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Age-Period-Cohort Analysis of Influenza in Koreans: the National Health Insurance Research Database, 2009–2018

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ABSTRACT



Background: This study aimed to identify the incidence rate of episodes diagnosed with influenza and the effects of age-period-cohort (APC) in Koreans.

Methods: The 2009–2018 National Health Insurance Research Database was used for analysis. All time-related claims connected relatively short window period in 100 days. The case definition was defined by all codes diagnosed with J09, J10, and J11. Calculation of the incidence rate and APC analysis adjusted income levels by insurance type, metropolitan city was performed to identify the characteristics of episodes diagnosed with influenza.

Results: Incidence rate by age and cohort gradually increased since 2014. The incidence rate of males aged 0–4 years was 171.02 and that of females was 173.31 in 2015–2016 season. In males, 29.19 in 1963 cohort and 243.79 in 2013 cohort were confirmed as high incidence rates in 2017–2018 season. In the females, a high incidence was confirmed in 1953–1967 cohort and 1978–1987 cohort, and the incidence was 251.38 in 2013–2017 cohort. APC effects showed a high relative risk in the infants, the pandemic influenza season in 2010 (1/7/2009 to 30/6/2010) and the adults of 1978–1987 cohort.

Conclusion: Since 2014, influenza outbreaks have been increasing every year. The start year of free vaccination decreased the incidence in infants and adults over 65 years of age but the incidence increased from the following year. Because influenza can be primarily prevented by vaccination, reinforcement of vaccination in infants may reduce the disease burden in their parents, and also the risk of infection caused by family transmission. A new vaccination strategy is needed to reduce the incidence and burden of diseases caused by influenza infection.

Keywords: Influenza; Episode of Care; Incidence; Age-Period-Cohort Effect

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Kim J, Choi BY. Data curation: Kim J, Byeon KH. Formal analysis: Kim J, Byeon KH, Lee N. Methodology: Kim J, Byeon KH. Writing - original draft: Byeon KH. Writing - review & editing: Kim J, Choi BY, Kim JY, Lee N.

INTRODUCTION

Influenza is an acute respiratory disease caused by infection of the influenza virus, which usually recovers in healthy adults, but in high-risk groups such as the elderly and chronic patients, the patients infected with influenza is at high risk for severe influenza contraction or complications such as pneumonia, and some patients may be led to death caused by severe complications.¹

In Korea, the influenza epidemic during the winter season continues every year. Statistical monitoring data of infectious disease portals operated by the Korea Centers for Disease Control and Prevention (KCDC) showed that the peak of influenza-like-illness proportion continued to increase since the 2014–2015 influenza season, especially during the 2016–2017 fifty-second influenza season, and the proportion of influenza-like-illness rose to 86.2.²

Influenza is a disease that can be prevented by vaccination, and the effects of vaccination vary from year to year depending on the age of the recipient, the immunity that accompanies underlying disease and vaccination, and the antigenic consistency of the vaccine and epidemic strains. When the vaccine and epidemic strains coincide, the prevention effect in the elderly was 70%–90% compared to healthy adults, vaccination was effective in 50%–60% to prevent hospitalization due to influenza, and in 80% to prevent death.^{3,4} In 82% of the chronic respiratory illnesses, vaccination was found to be effective to prevent hospitalization.⁵ However, it is known that the effect of vaccination cannot be confirmed when there is an antigenic mismatch.^{6,7}

In Korea, influenza vaccination is recommended to those who are recommended for prior vaccination according to the practical standards and methods of vaccination presented in notification by KCDC article 2018-1. Recommended influenza immunization priorities include health care workers, female in pregnancy, 50–64 aged group (population), the elderly (65 years or older), children and adolescents, and patients with chronic illness. In addition, children under age 2, the elderly (65 years or older), and patients with chronic diseases are classified into a high-risk group with severe influenza or complications.³ In Korea, as part of the national vaccination program, free vaccinations are provided for infants and the elderly (65 years or older). The vaccination rate in the 2017–2018 season was relatively high at 78.0% for children aged 6–59 months and 82.4% for those aged 65 or over in 2016–2017.^{1,3}

In Korea, free vaccinations for infants and the elderly (65 years or older) are provided during the winter season. Despite the high vaccination rates, the number of patients diagnosed with influenza is increasing every year.^{8,9} Hence, this study identified the effect of the age-period-cohort (APC) in order to comprehend the epidemiologic characteristics of influenza outbreaks by using the health insurance claims data of the National Health Insurance Service that include Korean nationals. If APC analysis that can identify age group, time and space, and specific generation at high risk based on national health insurance claims data is applied, various public health interventions including vaccination can take effect along with providing more specific and meaningful information for quantitative evaluation.

The specific purpose is as follows: Identify the number of episodes by year and age diagnosed with influenza; Calculate the crude incidence rate (CIR; per 1,000 person) by year, age, and cohort (= birth year); Identify the effect of APC.

