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Correspondence

Letter to the Editor: Effectiveness of the Varicella Vaccine Among Korean Children: Suggestions for Future Research

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Choi B, Cho H, Shin Y, and Lee EK are employees of GC Pharma, a pharmaceutical

We read with interest the paper by Hong et al.[1] about the effectiveness of one-dose universal varicella vaccination (UVV) among Korean children. In the first birth-cohort study among Korean children, the authors reported a moderate level (49.9–86.1%) of one-dose vaccine effectiveness (VE) against varicella. The authors' finding is in strong contrast with a low level (13.0%) of varicella VE reported in a previous case-control study.[2] But it was generally in line with our position[3,4] based on a case-coverage simulation analysis that the real VE against varicella in the previous case-control study would have been 65–90% if selection bias would have been corrected.

Having said that, in this letter, we would like to point out and discuss three major methodological and interpretational issues in the authors' paper with regard to the VE against varicella among Korean children. Also, we would like to make some suggestions for resolving the issues in future cohort studies.

First, we think that the moderate level of varicella VE reported in the authors' paper may have been underestimated. For estimating the VE, the authors compared the incidence rates of varicella between the vaccinated and unvaccinated groups in the 2011 Korean birth cohort. However, the unvaccinated group was very small (2.5%) relative to the large vaccinated group (97.5%) in the cohort, reflecting the contemporary high coverage of varicella vaccines among Korean children since the introduction of one-dose UVV program in 2005. Despite the authors' propensity score matching (PSM), we are not completely sure of the comparability between the vaccinated and unvaccinated groups. The authors did not show whether the number of outpatient visits per year was comparable between the vaccinated and unvaccinated groups after the PSM.[1] In addition, the unvaccinated group, defined as children without records of varicella vaccination in the national immunization registry, is likely to include either children who were actually vaccinated abroad, but misclassified as unvaccinated,[5,6] or children who were intentionally unvaccinated and when infected by varicella, did not seek needed health care due to their parents' belief for natural immunization over vaccination (e.g., national chickenpox party).[7] Thus, we think

company in Korea. However, the aim of the submitted manuscript as a correspondence is to discuss methodological and interpretational issues in epidemiological research on the effectiveness of the varicella vaccine in Korea. Any specific product of GC Pharma was not discussed in the submitted manuscript.

Author Contributions

Conceptualization: Choi B. Data curation: Choi B. Formal analysis: Choi B. Investigation: Choi B, Cho H, Shin Y, and Lee EK. Writing - original draft: Choi B. Writing - review & editing: Cho H, Shin Y, and Lee EK.

that the incidence rate of varicella could have been underestimated disproportionately in the unvaccinated group, which in turn may have resulted in an underestimated VE against varicella in the authors' study.

On the other hand, several researchers[8,9] have used historical controls (i.e., age-specific varicella incidence rates in unvaccinated children prior to the introduction of one-dose UVV program in the United States) as the comparator for estimating the VE of varicella in vaccinated children. However, such historical control information in Korean unvaccinated children is not yet available in the literature, although it seems to be possible to have access to the data of the Korean birth cohorts before the start of one-dose UVV program in 2005.[10] We think that, given the current high coverage of varicella vaccines among Korean children, using both internal and external (historical) controls for evaluating the varicella VE will generate more robust results in future cohort studies.

Second, we think that the authors may have inadvertently misled the readers to believe that the incidence rate of breakthrough varicella in Korea is comparatively high: "In this study, we found a substantial incidence density of breakthrough varicella of 23.3 per 1,000 person-year (95% CI, 23.1–23.4). In a pooled analysis… the incidence rate of breakthrough varicella…was 8.5 cases per 1,000 person-year (95% CI, 5.3–13.7) …" A summary estimate from a meta-analysis of extremely heterogeneous studies is very unlikely to represent individual studies included in the meta-analysis. In the paper, the authors neither presented nor considered a very high level of heterogeneity (I^2, 99.8%) among the thirty cohort studies included in the pooled meta-analysis[11]: the incidence rate of breakthrough varicella significantly varied from 0.5 to 61.9 cases per 1,000 person-years. The incidence of breakthrough varicella reported in the authors' study, whether the vaccine strain was Oka or MAV, fell within the aforementioned wide range of breakthrough varicella incidence from other countries in the literature. Also, as we said elsewhere,[4] it is generally comparable to those (21.7–28.3/1,000 person-years)[12,13] from the United States after one-dose UVV program. In future cohort studies, we think that more careful and appropriate comparisons should be made between Korea and other countries bearing in mind the very heterogeneous results of existing cohort studies in the literature.

Third, in the paper, the authors said "PSM analysis cannot be applied for the analysis of VE by the vaccine type. In the retrospective cohort analysis…the vaccine that contains MAV strain showed the highest incidence, while three remaining vaccine types that contain Oka strain had lower rates, indicating potential difference in VE between strains." We think that the potential vaccine strain-differential incidence suggested by the authors should be cautiously reexamined and confirmed in future cohort studies. The authors' observation is not consistent with the results of previous experimental and epidemiological studies. In the two experimental studies,[14,15] the immunogenicity between Oka-strain and MAV-strain varicella vaccines was very similar to each other. In the two case-control studies in Korean children,[2,16] there was no clear-cut difference in the VE against varicella by strain type. Furthermore, very little information about the analysis of the potential difference in VE by vaccine strain was provided in the authors' paper so we could not assess its validity. We think that in future cohort studies for addressing this issue, the following information needs to be clearly presented and considered in analysis: the degree of validity about the records of vaccine manufactures in the national immunization registry[17,18]; the ending point of the follow-up for estimating the VE of one-dose UVV considering potential differences by vaccine type in the rates and timings of the secondary vaccination (albeit currently not recommended as part

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of the national immunization program for children in Korea); and the extent of missing data by vaccine strain for the secondary vaccination.[6]

We agree with the authors that more cohort studies and cost-effectiveness studies for identifying and determining an optimal timing of secondary varicella vaccination among Korean children are urgently needed in the near future. We hope that the aforementioned three major issues and our suggestions for resolving the issues are taken into consideration in the future studies.

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