보건학석사학위논문

Recent increase of pertussis in South Korea: age-period-cohort analysis

한국의 최근 백일해 발생 증가에 대한 연령-기간-코호트 분석

2019 년 8 월

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이 논문을 보건학석사학위논문으로 제출함

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서울대학교 보건대학원

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ABSTRACT

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Pertussis is one of the most contagious disease, which is caused by a gram−negative bacterium called *Bordetella pertussis*. Pertussis is preventable by vaccination. Routine vaccination schedule of DTaP vaccine consists of 5−dose series at 2, 4, 6, 15−18 month and 4−6 years old. Despite the significant improvement in vaccination coverage, pertussis still attributes morbidity and mortality, particularly of infants and young. Resurgence of pertussis has been reported since 1980s in the developed countries, despite of their high vaccination coverage. After substantial decrease of pertussis by introduction of universal vaccination, South Korea also has experience resurgence of pertussis since 2000s. Many researches have tried to figure out the reason of pertussis resurgence. So far, few studies have addressed the cohort effect on the recent increase of pertussis. This study expects to figure out the specific birth cohorts who experienced the combined effects of various factors.

With secondary data from Infectious Disease Portal of Korea Center for Disease Prevention & Control and Korea Statistical Information Service of Statistics Korea, this study analyzed the incidence of pertussis in South Korea to figure out the factors contribute to the recent phenomena using age-period-cohort model.

Age effects indicates that the most vulnerable age group to pertussis is 0-2 years old group. After the sharp decrease at 3-5 years old group, the risk arises again until 9-11 years old, and then the decrease again 54-56 years old. After the lowest point at 54-56 years old, risk increases again. The period effect shows sharp increase after 2016. With cohort effect, significant decrease is observed from the introduction beginning at 1955 birth cohorts. However, since 2000s birth cohorts, the risk has started to rise again.

To explain the result of age effect, effectiveness of vaccination and age-specific social contact rates are suggested from previous studies. For period effect, following explanations are suggested from previous studies: antigenic variation, decreased opportunity of natural boosting due to lowered number of circulating pathogens, elated recognition and reporting, and improvement of diagnostic tools.

For cohort effect, this research suggested decreased maternal immunity as a factor that contributed to recent increase of pertussis in South Korea. Recent phenomenon is resulted from lack of passive immunity from maternal body due to waning immunity after vaccination combined with decreased opportunity of natural boosting.

From a view of public health, providing additional chance of boosting is available intervention. Considering the most significant increase of incidence rate occurred within infant aged under 1 year old, it is important to establish enough maternal immunity to provide passive immunity via placenta for babies.

keywords: pertussis, whooping cough, DTaP, immunization, vaccination, age−period−cohort analysis, apc, intrinsic estimator
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INTRODUCTION

■ Problem statement

Pertussis is one of the most contagious disease, which is caused by a gram−negative bacterium called *Bordetella pertussis* [1]. Another name of pertussis, whooping cough, is originated from its distinguishing symptom generating "whoop" sound during inhalation due to narrowed airways [1−3]. Pertussis is preventable by vaccination. Routine vaccination schedule of DTaP vaccine consists of 5−dose series at 2, 4, 6, 15−18 month and 4−6 years old (Table 1). After completion of DTaP vaccination, children aged 7 years old or older are recommended to be immunized by Tdap vaccine, which contains reduced dose of the diphtheria and pertussis (Table 1).

Table 1. Recommended Immunization Schedule of pertussis

Vaccine	2mo	4mo	6mo	12−15mo	4−6yr	≥7yr
DTaP	1st dose	2nd dose	3rd dose	4th dose	5th dose	
Tdap						6th dose

Since 1980s, the number of cases and deaths of pertussis have decreased significantly with increased proportion of the diphtheria−tetanus−pertussis (DTP3) vaccination coverage. (Figure 1) [4]. The reported cases of pertussis recorded 143,963 in 2017, and there were 89,000 deaths globally [4]. Despite this significant improvement, pertussis still attributes morbidity and mortality, particularly of infants and young [5].

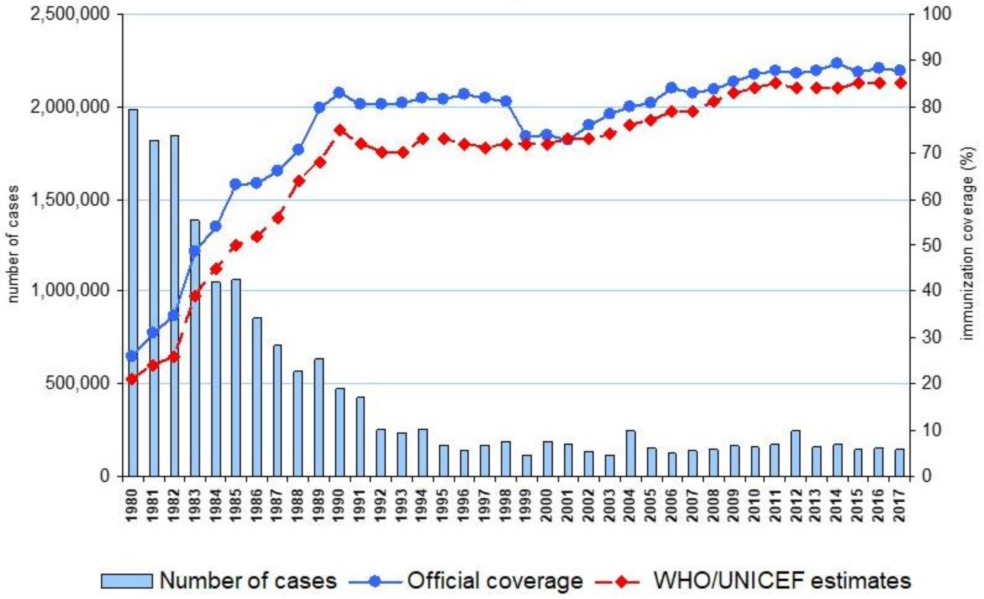

Figure 1. Pertussis global annual reported cases and DTP3 coverage, 1980–2017 [4]; DTP3, three doses of diphtheria–tetanus–pertussis; WHO, World Health Organization; UNICEF, United Nations of Children's Fund.

Though there is difference between country by country, resurgence of pertussis is reported from numerous countries despite of their mass vaccination strategy. South Korea is one of the countries where maintains high vaccination coverage since introduction of the DTaP vaccine in 1982 [3]. This research tries to explain the resurgence of pertussis by analyze the reported cases of pertussis in South Korea with age–period–cohort model.

■ Global epidemiology of pertussis

As pertussis has not been studied continuously, it is difficult to estimate exact incidence rate of all age groups in each country except for infants and young [3]. The latest study about global burden of pertussis estimated the 24.1 million cases of pertussis and 160,700 deaths from pertussis in children younger than 5 years in 2014 [6]. Compared to former publication about estimation of 1999 (30.6 million cases and 390,000 deaths), global disease burden of pertussis has decreased considerably [6].