METHODS

Study design and data source

In the National Health Information DB of the National Health Insurance Service, data from July 2008 to June 2018 were used, based on the sickness details tables, medical services statement tables, and the qualification and insurance tables.⁸ In addition, since health insurance database is a claims data, it was reconstructed as epidemiologic research unit, episode of care.

Influenza disease was reset from July 1 to June 30 of the following year, considering the characteristics of the disease that occurs during the winter season.

Establish an episode of care

Health insurance database is a claims data that may be claimed separately for a variety of reasons, even though it was actually one episode of case. Because a single disease uses different medical services for different periods and times, separate claims are generated, and therefore separate claims can be used as epidemiological data only after they are connected and integrated.¹⁰

In this study, the analysis process grouped all claims that were directly connected in time as one episode of care, that is, the time between the end date and the date within 1 day of the end date and the next start date. The interval between the leading end dates and trailing start dates for the same person, which is a window period, is as follows (Fig. 1). Assuming that claim events within the same season are considered as one and the same episode of care, 100 days were set as a window period. In this way, 94.9% of all segregation claims were included within 100 days. When the claims data was converted to episode of care after applying 100 days of window period, there were some differences from year to year, but about 99% of all influenza patients experienced one outbreak. That is, only about 1% of patients experience more than one outbreak (Table 1).

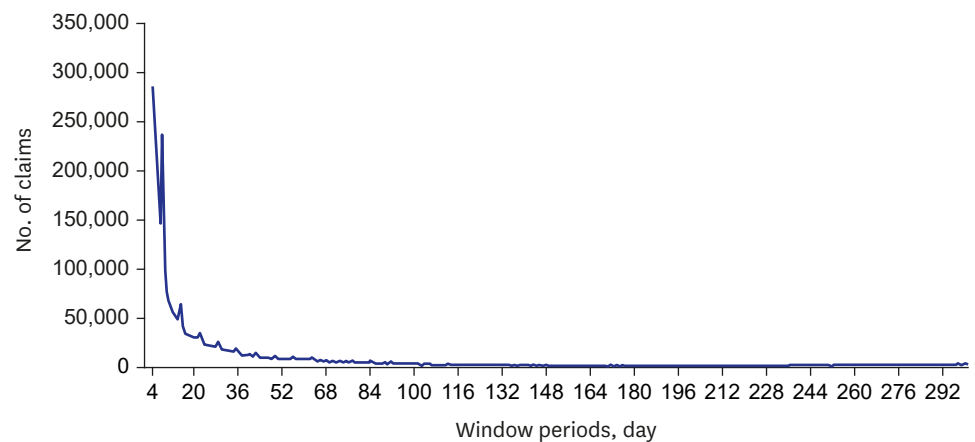


Fig. 1. Distribution of number of claims depending on window period for influenza.

Table 1. Number of episodes for 100 days' window period diagnosed with influenza by year

Year ^a	Episode 1	Episode 2	Episode 3	Episode 4
2009	425,175 (92.7)	32,021 (7.0)	1,287 (0.3)	1 (0.0)
2010	3,774,311 (98.0)	77,240 (2.0)	505 (0.0)	-
2011	394,494 (96.8)	12,872 (3.2)	293 (0.1)	-
2012	736,154 (98.5)	10,703 (1.4)	241 (0.0)	-
2013	304,846 (98.0)	6,074 (2.0)	169 (0.1)	-
2014	1,126,075 (99.3)	7,200 (0.6)	179 (0.0)	-
2015	1,140,143 (99.4)	6,243 (0.5)	150 (0.0)	-
2016	1,436,392 (99.5)	6,414 (0.4)	104 (0.0)	1 (0.0)
2017	1,876,398 (98.9)	21,669 (1.1)	143 (0.0)	2 (0.0)
2018	2,785,824 (99.5)	15,227 (0.5)	129 (0.0)	-

Data are presented as number (%).

^aEach year (starts from July 1st and ends at June 30th) is denoted by the calendar year in which it ends.

Case definition

In the health insurance claims data, primary diagnosis refers to the disease that causes the greatest demand for the treatment or examination (the disease that causes the most use of medical resources) and is listed first. Additional diagnosis is a condition that occurs with the main condition during the treatment period.⁸

Unlike severe diseases such as myocardial infarction, stroke, or cancer, influenza is less likely to be justified as a primary diagnosis. That is, if influenza occurs among existing chronic patients or other hospitalized patients, it is not likely to occupy the position of primary diagnosis but is likely to be added as an additional diagnosis or other illness. In consideration of these points, the influenza corporal subjects included all primary, additional and other diagnoses. The disease code was defined as J09, J10, and J11.

Study subjects

Using the 40T in the National Health Information DB, all cases of medical statement in 20T, qualifications, and insurance were combined, with the claims diagnosed as all sicknesses including primary, additional, and other diagnoses of influenza. A total of 24,605,290 claims were used to construct a 100-day episode of care. The final study consisted of 100-day episode of care constructed from all cases of influenza, and a total of 14,400,754 episodes were selected for analysis.

