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Changes in vaccination practices among infants after the introduction of DTaP-IPV/Hib combination vaccines

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ABSTRACT

Background: Diphtheria-tetanus-acellular pertussis, polio, and Haemophilus influenza type B (DTaP-IPV/Hib) combination vaccine was introduced as a part of the Korea National Immunization Program (NIP) on June 19, 2017. Combination vaccines can improve vaccination rates by simplifying the vaccination schedule.
Objective: To explain how the introduction of DTaP-IPV/Hib in the NIP has changed vaccination practices for infants.
Methods: Using a nationwide vaccine registry, the proportion of infants who completed the full recommended doses of the primary series of DTaP, IPV, and Hib (D-I-H) within 12 months of age was estimated among those born between 2013 and 2019. Among those, the proportions of those who received the same DTaP components for all 3 doses during the primary series were calculated for the 2013–2016 and the 2017–2019 birth cohorts. Those who received the same component of DTaP throughout the entire primary vaccination schedule were categorized into 3 groups by DTaP components to compare the average frequency of medical visits for vaccination.
Results: A total of 2,703,822 infants were born between 2013 and 2019, of which 96.7% completed full doses of the primary D-I-H series within 12 months of age. For the 2013–2016 birth cohorts, most received DTaP-IPV-only (75.4%), while most of the 2017–2019 birth cohorts received DTaP-IPV/Hib-only (81.0%) to complete the 3 doses for primary D-I-H series. The average frequency of medical visits for vaccination showed a significant difference across the 3 groups classified by DTaP components in every birth cohort ($p < 0.001$).
Conclusions: After the introduction of DTaP-IPV/Hib, most infants completed the primary D-I-H series with the combination vaccine and there was a significant reduction in the average number of medical visits for vaccination. Our findings provide important insights for countries considering the introduction of combination vaccines into their NIP.

1 Background

Vaccination during childhood can early prevent life-threatening infectious diseases that can lead to mortality. Thus, many countries encourage infant vaccination by providing guidance on regular immunization schedules and by implementing NIP [1,2]. Korea launched the NIP for children in 2009 to prevent various infectious diseases in children under 12, administering vaccines free-of-charge at public health centers or designated medical institutions. Many vaccines included in NIP are administered either as single or multiple doses to children.

Multiple visits to medical institutions are required especially for infants because of the various types of vaccines and their schedules. According to previous studies, the burden of multiple visits in a short period of time or receiving multiple shots per day to comply with the recommended vaccination schedule causes vaccine hesitancy [3,4]. Up to 20 doses against 10 diseases (diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* type b, hepatitis B, pneumococcal conjugate, Bacille Calmette-Guérin, Rotavirus, seasonal influenza) may be required by 12 months of age if all recommended vaccines are completed using separate stand-alone vaccines. Combination vaccines that have multiple antigens combined can serve as a solution to this problem, thereby increasing vaccination coverage. Indeed, several combination vaccines

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containing DTaP which is commonly required for infants worldwide have been developed, such as DTaP-IPV, DTaP-IPV/Hib, and diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* type b, and hepatitis B (DTaP-IPV-Hib-HepB). Korea introduced the DTaP stand-alone vaccine to NIP in March 2009, followed by DTaP-IPV combination vaccine in October 2011 and the DTaP-IPV/Hib combination vaccine in June 2017.

Although most previous studies have demonstrated that the convenience of combination vaccines has had a positive impact on improving vaccine coverage and timely administration [5–7], some studies have raised concerns from parents regarding the safety of administering multiple antigens simultaneously or receiving multiple DTaP products interchangeably [8–11]. This potential ambivalence surrounding the use of combination vaccines may bring changes in infant vaccination practices, but there are few studies that have comprehensively assessed this issue. Therefore, we aimed to assess the overall changes in vaccination coverage and practices for infants before and after the introduction of the DTaP-IPV/Hib combination vaccine into NIP.

