Received: 18 May 2019 | Accepted: 28 May 2019
DOI: 10.1111/jjns.12275

LETTER TO THE EDITOR

JAPAN JOURNAL OF NURSING SCIENCE WILEY

Authors' response to letter to the editor: Safety concerns with human papilloma virus immunization in Japan: Analysis and evaluation of Nagoya City's surveillance data for adverse events

See articles in *Japan Journal of Nursing Science*
DOI: 10.1111/jjns.12252
Safety concerns with human papilloma virus immunization in Japan: Analysis and evaluation of Nagoya City's surveillance data for adverse events
Yukari Yaju and Hiroe Tsubaki

DOI: 10.1111/jjns.12258
Letter to the editor: Safety concerns with human papilloma virus immunization in Japan: Analysis and evaluation of Nagoya City's surveillance data for adverse events
Sadao Suzuki

DOI: 10.1111/jjns.12282
Editor's Reply to the Letter to the Editor of Dr. Suzuki
William L. Holzemer

We wish to express our appreciation to Prof. Suzuki for his comments in his letter (Suzuki, 2019) on our paper. We have answered each of his points below.

1 | STUDY PERIOD

First, in our study, possible associations between human papilloma virus (HPV) vaccination and each possible post-vaccinated symptom were explored by comparing event rates in the vaccinated cases with those in the unvaccinated controls. Then, we excluded events in the vaccinated case group in which the first HPV vaccination was administered after the onset time of the symptom. In this regard, Prof. Suzuki stated as follows: "To do this is correct".

Second, for vaccinated cases, "length of time to recall the experienced symptom" was the period between time of the first vaccination and September 2015 while the length for the unvaccinated controls was the period between 12 years of age and the subject's age at September 2015. Then, it was considered that event rate depends on the "length of time to recall the experienced symptom". That is, when comparing the vaccinated cases with the unvaccinated controls, we need to consider the effect of the length. In our study, we defined the study period to refer to the "length of time to recall the experienced symptom" and used it as a covariate in the logistic regression model. Further, the study period is based on the concept of the method to control for bias due to misclassifying the non-exposure period before intervention commencement as the exposure period during analysis. Although the methods to control for such bias are still controversial issues in epidemiology, it is thought that a common approach to control for the bias is to reduce it (Suissa, 2007, 2008; Yang et al., 2014). Taking into consideration the factors mentioned above, we believe that the "study period" is acceptable. Moreover, we would like to note that we have already mentioned as follows in the discussion: "The difference in the study period between the vaccinated cases and the unvaccinated controls should be considered" and "The mean study period for the vaccinated cases was shorter than that for the unvaccinated controls. As a result of this difference, the event rates of the vaccinated cases were expected to be relatively underestimated, compared to those of the unvaccinated controls."

Third, we would like to note that Prof. Suzuki et al. did not mention that they excluded events in the vaccinated case group in which the first HPV vaccination was administered after the onset time of the symptom in the primary analysis (Suzuki & Hosono, 2018). Therefore, it is supposed that the number of events included the number of events which occurred before vaccination. For example, in our data the number of events for menstrual abnormality was 5,466 (including the events occurred before vaccination; nearly the same with the number of events 5,468 in their paper). It is assumed that they did not consider the bias due to misclassifying the non-exposure period before vaccination as

the exposure period. As previously stated, the methods to control for the bias are still controversial issues, but some measures should be taken to control for the bias.

Finally, we agree with Prof. Suzuki that we should make use of a control group, which would be an ideal counterfactual group. However, we could not specify "the time when the participants were supposed to have been vaccinated" for the unvaccinated controls from the data of the Nagoya Study. Therefore, we are unable to do the analysis. As for a counterfactual control group, we could propose the vaccinated age-matching methods as a proxy alternative to a counterfactual comparison. By applying this method we can use the vaccinated age-matched controls who were the same age as the vaccinated age of the vaccinated cases. It is expected that the healthy user bias would be reduced in the vaccination age-stratified analyses. This is because the impact of a healthy user bias varied by age would be well balanced by age-matching methods. However, we should be careful that it might be possible that the data from the present study has no sufficient accuracy and precision to perform the method because there was a significant imbalance in the numbers of vaccinated and unvaccinated women in the original data. For example, the numbers of patients of which the symptom onset time was available are far less than those of patients with symptoms through all symptoms (Table 7). Moreover, as will be described later in (3), it is evident that those are the preliminary results because of the interaction effect between vaccination and age on symptoms experience.

2 | CONCERNING THE INTERACTION

After careful consideration for similarity and linearity of the independent variables and log odds of event occurrence, it was suggested that logistic regression model 2, with the study period as the covariate, did not always fit the data and other approaches should be designed. That is, concerning the interaction, we have made histograms which show the distribution of event rates stratified by age or study period (age-stratified: 24 symptoms × 3 kinds of groups [vaccinated, unvaccinated, and total group] = 72 histograms; study period stratified: 24 symptoms × 2 kinds of groups [vaccinated, unvaccinated] = 48 histograms). Further, we confirmed that the test for interaction between vaccination and age was statistically significant in almost all of the symptoms and that the test for interaction between vaccination and study period was statistically significant in seven symptoms. Based on the above findings, we believe that model 3 is acceptable.