Variables

In the National Health Information DB, sickness details tables (40T), medical services statement tables (20T), qualification and insurance tables, and population group tables were used. 20T is a collection of medical services statement claimed by medical care institutions when patients use medical services. 40T includes disease codes extracted from 20T.⁸ The parameters of sex, age at onset of care, start year and month of treatment, start date of treatment, form code, disease number 1 (primary diagnosis), disease number 2 (secondary diagnosis), and disease treatment distribution were selected from sickness details tables. In the medical services statement tables, variables such as medical institution number, medical institution type code, medical department code, total hospital visit days, total prescription days, and payment status were selected. In the qualification and insurance tables, the month of care start date, adjusted address code, subscriber classification, and insurance variables were selected. Sex, base month, municipality, income level, and age variables were used in the population table and the insurance tables. The two tables were used as denominators representing the total population when we calculated incidence rate and APC effects. The keys connecting all the tables were a common key and a personal identification number.

Statistical analysis

The health insurance claims used in this study were reconstructed into 100-day episodes of care to be used as epidemiological data to perform basic analysis, calculation of CIR, and APC effect analysis.

In the basic and incidence analysis, the age was grouped on the unit of 5, the cohort was initiated with 3 years unit and reset to 5 years unit group. The incidence rate of influenza by age and cohort by year was calculated by using the number of the corresponding cases as a numerator. The entire population table was created using the population table and the insurance table was used as the denominator.

The APC effect analysis analyzed three effects related to time to summarize the social variation, causes of disease, increase in age, and population characteristics, which is different from the original method that uses only age and period. The identification problem of the APC analysis, in which the three effects cannot be estimated simultaneously due to collinearity, in which the sum of age and cohort is the period variable, was solved using the Glimmix model using the statistical package SAS (SAS Institute Inc., Cary, NC, USA).¹¹ In other words, the hierarchical APC (HAPC) analysis was performed using the mixed effect model. The specification of the model is as follows:

$$\log(\text{number of event}) = \log(\text{population}) + \mu + \alpha_i + \beta_j + \gamma_k + \varepsilon_{ij},$$

i , age group; j , time period; k , birth cohort.

In addition, assuming the Poisson distribution and correcting the population with the offset option, the relative risk was able to be calculated directly, rather than the odds ratio. In the HAPC analysis model, the fixed effect variables were analyzed using age, metropolitan city, income level by insurance type, and random effect variables with period and cohort (= birth year) variables.

Ethics statement

This study was exempted from deliberation by the Hanyang University Institutional Review Board (IRB) for the exemption from IRB deliberation that does not include personally identifiable information (HYU-2019-04-021).

RESULTS

Number of influenza episodes of care by year, sex and age

In terms of the number of episodes diagnosed as influenza, the number of episodes between the ages of males and females aged 0–9 was the highest in the 2017–2018 season after the 2009–2010 season (Table 2). In the 2016–2017 season a large number of episodes from 10 to 19 years were seen. In the 2017–2018 season, males and females over 45 years of age had more episodes than in the 2009–2010 season.

Incidence rates of influenza by year, sex and age

The incidence rate of males and females diagnosed with influenza CIR, (per 1,000 person) showed that between 2009 and 2010 0–9 years had the highest incidence rate (Table 3). Also, the incidence rate in school-age and adolescent ages was high. In 2016, the 2015–2016

