Effects of influenza vaccination on seasonal influenza symptoms: A prospective observational study in elementary schoolchildren in Japan

Mitsuo Uchida a,*, Shouhei Takeuchi b, Masaya-Masayoshi Saito c, Hiroshi Koyama a

a Department of Public Health, Graduate School of Medicine, Gunma University, 3-39-22, Showa-machi, Maebashi, Gunma, 371-8511 Japan
b Department of Nutrition Science, University of Nagasaki, 1-1-1, Manahino, Nagayo-machi, Nagasaki, 851-2195 Japan
c Research and Development Center for Data Assimilation, Institute of Statistical Mathematics, 10-3, Midorimachi, Tachikawa, Tokyo, 190-8562 Japan

ARTICLE INFO

Keywords:
Public health
Epidemiology
Infectious disease
Vaccines
Influenza
Elementary schoolchildren
Bayesian statistics
Public health
Vaccination

ABSTRACT

Although influenza vaccine has been shown to prevent influenza symptom onset, its further beneficial effects after vaccinated individuals become symptomatic remain undetermined. This epidemiological survey compared influenza symptoms in subjects diagnosed with influenza who were and were not vaccinated. A prospective survey was performed among the 13,217 schoolchildren who attended all 29 public elementary schools in Matsumoto City, Nagano Prefecture, Japan, during the 2014/2015 influenza season. Information about symptoms and background demographic and clinical factors were obtained from a questionnaire. Of these schoolchildren, 2,548 were diagnosed with influenza and 1,122 were previously vaccinated and 1,426 were unvaccinated. Fever duration and frequency of symptoms and hospitalization were compared in vaccinated and unvaccinated children. The hospitalization rate was lower in vaccinated children, whereas symptom frequency and fever duration were similar in the two groups. This study showed that hospitalization was less in vaccinated children. Vaccination may attenuate symptom intensity after symptom onset.

1. Introduction

Seasonal influenza vaccination is a standard pharmaceutical intervention usually used to prevent the onset of symptoms [1]. Although the effectiveness of influenza vaccine has been reported to be around 40–60% [2], vaccination is regarded as the best method of controlling influenza infection.

Vaccines that not only prevent symptom onset but reduce symptom severity may be more beneficial than those that prevent symptom onset alone. Influenza vaccines have been reported to reduce hospitalization rates in adult populations [3, 4], to reduce the risks of life-threatening influenza in children [5], to attenuate symptom severity in older adult outpatients [6] and to decrease the risks of fever in children [7]. All of these studies, however, had limitations, including selection bias; moreover, these studies differed in study settings and methods of analysis. Because community-based prospective studies can observe the study population and address selection bias, longitudinal epidemiological studies are needed in the field of infectious disease research.

Although influenza epidemics usually occur among schoolchildren, studies to date have not evaluated the effects of vaccination in school settings. We therefore conducted a prospective observational epidemiological study among all elementary schoolchildren in a moderately sized city in Japan during the 2014/2015 influenza season. That study showed that patterns of infection spread could be determined by simple mathematical modeling [8] and that vaccination and wearing a mask were effective in preventing the symptom onset [9]. However, the benefits of vaccination in symptomatic children remain undetermined. The present study therefore compared influenza symptoms in schoolchildren diagnosed with influenza who were and were not vaccinated.

2. Materials and methods

2.1. Study subjects

The study method and data collection have been described [8]. Briefly, a prospective survey was performed among the 13,217 schoolchildren who attended all 29 public elementary schools in Matsumoto City, Nagano Prefecture, Japan, during the 2014/2015 influenza season. In that study, information about symptoms and background demographic and clinical factors were obtained from a questionnaire administered to all children who were diagnosed with influenza. A case was defined as an individual who had an influenza-like illness (ILI), as shown by fever ≥37
and upper respiratory symptoms, and was diagnosed with seasonal influenza by a clinician at a medical institution. In Japan, if a schoolchild is diagnosed with influenza at a medical institution, the school nurse gives a certified document to the child's guardians, who are required to fill out the document and submit it to the school when the child returns to school. The questionnaire in the present study was distributed with the certified paper through school nurses. After questionnaires were distributed to households, parents/guardians of diagnosed children completed and submitted them to school nurses. Responses were received from the parents/guardians of 2,548 schoolchildren diagnosed with seasonal influenza; this number corresponded to 95.8% of the 2651 children who had been diagnosed as having influenza and for whom documents were submitted to their schools.