2. Methods

2.1. Database

To conduct this descriptive study, we used the national immunization registry from Korea Disease Control and Prevention Agency (KDCA) between 2009 and 2020. The database was linked to National Health Information database from National Health Insurance Service (NHIS) between 2009 and 2021. The KDCA database contains all vaccination records NIP as well as non-NIP for infants born between January 1, 2009 and December 31, 2019 who received at least one dose of DTaP-containing vaccine by 24 months of age. The KDCA database is collected through electronic submission of information by vaccine providers. It contains the details of all the vaccines administered to recipients, including their demographic characteristics, types of vaccines administered, the date of vaccination, dosing schedule, and medical institutions that provided vaccines. The NHIS database covers the entire Korean population and provides information on all medical services used by citizens and reimbursed by the government. However, the combined database we used for the study had access only to the medical records of children registered with the KDCA database. The diagnostic status was recorded with the International Classification of Diseases, 10th revision codes. All personal information from KDCA and NHIS database had been de-identified and provided to us by NHIS.

2.2. Recommended vaccines for infants by NIP

As of November 2023, the Korean NIP requires the following vaccinations for all infants up to 12 months of age: 3 doses of DTaP, 3 doses of IPV, 3 doses of Hib, 3 doses of Pneumococcal conjugate vaccine (PCV), 3 doses of HepB, 1 dose of Bacille Calmette-Guérin (BCG) and 2 or 3 doses of rotavirus (RV) **(Supplementary Table 1)**. The RV vaccine introduced into NIP after March 2023 was not applicable in our study period. The DTaP, IPV, HepB, and BCG vaccines were introduced in March 2009, followed by the DTaP-IPV vaccine in October 2011, the Hib vaccine in March 2013, and the PCV vaccine in May 2014 into NIP. The DTaP-IPV/Hib combination vaccine, which is the focus of our research, has been part of the NIP since June 19, 2017.

2.3. Study population

Our study population was limited to infants born between January 1, 2013 and December 31, 2019. This is to capture all of their DTaP, IPV, and Hib vaccination records, because the Hib vaccination records were included only after March 2013 in the KDCA database, while the DTaP and IPV administration records have been documented since March 2009. Among them, those who received at least one dose of the DTaP-containing vaccine within 12 months of age were eligible for our study. Infants who never received DTaP-containing vaccines or died within the first 12 months of age were excluded from this study. Moreover, to ensure data accuracy, infants with records of receiving more than one dose of DTaP, IPV, or Hib vaccines within 6 weeks of birth, four or more doses of DTaP, IPV, or Hib vaccines within the first 12 months of age, or inaccurate records related to the dosing schedule were excluded from our study.

2.4. Perspectives for observing changes in vaccine practices

Our study focused on three aspects to observe changes in vaccine practices among infants. First, we assessed the completion coverage rate of the primary D-I-H vaccine series. This was calculated by dividing the number of infants who received all three recommended doses of DTaP, IPV, or Hib vaccines within the first 12 months by the total number of births from Korean Statistical Information Service (KOSIS) [12]. The D-I-H vaccine series includes separate DTaP, IPV, and Hib vaccines classified as stand-alone, and DTaP-IPV and DTaP-IPV/Hib combination vaccines. Second, we estimated the proportion of infants who received the same DTaP component vaccine for all three doses among those who completed the primary D-I-H series. There are 27 [exp(3*ln(3))] possible administration patterns consisting of DTaP, DTaP-IPV, and DTaP-IPV/Hib, if infants complete the primary D-I-H vaccination series. However, the national vaccination guidance recommends administering the same components for all 3 doses of the primary DTaP series because of insufficient evidence for product interchangeability [13]. The DTaP-IPV/Hib combination vaccine expanded vaccination options and may have potentially influenced the established DTaP dosing practices. We categorized the birth cohort who completed the primary D-I-H series into two groups: those born in 2013–2016 and in 2017–2019. For each group, we then calculated the proportion of infants who completed the 1st to 3rd doses with the same DTaP component. Lastly, those who completed all primary D-I-H series with the same components were categorized into 3 groups (Group 1: 3 doses of DTaP, Group 2: 3 doses of DTaP-IPV, Group 3: 3 doses of DTaP-IPV/Hib) to calculate the average number of medical visits for their vaccination. The number of medical visits can include visits for non-NIP vaccination as well as NIP. Completing all NIP-recommended vaccines individually as separate products, except for the 3 doses of RV vaccine, by 12 months after birth, will require a maximum of 16 medical visits. However, this number can be lowered to fewer than 10 if combination vaccines are used.