Table 2. Number of episodes according to age group for influenza by year

Sex	Age group	Episodes of influenza by year ^a									
		2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Male	0–4	18,021	317,783	30,958	110,561	36,812	127,696	116,575	202,464	153,636	241,522
	5–9	17,555	360,446	22,756	73,451	19,696	122,679	122,792	176,690	216,604	230,143
	10–14	12,891	310,875	20,631	32,186	15,218	69,630	68,648	73,759	170,260	125,343
	15–19	7,521	259,822	11,256	12,720	8,295	26,754	26,971	29,593	86,393	60,627
	20–24	4,392	88,435	6,597	6,929	3,754	15,459	9,724	11,794	22,826	40,800
	25–29	7,615	109,788	12,919	9,901	5,079	17,502	11,386	14,092	22,647	44,894
	30–34	8,865	91,391	14,055	15,615	8,617	25,724	19,357	24,867	30,598	51,521
	35–39	11,850	96,363	14,253	17,255	9,288	26,930	25,038	33,363	37,042	75,897
	40–44	11,061	70,187	12,512	15,010	8,489	24,553	24,948	28,341	33,288	69,077
	45–49	11,884	52,374	10,631	12,243	6,589	18,266	19,408	20,103	27,105	71,798
	50–54	11,914	44,383	10,752	12,922	6,564	16,445	18,126	14,892	20,737	62,359
	55–59	10,120	30,502	8,223	9,924	5,151	13,370	15,819	13,700	19,568	61,646
	60–64	10,721	26,078	5,995	7,777	3,810	8,752	11,282	9,784	14,619	44,853
	65–69	15,771	26,216	5,100	6,906	3,285	7,653	10,177	7,501	11,537	30,788
	70–74	14,829	21,070	3,888	5,761	3,152	6,822	8,753	5,903	9,041	22,294
	75–79	8,851	12,397	2,262	4,052	2,107	4,880	6,932	4,229	7,114	19,584
	80–84	3,924	5,839	930	1,864	1,079	2,528	3,914	2,454	4,199	10,638
≥ 85	1,596	2,589	386	890	518	1,263	2,081	1,040	2,379	5,767	
Female	0–4	16,198	285,231	27,907	102,643	33,979	119,773	112,965	194,925	146,930	232,961
	5–9	16,178	317,913	20,117	71,259	18,883	118,715	121,179	174,179	213,778	231,722
	10–14	11,121	271,413	17,745	29,214	12,969	62,680	66,374	68,743	159,393	120,840
	15–19	7,723	222,860	12,007	12,385	7,836	26,606	31,138	30,718	90,053	70,203
	20–24	7,591	111,847	12,030	10,959	6,486	22,453	17,622	22,506	37,724	69,257
	25–29	11,306	130,899	17,477	15,673	7,646	24,528	19,460	25,042	35,353	64,757
	30–34	13,557	119,173	17,801	25,040	12,212	40,131	34,589	46,093	50,570	76,055
	35–39	15,816	118,791	16,292	22,531	11,198	36,474	38,580	51,765	59,962	105,123
	40–44	14,541	86,609	14,691	17,862	10,140	29,493	31,799	35,296	45,701	84,852
	45–49	18,287	69,602	13,957	15,717	8,495	23,065	25,896	25,408	36,836	87,418
	50–54	20,090	67,080	16,522	18,825	9,914	24,428	28,266	23,072	32,693	86,025
	55–59	19,213	48,430	12,516	15,816	7,984	21,942	28,221	24,874	36,168	95,372
	60–64	21,924	39,421	8,490	11,837	5,920	14,815	20,009	17,299	26,553	72,121
	65–69	35,839	41,423	7,144	10,125	4,769	11,965	16,022	11,931	18,636	47,598
	70–74	35,374	34,576	5,699	9,459	4,825	11,119	14,337	9,268	14,275	33,931
	75–79	23,869	22,029	3,844	6,833	3,506	8,239	11,667	6,940	11,818	32,014
	80–84	10,694	10,981	1,834	3,786	2,022	4,723	7,652	4,400	8,026	21,144
≥ 85	4,380	5,490	940	2,352	1,214	2,957	5,372	2,508	6,111	15,721	

^aEach year (starts from July 1st and ends at June 30th) is denoted by the calendar year in which it ends.

season, the incidence rate of males aged 0–4 was 171.02 episodes per 1,000 people, and females were 173.31. In 2017, the 2016–2017 season, the incidence rate was 139.48 for males aged 10–14, 140.94 for females, 52.96 for males aged 15–19, and 60.07 for females. The incidence rate of the 2017–2018 season, in the ages of 40–50 and 60–64 was higher compared to that in the pandemic influenza season.

Incidence rates of influenza by year, sex, and cohort

According to the CIR, (per 1,000 person) diagnosed as influenza, on 2010, the 2009–2010 season the incidence rate of males born in the 1923–1942 was 31.46–31.29 episodes per 1,000 people, 66.24 for males who were born between 1988–1992, and 172.24–253.39 for males who were born on 1993–1997 and higher (Table 4). The incidence of females was 63.32 for those who were born between 1978 and 1982, 69.54 for those who were born between 1983–1987, and 166.10–240.32 for those who were born on 1993–1997 and higher. There was an overall decline in 2009–2010 season after the pandemic influenza outbreaks but from 2014, cohort incidence rates continued to increase. In 2017, the 2016–2017 season, the incidence rate was 52.66 for males born in 1998–2002, 59.67 for females, 138.39 for males from 2003–2007,

