

Anaphylaxis following vaccination among children in Asia: A large-linked database study

To the Editor,

Anaphylaxis is a severe and potentially fatal systemic reaction that can be triggered by exposure to various allergens, including food, drugs, stings, and vaccines. According to the study in the United States, the estimated rate of anaphylaxis was 1.31 (95% confidence interval (CI), 0.90-1.84) cases per million doses for all vaccines.¹ Children are at risk of anaphylaxis following routine vaccinations, and yet the evidence for the incidence of anaphylaxis following vaccination was not established among children in South Korea. This study aimed to assess the incidence of anaphylaxis after vaccination.

By linking the Korea Immunization Registry Information System (KIRIS) and the National Health Information Database (NHID) (Appendix S1), we created a large-linked database (LLDB) including records for 4.4 million children born from 2008 and 2017 who were vaccinated with approved vaccines (the National Immunization Program (NIP) and non-NIP; Appendix S2) at least once in the South Korea. We retrieved information on vaccination from the KIRIS and information on demographics and healthcare utilization from the NHID. We used specified algorithms using diagnosis and prescription records to enhance the validity of anaphylaxis cases. Cases of anaphylaxis following vaccination were defined using both the diagnosis code and prescription data to ascertain cases accurately. We first identified all patients diagnosed with specific anaphylaxis codes (International Classification of Disease, 10th Revision codes: T78.2, anaphylactic shock, unspecified; T88.6 anaphylactic reaction due to adverse effect of correct drug or medicament properly administered) and prescribed with epinephrine (World Health Organization-Anatomical Therapeutic Chemical classification codes (WHO-ATC code): C01CA24) and/or corticosteroids (WHO-ATC code: H02AB04, H02AB06), concurrently. Among identified cases, we restricted to cases that occurred within two days (modified from the Brighton Collaboration criteria²) after vaccination.

First, we calculated the incidence per million doses administered and exact 95% confidence interval (CI) of anaphylaxis after vaccination by using the number of defined cases of anaphylaxis and the number of vaccine doses administered. Additionally, we calculated the incidence with 95% CI by using only inpatient information to identify the magnitude of cases of postvaccination anaphylaxis requiring hospitalization. Second, we described baseline characteristics of defined cases for demographics information, history of

allergic diseases (diagnosis information in the year preceding the date of anaphylaxis occurrence, Appendix S3), and concomitant vaccination. Third, we conducted stratified analyses according to age group and the number of doses.

Among 4 462 631 children, 4 404 367 (98.7%) children were vaccinated at least once, and a total of 112 799 043 vaccine doses were administered. We identified 137 cases of anaphylaxis after vaccination, and the incidence was 1.21 (95% CI, 1.02-1.44) per million doses (Table 1). When restriction to inpatient data only, we identified 33 cases (24.1%), with the incidence of 0.29 (95% CI, 0.20-0.41). In terms of individual vaccine, Vero cell-cultured inactivated Japanese encephalitis vaccine (IJEV) showed the highest rate (2.87; 95% CI, 1.15-5.92) followed by MMR vaccine (2.72; 95% CI, 1.59-4.36) and varicella vaccine (2.48; 95% CI, 1.24-4.45). A high rate was observed for the influenza vaccine (2.42; 95% CI, 1.70-3.36), and the quadrivalent influenza vaccine was higher than the trivalent influenza vaccine (1.98, 95% CI 1.29-2.90 vs. 5.87, 95% CI 2.81-10.79; Appendix S4). Most cases were aged between 12 months and 23 months (43.1%), and 61.3% were males (Table 2). 46% of cases had been diagnosed with asthma, and half of the cases (49.6%) had received other vaccines concomitantly. Similar results were observed between inpatient or outpatient cases, and results of stratified analyses according to age group and the number of doses were described in Appendix S5 and S6. When calculating the rate of anaphylaxis cases per million doses by income levels and residential region, children who were most affluent or who lived in metropolitan showed the highest rate in each characteristic (Appendix S7).