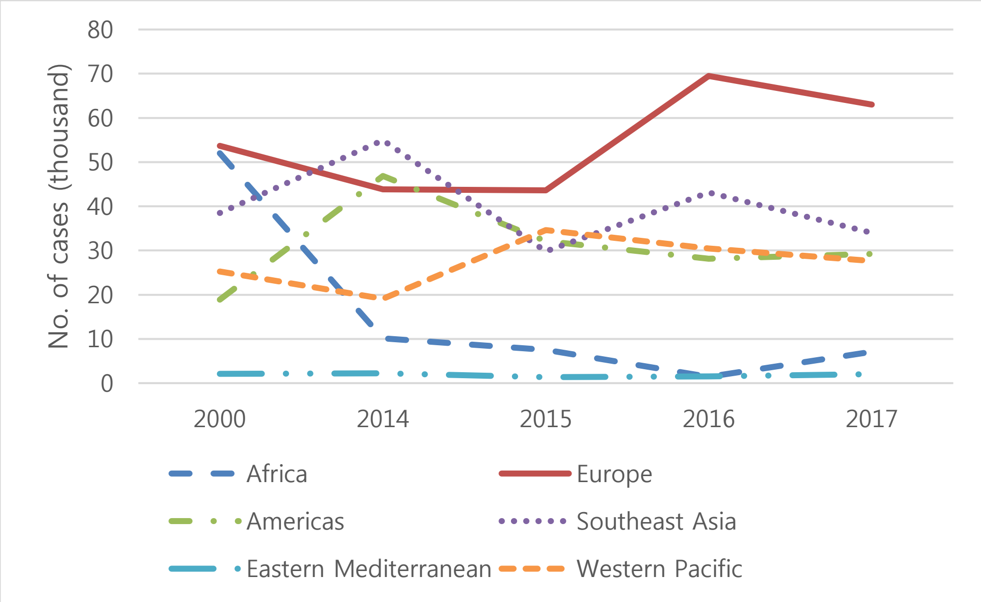

Figure 2. Number of reported pertussis cases across the 6 WHO regions in 2000 and 2014–2017 [7]

However, it is hard to conclude that the disease burden of pertussis has decreased successfully. According to data of World

Health Organization (WHO), not all regions demonstrate decreasing trend in number of reported pertussis cases (Figure 2) [7]. Considering gross improvement in vaccination coverage to target population from 2000s (Figure 3), the decreasing trend of pertussis across the regions is not as much as expected except for Africa. For European and Western Pacific regions, the number of pertussis increased recently rather than that of 2000 despite of their high vaccination coverage. The only region where shows significant progress in number of reported cases of pertussis is Africa, where also showed the most rapid increase in vaccination coverage.

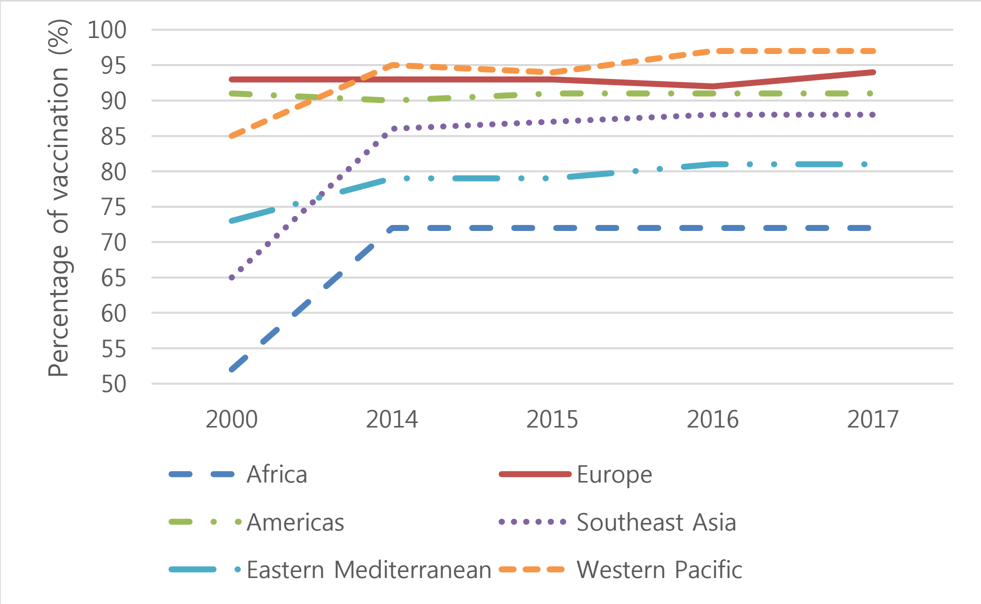

Figure 3. Percentage of target population vaccinated by DTP3 across the 6 WHO regions in 2000 and 2014–2017 [7]

The core problem of this phenomena is that the resurgence of pertussis located in highly vaccinated countries. Since 1990s, reemergence of pertussis observed in United States [8]. Like situation in South Korea, the incidence of pertussis in United States remained stable after introduction of DTP vaccination in mid-1940s (Figure 4) [9, 10]. However, the increasing trend in reported incidence of pertussis observed since the early 1980s, with repeated peak in every 3-4 years [8, 11]. Along with the steady increase, there was the largest outbreak of pertussis in the last 50 years in Washington, 2012 [12, 13]. This epidemic recorded a nearly 1,300% increased number of cases compared to the same period in 2011 and any of the highest number of cases recorded since 1942 [13]. Through the epidemiologic investigation, researchers found the evidence of the early waning of immunity from increased incidence in vaccinated adolescents aged 13-14 years [13].

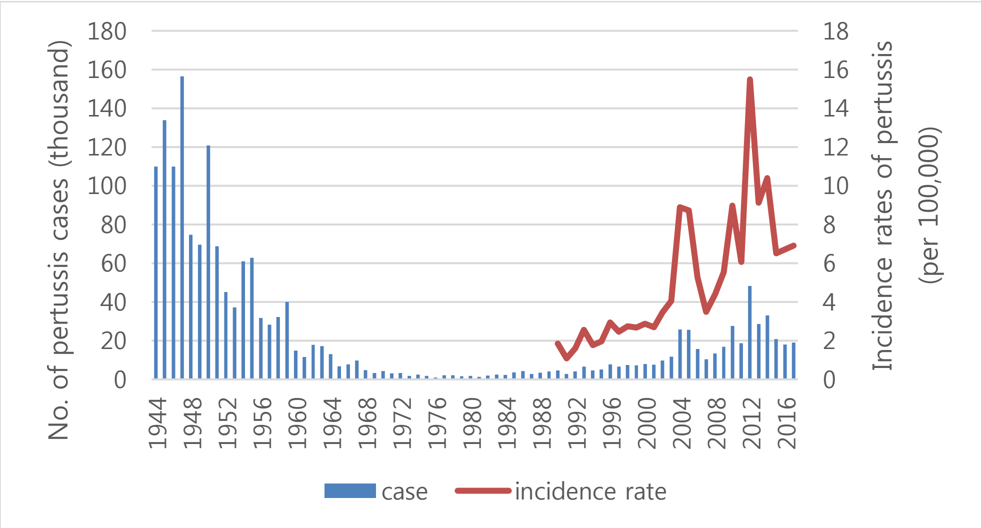

Figure 4. Number of cases and incidence rates of pertussis in United States, 1944–2017 (Incidence data is available since 1990) [9, 10]

Another resurgence was found in Canada. Similar to United States, Canada introduced universal vaccination program in the 1940s. Like many other countries where adopted pertussis vaccination, Canada also experienced dramatical decrease in pertussis incidence until 1980s (Figure 5).

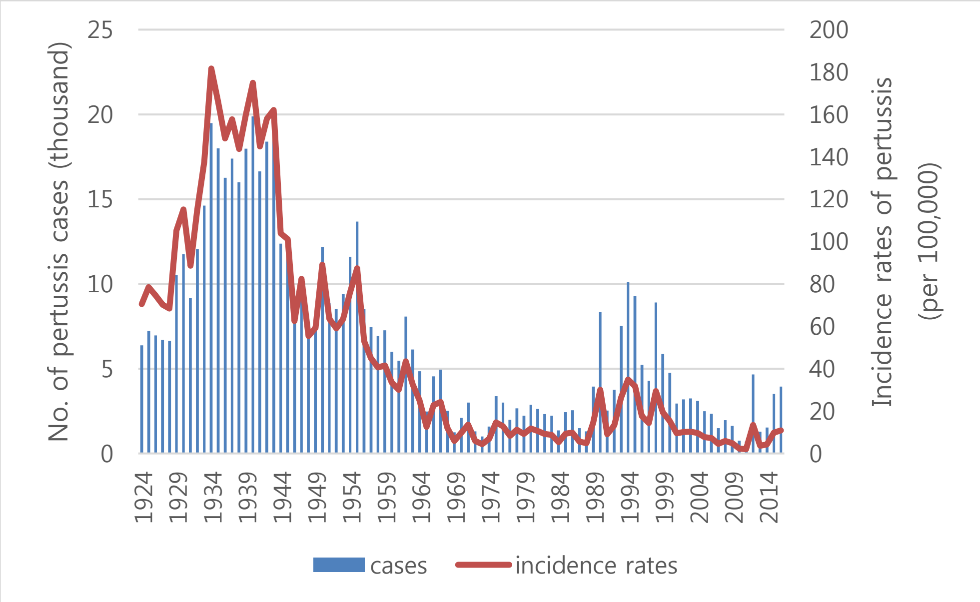

Figure 5. Number of cases and incidence rates of pertussis in Canada, 1924–2016 [14]

However, since 1990, the incidence of pertussis began to increase suggesting resurgence of pertussis in Canada (Figure 6) [14, 15]. It was hard to conclude that this resurgence were originated from unvaccinated children as vaccine coverage of the children who completed at least 3 doses of vaccination were estimated more than 95% of the target population [15].

