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# Seasonal Influenza Infection Risk Factors of Personnel at Shimane University Hospital

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***Objectives:*** A questionnaire survey is performed to investigate the factors associated with seasonal influenza infection at Shimane university hospital. ***Methods:*** From 2014 to 2017, questionnaire were distributed to hospital employees who were eligible for vaccination. The sheet includes the following information: age of responders, living situation with children, their preseason vaccination status, and their history of seasonal influenza infection. ***Results:*** We analyzed data of a total of 5450 employees, and 6.2% had seasonal influenza infection history in the preceding season. Female sex（odds ratio［OR］1.364, $P < 0.027$）, aged 30-39 years（vs 20-29 years, OR 2.023, $P < 0.001$; vs ≥ 60 years; OR 4.206, $P < 0.001$）, and living with children（OR 2.191, $P < 0.001$）were identified as factors associated with risk of influenza infection. ***Conclusion:*** Recognition of these risk factors may be beneficial to prevent and control influenza infection, and hospital employees should pay utmost attention for avoiding secondary influenza infection from households.

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## INTRODUCTION

Seasonal influenza infection control in hospitals is important for securing patient safety. An annual influenza vaccination for hospital employees has the potential to benefit their patients and their families as well as hospital administrators. Hospital employees often come into contact with patients, children, and older adults. The Annual vaccination is recommended for hospital employees to avoid contracting seasonal influenza and spreading it to others, especially hospitalized patients. According to the WHO fact sheet, the “seasonal flu vaccine is the most effective method of preventing infection.”

Influenza vaccination has been reported to have protective efficacy for healthy adults even if the vaccine differs from the subtype of the prevalent virus. Furthermore, influenza vaccination decreases the risk of complications and death among elderly people, children, and patients with underlying diseases, despite inadequate prevention［1-5］. In Japan, the vaccinations are performed once or twice a year for each applicant.

According to the website of the Ministry of

Health, Labor and Welfare (MHLW), influenza vaccination does not entirely prevent influenza infection but has a potent effect on the aggravation of the disease. However, the reported decrease in the incidence of influenza infection due to vaccination varies among studies [6-10]. Recently, an increasing number of immunocompromised patients and the spread of new influenza virus strains have led to an upsurge in the vaccination rate. Some reports have indicated that high-dose vaccination or twice inoculation can be useful for influenza prevention [11, 12]. It is difficult to provide the high-volume inoculation and twice inoculation for the hospital personnel in the season when vaccine is short in the market.

Moreover, some hospital employees have to be absent because of influenza infection despite undergoing vaccination, and this absence has a bad influence on their regular duties. In our hospital, prophylactic medication is prescribed at the hospital's expense for hospital employees who come into frequent contact with influenza patients without taking infection precautions. However, prophylactic medication is not common in Japan.

At our hospital which has already conducted vaccination and prophylactic medication use, some hospital employee has influenza. The aim of this observational study was to investigate factors associated with influenza infection and measures that can reduce the impact of influenza on hospital personnel.

## METHODS

### *Study Design*

A questionnaire survey was conducted to hospital employees at Shimane university hospital, Japan, between the last four seasonal influenza vaccination campaigns (2014/2015, 2015/2016, 2016/2017, 2017/2018). Shimane University Hospital is a tertiary, referral and advanced technology hospital with 600 beds approved by the MHLW in Japan.

Hospital employees who participated in the seasonal influenza vaccination campaign were enrolled in the study and received a questionnaire sheet. Seasonal influenza is prevalent from December until April of the following year. In the hospital, the seasonal influenza vaccination campaign starts on October 30 and ends by the second week in November. A questionnaire survey has been administered since 2014 for the purpose of investigating the factors associated with an influenza infection situation. The questionnaire sheet was distributed within two days before the date of seasonal influenza vaccination and collected with a preliminary examination sheet on the day of inoculation. This questionnaire included the next items; 1) age, 2) the gender, 3) occupation, 4) whether the person had been vaccinated in the preceding fiscal year (preseason vaccination status), 5) whether the individual lived with children aged less than 15 years, 6) the respondent's history of seasonal influenza infection in the preceding season. We excluded the responders who did not answer the question about the history of influenza infection. For diagnosing influenza infection, employees in whom diagnosis was not made by positive results of rapid antigen test were excluded from "infected" and were categorized as "unsure".