Our results were similar to previous studies. The incidence of vaccination-triggered anaphylaxis was 1.45 (95% CI, 0.86-2.29) among children and adolescents in the United States.¹ Also, the high proportion of male and the distribution of medical history among all cases also have been in line with earlier results.^{3,4} We also found identical results that most cases were between 12 and 23 months as in other study, when primary (influenza, MMR, and varicella vaccine) or booster (DTaP, PCV, Hib) schedules are concentrated in.⁵ Meanwhile, our results were significantly high when compared to the previous studies from Australia (Our study: DTaP 0.50, MMR 2.72 vs. Australia: DTaP 0.04, MMR 0.13).⁶ We consider that this discrepancy may have been observed due to the difference in the type of data used. These earlier Australian studies used databases collected by a spontaneous reporting system;

TABLE 1 Incidence of anaphylaxis cases following vaccination by type of vaccines among 4.4 million children in South Korea, 2008-2017

	Total doses	Anaphylaxis with in- and outpatient		Anaphylaxis with inpatient only	
		No. of cases ^a	Incidence (95% CI) per million doses	No. of cases ^a	Incidence (95% CI) per million doses
Total	112,799,043	137	1.21 (1.02-1.44)	33	0.29 (0.20-0.41)
BCG-PC	2,630,116	0	–	0	–
BCG-ID	1,392,353	0	–	0	–
DTaP	11,926,273	6	0.50 (0.18-1.10)	2	0.17 (0.02-0.61)
DTaP-IPV	6,114,357	8	1.31 (0.56-2.58)	1	0.16 (0.00-0.91)
DTaP-IPV/Hib	399,709	0	–	0	–
HepA	6,580,449	13	1.98 (1.05-3.38)	3	0.46 (0.09-1.33)
HepB	12,427,049	3	0.24 (0.05-0.71)	2	0.16 (0.02-0.58)
Hib	14,044,520	8	0.57 (0.25-1.12)	2	0.14 (0.02-0.51)
IJEV (Vero cell)	2,437,117	7	2.87 (1.15-5.92)	2	0.82 (0.10-2.96)
IJEV (Mouse brain)	7,786,803	13	1.67 (0.89-2.85)	3	0.39 (0.08-1.13)
IPV	8,174,466	5	0.61 (0.20-1.43)	2	0.24 (0.03-0.88)
LJEV	1,347,826	2	1.48 (0.18-5.36)	0	–
MMR	6,246,609	17	2.72 (1.59-4.36)	5	0.80 (0.26-1.87)
PCV10	1,649,005	1	0.61 (0.02-3.38)	0	–
PCV13	10,359,589	7	0.68 (0.27-1.39)	2	0.19 (0.02-0.70)
PPSV23	4,721	0	–	0	–
Varicella	4,427,195	11	2.48 (1.24-4.45)	3	0.68 (0.14-1.98)
Influenza vaccine	14,850,886	36	2.42 (1.70-3.36)	6	0.40 (0.15-0.88)

Abbreviations: BCG, Bacillus Calmette-Guérin vaccine; CI, confidence interval; DTaP, diphtheria-tetanus-acellular pertussis vaccine; HepA, hepatitis A vaccine; HepB, hepatitis B vaccine; Hib, *Haemophilus influenzae* type b vaccine; ID, intradermal; IJEV, inactivated Japanese encephalitis vaccine; IPV, inactivated polio vaccine; LJEV, live attenuated Japanese encephalitis vaccine; MMR, measles-mumps-rubella vaccine; PC, percutaneous; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

^aCases for anaphylaxis were defined as diagnosed with specific anaphylaxis codes (ICD-10 codes: T78.2, T88.6) and prescribed with epinephrine (ATC code: C01CA24) and/or corticosteroids (H02AB04, H02AB06) within two days after immunization, concurrently.

therefore, the incidence may be underestimated due to the limitation of under-reporting.