The questionnaire included factors regarded as associated with influenza symptoms [8]: sex (male/female); grade in school (description); number of household members (description); current underlying disease, if present (cardiovascular disease, pulmonary disease, kidney disease, liver disease, nerve disease, muscle disease, blood disease and diabetes); influenza vaccination during the 2014/2015 season before symptom onset (yes/no); dates of fever onset and diagnosis (calendar dates); date fever declined to <37 °C (calendar date); medication (oseltamivir, zanamivir, lamineaminivir, other); hospitalization (yes/no); symptoms (cough, sputum, sore throat, runny nose, chills, headache, nausea, arthralgia, diarrhea); mask wearing (yes/no); hand washing (yes/no); gargling (yes/no); and suspected route of transmission (description). Fever duration was defined as the time from the date of fever onset to the date of fever reduction to <37 °C. The data was checked by researchers and there was no evidence of missing data for the analysis in this study. As a result, data for 2548 children were included in the analysis.

2.2. Ethics

Because questionnaires were self-administered and answered anonymously, subjects who returned questionnaires were regarded as voluntary participants. The study procedure was approved by the Shinshu Medical Ethics Committee (approval number 2715), as described [8]. The ethical committee did not require informed consent because responses did not identify households or individuals. Moreover, this study was a secondary analysis of previously obtained data.

2.3. Influenza spread and vaccine information

During the 2014/2015 influenza season, almost all infected patients in Japan were found to be infected with the A/H3 subtype of seasonal influenza [10]. In the present survey, rapid diagnosis kits also found that almost all patients were infected with subtype A [8]. According to the National Institute of Infectious Disease of Japan (NIID), only one inactivated vaccine type was distributed during the 2014/2015 influenza season; that vaccine was directed against three viral strains; A/California/7/2009(H1N1)pdm09, A/New York/39/2012(H3N2) and B/Massachusetts/2/2012 [10]. The vaccine effectiveness was reported to be around 20% in a previous study [9]. The match between vaccine and circulating strain was small in this year according to an NIID report [10].

2.4. Statistical analysis

2.4.1. Null hypothesis method

All statistical analyses were performed with R software (ver. 3.4.0). Fever duration, symptoms and hospitalization in vaccinated and unvaccinated groups were compared using the Mann-Whitney U-test and Chi-square test, as applicable. A p value < 0.05 was considered statistically significant.

2.4.2. Propensity score matching

Many previous studies have shown limitations, including selection bias or inadequate adjustment for confounding factors. Propensity score is often used in observational studies to adjust for several background factors, mimicking randomized controlled trials [11, 12]. Because this study was observational in nature, selection bias was minimized by propensity score matching of patients in the vaccinated and unvaccinated groups. Factors used to calculate propensity scores included grade in school, sex, underlying diseases, number of siblings, number of days from symptom onset to diagnosis, medication, mask wearing, washing hand, gargling and suspected transmission route. The MatchIt package and the neighbor method were used for 1:1 propensity score matching [13]. The Hosmer-Lemeshow test was applied and the result was not significant, therefore, we confirmed that the allocation was valid.

2.4.3. Bayesian statistics

To estimate differences in symptoms between the vaccinated and unvaccinated groups, data were analyzed using the Bayesian method, resulting in a posterior distribution. Despite propensity score matching, unpaired tests were performed because the data were evaluated as groups. Then, Rstan (ver. 2.15.1) software which is used widely in the world was employed for Bayesian analysis. In this procedure, sampling was performed five times, with each consisting of 21,000 chains. The burn-in was 1,000, with a random value of 100,000 obtained and posterior distribution estimated by the Hamiltonian Monte Carlo (HMC) method which is one type of Markov chain Monte Carlo (MCMC) method. Each R hat was <1.1 and all samplings converged. All procedures were performed as described [14].

3. Results

Of the 2,548 schoolchildren diagnosed with influenza during the 2014/2015 season, 1,122 had been previously vaccinated and 1,426 had not. The factor of school grade to represent age of child showed no significant difference between groups. A comparison of fever duration showed no significant difference between vaccinated and unvaccinated groups (median [25%, 75%]: 3 [2,4] vs 3 [3,4]; p = 0.07). In addition, the frequency of all other symptoms did not differ significantly in these two groups. However, the hospitalization rate was significantly lower in the vaccinated than in the unvaccinated group (1.4% vs 2.6%; p = 0.04; odds ratio [OR] 0.54; Table 1).

After adjusting for individual background factors using the propensity score method, each group consisted of 1,065 subjects. The characteristics of both groups are shown in Supplement 1. Although the Hosmer-Lemeshow method showed the allocation was performed well, only the underlying disease factor remained different between groups. Posterior distribution was obtained by the HMC method. The expected a posteriori (EAP) fever duration was 3.17 days in the vaccinated group and 3.19 days in the unvaccinated group (Supplement 2), with a between group difference of -0.02 day (Supplement 3). Another estimation showed that the generated quantity of the area under the curve that fever duration would be lower in the vaccinated than in the unvaccinated group was 70.5%.