2.5. Statistical analysis

The coverage rates of completing the primary D-I-H vaccine series were calculated by dividing the number of infants who completed primary D-I-H series by the total number of births each year from KOSIS. The chi-square analysis was conducted to calculate the difference in terms of frequency and baseline characteristics between those who completed and those who did not complete D-I-H vaccinations. Baseline characteristics include demographic and socioeconomic status at the first administration of DTaP (gender, parental income level, type of medical institution that provided DTaP vaccine, status of parental health security, and residence) and comorbidities during the first 12 months of age (low birth weight, birth injury, perinatal infection, small for gestational age, congenital anomaly, cancer, anaphylaxis, Bell's palsy, and intussusception). For the three groups that we classified by the components of DTaP, we presented the average, median, and interquartile ranges (IQR) of visit numbers to medical institutions in each box plot stratified by birth cohort. IQR is the distance between the 25th percentile (Q1) and the 75th percentile (Q3). The upper whisker extends from the Q3 to the largest value no further than 1.5 times the IQR and the lower whisker extends from the Q1 to the smallest value at most 1.5 times the IQR. Within each birth cohort, the difference in the number of medical visits was evaluated for the two-group comparison by Wilcoxon test and for three- group comparisons by Welch's one-way analysis of

variance (ANOVA) with a post hoc Tamhane's T2. P-value <0.05 was considered to be statistically significant for the difference. All analyses were performed using SAS enterprise guide 7.15 (Cary, NC. SAS Institute Inc.).

3. Results

3.1. Completion rates for primary D-I-H series and characteristics of the study population

Of 2,703,822 infants born between 2013 and 2019 according to KOSIS, a total of 2,613,501 infants, who were extracted from the KDCA database, completed the D-I-H primary series, representing 96.7% of all births (Table 1). The number of births decreased every year, but completion rates for primary D-I-H series increased annually over the birth years from 2013 to 2019, with rates of 95.1% in 2013, 96.1% in 2014, 96.5% in 2015, 97.0% in 2016, 97.1% in 2017 and 97.8% both in 2018 and 2019. Compared to infants who did not complete the D-I-H series, those who completed were more likely to belong to high-income households (46.5% vs. 38.8%), receive vaccinations at more advanced healthcare institutions (32.2% vs. 25.0%), have perinatal infections (14.0% vs. 12.5%), or have congenital anomalies (18.9% vs. 14.8%) (Table 2).

3.2. Administration patterns of DTaP components during primary D-I-H series

In the entire birth cohort that completed the primary D-I-H vaccine series, 96.4% of those infants received all 3 doses with the same DTaP component. After categorizing birth cohorts before and after NIP introduction, we found that 98.8% of the 2013–2016 birth cohort and 92% of the 2017–2019 birth cohort received 3 doses with the same DTaP component (Table 3). In the 2013–2016 cohort, the majority completed all the primary doses of DTaP with the DTaP-IPV combination vaccine (75.4%), followed by the DTaP stand-alone vaccine (23.2%), and DTaP-IPV/Hib combination vaccine (0.2%). However, in the 2017–2019 cohort, the majority completed all primary doses of DTaP with DTaP-IPV/Hib combination vaccines (81.0%), followed by DTaP stand-alone vaccine (7.3%), and DTaP-IPV combination vaccine (3.7%). The overall DTaP administration pattern including infants who did not receive the same DTaP components, is detailed in **Supplementary Fig. 1**.

3.3. Frequency of medical visits for vaccination according to the DTaP components

Trends in the average and median medical visits for vaccination across the 3 groups categorized by components of DTaP vaccines in every annual birth cohort were illustrated in the boxplot (Fig. 1). Within each birth cohort, the estimates of average visits showed significant differences across the 3 groups ranging from 8.7 to 8.9 for the DTaP-IPV/Hib vaccine group (Group 3, green box), 9.7 to 10.5 for the DTaP-IPV vaccine group (Group 2, red box), and 10.7 to 11.3 for the DTaP vaccine group (Group 1, blue box) ($p < 0.001$). Group 3 had about 2 fewer mean medical visits than group 1 and about 1 fewer than group 2 ($p < 0.001$).