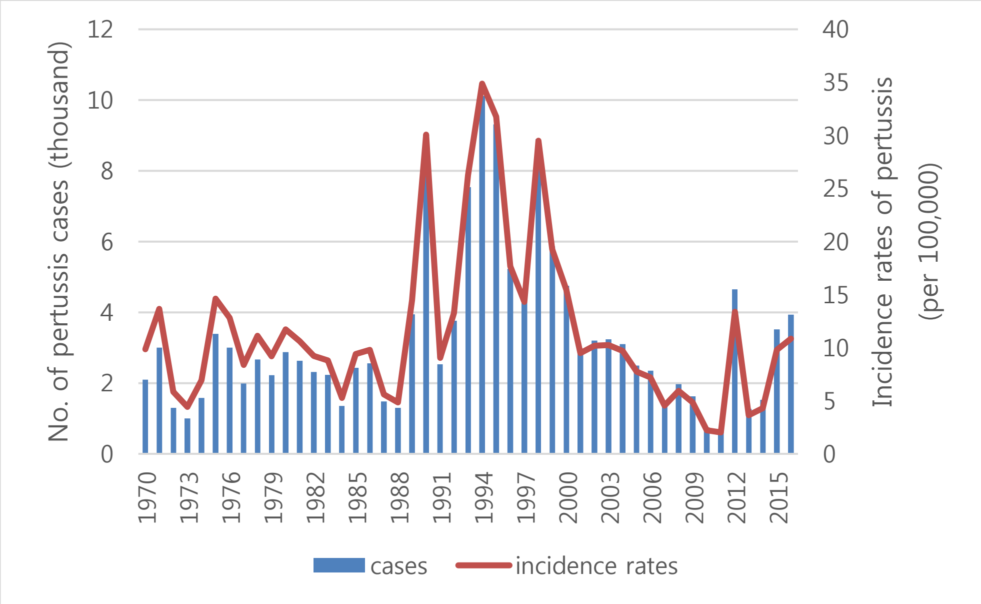

Figure 6. Number of cases and incidence rates of pertussis in Canada, 1970–2016 [14]

In addition to United States and Canada, resurgence of pertussis has been reported in Australia, United Kingdom and Europe [16, 17]. Considering that these countries including South Korea classified as highly vaccinated countries, the recent resurgence of pertussis is an unexpected phenomenon.

■ Epidemiology of pertussis in South Korea

In 1958, the DTwP vaccine was introduced to South Korea and the vaccination was actively carried out which continued after it was changed to the DTaP vaccine in 1982 due to safety concerns [3]. As a result, even small outbreaks had been found in South Korea for a while [3, 18] (Figure 7). Since 1990s, there was no reported case of death due to pertussis in South Korea [19].

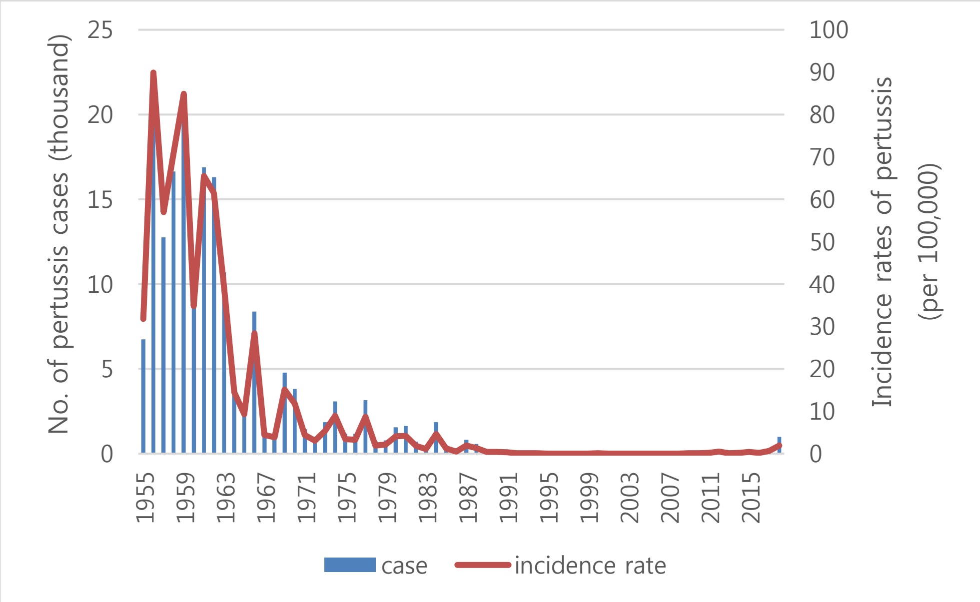

Figure 7. Number of cases and incidence rates of pertussis in South Korea, 1955–2018 [18, 20]

However, resurgence of pertussis has been observed in South Korea since 2000s, as it has in other highly vaccinated countries [3, 19]. Since 2012, small outbreaks were reported in South Korea [3]. Pattern of outbreak is also similar to other highly vaccinated countries, which has a cycle of 2 to 3 years [3].

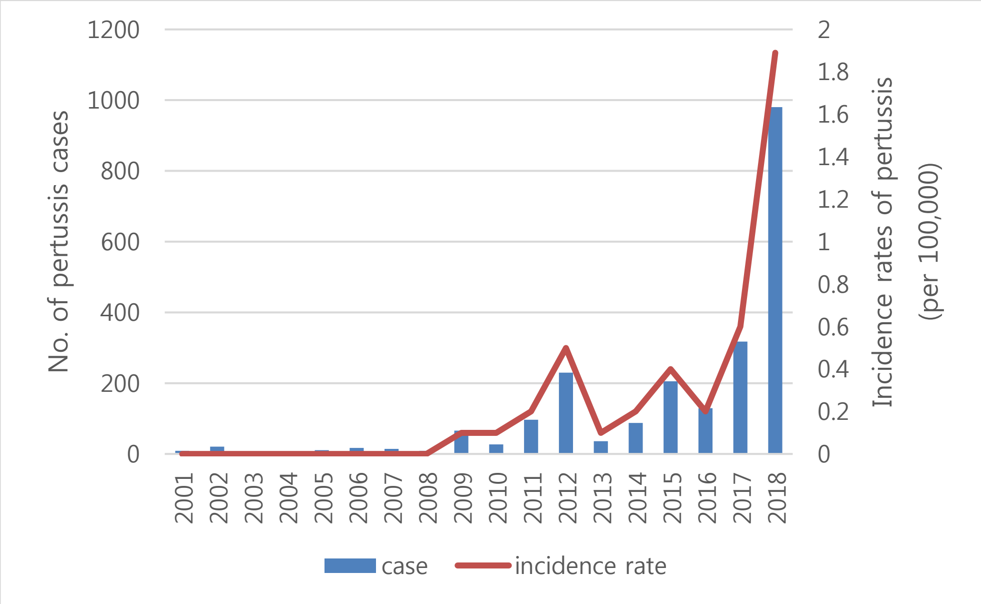

Figure 8. Number of cases and incidence rates or pertussis in South Korea, 2001–2018 [18, 20]

In 2012, there was an outbreak in dormitories for middle and high schools in Yeongam–gun [3, 21]. Another outbreak occurred in 2015 took place in postpartum care center in Andong–si and elementary schools in Chanwon–si [3, 22]. The most recent outbreak was found in 2017, which including small outbreaks of Gyeonggi–do, Gwangju and Sejong–si [3, 18].