In this regard, we would like to add that Shitara and Morikawa (2018) have also pointed out that we should consider the qualitative and quantitative interaction in their poster presentation at the 2018 Conference of Japanese Society for Pharmacoepidemiology held on October 13–14, 2018. We present the results of tests for qualitative and quantitative interaction in Table 0.

Additionally, in our paper, possible associations between HPV vaccination and each symptom were explored by using standardization with the reference group of the whole participants (Table 8). Moreover, we performed a Mantel–Haenszel analysis with age stratification (data not shown) and confirmed that those results were nearly the same as the results with logistic regression (age-adjustment). However, we would like to note again that the test for qualitative and quantitative interaction was statistically significant. Given those findings, it is evident that the logistic regression model with age as the only covariate, as well as the Mantel–Haenszel methods and the standardization methods do not fit the data of this study.

Now for the difference of the results between Tables 3 and 4, we have already explained our position in our paper as follows: "To explore the interaction effect of vaccination and study period on symptom experience, a multiple logistic regression was used in model 3 (in the section of Statistical analyses)." Further, we have stated as follows: after careful consideration for similarity and linearity of the independent variables and log odds of event occurrence [as described in (2)], it was suggested that logistic regression model 2 did not always fit the data and other approaches should be designed. (Omitted). Therefore we explored the interaction effect of vaccination and study period on symptom experience by using model 3.

3 | POTENTIAL CONFOUNDING BY AGE

When considering the age-adjustment, first of all, we need to confirm that the covariate can be a confounder. Specifically, it is needed that the following assumptions are made: biological age can affect the occurrence of symptoms. However, as described in our article, considering the participants in the present study are young women ranged in age from 15 to 21, it is unnatural that the risk of the disease is naturally higher in older participants compared to younger ones. That is because, age could not be a confounder because of the biological plausibility.

However, we do not necessarily deny that age can be a confounder if it was treated as an alternative to the length of time to recall the experienced symptom. Hence, we considered that age can be used as a confounder and estimated the age-adjusted odds ratios (ORs) by fitting multiple logistic regression model 1 (Table 2). Further, we confirmed that "interaction between vaccination and age (Table 2)" and "interaction between vaccination and study period (Table 3)"

TABLE 0 Results of test for interaction between human papilloma virus vaccination and age

		Vaccinated		Non-vaccinated				
No.	Symptoms	Event (+)	Event (−)	Event (+)	Event (−)	P^a	P^b	P^c
1	Menstrual abnormality	3,603	17,001	2,309	6,696	0.03	0.98	0.00
2	Menorrhagia	1,142	19,427	560	8,434	0.29	0.86	0.23
3	Arthralgia	1,163	19,411	720	8,276	0.00	0.98	0.00
4	Severe headache	1,529	19,083	925	8,097	0.00	0.98	0.01
5	Lassitude	1,831	18,775	1,037	7,984	0.00	0.98	0.00
6	Exhaustion	1,867	18,734	991	8,028	0.00	0.98	0.03
7	Impaired consciousness	1,159	19,425	723	8,294	0.00	0.98	0.11
8	Abnormal visual field	324	20,256	172	8,845	0.01	0.95	0.03
9	Severe photophobia	720	19,881	356	8,662	0.00	0.93	0.00
10	Reduced visual acuity	919	19,670	794	8,221	0.00	0.98	0.00
11	Dizziness	1,836	18,759	1,089	7,927	0.00	0.98	0.17
12	Cold sensation in the legs	1,775	18,807	1,144	7,873	0.06	0.98	0.65
13	Sleep disorder	1,226	19,372	692	8,320	0.00	0.98	0.00
14	Hypersomnolence	1,936	18,632	1,058	7,955	0.00	0.98	0.04
15	Skin roughness	1,497	19,100	1,062	7,950	0.89	0.98	0.96
16	Hyperpnea	536	20,075	335	8,694	0.00	0.98	0.00
17	Memory impairment	559	20,054	217	8,805	0.00	0.00	0.00
18	Dyscalculia	167	20,442	79	8,940	0.00	0.10	0.00
19	Dyslexia	386	20,224	181	8,846	0.00	0.22	0.00
20	Involuntary movement	175	20,436	58	8,964	0.04	0.18	0.01
21	Walking disability	65	20,540	22	8,990	0.06	0.65	0.29
22	Using a cane or wheel chair	26	20,581	16	8,994	0.26	0.98	0.39
23	Sudden attack of muscle weakness	253	20,340	100	8,909	0.01	0.43	0.01
24	Weakness	318	20,224	124	8,862	0.06	0.59	0.64

P-value:
[a]Logistic regression test for interaction.
[b]Gail-Simon test for qualitative interaction.
[c]Breslow-Day test for quantitative interaction.

were statistically significant for many of the symptoms. Based on these findings, we explored the interaction effect of vaccination and study period on symptom experience by using model 3. We believe that the model 3, in which the covariates were vaccination, study period, and the interaction covariate, is at least better than model 1.