Table 1
Proportion of infants who completed the primary DTaP, IPV and Hib vaccine series within 12 months of age.

Birth year	Number of births[a] N	Complete primary D-I-H series N (%)	Incomplete primary D-I-H series N (%)
Total	2,703,822	2,613,501 (96.7)	64,300 (2.4)
2013	436,455	415,003 (95.1)	14,849 (3.5)
2014	435,435	418,346 (96.1)	12,078 (2.8)
2015	438,420	423,151 (96.5)	11,361 (2.6)
2016	406,243	393,976 (97.0)	8,930 (2.2)
2017	357,771	347,476 (97.1)	7,519 (2.1)
2018	326,822	319,527 (97.8)	4,990 (1.5)
2019	302,676	296,031 (97.8)	4,573 (1.5)

Abbreviations: D-I-H = DTaP, IPV, and Hib vaccine.

[a] Referred from Statistics Korea. There is a slight gap between the total number of births reported by Statistics Korea and the sum of complete and incomplete vaccination births in our study population. This gap could occur because of such as infants who have never received DTaP vaccinations by 2 years of age or who meet our study exclusion criteria.

Table 2
Characteristics of study population.

	Complete primary D-I-H series		Incomplete primary D-I-H series	
	N	(%)	N	(%)
Total (in KDCA vaccine registry)	2,613,501		64,300	
Total (in NHIS claims database)[a]	2,604,939	(100.0)	62,357	(100.0)
Gender				
Male	1,335,667	(51.3)	32,733	(52.5)
Parental health security				
Employer-sponsored	2,056,829	(79.0)	38,568	(61.9)
Self-employed	537,951	(20.7)	22,905	(36.7)
Medical aid	10,159	(0.4)	884	(1.4)
Household income level[b]				
Low	324,963	(12.5)	12,077	(19.4)
Middle	973,648	(37.4)	23,340	(37.4)
High	1,211,021	(46.5)	24,197	(38.8)
Unknown	95,307	(3.7)	2,743	(4.4)
Type of medical institutions for 1st dose of DTaP				
Hospitals	837,237	(32.2)	15,514	(25.0)
Clinics	1,495,834	(57.4)	38,423	(61.6)
Public centers	271,313	(10.4)	8,307	(13.3)
Unknown	555	(0.0)	113	(0.1)
Residence				
Urban	1,178,982	(45.3)	26,241	(42.1)
Comorbidities during first 12 months of age				
Small for gestational age	13,171	(0.5)	251	(0.4)
Low birth weight	140,792	(5.4)	3,447	(5.5)
Birth injury	38,941	(1.5)	690	(1.1)
Perinatal infections	365,434	(14.0)	7,781	(12.5)
Congenital anomaly	491,085	(18.9)	9,242	(14.8)
Cancer	4,136	(0.2)	301	(0.5)
Anaphylaxis	1,173	(0.1)	28	(0.0)
Bell's palsy	696	(0.0)	17	(0.0)
Intussusception	10,818	(0.4)	284	(0.5)

Abbreviations: D-I-H = DTaP, IPV and Hib vaccine; KDCA = Korea Disease Control and Prevention Agency; NHIS = National Health Insurance System.

[a] Demographic data for 10,505 (8,562 + 1,943) infants recorded in KDCA vaccination registry were not available in the National Health Insurance System claims database.

[b] Income level ranges from 1 to 10, where higher numbers indicate higher levels. We categorized the 1–4 level as low, the 5–7 level as middle, and the 8–10 level as high.

4. Discussion

This nationwide study sought to evaluate the impact of introducing the DTaP-IPV/Hib vaccine into NIP on infant vaccination practice. In total, 96.7% of infants born between 2013 and 2019 completed primary vaccination series of D-I-H by 12 months of age, exhibiting a higher coverage rate than global averages [14–17]. There was a steady increase in the rate over the birth years (from 95.1% in 2013 to 97.8% in 2019). In particular, in 2018, when the DTaP-IPV/Hib vaccine was introduced, there was 0.7 percentage point increase from the previous year, the largest increase except for the 2013–2014 period when the Hib vaccine was introduced into NIP. Previous clinical trials conducted among Korean infants before the introduction of DTaP-IPV/Hib into NIP demonstrated the immunological non-inferiority of the DTaP-IPV/Hib combination vaccine compared to separate DTaP-IPV and Hib vaccine administration. Although there was no significant difference in the

Table 3
Patterns of DTaP-containing vaccine series administered to infants born between 2013 and 2019.