Safety profile of Mouse brain cultured IJEV, which was administered more frequently over Vero cell-cultured IJEV in our study, had been established previously; the adverse events ranged from non-specific localized reactions to systemic reactions such as severe allergic reaction including anaphylaxis.⁷ In 2009, Vero cell-cultured IJEV was approved worldwide and was reported to be safer than mouse brain cultured IJEV due to not containing impurities from mouse brain tissue. In fact, multicenter clinical trials conducted in Asia concluded that the safety and immunogenicity of Vero cell-cultured IJEV was comparable to that of mouse brain cultured IJEV.^{8,9} However, the difference in the incidence of anaphylaxis between these IJEVs (Vero cell, 2.87 vs. Mouse brain, 1.67) in our study calls for an additional study to confirm the comparable safety outcome observed in the previous clinical trials as these studies were limited due to small study population for detecting rare systemic adverse events.

We observed a relatively high incidence of anaphylaxis for IJEV, MMR, varicella, and influenza vaccine. Hypersensitivity reactions following vaccination may be caused by various excipients

(preservatives, stabilizers, and adjuvants) in vaccine; especially, vaccines containing gelatin as stabilizer and egg-based vaccines were most frequently associated with postvaccination anaphylaxis.¹⁰ It has previously been documented that patients without egg allergy developed anaphylaxis following IJEV, MMR, and influenza, and these vaccines contained gelatin as stabilizer. Particularly, more than 20% of patients who experienced anaphylaxis following influenza vaccine containing gelatin had a food allergy to gelatin. MMR and influenza vaccines contain ovalbumin, which can potentially trigger anaphylaxis in patients allergic to egg. Besides, traces of antibiotics, such as neomycin, polymyxin B, streptomycin, and gentamicin, contained in MMR and influenza vaccines also could induce hypersensitivity reactions. In fact, past studies, though lacking complete allergic workup on the individual cases, suspected that these traces of antibiotics were responsible for postvaccination dermatitis and/or immediate hypersensitivity reactions.¹¹ These findings highlight the importance of in-depth evaluation of individual's past medical history prior to vaccination.

We also found that the boys were more likely to be diagnosed with postvaccination anaphylaxis than girls, which is in line with

TABLE 2 Demographic and clinical characteristics of anaphylaxis cases following vaccination among 4.4 million children in South Korea, 2008-2017

	Anaphylaxis with in- and outpatient (n = 137)	Anaphylaxis with outpatient only (n = 104)	Anaphylaxis with inpatient only (n = 33)
Age group			
0-11 mo	9 (6.6)	7 (6.7)	2 (6.1)
12-23 mo	59 (43.1)	39 (37.5)	20 (60.6)
24-59 mo	42 (30.7)	37 (35.6)	5 (15.2)
5-9 y	27 (19.7)	21 (20.2)	6 (18.2)
Sex			
Female	53 (38.7)	38 (36.5)	15 (45.5)
Male	84 (61.3)	66 (63.5)	18 (54.5)
Income level ^a			
1st quantile (Most deprived)	13 (9.5)	12 (11.5)	1 (3.0)
2nd quantile	10 (7.3)	8 (7.7)	2 (6.1)
3rd quantile	16 (11.7)	11 (10.6)	5 (15.2)
4th quantile	57 (41.6)	42 (40.4)	15 (45.5)
5th quantile (Most Affluent)	41 (29.9)	31 (29.8)	10 (30.3)
Residential region ^b			
Metropolitan	94 (68.6)	76 (73.1)	18 (54.5)
Urban	19 (13.9)	13 (12.5)	6 (18.2)
Rural	24 (17.5)	15 (14.4)	9 (27.3)
Medical history ^c			
Asthma	28 (20.4)	20 (19.2)	8 (24.2)
Allergic rhinitis	63 (46.0)	47 (45.2)	16 (48.5)
Atopic dermatitis	54 (39.4)	44 (42.3)	10 (30.3)
Urticaria	50 (36.5)	39 (37.5)	11 (33.3)
Other concomitant vaccines			
Yes	68 (49.6)	48 (46.2)	20 (60.6)

^aIncome levels are classified into 11 groups ranging from 0 to 10, according to the type of health insurance. 10 of the groups are for both employee subscribers and district subscribers, group 0 indicates medical aid.