4 | SELECTION OF UNVACCINATED CONTROLS

First, Prof. Suzuki mentioned as follows: if the authors want to use these unvaccinated controls then they should also use the vaccinated subjects of the same age (15–16-year-olds). As regards this point, we have already described the results comparing the 15–16-year-old vaccinated cases and 15–16-year-old unvaccinated controls in Table 5.

Second, we showed the results of age-stratified analysis as an example of analysis to minimize the impact of healthy user bias (Table 5). We considered that the 15-year-old group and 16-year-old group can be treated as one group because the impact of healthy user bias is similar in the two groups and presented the crude ORs.

Third, Table 6 also showed the results of the analysis as an example of the exploratory methods to minimize the impact of healthy user bias. We have already stated that in our article. That is, we performed a subgroup analysis using the vaccinated case group in all age groups (they were supposed to have been healthy because they could get vaccinated) and the unvaccinated control group in the 15–16-year-old group (they also were supposed to have been healthy because they chose not to be vaccinated of their own accord). In light of healthy user bias, we believe that comparing the vaccinated cases in all age groups with the unvaccinated controls in the

15–16-year-old group is acceptable as an exploratory analysis to minimize the healthy user bias. We have discussed the limitation of the method of age-adjustment in (3).

Additionally, we could suggest the propensity score analysis as an example of the exploratory methods to control the healthy user bias. For example, we might be able to use the propensity score, defined as the conditional probability of being vaccinated given the baseline data of the participants. However, we would be unable to do the propensity score matching or regression analysis because there is no information on comorbidity or underlying disease of participants. Again, we therefore believe that in light of the limitations of the data, the subgroup analysis using the vaccinated case group in all age groups and the unvaccinated control group in the 15–16-year-old group as an example of the exploratory methods is acceptable.

5 | MULTIPLE COMPARISONS

First, in this regard, we clearly stated as follows in the section of statistical analysis: the results of two-sided testing were shown if necessary with *P*-values, without adjusting for multiplicity. Further, in the Results section, we described as follows: Moreover, in the multivariate analysis, the study period-adjusted ORs (omitted) were >1 and the ORs (omitted) were statistically significant, although they were not adjusted for multiplicity (Table 3).

Second, we agree with Prof. Suzuki's comment that multiplicity issues caused by multiple statistical tests need to be adequately handled. However, we should note that although multiple comparison procedures should be applied in confirmatory trials the main objective of which is to test the effectiveness of the intervention with clear hypothesis, it should not be called in the exploratory studies in which the main objective was to explore some preliminary facts without clear or precise hypotheses or to screen several hypotheses, particularly for safety issues. In light of these considerations, we considered that our method was appropriate.

6 | DECLARATION OF CONFLICT OF INTEREST

As explained in the Editor's reply (Holzemer, 2019), we are confident that there was no irregularity in the proceedings in terms of the fact that the authors disclosed conflicts of interest and the proper reviewing process was carried out.

Yukari Yaju[1]
Hiroe Tsubaki[2]

[1]*Department of Statistics, Graduate School of Nursing Science, St. Luke's International University, Tokyo, Japan*
[2]*The Institute of Statistical Mathematics, Tokyo, Japan*

REFERENCES

Holzemer, W. (2019). Editor's Reply to Letter to the Editor of Dr. Suzuki. *Japan Journal of Nursing Science*, 16, 507–508. https://doi.org/10.1111/jjns.12282.

Shitara, S., & Morikawa, T. (2018). To explore the bias in 'Nagoya City cervical cancer immunization program survey'. *Proceedings of the 24th Conference of Japanese Society for Pharmacoepidemiology* 2018, P1-7, 132 (in Japanese).

Suissa, S. (2007). Immortal time bias in observational studies of drug effects. *Pharmacoepidemiology and Drug Safety*, 16, 241–249.

Suissa, S. (2008). Immortal time bias in pharmaco-epidemiology. *American Journal of Epidemiology*, 167, 492–499.

Suzuki, S. (2019). Letter to the editor: Safety concerns with human papilloma virus immunization in Japan: Analysis and evaluation of Nagoya City's surveillance data for adverse events. *Japan Journal of Nursing Science*, 16, 500–502. https://doi.org/10.1111/jjns.12258.

Suzuki, S. & Hosono, A. (2018). No association between HPV vaccine and reported post-vaccination symptoms in Japanese young women: Results of the Nagoya study. *Papillomavirus Research*, 5, 96–103. https://doi.org/10.1016/j.pvr.2018.02.002.

Yang, X., Kong, A. P., Luk, A. O., Ozaki, R., Ko, G. T., Ma, R. C. *et al*. (2014). Validation of methods to control for immortal time bias in a pharmacoepidemiologic analysis of renin-angiotensin system inhibitors in type 2 diabetes. *Journal of Epidemiology*, 24, 267–273.