	Total birth cohort		Birth cohort 2013–2016		Birth cohort 2017–2019	
	N	(%)	N	(%)	N	(%)
Completed primary D-I-H vaccination series	2,613,501		1,650,476		963,025	
Three doses of the same components	2,517,099	(96.4)	1,630,093	(98.8)	887,006	(92.0)
Three doses of DTaP	453,616	(17.4)	383,079	(23.2)	70,537	(7.3)
Three doses of DTaP-IPV	1,280,541	(49.0)	1,244,497	(75.4)	36,044	(3.7)
Three doses of DTaP-IPV/Hib	782,942	(30.0)	2,517	(0.2)	780,425	(81.0)

Abbreviations: D-I-H = DTaP, IPV and Hib vaccine; DTaP = diphtheria-tetanus-acellular pertussis; DTaP-IPV = diphtheria-tetanus-acellular pertussis and polio; DTaP-IPV/Hib = diphtheria-tetanus-acellular pertussis, polio and Haemophilus influenzae type b.

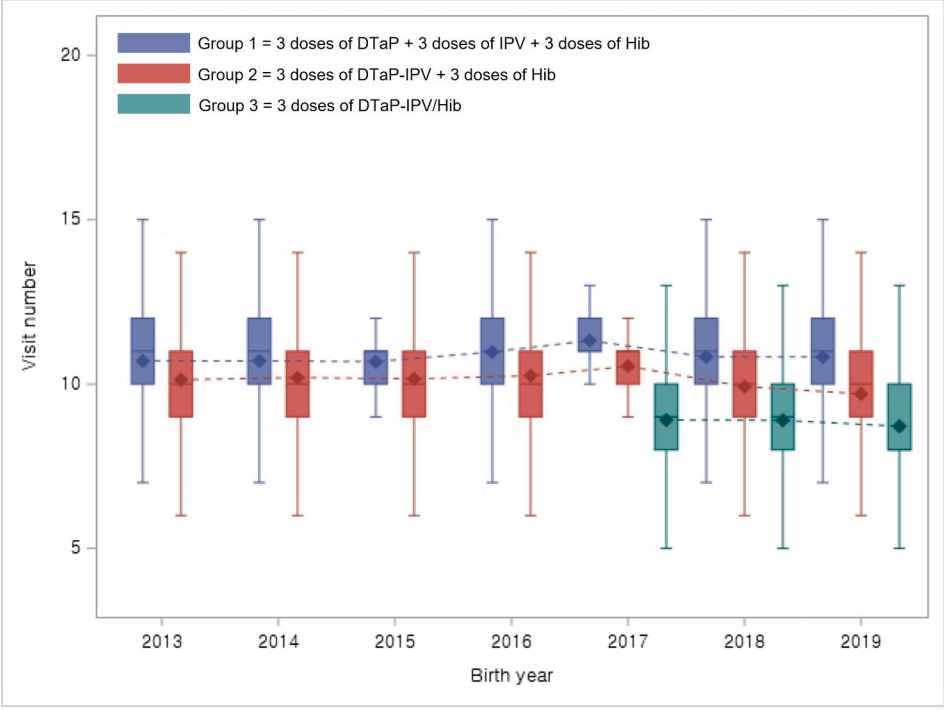

Fig. 1. Numbers of medical visits for vaccination among infants born between 2013 and **2019.** *Abbreviations:* DTaP = diphtheria-tetanus-acellular pertussis; DTaP-IPV = diphtheria-tetanus-acellular pertussis and polio; DTaP-IPV/Hib = diphtheria-tetanus-acellular pertussis, polio and Haemophilus influenzae type b. The filled diamond and line across the middle of the box indicate the mean and median, respectively. The blue boxes represent IQR of infants who completed all 3 doses of primary D-I-H series with separate DTaP, IPV, and Hib vaccines, the red boxes with DTaP-IPV and Hib vaccines, and the green boxes with DTaP-IPV/Hib vaccines. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

safety profile between the two vaccination groups, local injection site reactions were lower in the DTaP-IPV/Hib group than in the separate vaccination groups [18]. This suggests that combined vaccines could improve vaccination coverage by addressing parental concerns about multiple injections.