^bResidential region is classified into 3 groups: metropolitan (metropolitan cities with population > 1 million); urban (municipalities with population 50 000-1 million); and rural (county-level with population < 50 000).

^cMedical history was identified by using all diagnosis data preceding year.

previous report on gender effect in incidence of allergy in children.¹² Although the risk of postvaccination anaphylaxis seemed be higher for boys than girls during childhood, gender difference from adolescence onwards should be investigated further. Moreover, as in other allergic conditions, our result may have been influenced by sociodemographic and environmental factors. We found more affluent children who experienced postvaccination anaphylaxis than children with lower socioeconomic status (SES), which may be a surrogate for living conditions and lifestyle. Our results point out the importance of SES as a risk marker for vaccine-associated reactions.

Our study has several strengths. First, we utilized a LLDB approach by combining vaccine registry data with claims data over the 10-year period. Second, cases were defined using all in- and outpatient data to overcome under-reporting problem. Third, we defined anaphylaxis cases by using both diagnosis codes and prescription

data, thereby improving the validity of the case ascertainment. Nevertheless, our findings should be interpreted with caution. Due to the lack of relevant clinical information in claims data, we could not assess the validity of anaphylaxis using the Brighton Collaboration definition; the possibility of over- or underestimation for anaphylaxis following vaccination exists. To overcome this, we used the predefined algorithm using both anaphylaxis-related diagnostic code and prescription of epinephrine and/or corticosteroids. Moreover, we did not adjust according to potential confounders. Despite limitations, our results provide the most recent population-based incidence of postvaccination anaphylaxis.

Based on vaccine safety surveillance study using the LLDB, anaphylaxis following vaccination was rare among children, but the incidence varied by different types of vaccines. Therefore, vaccine providers should be prepared to manage this life-threatening hypersensitivity reaction.

ACKNOWLEDGMENTS

The National Health Insurance Service-National Health Insurance Data (NHIS-2019-1-622) was provided by the National Health Insurance Service of South Korea.

CONFLICTS OF INTEREST

Dr Shin reported receiving grants from the Ministry of Food and Drug Safety, the Ministry of Health and welfare, the National Research Foundation of Korea, and Government-wide R&D Fund for infectious disease research; grants from pharmaceutical companies including Amgen, Pfizer, Hoffmann-La Roche, Dong-A ST, Yungjin outside the submitted work. No other disclosures were reported.

Young June Choe¹ 

Hyesung Lee² 

Ju Hwan Kim² 

Won Suk Choi³ 

Ju-Young Shin^{2,4} 

¹Department of Social and Preventive Medicine, Hallym University College of Medicine, Chuncheon, South Korea

²School of Pharmacy, Sungkyunkwan University, Suwon, South Korea

³Division of Infectious Diseases, Department of Internal Medicine, Korea University College of Medicine, Ansan Hospital, Ansan, South Korea

⁴Samsung Advanced Institute for Health Sciences & Technology (SAIHST), Sungkyunkwan University, Seoul, South Korea

Correspondence

Ju-Young Shin, School of Pharmacy, Sungkyunkwan University, Suwon, South Korea.
Email: shin.jy@skku.edu

Choe and Lee contributed equally to this manuscript.