When we compared the frequency of all symptoms in the propensity score matched groups, we found that the EAP for all symptom ORs ranging from 0.92 to 1.11 and 95% credible intervals (CIs) ranging from 0.72 to 1.33 (Table 2).

The EAP frequency of hospitalization yielded an OR of 0.68 (Supplement 4). The adjusted OR was higher than the crude OR (0.54). The area under the curve that the OR of the vaccinated compared with the unvaccinated group would be below 1.00 was calculated as 92.2% (Supplement 5). This result indicated that the likelihood of hospitalization would be lower in vaccinated than in unvaccinated symptomatic individuals.
4. Discussion

This study was performed to evaluate the effects of seasonal influenza vaccination on influenza symptoms by comparing outcomes in vaccinated and unvaccinated individuals. We evaluated the entire population of elementary schoolchildren in one city and almost all (95.8%) of symptomatic cases could be analyzed. Therefore, we believed that selection bias was excluded as far as can be possible. This study showed that fever duration and symptoms were similar in the vaccinated and unvaccinated groups, whereas hospitalization rates were lower in the vaccinated group. Similar results were obtained after propensity score matching.

In this study, we found that hospitalization was less in vaccinated children. This agrees with findings in many previous studies. For example, influenza vaccination was found to reduce the rates of influenza diagnosis and hospitalization and was associated with reduced severity and a better prognosis in inpatients with influenza [3]. In addition, a large scale national survey in the US showed that influenza vaccination programs provided substantial health benefits, including reducing the rate of hospitalization [4]. High vaccination coverage was estimated to avert hospitalization in several age groups, and influenza vaccination was associated with reduced symptom severity in the outpatient setting [6]. Because few patients in the present study were hospitalized, we also found that vaccination had a beneficial effect on the rate of hospitalization in Japanese schoolchildren. According to Supplement 1, we found that underlying disease factor was frequent in the vaccinated group. This bias could not be adjusted for fully because children with underlying disease might be given more vaccination to prevent their disease worsening. Nevertheless, hospitalization was less in the vaccinated group. This phenomenon shows that underlying disease was not directly associated with hospitalization, and vaccination may prevent hospitalization as we had assumed. In other words, the effect of vaccination to prevent hospitalization may be underestimated in this study. In contrast, we found that vaccination did not decrease symptom frequency or fever duration. However, a previous study reported that vaccination was associated with reductions in the duration of numerous symptoms among young healthy adults [15], suggesting that vaccination could attenuate symptoms. The discrepancy between these studies may be due to differences in age groups and/or study settings.

Because most clinical studies have analyzed patients who visited a specific hospital, these studies might show a selection bias such as residence of patient or degree of urbanization because of the hospital environment. In this study, we considered these factors and analyzed data from all schoolchildren in one city.

Table 1. Influenza symptoms of vaccinated and unvaccinated schoolchildren.

| Factor              | n = 2548 | Vaccinated (n = 1122) | Unvaccinated (n = 1426) | p-value |
|---------------------|----------|-----------------------|-------------------------|---------|
| Fever duration      | Median [25%, 75%] | 3 [2, 4]              | 3 [3, 4]                | 0.07    |
|                     | Mean [SD] | 3.2 [1.1]             | 3.2 [1.1]               |         |
| Hospitalization     | Yes       | 16 (1.4)              | 37 (2.6)                | 0.04    |
|                     | No        | 1106 (98.6)           | 1389 (97.4)             |         |
| Arthralgia          | Yes       | 270 (24.1)            | 366 (25.7)              | 0.35    |
|                     | No        | 852 (75.9)            | 1060 (74.3)             |         |
| Chills              | Yes       | 335 (29.9)            | 453 (31.8)              | 0.30    |
|                     | No        | 787 (70.1)            | 973 (68.2)              |         |
| Cough               | Yes       | 835 (74.4)            | 1039 (72.9)             | 0.38    |
|                     | No        | 287 (25.6)            | 387 (27.1)              |         |
| Diarrhea            | Yes       | 92 (8.2)              | 124 (8.7)               | 0.66    |
|                     | No        | 1030 (91.8)           | 1302 (91.3)             |         |
| Headache            | Yes       | 588 (52.4)            | 752 (52.7)              | 0.87    |
|                     | No        | 534 (47.6)            | 674 (47.3)              |         |
| Nausea              | Yes       | 219 (19.5)            | 292 (20.5)              | 0.55    |
|                     | No        | 903 (80.5)            | 1134 (79.5)             |         |
| Runny nose          | Yes       | 695 (61.9)            | 841 (59.0)              | 0.13    |
|                     | No        | 427 (38.1)            | 585 (41.0)              |         |
| Sore throat         | Yes       | 496 (44.4)            | 596 (41.8)              | 0.19    |
|                     | No        | 624 (55.6)            | 830 (58.2)              |         |
| Sputum              | Yes       | 311 (27.7)            | 363 (25.5)              | 0.20    |
|                     | No        | 811 (72.3)            | 1063 (74.5)             |         |

