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LETTER TO THE EDITOR

Letter to the Editor: 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

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Authors' response to letter to the editor, letter to the editor: 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
Yukari Yaju and Hiroe Tsubaki

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Editor's Reply to the Letter to the Editor of Dr. Suzuki
William L. Holzemer

Dear Editor,

The response letter entitled "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" (Yaju & Tsubaki, 2019b) is extremely disappointing since the authors did not admit their biased analyses and insisted their fairness including the acceptability of model 3. Furthermore, in the reply by the Editor-in-Chief of *JJNS* (Holzemer, 2019), he only described "the purpose of the Letter to the Editor in *JJNS*" is to stimulate discussion". No expert's opinion was published and *JJNS* avoided scientific decision after more than 6 months since I had sent the letter to *JJNS*.

In this short letter, among all invalid concepts and analyses that Yaju and Tsubaki used, I try to explain the reason why the use of study period, especially in model 3 with interaction term, is biased. In Figure 1, the summary of odds ratios of three models in Tables 2–4 in the paper (Yaju & Tsubaki, 2019a) is shown. In several symptoms, considerable differences are observed among three models. In symptom #20, for example, age-adjusted odds ratio was 1.05 (95% CI: 0.76–1.48). However, the odds ratios grew up to 1.53 (95% CI: 1.11–2.13) by study period adjustment, and at last, reached 3.19 (95% CI: 1.17–8.66) with the use of interaction term. They are due to bias and misleading presentation of results. One is the use of biased variable, that is, study period, and the other is the

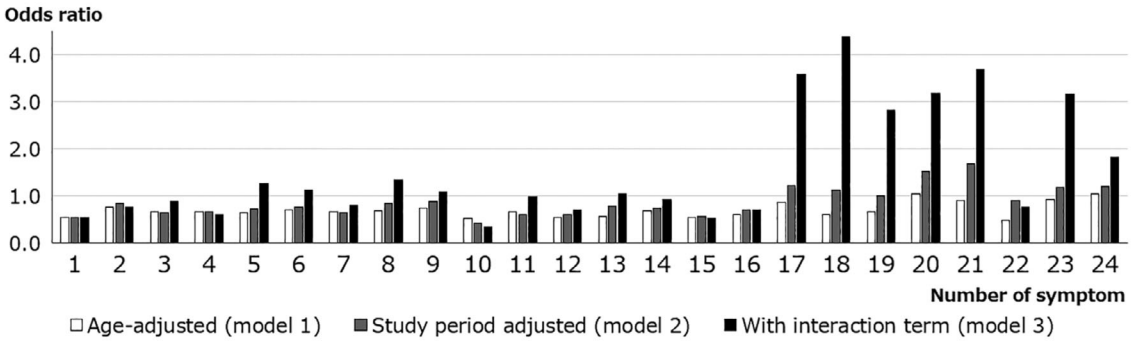

FIGURE 1 The summary of odds ratios of three models

misleading use of the odd ratio of HPV vaccination under the use of interaction term.

1 | STUDY PERIOD

Generally, in an analytic epidemiologic study like this, and as I pointed out in my letter (Suzuki, 2019), comparability between subjects with/without factor is the most important for valid results, and different definitions of variables between these groups easily generates information bias. Yaju and Tsubaki defined the study period as follows (italicized for emphasis by me): "the questionnaire survey period was *defined differently between the vaccinated cases and the unvaccinated controls*: the questionnaire survey period for the vaccinated cases was restricted to the postvaccination period, while the period for the unvaccinated controls was the complete period of the questionnaire survey period (from 12 years of age to the participant's age at September, 2015)." For reference, the distribution of study period by vaccination status from the Nagoya Study (Suzuki & Hosono, 2018) is shown in Table 1. By the definition, "the mean study period for the vaccinated cases (3.9 years) was 0.6 years shorter than that of the unvaccinated controls (4.5 years)" as the authors mentioned in their original article. This description is the same, as vaccinated subjects are older for the same study period than unvaccinated subjects as shown in Figure 2. In the study period adjusted analysis, the vaccinated subjects are compared to younger unvaccinated controls automatically without adjustment for age. That is the reason for the larger odds ratio by study period adjustment than adjustment ones, which is of course invalid.