ORCID

Young June Choe  <https://orcid.org/0000-0003-2733-0715>

Hyesung Lee  <https://orcid.org/0000-0001-6556-9984>

Ju Hwan Kim  <https://orcid.org/0000-0001-7253-6515>

Won Suk Choi  <https://orcid.org/0000-0001-5874-4764>

Ju-Young Shin  <https://orcid.org/0000-0003-1010-7525>

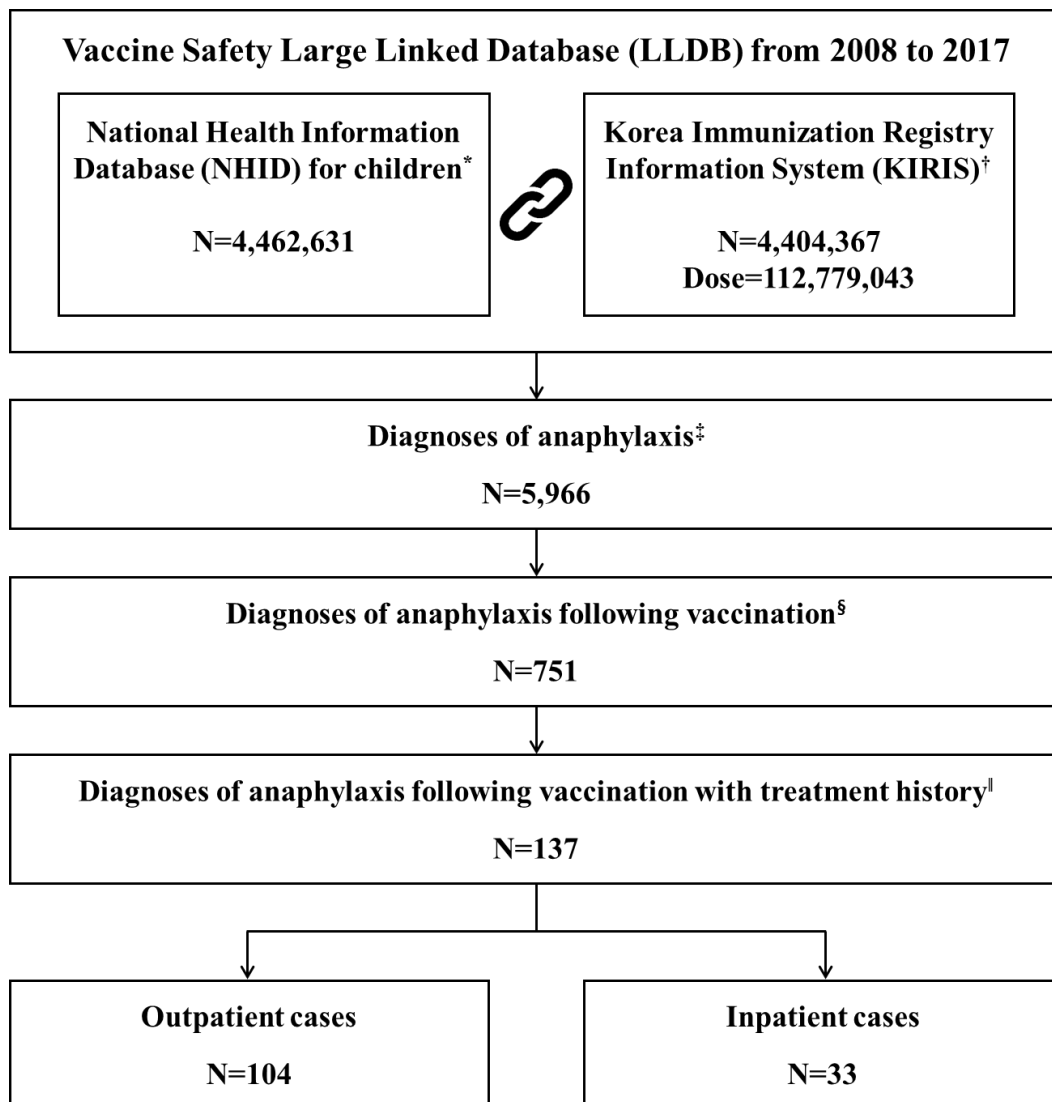
REFERENCES

1. McNeil MM, Weintraub ES, Duffy J, et al. Risk of anaphylaxis after vaccination in children and adults. *J Allergy Clin Immunol*. 2016;137(3):868-878.
2. Ruggeberg JU, Gold MS, Bayas JM, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine*. 2007;25(31):5675-5684.
3. Su JR, Moro PL, Ng CS, Lewis PW, Said MA, Cano MV. Anaphylaxis after vaccination reported to the Vaccine Adverse Event Reporting System, 1990-2016. *J Allergy Clin Immunol*. 2019;143(4):1465-1473.
4. Motosue MS, Bellolio MF, Van Houten HK, Shah ND, Campbell RL. Risk factors for severe anaphylaxis in the United States. *Annals Allergy Asthma Immunol*. 2017;119(4):356-361.
5. Jeong K, Lee JD, Kang DR, Lee S. A population-based epidemiological study of anaphylaxis using national big data in Korea: trends in age-specific prevalence and epinephrine use in 2010-2014. *Allergy Asthma Clin Immunol*. 2018;14(1):2010-2014.
6. Cheng DR, Perrett KP, Choo S, Danchin M, Buttery JP, Crawford NW. Pediatric anaphylactic adverse events following immunization in Victoria, Australia from 2007 to 2013. *Vaccine*. 2015;33(13):1602-1607.
7. Chanthavanich P, Limkittikul K, Sirivichayakul C, et al. Immunogenicity and safety of inactivated chromatographically purified Vero cell-derived Japanese encephalitis vaccine in Thai children. *Human Vacc Immunother*. 2018;14(4):900-905.
8. Miyazaki C, Okada K, Ozaki T, et al. Phase III clinical trials comparing the immunogenicity and safety of the vero cell-derived Japanese encephalitis vaccine Encevac with those of mouse brain-derived vaccine by using the Beijing-1 strain. *Clin Vaccine Immunol*. 2014;21(2):188-195.