Note: Mann–Whitney U test, Chi-square test. Proportion (%) was calculated by each cell value divided by the total number of vaccinated (n = 1122) or unvaccinated (n = 1426) children.

Table 2. Posterior distribution of Odds Ratio of influenza symptoms between vaccinated and unvaccinated groups after propensity score matching.

| Symptoms    | Odds Ratio | SE | SD | 2.5% | 5%  | 50%  | 95%  | 97.5% | Sampling | R hat |
|-------------|------------|----|----|------|-----|------|------|-------|----------|-------|
| Arthralgia  | 0.92       | 0.00| 0.09| 0.75 | 0.78| 0.92 | 1.08 | 1.11  | 86154    | 1     |
| Chills      | 0.93       | 0.00| 0.09| 0.77 | 0.79| 0.92 | 1.08 | 1.11  | 82002    | 1     |
| Cough       | 1.10       | 0.00| 0.11| 0.90 | 0.93| 1.09 | 1.28 | 1.33  | 81864    | 1     |
| Diarrhea    | 0.99       | 0.00| 0.15| 0.72 | 0.76| 0.98 | 1.26 | 1.32  | 84077    | 1     |
| Headache    | 1.03       | 0.00| 0.09| 0.86 | 0.89| 1.02 | 1.18 | 1.21  | 86865    | 1     |
| Nausea      | 0.94       | 0.00| 0.10| 0.76 | 0.78| 0.93 | 1.11 | 1.15  | 77600    | 1     |
| Runny nose  | 1.09       | 0.00| 0.10| 0.91 | 0.93| 1.08 | 1.25 | 1.29  | 93643    | 1     |
| Sore throat | 1.10       | 0.00| 0.10| 0.92 | 0.95| 1.09 | 1.26 | 1.30  | 83722    | 1     |
| Sputum      | 1.11       | 0.00| 0.11| 0.91 | 0.94| 1.10 | 1.29 | 1.33  | 82295    | 1     |
location. In contrast, the present study included all elementary schoolchildren in a moderately-sized city. We were therefore able to obtain data about all schoolchildren who had been diagnosed with seasonal influenza, thus eliminating possible selection bias. In contrast to other studies, we found that influenza vaccination was not associated with fever duration or symptoms. This difference may be due to our inclusion of all individuals diagnosed with influenza, not only those with severe disease but those with mild or slight disease, who were diagnosed by a family doctor or in a clinic. The strength of the present study was its determination of the effects of vaccination in all schoolchildren in an entire city, while adjusting for individual background factors.

Nevertheless, this study had several limitations. First, because data were obtained from questionnaires, biological findings, such as those obtained from blood samples, were not analyzed. This method may have a limitation of measurement error or recall bias. In general, a definitive diagnosis of influenza requires a PCR-based method. Therefore, this study may have included patients with ILL or other respiratory diseases. However, in fact, other public health studies often utilize self-administered questionnaires to determine the tendency of influenza spread. We obtained influenza diagnosis information based on use of rapid diagnosis kits by medical institutions, therefore, we believe the diagnosis information was reliable. Second, a selection bias among children who showed symptoms and visited hospitals may be present. The motivation of guardians on whether or not to take their charges to hospitals was unknown. Although the hospitalization rate was lower in the vaccinated group, this might have been influenced by child vaccination history because guardians might be less likely to take their children to hospital if they have been vaccinated. Such limitations should be addressed in future studies. Third, the vaccinated groups included all children who had been vaccinated at least once. We did not compare subjects who had been vaccinated once with those who had been vaccinated twice. Fourth, this study was performed in Japan, a country with an advanced medical system that includes requirements for certified reporting of illness, the use of a uniform strain and the availability of medical materials. Therefore, the results of this study may be limited to countries with similar medical systems. Longitudinal studies in several study settings are therefore required.