Table 3. Age-specific CIR for influenza by year

Sex	Age group	CIR by year ^a									
		2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Male	0–4	15.01	267.87	25.68	90.82	30.32	106.24	97.25	171.02	133.34	222.54
	5–9	11.97	259.69	17.79	60.20	16.19	102.02	103.35	146.31	177.45	189.44
	10–14	7.15	178.17	12.11	19.71	9.87	47.55	49.49	57.67	139.48	103.20
	15–19	4.16	139.96	5.96	6.76	4.50	14.87	15.49	17.40	52.96	39.44
	20–24	2.61	53.06	3.95	4.04	2.10	8.40	5.14	6.13	11.92	21.81
	25–29	3.57	53.25	6.54	5.29	2.88	10.16	6.60	8.14	12.77	24.50
	30–34	4.35	45.21	6.84	7.45	4.07	12.03	9.35	12.53	16.22	28.88
	35–39	5.01	41.22	6.28	7.94	4.43	13.28	12.43	16.31	17.74	35.90
	40–44	5.03	31.29	5.48	6.43	3.60	10.48	10.76	12.61	15.45	33.17
	45–49	5.31	23.47	4.85	5.67	3.10	8.35	8.70	8.87	11.69	30.65
	50–54	6.47	22.72	5.24	6.00	2.98	7.42	8.19	6.84	9.67	29.56
	55–59	8.05	22.89	5.64	6.25	3.07	7.40	8.24	6.78	9.24	28.42
	60–64	10.79	24.93	5.43	6.90	3.22	7.20	8.73	6.91	9.45	27.43
	65–69	17.91	29.79	5.81	7.87	3.71	8.18	10.29	7.17	10.78	27.33
	70–74	24.48	32.60	5.82	8.16	4.09	8.66	11.05	7.44	11.32	27.48
	75–79	27.85	35.50	5.81	9.47	4.57	9.82	12.97	7.59	11.99	29.96
80–84	26.06	35.70	5.31	9.91	5.23	11.20	15.62	8.68	13.39	31.22	
≥ 85	19.53	29.56	4.18	9.13	4.95	11.11	16.63	7.74	16.38	35.76	
Female	0–4	14.42	256.31	24.64	89.43	29.65	105.41	99.47	173.31	134.08	225.83
	5–9	12.04	249.28	17.04	63.09	16.65	105.48	108.62	153.32	185.60	201.92
	10–14	6.87	171.57	11.42	19.52	9.20	46.68	52.05	58.20	140.94	106.66
	15–19	4.81	136.02	7.18	7.44	4.76	16.43	19.68	19.75	60.07	49.82
	20–24	4.89	72.82	7.90	7.04	4.06	13.74	10.58	13.26	22.35	41.67
	25–29	5.59	67.58	9.45	8.98	4.65	15.45	12.37	16.04	22.18	39.78
	30–34	7.00	61.74	9.12	12.57	6.08	19.74	17.73	24.73	28.71	45.79
	35–39	7.00	53.38	7.52	10.84	5.52	18.83	19.98	26.51	30.06	52.30
	40–44	6.85	39.88	6.68	7.86	4.46	13.04	14.28	16.28	21.98	41.88
	45–49	8.42	32.29	6.60	7.66	4.14	10.82	11.87	11.50	16.14	38.37
	50–54	11.11	34.79	8.17	8.84	4.56	11.20	13.04	10.83	15.82	41.69
	55–59	15.06	36.02	8.46	9.83	4.72	12.11	14.60	12.25	16.96	43.86
	60–64	20.76	35.89	7.35	10.04	4.80	11.67	14.93	11.72	16.52	42.72
	65–69	34.25	39.92	6.99	10.08	4.77	11.54	14.83	10.48	16.02	39.12
	70–74	42.38	39.64	6.42	10.26	4.88	11.10	14.39	9.43	14.73	35.11
	75–79	41.70	36.24	5.92	9.88	4.84	10.81	14.57	8.47	13.85	34.86
80–84	31.76	29.83	4.64	9.00	4.52	9.98	15.10	8.05	13.71	34.31	
≥ 85	18.48	21.87	3.49	8.20	3.91	8.73	14.53	6.27	14.25	33.87	

CIR = crude incidence rate.

^aEach year (starts from July 1st and ends at June 30th) is denoted by the calendar year in which it ends.

139.76 for females, 176.06 for males born in 2008–2012, and 184.11 for females, which showed high incidence rates. In 2018, the season of 2017–2018, males were found to have a high incidence of 29.19 for 1963–1967 born and 243.79 for 2013–2017 born. Females had a higher incidence for 1953–1967 born and 1978–1987 born, 41.13 for the 1993–1997 born and 251.38 for 2013–2017 born. Overall incidence rate was higher in females.

Analysis of APC effect on influenza outbreaks

The APC effect analysis was conducted in all episodes diagnosed with influenza. As a result, on age effect, the relative risk was 1.38 for males and 1.48 for females at age 4 based on age 13 (Fig. 2). In addition, it was confirmed that the relative risk was 1.23 for males and 1.32 for females at age 8 or school age. At age 13, higher relative risks were observed in females. The period effect was identified at the highest relative risk in 2010, the season of 2009–2010, and has been continuously increasing since the 2013–2014 season. The cohort effect was gradually high in males and females born in the 1937's or lower. Males were found to have higher relative risks for 1970–1988 born and females in 1977–1988 born and the relative risk