9. Yun KW, Lee HJ, Kang JH, et al. Safety and immunogenicity of a freeze-dried, Vero cell culture-derived, inactivated Japanese encephalitis vaccine (KD-287, ENCEVAC(R)) versus a mouse brain-derived inactivated Japanese encephalitis vaccine in children: a phase III, multicenter, double-blinded, randomized trial. *BMC Infect Dis*. 2015;15:7.
10. Caubet J-C, Ponvert C. Vaccine allergy. *Immunol Allergy Clin North Am*. 2014;34(3):597-613.
11. Kwittken P, Rosen S, Sweinberg S. MMR vaccine and neomycin allergy. *Am J Dis Child*. 1993;147(2):128-129.
12. Grabenhenrich LB, Dölle S, Moneret-Vautrin A, et al. Anaphylaxis in children and adolescents: The European Anaphylaxis Registry. *J Allergy Clin Immunol*. 2016;137(4):1128-1137.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Appendix S1. Flow diagram of defining anaphylaxis cases.



* The NHID collected by the National Health Insurance Service (NHIS) serves as a single-payer program in the country covering 97% of total population (~50 million). The overall positive predictive value of the diagnoses in the NHID is 82%.

† The KIRIS has been operational since 2008, and collects information on age, sex, type of the vaccine (and lot number), vaccinating healthcare provider, and the date of vaccination. In 2017, the vaccination coverage for all NIP vaccines ranged between 92.9% (Japanese encephalitis vaccine) to 98.0% (BCG vaccine).

‡ All patients diagnosed with specific anaphylaxis-related code (ICD-10 codes: T78.2, anaphylactic shock, unspecified; T88.6 anaphylactic reaction due to adverse effect of correct drug or medicament properly administered) were included.

§ Cases were defined as specific anaphylaxis-related code occurred within 2 days after vaccination.

16 [†] Treatment history was defined as prescriptions with epinephrine (ATC code: C01CA24)
17 and/or corticosteroids (ATC code: H02AB04, H02AB06).