### *Statistical Analyses*

JMP14.2® software (SAS Institute Japan) and STATA14.0® software (STATACorp USA) were used for statistical analysis. A chi-squared test was used for the comparison between the two groups. Odds ratio for the influenza infection risk was calculated, and predictive factors for influenza infection were determined by using logistic regression analysis. The level of significance was set at $p < 0.05$.

Table 1. Number of vaccinated subjects, number of vaccines used and questionnaire responses
Valid response, the number of responses that was excluded the responders who did not answer the question about the history of influenza infection.

| Year | 2014 | 2015 | 2016 | 2017 | Total |
|---|---|---|---|---|---|
| Vaccine applicants | 1676 | 1700 | 1853 | 1901 | 7130 |
| Responders to questionnaires | 1111 | 1455 | 1642 | 1683 | 5891 |
| Eligible responders* | 1091 | 1408 | 1452 | 1499 | 5450 |

*Exclude the responders who did not answer the question about the history of influenza

## RESULTS

### *Basic Characteristics*

The number of vaccine inoculators and responders to questionnaire during study periods is shown in Table 1. Of 5891 responders, we excluded 441 responders who did not answer the question about the history of influenza infection, data of a total of 5450 employees were analyzed.

The characteristics of the responders in this study are shown in Table 2. Of 5450 responders, 2194 were nurses, 724 were physicians, 868 were office workers, and 1580 were other employees (including laboratory technicians and other medical staff). 5052 received influenza vaccine and 366 did not receive in the preceding fiscal year. 1716 lived with children, and 2829 did not live with children.

Table 2. Characteristics of questionnaire responders
With children, respondents living with children aged <15 years old; without children, responders not living with children aged <15 years old; vaccinated, vaccinated responders; unvaccinated, nonvaccinated responders

| | Number |
|---|---|
| Gender* | |
| Male | 1267 |
| Female | 4099 |
| Age (years old)** | |
| 20-29 | 1554 |
| 30-39 | 1489 |
| 40-49 | 1106 |
| 50-59 | 909 |
| ≥ 60 | 341 |
| Occupation† | |
| Nurse | 2194 |
| Physician | 724 |
| Office worker | 868 |
| Others | 1580 |
| Vaccination§ | |
| Vaccinated | 5052 |
| Un-vaccinated | 366 |
| Living situation¶ | |
| With children | 1716 |
| Without children | 2829 |
| Influenza infection# | |
| Infected | 333 |
| Uninfected | 5053 |
| Unsure | 64 |

Excludes unknown number as below; 84 (*), 51 (**), 84 (†), 32 (§), 905 (¶)
# For diagnosing influenza infection, employees in whom diagnosis was not made by positive results of rapid antigen test were excluded from "infected" and were categorized as "unsure".

### *Incidence Rate of Seasonal Influenza Infection*

The seasonal influenza infection incidence during the whole period was 6.2%. The incidence rate was 5.3% in 2013/2014, 4.9% in 2014/2015, 6.7% in 2015/2016, and 7.5% in 2016/2017.

The incidence rates of the seasonal influenza infection were significantly different among sexes (Table 3). The total infection rate of females for all 4 seasons was significantly higher ($p = 0.027$, Odds Ratio (OR) 2.19, 95% Confidence Interval (95% CI) 1.72-2.80) (Table 3).

A significant difference in the distribution of infected subjects was found according to age (Table 3). The incidence rate of seasonal influenza infection was the highest among subjects in their 30s in all seasons.

As we show in Table 4, level 1 and level 2 logistic regression analysis was performed among age generations, and the corresponding odds ratios were determined.

Employees aged 30-39 years were more susceptible to seasonal influenza infection as compared with those aged 20-29 years (OR 2.023, 95% CI 1.509-2.712, $P < 0.001$), and those aged ≥ 60 years (OR 4.206, 95% CI 2.040-8.669, $P < 0.001$) (Table 4).

No difference was found in the incidence according to occupation.