TABLE 1 The distribution of study period by vaccination status

Study period	Vaccinated	Unvaccinated	Total
0 year	29	0	29
1 year	84	0	84
2 years	1,376	0	1,376
3 years	3,491	3,761	7,252
4 years	8,652	2,038	10,690
5 years	3,805	1,260	5,065
6 years	264	663	927
7 years	0	452	452
8 years	0	428	428
9 years	0	496	496
Total	17,701	9,098	26,799

Here is an interesting simulation using data among 9,098 unvaccinated subjects using data from the Nagoya Study (Suzuki & Hosono, 2018) in order to show the systematic error due to different defined variables between groups. (3)–(5) are performed adhering to the methods by Yaju and Tsubaki.

1. Divide the unvaccinated subjects into two groups quasi-randomly using ID, odd and even group.
2. Give a first vaccinated date to the odd group, median date by age in vaccinated group, under the assumption of odd ID group had been vaccinated. Even ID group was treated as unvaccinated group.

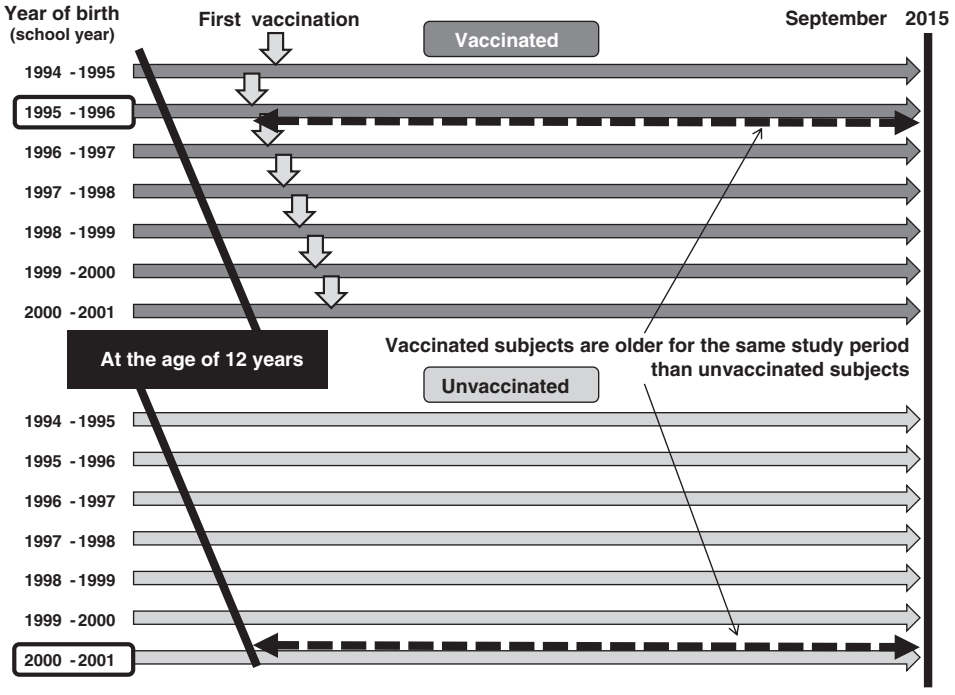

FIGURE 2 The scheme of study period by vaccination status

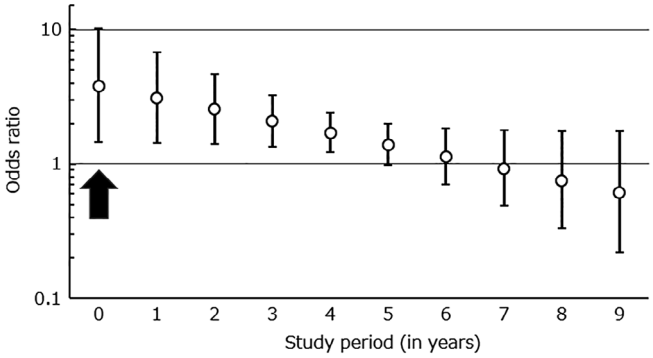

FIGURE 3 Change in the odds ratio and 95% confidence interval with study period for symptom #20