Appendix S2. List of vaccines for children aged 9 years old or younger in the Korea Immunization Registry Information System

Type of vaccine	Subtype
BCG	BCG Danish strain BCG Tokyo strain
Diphtheria, Tetanus, Pertussis	DTaP DTaP-IPV DTaP-IPV/Hib
<i>Haemophilus influenzae</i> type B	<i>Haemophilus influenzae</i> type b, conjugated
Hepatitis A	Hepatitis A, inactivated
Hepatitis B	Hepatitis B, recombinant
Influenza	Inactivated influenza vaccine
Japanese encephalitis	Inactivated Japanese encephalitis vaccine (IJEV; Vero cell cultured, Mouse brain cultured) Live-attenuated Japanese encephalitis vaccine (LJEV)
MMR	Measles, Mumps, Rubella, live attenuated
Pneumococcus	10-valent Pneumococcal conjugate vaccine 13-valent Pneumococcal conjugate vaccine 23-valent Pneumococcal polysaccharide vaccine
Polio	Inactivated poliovirus vaccine
Varicella	Varicella vaccine

Abbreviations: BCG, Bacille Calmette-Guérin; DTaP, Diphtheria-tetanus-acellular pertussis vaccine; acellular pertussis; IPV, inactivated polio virus; Hib, *Haemophilus influenzae* type b vaccine; MMR, measles-mumps-rubella vaccine.

Appendix S3. List of diagnosis codes and drug codes used in definition of anaphylaxis cases and medical history

Type	Name	Codes
Anaphylaxis		
Diagnoses	Anaphylactic shock, unspecified	T78.2
(ICD-10 codes)	anaphylactic reaction due to adverse effect of correct drug or medicament properly administered	T88.6
Drugs	Epinephrine	C01CA24
(WHO ATC code)	Corticosteroids	H02AB04, H02AB06
Medical history		
Diagnoses	Asthma	J45
(ICD-10 codes)	Allergic rhinitis	J30
	Atopic dermatitis	L20
	Urticaria	L50

Abbreviations: ICD-10 codes, the International Classification of Disease, 10th Revision codes; WHO ATC code, World Health Organization-Anatomical Therapeutic Chemical classification codes.

29 **Appendix S4.** Number of anaphylaxis cases following vaccination by influenza vaccines and their subtypes among 4.4 million children in
30 South Korea, 2008-2017

	Total doses	Anaphylaxis with in- and outpatient		Anaphylaxis with inpatient only	
		No. of cases*	Incidence [†] (95% CI)	No. of cases*	Incidence [†] (95% CI)
Influenza vaccine	14,850,886	36	2.42 (1.70-3.36)	6	0.40 (0.15-0.88)
Trivalent	13,146,480	26	1.98 (1.29-2.90)	5	0.38 (0.12-0.89)
Quadrivalent	170,4406	10	5.87 (2.81-10.79)	1	0.59 (0.01-3.27)

31 * Cases for anaphylaxis were defined as diagnosed with specific anaphylaxis codes (ICD-10 codes: T78.2, T88.6) and prescribed with
32 epinephrine (ATC code: C01CA24) and/or corticosteroids (H02AB04, H02AB06) within two days after immunization, concurrently.

33 [†] Incidence was calculated per million doses.

34 Abbreviations: CI, confidence interval.

35

Appendix S5. Number of anaphylaxis cases following vaccination by type of vaccines and age groups among 4.4 million children in South Korea, 2008-2017

	No of cases (n=137)			
	Age group			
	0-11 months	12-23 months	24-59 months	5-9 years
Total	9	59	42	27
BCG-PC	0	0	0	0
BCG-ID	0	0	0	0
DTaP	1	0	3	2
DTaP-IPV	2	1	2	3
DTaP-IPV/Hib	0	0	0	0
HepA	0	9	3	1
HepB	1	2	0	0
Hib	1	6	1	0
IJEV (Vero cell)	0	4	3	0
IJEV (Mouse brain)	0	7	3	3
IPV	1	0	2	2
LJEV	0	0	2	0
MMR	0	8	5	4
PCV10	0	1	0	0
PCV13	2	4	1	0
PPSV23	0	0	0	0
Varicella	0	7	3	1
Influenza vaccine	1	10	14	11

