-15} The study by Watanabe was conducted in Japanese facility.\textsuperscript{10} The frequency of headache and myalgia was less 3.0\%, and not common as was shown in our study. The frequencies of AEs, both at injection site and systemic, were much less in India.\textsuperscript{7} We cannot explain these differences. There might be differences in the threshold to claim AEs among countries. If we have set the background factors as follows, age, sex, type of work, history of medical and allergy in this questionnaire, we might show additional findings.

A few severe cases with both IIV4 and monovalent vaccine were reported. The grade difference between IIV4 and monovalent vaccine was not significant. The frequency of systemic AEs was relatively restricted to 10\% to 30\%.\textsuperscript{11,13,16,18} The systemic AEs frequency of 25.5\% in this study also equivalent to other study. There was not significant difference between IIV4 and monovalent vaccine, then occurrence of systemic AEs might not depend on the dose of antigens.

There are some limitations to this study. First, this study was conducted in a single setting. Second, the subjects were HCWs, and there were a few subjects aged 60 years or older. Most HCWs were healthy persons without severe underlying conditions. This result may not be generalizable to other populations. Elderly persons possibly have some underlying conditions. They are thought to claim AEs less frequently compared to younger generations.\textsuperscript{10} IIV4 vaccination was strongly recommended for elderly persons aged \(\geq 65\) years in Japan, and a financial support system has been provided for this vaccination. In consideration of the above evidence, AEs information would be useful for promoting IIV4 vaccination for elderly persons. Third, we tried to assess IIV4 safety with a solicited AEs check sheet like a diary, and most of the check indices were subjective ones depending on self-estimation by every HCW. Fourth, we did not collect the age among those with AEs in the questionnaire, therefore the distribution of actual age was unknown. Despite this limitation, we were able to collect the questionnaire from 67–68\% of the vaccine recipients, therefore we believe that the age distribution is similar.
IIV4 caused injection site AEs in about 80% of HCWs, which was significantly higher than with AH1pdm monovalent vaccine, but its grade was mild to moderate in most HCWs. A few HCWs reported severe AEs, but there was no case of anaphylaxis or death. In contrast, there was no significant difference in the frequency of systemic AEs between IIV4 and monovalent vaccine. The higher frequency of injection site AEs might be due to the dose of hemagglutinin contained in vaccines. AEs resolved within 7 d of vaccination in most HCWs. In total, IIV4 was well tolerated by HCWs in consideration of the grade and duration of AEs.

Acknowledgements We would like to express our thanks to the staff in the division of occupation management for coordinating the influenza vaccination program and preparing the data.

Conflict of Interest The authors have no conflicts of interest to declare.

REFERENCES