Table 4. Cohort-specific CIR for influenza by year

Sex	Cohort group	CIR by year ^a									
		2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Male	1923–1927	22.08	31.46	4.30	9.09	-	-	-	-	-	-
	1928–1932	27.76	36.14	5.58	9.88	5.20	11.21	16.82	7.94	16.29	-
	1933–1937	26.09	34.15	5.81	9.45	4.58	10.29	14.14	8.32	13.31	33.02
	1938–1942	20.57	31.29	5.67	8.14	4.22	9.07	12.20	7.69	11.93	30.19
	1943–1947	13.57	28.23	5.88	7.86	3.86	8.45	10.80	7.34	11.24	28.05
	1948–1952	9.00	23.43	5.46	6.88	3.28	7.48	9.59	7.05	10.70	26.90
	1953–1957	7.00	23.09	5.62	6.24	3.07	7.30	8.41	6.78	9.39	27.15
	1958–1962	5.67	22.53	5.08	5.99	3.00	7.41	8.21	6.69	9.17	28.08
	1963–1967	5.01	25.40	4.88	5.66	3.02	7.72	8.17	6.98	9.60	29.19
	1968–1972	5.08	35.99	5.65	6.42	3.44	9.39	9.27	9.40	11.57	30.23
	1973–1977	4.68	43.02	6.44	7.92	4.23	12.46	11.80	13.33	15.26	32.15
	1978–1982	3.85	47.69	6.84	7.44	4.35	12.85	11.43	15.92	17.51	35.63
	1983–1987	3.11	56.81	6.19	5.29	3.05	10.74	8.01	11.33	16.05	30.53
	1988–1992	3.00	66.24	3.66	4.03	2.33	9.50	6.08	7.63	12.68	24.83
	1993–1997	5.82	172.24	6.89	6.76	3.52	9.65	5.85	6.24	11.87	22.30
	1998–2002	9.72	195.08	13.38	19.67	8.83	31.48	26.89	22.46	52.66	32.20
	2003–2007	15.32	290.27	19.91	60.06	13.99	78.07	70.46	71.08	138.39	88.72
	2008–2012	13.24	253.39	25.66	90.57	30.62	120.10	110.70	168.81	176.06	164.22
	2013–2017	-	-	-	-	19.61	82.34	88.38	155.45	132.30	243.79
	2018	-	-	-	-	-	-	-	-	-	95.87
Female	1923–1927	23.00	23.58	3.61	8.17	-	-	-	-	-	-
	1928–1932	37.61	32.17	4.93	8.99	4.19	9.14	14.66	6.42	14.15	-
	1933–1937	43.35	37.89	6.04	9.86	4.77	10.65	14.96	8.04	13.60	33.87
	1938–1942	38.24	39.78	6.50	10.24	4.89	10.95	14.52	8.71	13.75	34.79
	1943–1947	26.41	38.74	7.10	10.07	4.82	11.26	14.36	9.51	14.63	34.84
	1948–1952	17.03	35.55	7.59	10.03	4.74	11.61	14.92	10.70	15.90	37.48
	1953–1957	12.35	36.00	8.49	9.82	4.76	11.90	14.68	11.72	16.40	41.92
	1958–1962	9.41	33.23	7.87	8.83	4.65	11.74	14.12	11.93	16.83	43.82
	1963–1967	7.16	33.62	6.40	7.65	4.16	10.73	12.30	10.66	15.71	42.05
	1968–1972	6.80	45.16	6.75	7.85	4.33	11.50	12.09	11.87	15.99	38.55
	1973–1977	7.22	57.99	7.92	10.83	5.19	16.41	16.62	17.69	21.70	39.98
	1978–1982	6.08	63.32	9.32	12.55	6.23	20.70	20.15	27.55	29.68	50.37
	1983–1987	5.16	69.54	9.20	8.98	4.90	16.67	15.26	22.21	28.38	48.10
	1988–1992	4.65	82.61	7.36	7.02	4.10	14.52	11.41	15.15	22.01	39.37
	1993–1997	5.53	166.10	7.64	7.43	4.46	13.67	10.98	13.01	22.23	41.13
	1998–2002	9.89	186.97	12.53	19.47	7.93	29.85	29.52	23.26	59.67	45.99
	2003–2007	15.20	278.18	19.24	62.91	14.25	81.40	75.05	73.37	139.76	90.52
	2008–2012	11.81	240.32	24.37	89.15	30.65	122.16	116.18	176.05	184.11	176.00
	2013–2017	-	-	-	-	17.04	77.59	87.60	156.16	133.04	251.38
	2018	-	-	-	-	-	-	-	-	-	87.09

CIR = crude incidence rate.

^aEach year (starts from July 1st and ends at June 30th) is denoted by the calendar year in which it ends.

was higher in males. From people born in 2008 or later, the relative risk was high in females. Males born in 2015, and females born between 2012 and 2013, the relative risk was high.