■ Age−period−cohort analysis for pertussis

Since the 1930s, the importance of birth cohort's impact on disease and human behavior has been rising [23]. Birth cohort refers the component of the population born during a particular period and identified by period of birth so that its characteristics can be ascertained as it enters successive time and age periods [24]. Age−period−cohort analysis is a systematic study of temporally ordered datasets [25]. It helps understand the effect of age, period and cohort on the health outcome, respectively [24].

There have been numerous studies which temporally analyzed the recent increase of pertussis despite the high vaccination coverage in many countries. One of these studies which analyzed epidemiological data of pertussis across the world from 2000 to 2013 through systematic review provided two key findings: 1. Despite the effective vaccination strategies, still pertussis is a serious health problem especially for infants. 2. There was remarkable increase in school−aged children and adolescents [26]. This study suggested several factors which contributed to the resurgence of pertussis: lack of booster immunizations, low vaccine coverage, improved diagnostic methods, and genetic changes in the organism [26].

Another study analyzed nationally reported data of pertussis in United States from 2000 to 2016 [27]. According to this study, the baseline incidence of pertussis in Unites States increased about 2-fold from earlier part of the study period to that of the later part [27]. This study suggested contributors to the resurgence including improved diagnostic tools, heightened recognition and reporting, molecular changes of organism, and waning of vaccine-induced immunity [27].

Similar study was published in 2012 using national data of South Korea [28]. Like many other highly vaccinated countries, South Korea experienced decrease in the reported number of cases after introduction of vaccination until the late 1990s, but the increase began in the early 2000s [28]. They also experienced age-shift of increase in trend among adolescents and adults aged 15 years old or more [28].

However, very few explained the recent reemergence of pertussis and suggested the possible factors which contributed to recent resurgence of pertussis focusing on the cohort effect, rather simply comparing the situation of past and present. In this day and age, in where birth cohorts who experienced difference eras including pre- and post-vaccine era, different exposure rate of natural boosting to naturally circulating pathogen due to introduction of vaccination coexist and many other improvement in medical settings, it is necessary to figure out cohort effect over resurgence of pertussis.

RESEARCH PURPOSE

Pertussis is one of the vaccine preventable diseases, which can be prevented by appropriate vaccination policy. But recently, incidence rate of pertussis increases significantly with high enough vaccine coverage rate. In South Korea, vaccine coverage rate of children who completed 4^{th} dose have been maintained more than 95% [29], which is sufficient to eradicate the disease, considering the basic reproductive number (R_0) of pertussis [30].

As mentioned earlier, many researches have tried to figure out the reason of pertussis resurgence including relatively short immune duration of DTaP vaccine [2, 16], genetic change of circulating pathogen [31–33] and reduced boosting opportunities due to decreased incidence [34], etc.

However, resurgence of a disease cannot be explained by a single factor. The cohort effect provides appropriate explanation to describe the mixed effect of various factors, which reflects the effect of age–related and periodical changes at the same time. So far, few studies have addressed the cohort effect on the recent increase of pertussis.

This study aims to find the specific birth cohorts who experienced the combined effects of those factors mentioned by various studies. Detecting the high–risk population, specific birth cohorts in this study, would be helpful to react to the difficult pattern of recent re-emerging infectious diseases.

MATERIALS and METHODS

■ Ethical statement

The Institutional Review Board of Seoul National University confirmed that the data used in this study are statistical data for the group, not for the individual, and are not subject to review.

■ Data source

Data of pertussis cases and mid-year population was gathered to calculate annual age-specific incidence rate of pertussis. In South Korea, All physician ought to notify the all pertussis cases including laboratory-confirmed cases and clinically suspected cases when they recognize the patients. The aggregated data of notifiable diseases are open to public through Infectious Disease Portal of Korea Center for Disease Prevention & Control (http://www.cdc.go.kr/npt). This study used the age-specific data of pertussis from 2001 to 2018. Also, the age-specific mid-year population data were obtained from Korea Statistical Information Service of Statistics Korea (http://www.kosis.kr).

South Korea started DTwP vaccination in 1955, which changed to DTaP vaccine in 1989 due to safety issues. It indicates that the birth cohorts before 1955 (~1954) hadn't received any artificial immunity, whereas the birth cohorts from 1955 to 1988 received DTwP vaccine, and the birth cohorts after 1988 (1989~) received DTaP vaccine.

■ Statistical analysis

Before the APC analysis, the annual age-specific incidence rate of pertussis in each age group were plotted using data from Infectious Disease Portal (pertussis cases) and Korea Statistics (mid-year population). The age group was divided into 7 groups: infant (0years old), toddler (1-3years old), preschooler (4-6years old), school-aged (7-11years old), adolescent (12-19years old), adult (20-59years old), senior young (60-74years old) and senior old (75 over). This grouping can identify the different patterns of change between age groups.

Goodness-of-fit statistics provide the necessity to assume that all three of the age, period, and cohort effects are present and to estimate them simultaneously[25]. By evaluating the model fit statistics with possible sets and combinations of coefficients, A, P, C, AP, AC, PC, and APC, the best model can be identified[25]. Deviance of a model close to the df means the model is well-fitted, whereas large deviance indicates a poor fit of the model[23].

Usually, the multiple regression model was used to estimate each effects: $Y = \alpha + \beta_1 age + \beta_2 period + \beta_3 cohort + \varepsilon$ [24]. However, this study adopted the Poisson age-period-cohort (APC) model since the analysis in this study is based on count data. Formula for the model is as follows: $\ln[\lambda(a, p)] = f(a) + g(p) + h(c)$, where a stands for age,

p for period, and **c** for cohort effect.

As mentioned earlier, APC analysis is kind of multiple regression which composed of age, period, and cohort. The basic assumption of multiple regression is that each variable is independent each other. But APC model fails to meet this assumption due to linear−dependent relationship between the three variables (cohort=period−age), which called "identification(ID) problem." [24]

There have been developed many statistical models and methods to manage the identification problem arising from the linear dependence of the three factors including the intrinsic estimator (IE), cross−classified random effect (CCREM), and hierarchical APC (HAPC)−growth curve model. This study adopted the intrinsic estimator (IE) method was applied as it provides more objective estimates traditional constraining model (Constrained general linear models, CGLM) by which a researcher choose one variable to constrain out of three[35].

Plotting incidence rates by age groups as described earlier is useful to understand the overall trend of the disease, but it is necessity to set the equally spaced blocks for APC analysis. Blocks were set by 3−year units for age, calendar year, and birth cohorts. Reported cases of aged over 80 were excluded because of their low incidence (67 out of total 2,268, 0.03%), resulting 27 age groups from 0−2 to 78−80 years old, 18 calendar year from 2001 to 2018, and 32 birth cohorts from 1923−1925 to 2016−2018. Still, after excluding data of aged over 80 years old, there are many cells which have zero value. To analyze as many data as possible, the lowest incidence rate was replaced with zero value [36]. All statistical analysis was performed using STATA/MP V.13.

RESULT

Figure 9 shows the secular trend of pertussis incidence from 2001 to 2018 in South Korea. Incidence rates of all 7 groups increased after 2017, so that the highest incidence rates were founded in 2018 during study period. While maintaining the highest incidence rates, the infant group shows the sharpest increase during 2017 to 2018. Next to the infant group was the school-aged group (7-11years old). According to Table 2, which shows the incidence rate of pertussis cases by age and calendar year, the incidence rate of infant group shows 17.6-fold increase in 2018 compared to 2001.