### *Vaccination Situation*

The incidence rate of seasonal influenza infection was 6.2% in vaccinated employees and 5.8% in unvaccinated employees ($p = 0.75$) (Table 3). The annual infection incidence rates were 5.3% in the vaccinated employees and 5.4% in the unvaccinated employees ($p = 0.99$) in 2013/2014, 4.9% in the vaccinated employees and 4.9% in the unvaccinated employees ($p = 1.00$) in 2014/2015, 6.8% in the vaccinated employees and 5.1% in the unvaccinated employees ($p = 0.57$) in 2015/2016, and 7.5% in the vaccinated employees and 8.7% in the unvaccinated employees ($p = 0.67$) in 2016/2017, and no significant differences were observed between the groups.

### *Living Situation with/without Children Younger than 15 Years Old*

The incidence rate of seasonal influenza was higher in respondents living with children aged < 15 years old (With-children) than in those not living with children aged < 15 years old (Without-children) ($p$

Table 3. Number and percentage of individuals with seasonal influenza among hospital staff by vaccination status, gender, living situation with children, and age, relative risk and odds ratio
Shimane, Japan, September 1, 2013-August 20, 2017
Infected means people who contracted seasonal influenza infection.
Uninfected means people who did not contract seasonal influenza infection.
Vaccinated, vaccinated respondents; unvaccinated, nonvaccinated respondents; with children, respondents living with children aged <15 years old; without children, respondents not living with children aged <15 years old; OR: Odds ratio; 95% CI: 95% confidence interval.

| | Infected no.(%) | Uninfected no.(%) | *P*-value | OR (95%CI) |
|---|---|---|---|---|
| Gender | | | | |
| Male | 62 (4.9) | 1193 (95.1) | | 1 |
| Female | 268 (6.6) | 3780 (93.4) | 0.0274 | 1.364 (1.027-1.812) |
| Age (years old) | | | | |
| 20-29 | 74 (4.8) | 1473 (95.2) | < 0.0001 | |
| 30-39 | 135 (9.2) | 1328 (90.8) | | |
| 40-49 | 67 (6.2) | 1017 (93.8) | | |
| 50-59 | 45 (5.0) | 857 (95.0) | | |
| ≥ 60 | 8 (2.4) | 331 (97.6) | | |
| Vaccination | | | | |
| Vaccinated | 311 (6.2) | 4683 (93.8) | 0.7527 | |
| Un-vaccinated | 21 (5.8) | 340 (94.2) | | |
| Living situation | | | | |
| With children | 154 (9.2) | 1529 (90.9) | < 0.0001 | 2.191 (1.715-2.800) |
| Without children | 123 (4.4) | 2677 (95.6) | | 1 |

OR: Odds ratio; 95% CI: 95% confidence interval

Table 4. Level 1 and level 2 logistic regression analysis of age generation and corresponding odds ratios

| Level 1 | Level 2 | *P*-value | OR | 95%CI |
|---|---|---|---|---|
| 20-29 | 30-39 | < 0.0001 | 2.023 | 1.509-2.712 |
| 20-29 | 40-49 | 0.1182 | 1.311 | 0.933-1.842 |
| 20-29 | 50-59 | 0.8196 | 1.045 | 0.714-1.528 |
| 20-29 | ≥ 60 | 0.0524 | 0.481 | 0.229-1.007 |
| 30-39 | 20-29 | < 0.0001 | 0.494 | 0.368-0.662 |
| 30-39 | 40-49 | 0.0052 | 0.648 | 0.478-0.878 |
| 30-39 | 50-59 | 0.0002 | 0.516 | 0.364-0.731 |
| 30-39 | ≥ 60 | < 0.0001 | 0.237 | 0.115-0.490 |
| 40-49 | 20-29 | 0.1182 | 0.762 | 0.542-1.071 |
| 40-49 | 30-39 | 0.0052 | 1.543 | 1.138-2.091 |
| 40-49 | 50-59 | 0.2525 | 0.797 | 0.540-1.175 |
| 40-49 | ≥ 60 | 0.0082 | 0.366 | 0.174-0.771 |
| 50-59 | 20-29 | 0.8196 | 0.956 | 0.654-1.398 |
| 50-59 | 30-39 | 0.0002 | 1.935 | 1.366-2.742 |
| 50-59 | 40-49 | 0.2525 | 1.254 | 0.850-1.850 |
| 50-59 | ≥ 60 | 0.0462 | 0.46 | 0.214-0.986 |
| ≥ 60 | 20-29 | 0.0524 | 2.078 | 0.992-4.352 |
| ≥ 60 | 30-39 | < 0.0001 | 4.206 | 2.040-8.669 |
| ≥ 60 | 40-49 | 0.0082 | 2.725 | 1.295-5.733 |
| ≥ 60 | 50-59 | 0.0462 | 2.172 | 1.013-4.657 |

OR: Odds ratio; 95% CI: 95% confidence interval

< 0.001）（Table 3）. During 2015-2017, the infection rates were markedly higher in the With-children group than in the Without-children group.