3. Define the study period differently between odd and even groups.
4. Treat symptom cases as without symptom if given vaccinated date is after the symptom occurrence among the odd group.
5. Calculate the odds ratios of unadjusted and adjusted for study period in symptoms #17, #18, #19, and #20 using logistic regression.

The unadjusted odds ratios of the odd ID group for symptoms #17, #18, #19, and #20 were 0.86 (95% CI: 0.65–1.13), 1.02 (95% CI: 0.65–1.61), 1.02 (95% CI: 0.76–1.38), and 1.10 (95% CI: 0.65–1.88), respectively. The results are very natural since odd ID is not a risk factor. However, by adjustment for study period the odds ratios elevate with significance as follows: 2.19 (95% CI: 1.46–3.28) for symptom #17, 3.61 (95% CI: 1.77–7.38) for symptom #18, 2.72 (95% CI: 1.74–4.25) for symptom #19, and 2.20 (95% CI: 1.00–4.83) for symptom #20. Of course, odd ID could not be a risk factor, and this systematic error is due to the biased definition of study period that Yaju and Tsubaki used in their analysis. In addition, almost identical results were obtained when odd and even groups were switched.

Therefore, the significantly high odds ratio that Yaju and Tsubaki presented in Table 3 in their paper using model 2 is due to invalid adjustment for study period, not due to HPV vaccination.

2 | INTERACTION

After reading the section "2. concerning the interaction" in the response to the letter, how many readers could understand the difference of models 3 and 4 (see Figure 1 in this letter)? Yaju and Tsubaki never answer the question, to whom the odds ratios in model 4 are applied which are not common and should be applied to only specific subjects. In the question I insisted that it is quite unfair to present only one specific odds ratio in their Table 4 without any explanation in it (see Figure 3 in this letter).

By taking an interaction term into account, different odds ratios are allowed by strata, that is, study period in this case. If the interaction term is defined by the product of study period in year (0–9) and HPV vaccination (vaccinated = 1, unvaccinated = 0), the odds ratios for HPV vaccination term decreased with study period (Figure 3, for symptom #20). Therefore, presentation of only one odds ratio in Table 4 in their paper, being the highest, is misleading, and Yaju and Tsubaki never answered the question in the response. Furthermore, odds ratios for study periods of 0, 1, 2, 7, 8, and 9 years are meaningless, since there is no vaccinated or unvaccinated subject by definition (Table 1), and they are only extrapolated from the regression model. Therefore, the odds ratios in Table 4 in the paper by Yaju and Tsubaki using model 3 are extremely misleading and totally unfair.

3 | COI

Yaju and Tsubaki wrote "there was no irregularity in the proceedings in terms of the fact that the authors disclosed conflicts of interest". However, the fact is that Dr. Yaju did not declared that she is a member of Medwatcher Japan. How can the readers believe in the paper without knowing who/what she is? Furthermore, Yaju and Tsubaki, and also *JJNS*, should explain how Yaju and Tsubaki could see the Editor's reply that Yaju and Tsubaki cited (Holzemer, 2019, first published: August 26, 2019) before the received date (May 18, 2019). Of course, I did not know what the Editor replied to me before the publication date. It is obvious that Yaju and Tsubaki, and *JJNS* communicated improperly. It is impossible to believe that the policy of *JJNS* is fair.

In conclusion, I request the retraction of the paper by Yaju and Tsubaki (2019a) again.

ORCID

Sadao Suzuki https://orcid.org/0000-0001-5988-4849

Sadao Suzuki

Department of Public Health, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

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