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LETTER TO THE EDITOR

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

We write to express our concerns and extreme disappointment at the publication of the article entitled "Safety concerns with human papilloma virus immunization in Japan: Analysis and evaluation of Nagoya City's surveillance data for adverse events" by Yaju and Tsubaki (2019) in the *Japan Journal of Nursing Science* on January 28, 2019. This publication came just 1 week after the World Health Organization (WHO) announced that vaccine hesitancy was one of the top 10 threats to global health (WHO, 2019).

This paper is a re-analysis of the publicly available human papillomavirus (HPV) vaccine surveillance of Nagoya City and reaches a completely different conclusion from that of the original analysis by Suzuki and Hosono (2018). While we strongly support stringent safety monitoring for all vaccines and actively encourage research that helps to investigate and elucidate all reported adverse events, we believe the methods used in the analysis by Yaju and Tsubaki (2019) are incorrect and as a result, the interpretation and conclusions erroneous. Furthermore, we also feel it is important to draw the editor's attention to the fact that the first author, Yukari Yaju, failed to disclose she is a member of Medwatcher Japan (http://www.yakugai.gr.jp/en/), an organization which continues to promote anti-HPV vaccine activity, both in Japan and globally, and the Secretary General of which, Ms Masumi Minaguchi, is the Joint Representative of the National Attorneys' Association for the HPV Vaccines Lawsuits in Japan.

Close to 300 million doses of HPV vaccines have been globally distributed. Prior to their introduction HPV vaccines have been successfully tested for both effectiveness and safety. Post licensure investigations have been performed by the US Centers for Disease Control, the European Medicines Agency (2015), as well as repeated systematic investigations by the WHO's Global Advisory Committee on Vaccine Safety on all safety allegations toward HPV vaccination (WHO, 2013; WHO, 2017). As with our original analysis of the data, these investigations continue to conclude there are no issues with HPV vaccine safety. The paper by Yuji and Tsubaki adds nothing to the scientific discourse concerning the alleged adverse events following HPV vaccination in Japan. However, it does seek to erode trust in HPV immunization programs, both in Japan and globally, the public health consequences of which can be devastating.

Major issues with the article are as follows:

1 | SYSTEMATICALLY DIFFERENT "STUDY PERIOD" BETWEEN VACCINATED AND UNVACCINATED SUBJECTS

In order to investigate "causality" the authors introduce the concept of "study period". They treated vaccinated subjects with symptoms prior to the first vaccination as vaccinated

cases with no symptoms. To do this is correct if data on time frame are comparable between vaccinated girls and unvaccinated controls. However, we only have data on this time period for vaccinated subjects. The time period investigated for the unvaccinated girls is the whole study period. For valid causal inference, the concept of counterfactual is indispensable. For the unvaccinated controls, the counterfactual commencement period should be "the time when the girls should have been vaccinated" and not the commencement of the study time frame as used by Yaju and Tsubaki. This systematic difference between vaccinated girls and unvaccinated controls generates bias. Thus, the "study period" should not be used throughout the study for internal validity. If the time frame is systematically longer in one group and shorter in the other, the resulting odds ratios will be biased. Therefore, it is improper to use the study period as a variable in the regression analysis. The reason why the authors have chosen to use the study period as a variable is unclear, unless by intentionally not adjusting for age where the age of those in the vaccinate group would be higher than those in the unvaccinated group, they wanted to obtain inflated odds ratios.

2 | MISLEADING MEANING OF THE MAIN EFFECT UNDER THE INTERACTION TERM

In model 3, (Table 4) the authors claim there is interaction between vaccination and the study period. In this context, interaction means the effect of the HPV vaccine is different depending on the study period. Therefore, when the authors present the odds ratios for vaccination, they should mention to which subjects the odds ratios apply since they will differ by group. For example, the odds ratio for dyscalculia (#18) is high at 4.37. However, this only applies to a specific group (or even imaginary subjects since it depends on the definition of the interaction term which is not stated). The way in which the discussion is written implies that this applies to all subjects. To be more specific, the authors write: "four symptoms demonstrated [odds ratios] that were >1 with statistical significance (p.9, left column, l.5)" and "suggesting that there is an association between HPV vaccination and these symptoms (p.9, left column, l.13)". However, to whom these odds ratios refer is unclear. They write the discussion as if the interaction term were a confounder. The uninformed reader may easily misunderstand what is being presented and think the odds ratios are general ones after some "adjustment" for a significant interaction. The meaning of the "study period-adjusted" odds ratios in Table 3 and Table 4 is conceptually different. However, nothing is mentioned about the difference, which is intentionally misleading and unacceptable.