The annual infection incidence rates were 7.0% in the With-children group and 4.5% in the Without-children group in 2013/2014, with no significant difference（$p = 0.09$）; 7.8% in the With-children group and 3.3% in the Without-children group（$p <$

0.001, OR 2.46, 95%CI 1.44-4.23) in 2014/2015; 10.5% in the With-children group and 4.4% in the Without-children group ($p < 0.001$, OR 2.55, 95%CI 1.52-4.33) in 2015/2016; and 11.1% in the With-children group and 5.7% in the Without-children group ($p = 0.001$, OR 2.11, 95%CI 1.32-3.39) in 2016/2017.

***Relationship between Vaccination Situation and Living-with-Children Situation***

In the With-children group, the infection rates during four seasons in the vaccinated and unvaccinated were 9.1% and 8.9%, respectively, and there was no significant difference between groups ($p = 0.95$).

Simultaneously, in the With-children group, the annual infection incidence rates in the vaccinated and unvaccinated groups were 7.3% and 2.8% in 2013/2014, 7.6% and 11.1% in 2014/2015, 10.3% and 13.0% in 2015/2016, and 11.2% and 11.5% in 2016/2017, respectively, and no significant differences were observed between the two groups ($p$ values: 0.31 in 2013/2014, 0.50 in 2014/2015, 0.68 in 2015/2016, and 0.96 in 2016/2017).

In the Without-children group, the infection rates in the vaccinated and unvaccinated groups were 4.4% and 4.2%, respectively, with no significant difference between groups ($p = 0.86$).

Moreover, the annual incidence rates in the vaccinated and unvaccinated groups were 4.5% and 5.8% ($p = 0.61$) in 2013/2014, 3.4% and 1.9% ($p = 0.56$) in 2014/2015, 4.8% and 0.0% in 2015/2016, and 5.5% and 8.2% ($p = 0.44$) in 2016/2017, respectively, and there were no significant differences between the two groups.

## DISCUSSION

***The Relationship between Influenza Infection and Living-with-Children Situation***

This report determined the relationship between seasonal influenza infection and living-with-children situation by using statistical method.

On the basis of the chi-squared quadratic profile, there were significant differences in the incidence of influenza infection by age (Table 3). A significant difference was found for hospital employees in their 30s (Table 4). Next to 30s, the person in the 40s had influenza at a higher percentage as compared with the person of other generations. When we added an investigation, the living together rate with children was found to be 66% in the 30s group. The living together rate with children was 57% in the 40s group, and the rate was 15% in the 20s group, and the rate was 15% in the 50s group, and the rate was 10% in the 60s group. It may influence that prevalence of influenza is high in 30s group that a rate to live together with children is high. It is inferred that the difference in prevalence by the generation is due to the difference in living together rate with children.

The incidence rate of seasonal influenza infection for females was significantly higher than that for males (6.62% for females and 4.94% for males; $p = 0.03$), and the odds ratio of influenza infection for females was 1.364 (95% CI: 1.03-1.81). A living together rate with the children of males was 37.1%, and the rate of females was 37.9%. It cannot be said that the frequency that females live together with children is higher than males (P = 0.33). According to the hospital employees' comments on the questionnaire sheets, many female hospital employees stated that they did not want to part from their children. According to some reports, 37-51.7% of families share a bed until a child reaches approximately 12 years old, which is the age of a primary schoolchild in Japan [13-17]. We cannot judge it from this study, but the behavior of female staff in the home may be different from it of male staff. The people living together with children seem to increase clearly at an opportunity to come in contact with children.