DISCUSSION

Influenza is a disease that can be prevented by vaccination, and in Korea, influenza vaccination is recommended to those who are recommended for vaccination. As part of the National Immunization Support Program, free vaccinations are provided every year for infants and seniors aged 65 and over. Since 2015, free influenza vaccination was provided for the elderly aged 65 and older born before 1950.12.31. Infants born between 2015.10.1 and 2016.6.30 in 2016–2017 season, and infants born between 2012.9.1 and 2017.8.31 in 2017–2018 season were given vaccination.^{3,12,13}

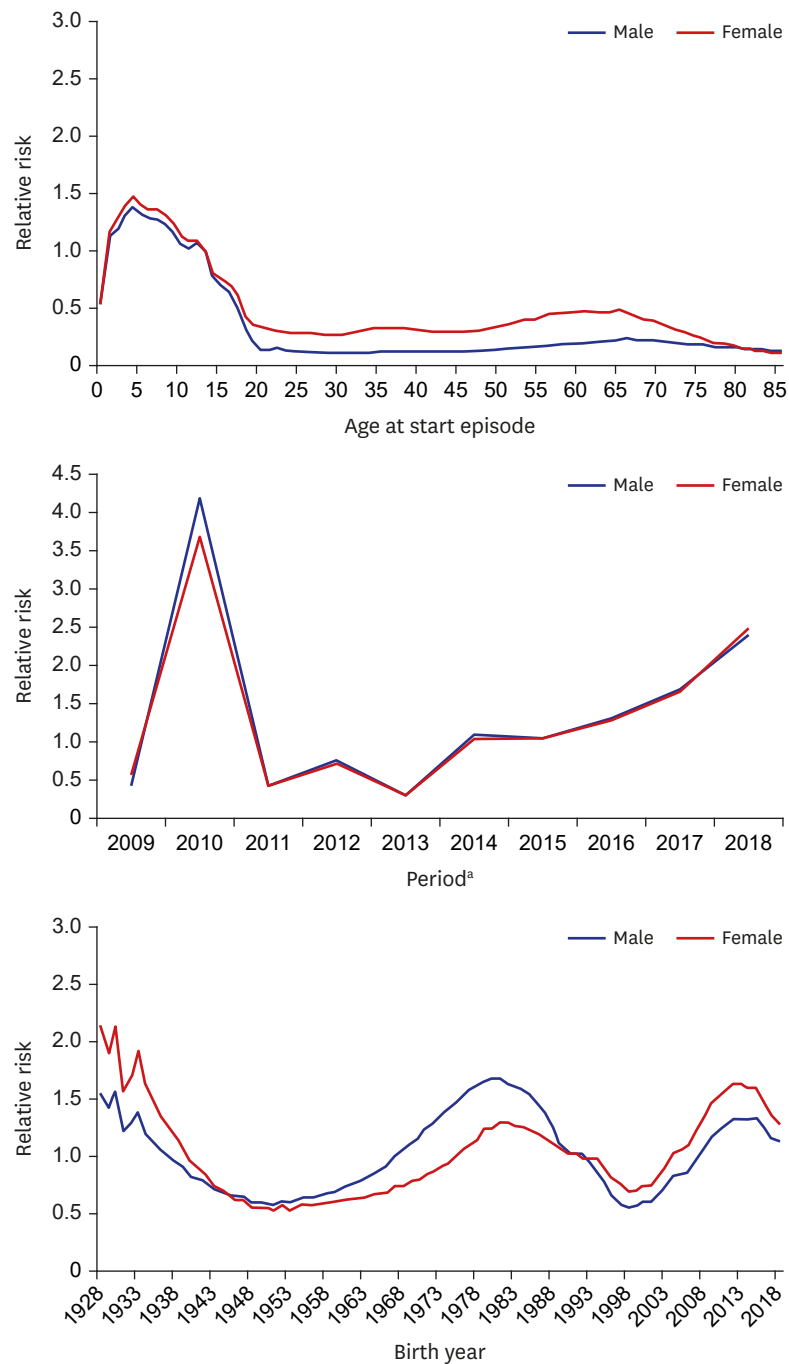


Fig. 2. APC effect of influenza incidence, by total episode.

APC = age-period-cohort.

^aEach year (starts from July 1st and ends at June 30th) is denoted by the calendar year in which it ends.

Although infants and the elderly aged 65 years or older who are part of the National Immunization Complimentary Support Program are included in the high-risk group and given priority for influenza vaccination resulting in high vaccination rate, patients diagnosed with influenza tend to continuously increase.^{8,9} This study aims to identify the epidemiological characteristics associated with influenza outbreaks and to use it as basic data for reducing influenza outbreaks.

This study reconstructed the data of the medical specification unit into the episode of care unit, which was claimed as influenza, by using the data of the health insurance claims data of the National Health Insurance Service. The interval between episodes of care was determined to be 100 days and the task of grouping the reclaim within 100 days into the same episode was performed. In addition, after 100-day episodes of care were established for influenza, calculation of CIR by year, age, and cohort, and analysis of APC effect adjusted for income level by insurance type, and metropolitan city were performed at the episode level.