In conclusion, this study, based on data from an observational epidemiological study, showed that influenza vaccination reduced hospitalization but did not affect fever duration or symptoms in symptomatic schoolchildren. Influenza vaccine may therefore have a protective effect, even after symptom onset.

Declarations

Author contribution statement

M. Uchida: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.
M. Saito, S. Takeuchi: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.
H. Koyama: Analyzed and interpreted the data; Wrote the paper.

Funding statement

This work was supported by grants JSPS KAKENHI (JP26860413, JP16K09052, JP19K10614) and AMED (16fk0108316h0003).

Competing interest statement

The authors declare no conflict of interest.

Additional information

Supplementary content related to this article has been published online at https://doi.org/10.1016/j.heliyon.2020.e03385.

Acknowledgements

The authors thank all staffs of Department of Public Health, Graduate School of Medicine, Gunma University and Center for Health, Safety and Environment Management, Shinshu University.

References

[1] WHO, Influenza (Seasonal). 2014. http://www.who.int/mediacentre/factsheets/fs211/en/. (Accessed 4 May 2018).
[2] CDC, Vaccine Effectiveness - How Well Does the Flu Vaccine Work?, 2016. http://www.cdc.gov/flu/about/qa/vaccineeffect.htm. (Accessed 4 May 2018).
[3] J. Castilla, P. Godoy, A. Dominguez, I. Martinez-Baz, J. Astray, V. Martin, et al., Influenza vaccine effectiveness in preventing outpatient, inpatient, and severe cases of laboratory-confirmed influenza, Clin. Infect. Dis. 57 (2) (2013) 167–175.
[4] D. Kostova, C. Reed, L. Finelli, P.Y. Cheng, P.M. Gargiullo, D.K. Shay, et al., Influenza illness and hospitalizations averted by influenza vaccination in the United States, 2005-2011, PLoS One 8 (6) (2013), e66312.
[5] J.M. Ferdinands, L.E. Olibo, A.A. Agan, N. Bhat, R.M. Sullivan, M. Hall, et al., Effectiveness of influenza vaccine against life-threatening RT-PCR-confirmed influenza illness in US children, 2010-2012, J. Infect. Dis. 210 (5) (2014) 674–683.
[6] J.J. VazWormer, M.E. Sundaram, J.K. Meece, E.A. Belongia, A cross-sectional analysis of symptom severity in adults with influenza and other acute respiratory illness in the outpatient setting, BMC Infect. Dis. 14 (2014) 231.
[7] V.K. Jain, L. Rivera, K. Zaman, R.A. Espos Jr., C. Srivichayakul, B.P. Quiambao, et al., Vaccine for prevention of mild and moderate-to-severe influenza in children, N. Engl. J. Med. 369 (26) (2013) 2481–2491.
[8] M. Uchida, M. Kaneko, Y. Hidaka, H. Yamamoto, T. Honda, S. Takeuchi, et al., Prospective epidemiological evaluation of seasonal influenza in all elementary schoolchildren in Matsumoto City, Japan, in 2014/2015, Jpn. Influenza J. Infect. Dis. 70 (3) (2017) 333–339.
[9] M. Uchida, M. Kaneko, Y. Hidaka, H. Yamamoto, T. Honda, S. Takeuchi, et al., Effectiveness of vaccination and wearing masks in seasonal influenza in Matsumoto City, Japan, in the 2014/2015 season: an observational study among all elementary schoolchildren, Prev. Med. Rep. 5 (2017) 86–91.
[10] National Institute of Infectious Diseases of Japan, A Report of Seasonal Influenza in 2014/15, 2015. http://www.niid.go.jp/niid/images/sdcn_disene/inflnu_flu2014/2015_report.pdf. (Accessed 4 May 2018).
[11] P. Rosenbaum, D. Rubin, The central role of the propensity score in observational studies for causal effects, Biometrika 70 (1) (1983) 41–55.
[12] P.C. Austin, An introduction to propensity score methods for reducing the effects of confounding in observational studies, Multivariate Behav. Res. 46 (3) (2011) 399–424.
[13] J. Randolph, K. Falbe, A. Manuel, J. Balloun, A step-by-step guide to propensity score matching in R, Practical Assess. Res. Eval. 19 (18) (2014) 1–6.
[14] H. Toyota, A First Step of Statistical Analysis, Bayesian Statistics, Asakura Shoten, Tokyo, 2016.
[15] R.G. Deiss, J.C. Arnold, W.J. Chen, S. Echols, M.P. Fairchok, C. Schofield, et al., Vaccine-associated reduction in symptom severity among patients with influenza A/H1N2 disease, Vaccine 33 (51) (2015) 7160–7167.