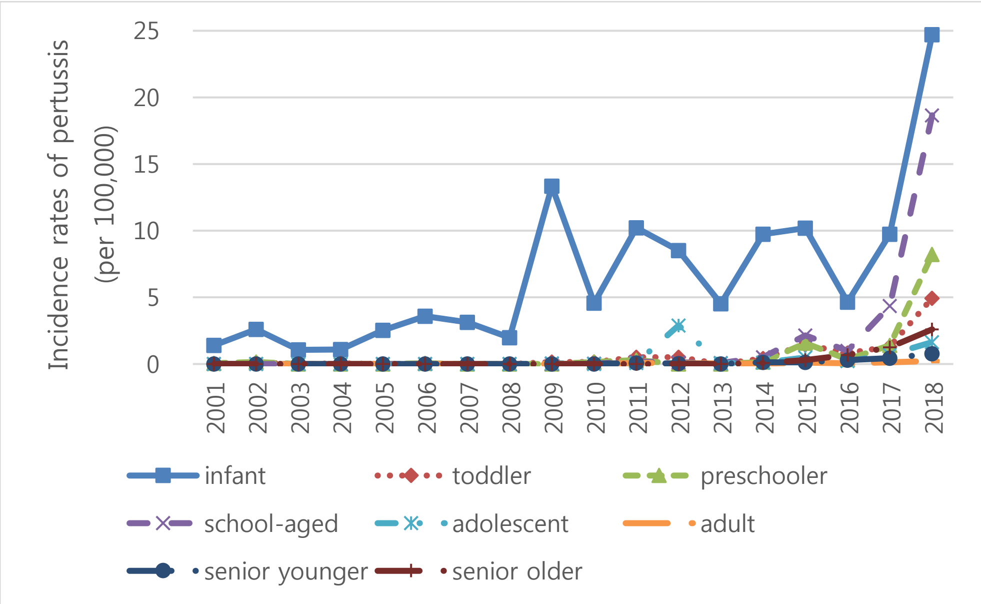

Figure 9. Incidence rate of pertussis by year and age groups, South Korea, 2001-2018

Table 2. Annual incidence rates (per 100,000) and number of cases of pertussis by age groups and calendar year (2001−2018) in South Korea

Age Groups (Age range)	Calendar Year																	
	‘01	‘02	‘03	‘04	‘05	‘06	‘07	‘08	‘09	‘10	‘11	‘12	‘13	‘14	‘15	‘16	‘17	‘18
Infant (0)	1.403 (8)	2.592 (13)	1.064 (5)	1.086 (5)	2.543 (11)	3.577 (15)	3.129 (14)	1.968 (9)	13.349 (58)	4.582 (20)	10.222 (46)	8.516 (39)	4.516 (20)	9.747 (41)	10.185 (43)	4.644 (19)	9.737 (36)	24.719 (82)
Toddler (1−3)	0 (0)	0.108 (2)	0 (0)	0.062 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0.144 (2)	0.143 (2)	0.503 (7)	0.505 (7)	0 (0)	0.423 (6)	1.445 (20)	0.819 (11)	1.301 (17)	4.944 (62)
Preschool (4−6)	0.048 (1)	0.147 (3)	0 (0)	0 (0)	0 (0)	0.057 (1)	0 (0)	0 (0)	0 (0)	0.145 (2)	0.293 (4)	0 (0)	0 (0)	0.143 (2)	1.581 (22)	0.353 (5)	1.407 (20)	8.215 (114)
School−aged (7−11)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.035 (1)	0.183 (5)	0.117 (3)	0.083 (2)	0.511 (12)	2.142 (50)	0.996 (23)	4.363 (101)	18.662 (438)
Adolescent (12−19)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.054 (3)	0 (0)	0.091 (5)	2.895 (157)	0.057 (3)	0.098 (5)	0.49 (24)	0.235 (11)	0.694 (31)	1.646 (70)
Adult (20−59)	0 (0)	0.01 (3)	0 (0)	0 (0)	0 (0)	0.003 (1)	0 (0)	0 (0)	0.01 (3)	0.003 (1)	0.084 (26)	0.071 (22)	0.032 (10)	0.038 (12)	0.093 (29)	0.067 (21)	0.138 (43)	0.233 (72)
Senior young (60−74)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.018 (1)	0.07 (4)	0.034 (2)	0.016 (1)	0.127 (8)	0.136 (9)	0.289 (20)	0.444 (32)	0.77 (58)
Senior old (75+)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.08 (2)	0.3 (8)	0.671 (19)	1.251 (38)	2.601 (84)

Values are presented as incidence rates (number of cases)

Also, school-aged group shows 93.5-fold increase in 2018 compared to 2011. This increase in school-aged group is the most explosive increase among all age groups, which is similar to many other highly vaccinated countries (Figure 10). The exceptional high proportion of adolescent in 2012 seems to be resulted from the pertussis outbreak in dormitories for middle and high schools in Yeongam-gun. From 2001 to 2018, the average of reported number of cases in adolescent is 17.1 cases per 100,000. However, in 2012, total 157 cases were reported, among which 113 cases and 41 cases were reported from high school and middle school in Yeongam-gun, respectively [37].

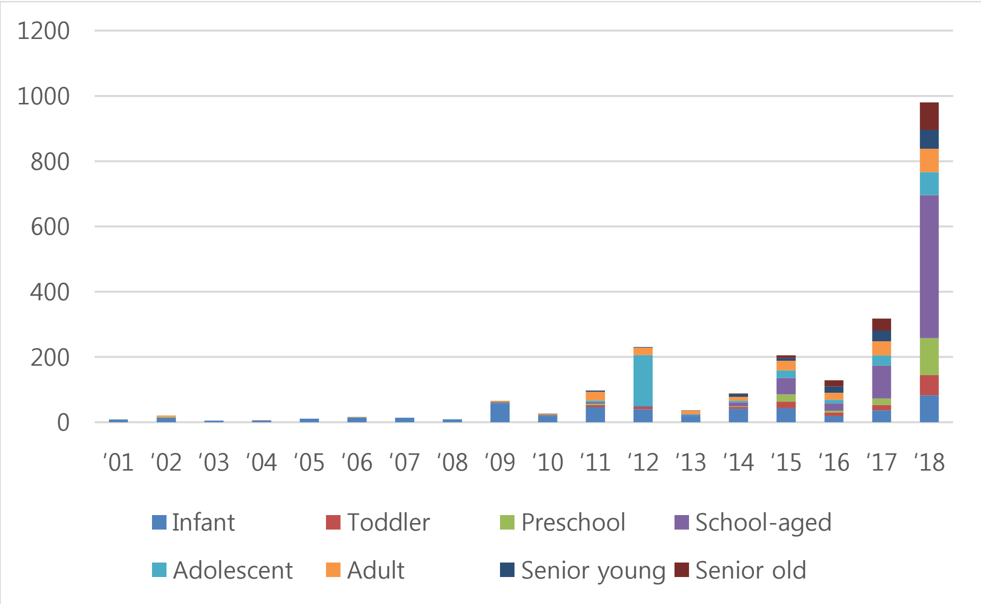

Figure 10. Annual cumulative number of pertussis by year and age groups, South Korea, 2001-2018

For age−period−cohort analysis, the result of goodness−of−fit test suggested that the full APC (IE) model fits best for the analysis (Table 3). Residual deviance represents the goodness−of−fit of the models. According to residual deviance, the full APC model which showed the smallest residual deviance most appropriately explains the data.

Table 3. Goodness−of−fit test for each model

Model	Deviance (*df*)	Log likelihood	AIC
Age	5997.32(160)	−3231.19	39.92
Age−period	3095.69(159)	−1780.38	22.02
Age−cohort	3095.69(159)	−1780.38	22.02
Age−period−cohort (intrinsic estimator)	345.65(100)	−405.36	5.77

Figure 11 presents all three effects—age, period and cohort—derived from the model on the incidence rate of pertussis in South Korea. All the three effects showed clear patterns of change according to each age, period, and cohort groups. Considering that infants are the most vulnerable population to pertussis, the highest coefficient of age effect in 0−2 years old groups is not surprising. More than that, rapid increase in period effect of 2016−2018 and cohort effect of recent birth cohorts are remarkable results.