Since pandemic influenza in 2014, the CIR by age and cohort has increased continuously. Especially, influenza incidence was high in infants and the elderly by age, while high incidence was observed in cohorts born between 1973 and 1982. The APC effect analysis revealed that the age group with the highest relative risk was infants. In addition, the risk of influenza outbreaks was the highest in 2010 (1/7/2009 to 30/6/2010) due to the novel influenza virus pandemic. Its vaccine was subsequently developed and early intervention with the vaccine could decrease the risk for several years, but the risk has increased since 2014. The cohort effect was found with a higher relative risk in children born in 2012–2018, 1978–1987, and 1937.

In multivariate analysis, which took into account APC effect (= birth year), the group at highest risk for influenza was the newly born infants. In the overall age effect, people in their 30s and 40s were not at high risk. Nevertheless, in the cohort effect, high relative risks were observed in children born after 2010 and adults born in the 1980s presumed to be parents' generation of the children. The recent simultaneous increase in the relative risks in infants and their parents has suggested the potential impact of family propagation.

Influenza caused by droplet infection can be transmitted through cough, sneeze and conversation within easy distance. Family in the community is one of important factors of influenza transmission. Contact between family members is frequent and, therefore, households can provide easy transmission of influenza.¹⁴ In addition, children among family members are more vulnerable to infection to play an important role in transmission because they spend a lot of time in nurseries, kindergartens and schools with others.^{15,16} In the previous study on the risk of infectious disease transmission, it was suggested that close contact increased the risk of transmission and the closest contact occurred at home or during leisure activities.¹⁷

In other terms, strengthening immunizations for infants may reduce the burden of influenza disease among young parents who are an active socioeconomic population.

Infants and the elderly aged 65 years or older who were eligible for the National Immunization Vaccine Support Project revealed decreased CIRs due to free vaccination in the first season but incidence increased from the following year. Free vaccinations were expanded and enforced for infants, but the incidence of influenza was high. As well as in the elderly aged 65 years or older, free vaccinations were expanded to private medical institutions but the incidence increased. Influenza immunization effects vary from year to year depending on the age of the vaccinated, the accompanying underlying diseases, the immune status, and the antigenic consistency of the vaccine and epidemic strains of the year. Antigenic mismatch can lead to high influenza prevalence in the vaccinated subjects,¹⁸ but despite the high immunization rates in infants and the elderly aged 65 years or older, the patients continue to increase and therefore it will be needed to consider the effects of vaccination.

Recently, two strains of influenza B virus were prevalent in Korea, and the quadrivalent influenza vaccine showed excellent immunogenicity against the virus that was not included in the trivalent vaccine.^{18,19} Currently, the vaccine used in free vaccination in Korea is inactivated influenza vaccine (trivalent, IIV3), and it is recommended that the trivalent vaccine should contain one type of B virus other than the recommended strain.³ Since influenza viruses cause large and small epidemics through antigenic drift, it is necessary to switch to quadrivalent vaccines containing influenza B antigens to reduce antigenic mismatch caused by antigenic drift. In addition, converting the vaccine to a quadrivalent vaccine, in the free immunization support program, will reduce medical expenses due to the decreased burden of disease in infants and the elderly.

The limitations of this study were as follows: First, since the National Health Insurance Service's data were billing claims data, the influenza diagnosis information could only be confirmed by the disease codes. The clinical data of medical institutions can confirm the type of virus based on symptoms and test results to reflect the accuracy of influenza diagnosis, the number of morbidity experiences and severity of influenza-induced illnesses caused by the virus type, but the National Health Insurance Service's data cannot confirm clinical results. Analysis of Tamiflu and Relenza was possible, but it was necessary to reduce the year of use in the data considering the timing of stabilization of prescription. Second, since influenza is a disease that can be prevented by vaccination, vaccination information is very important, but because it is not claimed due to non-payment, it was not possible to use vaccination information from the claims data. Therefore, influenza diagnosis and vaccination could not be confirmed. Further studies will be needed to determine the influenza outbreak according to influenza vaccination.

In the APC effect analysis, the influenza outbreak was confirmed by reconstructing data by billing statement units at 100-day intervals using the National Health Insurance Service's health insurance claims data including the whole nation. After the outbreak of pandemic influenza, from 2014 the influenza incidence has been increasing every year, and high influenza incidence and relative risk were confirmed in the cohort covered by free vaccination. In addition, the simultaneous increase in influenza outbreaks among high-risk infants and their parents' generations may suggest the possibility of family transmission.

Since influenza can be primarily prevented by vaccination, reinforcement of vaccination in infants may reduce the disease burden in their parents, and also the risk of infection caused by family transmission. Furthermore, a new national vaccination program may be needed to reduce secondary complications such as pneumonia and medical uses caused by influenza infection.

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