The association between the influenza infection of children and the influenza infection of the hospital personnel was not able to evaluate in this investigation. Why is the person living together with children easy to have influenza? The reason may be that children living together had influenza and may be the difference of the lifestyle (e.g., the participation of the children's association) by there being children. In future, we want to investigate more why a person living together with children tend to get influenza.

***Influenza infection risk of the vaccinated respond-***

***ers***

The incidence rates of female were significantly high. The incidence rates were 5.0% for males and 6.7% for females ($p < 0.001$, OR 1.36, 95%CI 1.01-1.86). The incidence rate was the highest among subjects in their 30s, with rates of 9.3%. A significant difference in the distribution of infected subjects was found according to age ($p < 0.001$). The annual infection incidence rates were 9.1% in the With-children group and 4.4% in the Without-children group. The incidence rates of the With-children group were significantly high ($p < 0.001$, OR 2.16, 95%CI 1.66-2.81)

It is important for hospital employees to reduce opportunities against influenza virus exposure both at home and in the workplace. In other words, to control hospital-acquired infection, hospital employees need to be educated about influenza infection prevention in outside of the hospital.

According to the report, the prophylactic administration of oseltamivir (75 mg/day for 4 days) could prevent hospital employees from developing influenza after contact with patients with influenza [18]. If prophylaxis is recommended when the staff came into contact with patients with influenza in home, the influenza infection of the hospital personnel may decrease. In addition to influenza vaccination, precautions of wearing a mask and hand hygiene should be promoted during the influenza season [19]. Separating and isolating family members with influenza from healthy family members at home may be an effective measure to prevent influenza infection. It should be further considered whether vaccination of children could reduce the incidence of seasonal influenza in hospital personnel.

The incidence of influenza infection is reduced by employee influenza vaccination, and vaccination reduces sick leave of employee [20]. From our results, the next phenomenon seems to a fact. We cannot prevent influenza infection by a certain one measure, for example a “vaccination”. The hospital personnel should perform many precautions against influenza infection in parallel not to get seasonal influenza. In 2020/2021, mask wearing and hand washing, securing of sociological distance are recommended to not only the hospital personnel but also a citizen for prevention of infection of the new coronavirus infection. We are getting a custom to avoid a crowd as a new lifestyle. We could not know the change of the real vaccination rate, but vaccination was strongly recommended. An infected person begins to increase the seasonal flu from December in an average year, but the number of the reports of influenza does not show a tendency of the increase at the end of January in 2020/2021 season.

***Limitations***

This study has several limitations. Some factors associated with influenza infection differ during the four seasons.

Firstly, it is generally thought that the efficacy of vaccines might be different according to season. We could not evaluate differences in influenza vaccine efficacy between hospital personnel and individuals who do not work in the hospital. Secondly, we were not able to accurately determine the number of subjects present when the questionnaire was administered. The subject of a distributor and the respondent of the questionnaire became extended. Third, precautions taken against infection vary among families. Therefore, it is difficult to conclude that all people living with children are at increased risk of influenza infection.

Finally, frozen section diagnosis was not performed in all individuals with fever. A prospective study is necessary to evaluate the effect of the vaccination.

## CONCLUSIONS

For hospital employees living with children younger than 15 years old, the odds ratio of seasonal influenza infection was 2.19. They were at increased risk of the influenza infection. It is suggested that it reduce an incidence of the seasonal influenza infection among another employee and patients at a hospital that a staff takes the infection-related precautionary measures at home. In other words, influenza vaccination is necessary for the prevention of influenza infection, but even a person inoculated vaccine into has influenza. It is also important to reduce influenza virus exposure opportunity anytime. Next is inferred by an influenza outbreak trend in 2020/2021.

Social behavior modification and the rise in vaccination rate reduce the influenza infection of the hospital personnel.

***Ethics Statement***

This study was approved by the Medical Ethics Committee at Shimane University Faculty of Medicine "Shimane University Institutional Committee on Ethics" on October 10, 2018. The ethics code is 20180914-1.

***Contributors***

Conceived of and designed the experiments: YJ, CS, and SK. Performed the experiments: YJ, TK and MH. Analyzed the data: YJ and MH. Wrote the paper: YJ, MH, JS and SK. Managed the study: KN

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None.

***Conflicts of Interest***

The authors declare that they have no conflicts of interest.

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