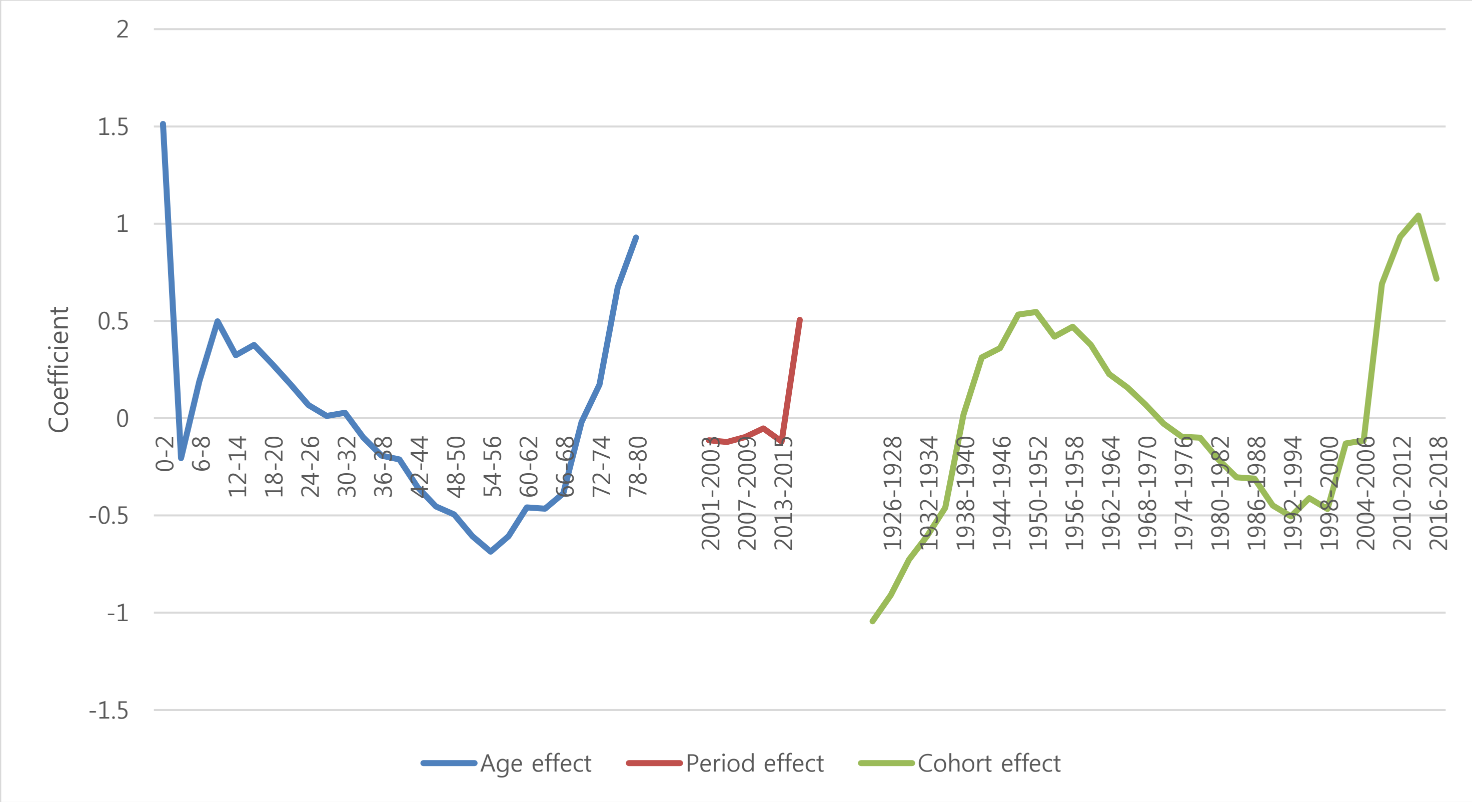

Figure 11. Intrinsic estimator (coefficient) of age, period and cohort effect from age−specific incidence rates (100,000 person) of pertussis in South Korea.

Age effects over incidence rates of pertussis are shown in Figure 11 and 12. The result indicates that the most vulnerable age group to pertussis is 0–2 years old group in which the babies who are subjected to initial 3rd vaccination of DTaP. After 3rd vaccination, there was sharp decrease in the risk of pertussis in 3–5 years old group. However, the risk arises again until 9–11 years old, and then the second decrease appeared until the 54–56 years old. After the lowest point at 54–56 years old, risk increases again until the end.

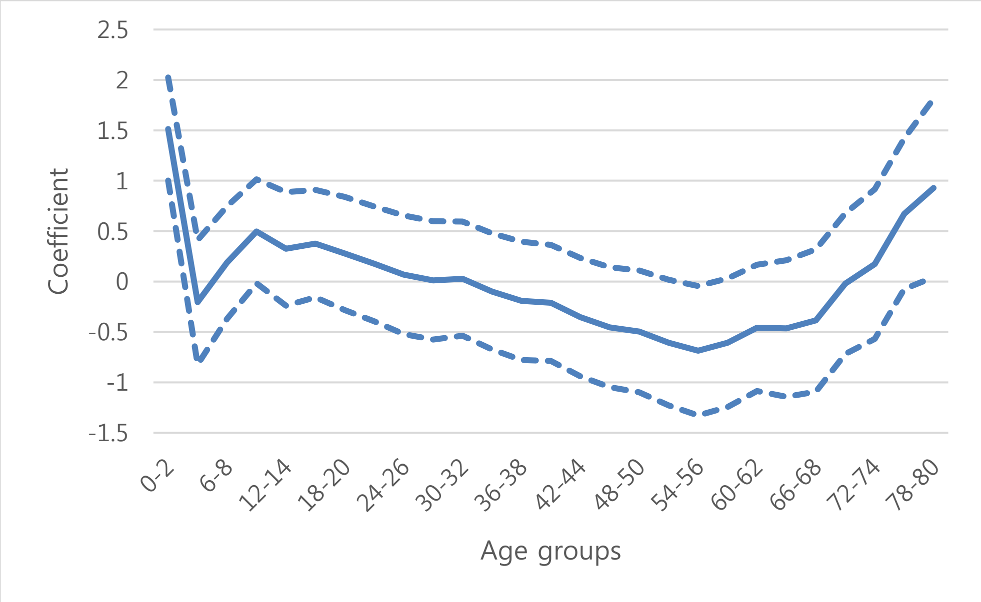

Figure 12. Intrinsic estimator (coefficient) of age effect from age-specific incidence rates (100,000 person) of pertussis by age groups.

The period effect was also significant as shown in Figure 11 and 13. From 2001 to 2015, there were no significant change in the risk of pertussis. Since 2016, the risk of pertussis sharply increased, which shows the similar trend with overall incidence rates of pertussis in South Korea, from 2001 to 2018.

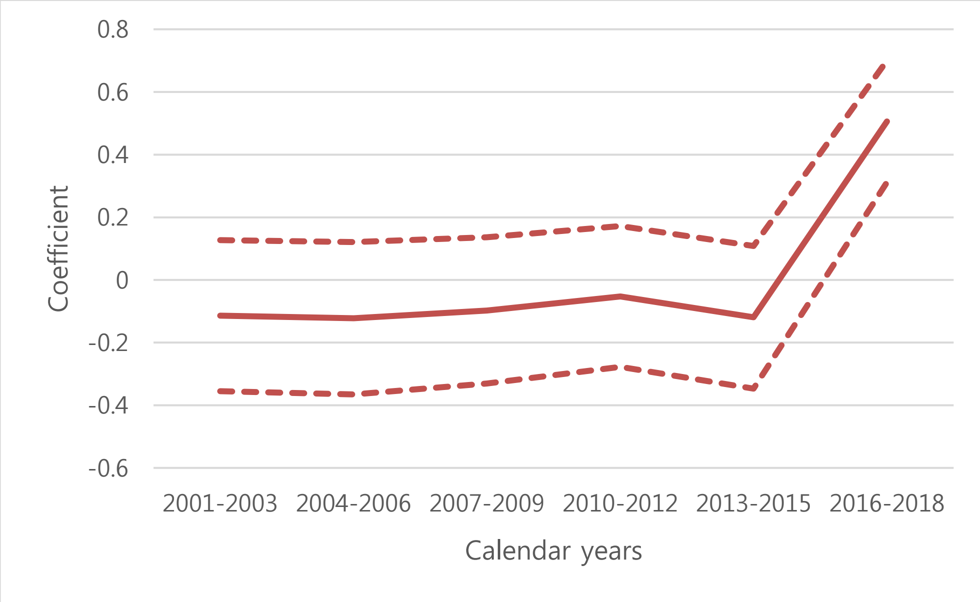

Figure 13. Intrinsic estimator (coefficient) of period effect from age−specific incidence rates (100,000 person) of pertussis by calendar years

Another increased risk of pertussis was observed from cohort effect (Figure 11 and 14). The risk of pertussis had increased gradually until before the introduction of vaccination in 1955. After then, there was a steady decrease in risk of pertussis until the early 1990s birth cohorts. Since 2000s birth cohorts, the risk has started to rise again, indicating a risk as high as it was before the vaccine was introduced.