Among infants who completed the first D-I-H vaccine series, the majority (94.3%) received the same components for all doses, indicating high compliance with vaccination regulations. In addition, the proportion of infants born between 2013 and 2016 who received DTaP and DTaP-IPV to complete the primary D-I-H vaccination series was 23.2% and 75.4%, respectively, however, for infants born between 2017 and 2019, these proportions decreased to 7.3% and 3.7%, respectively. Instead, 81% received the DTaP-IPV/Hib combination vaccine, indicating that many parents replaced the existing vaccines with the DTaP-IPV/Hib combination vaccine following the introduction of the new vaccine.

Our study revealed a significant difference in the average number of visits for vaccination across the 3 groups: DTaP, DTaP-IPV, and DTaP-IPV/Hib vaccines and the difference was consistent in all birth cohorts. The DTaP-IPV/Hib combination vaccine led to an average of two fewer medical visits than the DTaP stand-alone vaccine. This reduction may have occurred for several reasons. First, the combination vaccine that includes DTaP, IPV, and Hib components in a single vaccine has reduced the absolute number of necessary visits. Second, there is no longer a need for separate shots for IPV and Hib at the time of DTaP vaccination visits, which may have facilitated simultaneous administrations with other recommended vaccines like PCV and HepB. It allowed for more efficient scheduling, leading to a reduction in the number of visits. Reducing the number of medical visits enhances the efficiency of the vaccination process and ultimately increases overall vaccination coverage rates.

The study used a large nationwide database containing more than 99% of Korean infants born over 7 years to evaluate the impact of adding DTaP-IPV/Hib combination vaccine to NIP and its influence in vaccination practice. Despite its extensive scope, the study has several potential limitations. First, the definition of completing DTaP, IPV, and Hib vaccinations did not consider the recommended intervals between doses, as it was simply defined as the administration of the first 3 doses between 6 weeks and 12 months after birth, regardless of recommended intervals. Therefore, it's possible that some infants may have received

invalid doses if they did not adhere to the recommended intervals. However, it was assumed that the majority of infants who completed all recommended vaccinations by 12 months after birth would naturally adhere to the vaccination interval. Second, although the database contains administration records on non-NIP as well as NIP vaccines, those on non-NIP vaccines might not be fully captured because reporting of non-NIP is not mandatory, potentially leading to an underestimation of vaccination visits.

DTaP-IPV-Hib-HepB combination vaccine (Sanofi Pasteur) was approved in Korea on April 6, 2020, but has not yet been introduced into the NIP [19]. Many countries including the United States, United Kingdom, Australia, and Canada, have already introduced the DTaP-IPV-Hib-HepB combination vaccine into their NIPs based on its high safety and immunogenicity profile [20]. Korea recently conducted a cost-effectiveness analysis of the DTaP-IPV-Hib-HepB combination vaccine, which demonstrated the potential to reduce costs by $36.22 per infant and a total savings of $9,236,417 compared to the DTaP-IPV/Hib combination vaccine [21]. Our study supports the theory that DTaP-containing combination vaccines can decrease indirect costs by substantially reducing hospital visits for vaccination and the total number of required doses, while also enhancing vaccination coverage rates.

5. Conclusion

Our study found that the introduction of DTaP-IPV/Hib combination vaccine into NIP has several positive effects. It reduced the number of medical visits for vaccination and improved vaccine coverage rates. Fewer number of medical visits enhances the efficiency of the vaccination process and, as a result, increases coverage rates, which benefits infant health. Most infants have completed the primary D-I-H series with the consistent use of the same DTaP component, particularly, with the newly introduced DTaP-IPV/Hib combination vaccine. Our findings offer valuable evidence for countries planning to introduce DTaP-containing combination vaccines, including Korea.

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CRediT authorship contribution statement

Hee-Jin Kim: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Suvin Park:** Validation, Investigation, Formal analysis. **Na-Young Jeong:** Writing – review & editing, Methodology. **Nam-Kyong Choi:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors do not have permission to share data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2024.100484.

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