Abbreviations: BCG, Bacillus Calmette–Guérin vaccine; PC, percutaneous; ID, intradermal; DTaP, diphtheria-tetanus-acellular pertussis vaccine; Hib, *Haemophilus influenzae* type b vaccine; HepA, hepatitis A vaccine, HepB, hepatitis B vaccine; IJEV, inactivated Japanese encephalitis vaccine; IPV, inactivated polio vaccine; LJEV, live-attenuated Japanese encephalitis vaccine; MMR, measles-mumps-rubella vaccine; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

Appendix S6. Number of anaphylaxis cases following vaccination by type of vaccines and number of doses among 4.4 million children in South Korea, 2008-2017

	No of cases (n=137)				
	Number of doses				
	1	2	3	4	5
Total	45	27	43	19	3
BCG-PC	0	0	0	0	0
BCG-ID	0	0	0	0	0
DTaP	0	0	1	2	3
DTaP-IPV	0	1	2	5	0
DTaP-IPV/Hib	0	0	0	0	0
HepA	9	4	0	0	0
HepB	1	0	2	0	0
Hib	0	0	5	3	0
IJEV (Vero cell)	3	3	1	0	0
IJEV (Mouse brain)	5	4	2	2	0
IPV	0	0	1	4	0
LJEV	1	1	0	0	0
MMR	9	8	0	0	0
PCV10	0	0	1	0	0
PCV13	1	0	3	3	0
PPSV23	0	0	0	0	0
Varicella	8	3	0	0	0
Influenza vaccine	8	3	25	0	0

Abbreviations: BCG, Bacillus Calmette–Guérin vaccine; PC, percutaneous; ID, intradermal; DTaP, diphtheria-tetanus-acellular pertussis vaccine; Hib, *Haemophilus influenzae* type b vaccine; HepA, hepatitis A vaccine, HepB, hepatitis B vaccine; IJEV, inactivated Japanese encephalitis vaccine; IPV, inactivated polio vaccine; LJEV, live-attenuated Japanese encephalitis vaccine; MMR, measles-mumps-rubella vaccine; PCV10, 10-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine.

Appendix S7. Rate of anaphylaxis cases in the respective group according to income level and residential region.

	Anaphylaxis with in- and outpatient (n=137)	Total number of vaccination doses (n=112,779,043)	Rate of anaphylaxis cases in the respective income level per million doses
Income level*			
1st quantile (Most deprived)	13 (9.5)	12,004,667 (10.6)	1.08
2nd quantile	10 (7.3)	12,506,138 (11.1)	0.80
3rd quantile	16 (11.7)	26,264,261 (23.3)	0.61
4th quantile	57 (41.6)	37,875,913 (33.6)	1.50
5th quantile (Most Affluent)	41 (29.9)	24,130,785 (21.4)	1.70
Missing	0 (0.0)	17,279 (0.0)	N/A
Residential region†			
Metropolitan	94 (68.6)	57,414,214 (50.9)	1.64
Urban	19 (13.9)	21,512,878 (19.1)	0.88
Rural	24 (17.5)	33,773,081 (29.9)	0.71
Missing	0 (0.0)	98,870 (0.1)	N/A

* Income levels are classified into 11 groups ranging from 0 to 10, according to the type of health insurance. 10 of the groups are for both employee subscribers and district subscribers, group 0 indicates medical aid.

† Residential region is classified into 3 groups: metropolitan (metropolitan cities with population >1 million); urban (municipalities with population 50,000 – 1 million); and rural (county-level with population <50,000).