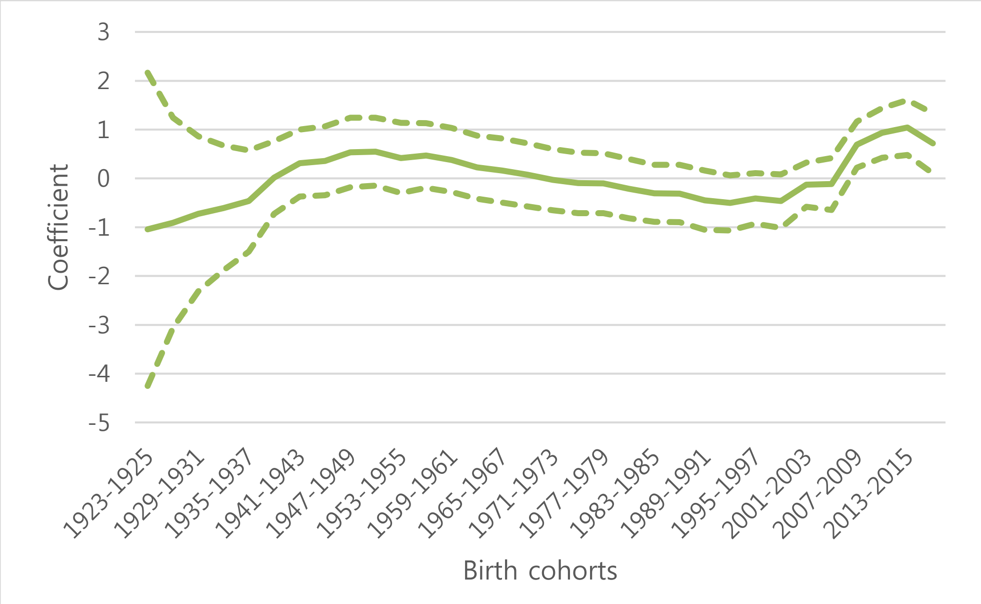

Figure 14. Intrinsic estimator (coefficient) of cohort effect from age−specific incidence rates (100,000 person) of pertussis by birth cohorts.

DISCUSSION

I described the secular trend of pertussis incidence and estimated the effect of age, period, and cohort during 2001–2018 in South Korea. The most significant increase appeared in infant (8 to 82 cases, 1.403 to 24.719 per 100,000 persons in 2001 and 2018 respectively), school–aged (1 to 433 cases, 0.035 to 18.662 per 100,000 persons in 2010 and 2018 respectively) and preschooler (1 to 114 cases, 0.048 to 8.215 in 2018 and 2018 respectively) groups.

These results suggest waning of vaccine–induced immunity in accordance with decreased opportunity of natural boosting due to successful control over pertussis by vaccination. According to case–control study conducted in California, United States, vaccine–induced protection begins to wane during 5 years after the 5th dose of vaccination [38]. Another nested case–control study which included test–negative participants as controls in Ontario, Canada, the decline of the vaccine effectiveness was observed since 4 years after last vaccination [39]. In South Korea, School Entry Requirement Certification Program conducted by Korea Centers for Disease Control and Prevention requires 5th dose of vaccination by DTaP before admission to an elementary school. Considering the duration of immunity calculated from the previous studies, increased incidence among school–aged in South Korea is quite reasonable.

According to the age effect, the preventive effect is found after the first 5 dose of the vaccination, which finished at the age between 4 to 6 years old. However, despite of its effectiveness, the risk increases soon later at the age of 6−8 to 9−11 years old groups. Increased contact rate by school environment may result this increased risk among children. According to previous study regarding age−specific contact rate of respiratory disease, the highest contact rate was observed at the age of 10−14 years old [40]. Previous studies supporting this pattern of contact rate conducted in Japan and Netherland. In Japan, elementary school children are more vulnerable to pertussis than junior high school student because of their lower exposure rate to pertussis [41]. Similarly, in Netherland, the children who completed their 5−dose of vaccination already had high−enough immunity at 9 years old thanks to natural boosting [42].

The age−specific contact rate also explains the decreasing pattern which appeared after 9−11 years old, in which age−specific contact rates begin to decrease at the age of 15−19 years old [40]. Also, in Korea, by the School Entry Requirement of Certification Program conducted by Korea Centers for Disease Control and Prevention, not only elementary school but also middle school requires the certification of Tdap immunization. This boosting vaccination may attribute to the decrease of the risk beginning after the 9−11 years old age group.

With the result of age effect, it can be concluded that despite the lowered incidence, still there are circulating pathogens of pertussis which stimulate the boosting reaction of immunity. This effect may accumulate with ageing, resulting the decreasing trend of risk until middle age. Lastly, the increasing trend observed at aged over 60 indicates that the depression of immunity with ageing [43].

The period effect over risk of pertussis was also significant, representing the sharpest increase of risk during 2016−2018. According to overall incidence rate (Figure 8), the most significant increase of pertussis occurred in 2018, and the result of period effect reflects this pattern. Several possible explanations have been suggested by previous studies.

First, one reason of this phenomena is antigenic variants which is not correspond to vaccine type [44]. In Korea, type of circulating pathogen in 2011 to 2012 is different compared to that of 2000 to 2009 [44]. The study also point out that changes of genotypes in South Korea have notably emerged, especially in genes that determine antigenicity, as has already been reported in many other countries [44]. This adaptation of pathogen induced the period in which vaccination is effective, resulting enhancement of waning immunity [43].

Secondly, the other research supporting the period effect is the decreased opportunity of natural boosting due to lowered number of circulating pathogens [34]. Because of the decreased force of infection came from lowered incidence, size of population who cannot experience reexposure to the pertussis pathogen grows bigger than the past [34]. At some points, cumulation of this population across the threshold of protection, resulting a rapid increase of pertussis incidence [45].

Actually, one of the vaccine−preventable diseases, measles and mumps also has experienced resurgence. Despite the declaration of the measles elimination, South Korea experienced measles outbreak in early 2019. Mumps also maintain high burden of disease in South Korea. Especially for mumps, the previous study conducted in South Korea suggested that the decreased opportunities for subclinical boosting by naturally circulating mumps virus may be resulted recent increase in mumps cases, like pertussis [46].

Another possible explanation is elated recognition and reporting by physicians. South Korea has been equipped with a strict surveillance system since 1954 which involved passive surveillance reported toward clinically diagnosed patients by physicians [28, 47]. This was updated in 2001 under the WHO recommended clinical case definition and again in 2010 to collect more complete and detailed information [28]. Combined effect of heightened awareness of pertussis after 2012 epidemic in Yoengam−gun and upgraded surveillance system would affect to recent increased number of reported pertussis. Because there had been no death case in South Korea since 1990, it is hard to conclude that the true disease burden has been increased so far [8]. To verify this problem and evaluate the true disease burden of pertussis, further research is needed about proportion of hospitalization from pertussis.