3 | INABILITY TO UNDERSTAND THE CONCEPT OF AGE ADJUSTMENT

With regard to age as a confounder, in the Discussion section, the authors insist that the data "did not meet the assumption' (p.13, right column, l.1)" for confounding effect for age. This is incorrect. If and only the following three conditions are met, then age is a cofounder between HPV vaccination and the symptom: (a) age is an independent risk factor for the symptom, (b) age is associated with HPV vaccination, and (c) age is not an intermediate factor between the causal pathway of HPV vaccination to the symptom. Put simply, if the unadjusted and age-adjusted odds ratios differ, this difference comes from the confounding effect of age, and therefore we should use age-adjusted odds ratios. For example, in Table 5, the odds ratio for dyscalculia (#18) among subjects aged 15 years is 2.30. That of subjects 16 years is 2.25. These numbers are similar and the odds ratio among subjects 15–16 years should be somewhere between 2.25 and 2.30. However, it is 1.77; this is due to the fact that age is a confounder. To say age should not be adjusted for is incorrect and to not adjust for age would be unscientific. Unadjusted odds ratios are therefore biased and should not be used in the final results. Finally, the authors state, "it appears more reasonable to assume that the study period is more appropriate than age as a covariate (p.14, left column, l.13)". All necessary covariates should be incorporated into the model. The argument of which covariate is more appropriate is meaningless here. The fact that age is not adjusted for, not only implies a lack of scientific rigor on the authors' part, but also on that of the reviewer(s), suggesting they were not qualified to review the paper.

4 | BIASED SELECTION OF UNVACCINATED CONTROLS

In Table 6, the authors used the unvaccinated girls aged 15–16-years old as the controls. This will result in bias. This age group could only be used as the controls if there were no confounding effect of age which we have explained above in section (3) that this is not the case. 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). The biased setting of the control group generates higher odds ratios. Furthermore, even for an analysis of the subgroup, 15–16-year-olds, age adjustment is also necessary.

5 | LACK OF MULTIPLE COMPARISON

In statistics, the multiple comparisons, or multiplicity problem occurs when a set of statistical inferences is considered

simultaneously. In this case some will have *p* values less than .05 purely by chance, even if all the null hypotheses are true. To address this issue multiple comparisons should be done to prove the association. For example, this is often done by dividing .05 by the number of inferences, in this case 24 (Bonferroni correction) and statistical significance should therefore be set at .05/24 which is <.002. The authors ignored the alpha error on purpose and applied 5% error level to each comparison. The lack of multiple comparison overestimates the probability of the association between HPV vaccination and symptoms. Once again this should have been pointed out by the reviewers and further suggests the paper did not undergo robust peer review.

6 | LACK OF DECLARATION REGARDING POTENTIAL OR ACTUAL CONFLICTS OF INTEREST AND FUNDING

As mentioned previously, Yukari Yaju, failed to disclose she is a member of Medwatcher Japan, an organization that continues to promote anti-HPV vaccine activity, both in Japan and globally, and the Secretary General of which, Ms Masumi Minaguchi, is the Joint Representative of the National Attorneys' Association for the HPV Vaccines Lawsuits in Japan. While Medwatcher is vague on how its activities are funded, if they were to benefit financially from the class-action lawsuit then publishing a paper to help achieve this aim would be considered a conflict of interest. Even if Medwatcher did not directly benefit financially, the publicity it would receive if they were to win the lawsuit would be great and as such the first author's affiliation with the organization is at least a potential conflict of interest. The International Committee of Medical Journal Editors declaration form used by the *Japan Journal of Nursing Science* requires that any potential conflict of interest also be declared. The first author had to disclose she was a member of Medwatcher in a previous paper on the HPV vaccine (Beppu et al., 2017). Furthermore, no mention is made on where the authors got funding for the study. The paper is open access so the source of the funding ($2,500?) for this needs to be declared, as does the source of any funding if a professional English editing service was used. Finally, the role of both authors in the analysis and writing of the paper should be declared.

In general, two completely different sets of results from the same data investigating the same outcomes are not acceptable. The overwhelming conclusion of experts globally is that a large volume of scientifically robust evidence demonstrates the safety of HPV vaccines. We believe our original paper with the analysis of the Nagoya data is part of this evidence. In our opinion, the *Japan Journal of Nursing Science* published this paper without a sufficiently rigorous peer review process. If reviewers were selected by the authors or were selected from authors in the reference list of the paper, there is a chance that these reviewers have published similar anti-vaccine pseudo-science. We are confident that Wiley Publishing Group and the *Japan Journal of Nursing Science* would not wish to support pseudo-science. This severely flawed work by Yaju and Tsubaki will feed anti-vaccine groups with more misinformation with which they seek to damage the reputation of one of the most important advances in medicine in the last half-century, the development of a vaccine to prevent HPV-related cancer morbidity and mortality and for this reason we ask that the paper is retracted.

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