Also, improvement of diagnostic test can be an additional factor to affect recent increase of pertussis. As diagnostic sensitivity of polymerase chain reaction assays ranged from 73 to 100% [48], investment of more stable diagnostic test may have influenced to recent increase of pertussis [49, 50]. Even though the patient who screened by PCR finally was diagnosed as a confirmed case, the patient may be reported as suspected case.

Differ from age effect and period effect, which can be explained by previous studies, cohort effect is the most distinguishing result of this study. According to the result of the cohort effect, the risk of pertussis was increasing until the introduction of the DTwP vaccine in 1955. From 1955 birth cohort, the risk started to drop until late 1990s birth cohorts. Resurgence of risk beginning with 2000s birth cohort may be induced from the reduced maternal passive immunity. During the pre-vaccine era, the most vulnerable population was not the infants aged under 1 year old, but the toddlers aged between 1 to 4 years old [51, 52]. Also, during pre-vaccine era, case-fatality rates of pertussis in the 2^{nd} and 3^{rd} months old babies were higher than that of 1st month old babies, which representing indirect evidence of maternal immunity to infants [53]. However, waning immunity after vaccination accompanied with decreased rate of circulating pathogen, make pregnant women hard to have enough antibodies against pertussis to provide their babies [53]. The increased risk of 2000s birth cohorts represented in cohort effect may be resulted from the decreased immunity of mother cohorts.

From a view of public health, providing additional chance of boosting based on the result of cohort effect is available intervention to improve the current situation among age, period, and cohort effects. Considering the most significant increase of incidence rate occurred within infant aged under 1 year old, it is important to establish enough maternal immunity to provide passive immunity via placenta for babies who are too young to begin vaccination.

According to randomized clinical trial conducted in U.S., There was no increased risk of adverse events in women or infants receiving the Tdap vaccine on week 30−32 of pregnancy, as well as high concentrations of regent antibodies in infants during the first two months of pregnancy and did not substantially alter the infant response to DTaP [54]. Another randomized controlled trial conducted in Netherland also indicate that maternal immunity during pregnancy prevents neonates from contracting to the pertussis [55].

In U.S., Tdap vaccination for women during pregnancy is official recommendation of Centers for Disease Control and Prevention [56]. As a result, the proportion of women who vaccinated with Tdap during pregnancy is increasing every year [56].

In South Korea, Korea Centers for Disease Prevention and Control operates several businesses dealing with vaccination, mainly targeting children and old adults. Pregnant women are not included in the vaccination businesses of Korea Centers for Disease Prevention and Control. Therefore, of course, no statistics have been established on the vaccination of pregnant women. At this point, this study can be used as a scientific evidence to establish vaccination policies targeting the pregnant women.

Although our study is coherent with previous studies, this study subjects to few limitations. First, the data used to this study contains suspected case of pertussis. Korea Centers for Disease Prevention and Control provides age-specific data as a sum of confirmed cases and suspected cases. As a result, the size of pertussis cases may be overestimated due to other respiratory diseases during the peak season of them. On the contrary, the possibility of underestimation also exists due to different clinical setting. Secondly, this data does not provide the information about vaccination history. To accurately evaluate the effect of vaccination, the vaccination history is key information. Lastly, the fundamental limitation of age-period-cohort analysis is the tool cannot find exact association between the events and the phenomena. Previous studies can explain the results of age-period-cohort analyses, but this study cannot explain the direct relationship between them.

Despite these limitations, this study provides epidemiological contemplation over patterns of pertussis in South Korea. Further data on vaccination histories and age-specific data from previous periods would enable more accurate estimates.

CONCLUSION

In conclusion, this study discovered age, period, and cohort effect of pertussis in South Korea. The standard vaccination schedule of South Korea mainly focuses on children. However, this study suggests the necessity for adult vaccination, especially for pregnant women, through age−period−cohort analysis. South Korea is one of the countries with best prenatal care. It is necessary to promote the importance of maternal vaccination through cooperation with local hospitals during prenatal stage, along with improvements to the relative alienation of pregnant women in national vaccination projects.

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국문초록

한국의 최근 백일해 발생 증가에 대한 연령-기간-코호트 분석

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김찬희

백일해는 전염성이 높은 호흡기 질환 중 하나로, *Bordetella pertussis* 라 불리는 그람 음성균에 의해 발생한다. 백일해는 백신을 통해 예방이 가능한 예방접종대상 감염병 중 하나이다. 세계보건기구(WHO)의 통계에 따르면 1980년대 이후 디프테리아-파상풍-백일해 백신 (DTP3) 예방접종이 증가하면서 백일해 환자 수와 사망률이 크게 감소했다. 그러나 1980년대 이후부터는 높은 예방접종률을 유지하고 있던 선진국에서 백일해 재출현이 보고되기 시작했다. 한국의 경우 백신 도입 이후 눈에 띄게 백일해 발생이 감소하였으나, 2000년대부터는 한국에서도 백일해의 재출현이 관찰되었다.

많은 연구들이 백일해 재출현의 이유를 알아내려고 노력해왔으나, 연령 및 시대적 배경을 동시에 고려한 연구는 거의 없었다. 이러한 의미에서 코호트 효과를 분석하는 본 연구의 필요성이 제기된다고 볼 수 있다.

본 연구는 질병관리본부의 감염성 질병 포털과 통계청의 2차 데이터를 연령-기간-코호트 모델을 활용하여 분석하였다. 이를 통해 최근 백일해 발생 증가에 기여한 요인들을 파악하고 설명하고자 한다.

연령 효과의 결과에 따르면 백일해에 가장 취약한 연령층이 0-2세 집단임이 확인되었다. 그 후, 3-5세 집단에서 섭정증의 위험이 급격히 감소하였다. 그러나 그 위험은 9-11세에 최고점을 나타낸 후, 54-56세까지 꾸준히 감소하였다. 54-56세에 가장 낮은 위험을 나타낸 후 노년기에 접어들면서 위험은 다시 증가한다. 기간 효과에서는 2001년부터 2015년까지 위험에 큰 변화가 없었으나 2016년 이후 위험이 급격히 증가했다. 코호트 효과에서는 한국에 백신이 도입된 1955년 이후로 위험의 감소가 나타난다. 그러나 2000년대 탄생 코호트 이후 위험성은 다시 높아지기 시작했다.

연령 효과의 결과는 백신 접종으로 유도된 면역 효과와 연령별 사회적 접촉률(social contact rate)로 설명할 수 있다. 기간 효과의 경우 병원체 변이, 순환하는 병원체 감소에 따른 자연 추가 접종의 기회가 감소, 백일해에 대한 인식과 신고의 증가, 그리고 진단 도구의 발전 등으로 설명이 가능하다.

코호트 효과의 결과를 설명하기 위해 본 연구는 모체로부터 제공받는 수동 면역의 감소가 최근의 백일해 재출현을 일으켰다는 가설을 제시한다. 병원체 감소에 따른 자연 추가 접종의 기회가 감소함에 따라, 최근 코호트의 부모 세대인 가임기 여성은 태아에게 전달할 수 있을 만큼 충분한 항체를 보유하기 어렵다. 이는 백일해 환자 중 1세 미만 영아가 가장 많은 비율을 차지한다는 점을 통해서도 추측할 수 있다.

보건학적 관점에서, 본 연구를 통해 도출된 세 가지 효과 중 중재가 가능한 것은 추가 접종의 기회를 제공하는 것이다. 많은 선행 연구에서 산모 예방접종을 통해 예방접종이 시작되지 않은 2개월 미만 월령의 신생아 백일해 발생을 낮출 수 있다는 결과가 보고된 바 있다. 신생아에서 가장 큰 질병부담이 확인된다는 점을 고려하여, 신생아에게 충분한 수동 면역을 제공할 수 있도록 산모 예방접종을 권장해야 할 필요성이 있다.

주요어: 백일해, DTaP, 백신, 예방접종, 예방접종대상감염병, 연령-기간-코호트 분석, apc, intrinsic estimator

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