보건학박사학위논문

Impact of National Immunization Program on the Incidence of Mumps in the Republic of Korea: from the National Notifiable Disease Surveillance Data

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이 논문을 보건학박사학위논문으로 제출함

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2017년 8월

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ABSTRACT

Objective:

Mumps is a highly communicable disease characterized by painful swelling of parotid glands. There have been growing reports which indicate increase of mumps globally including the Republic of Korea. The mumps vaccines have proven to be very effective in decreasing the overall incidence and prevalence of disease. However, different vaccination policy and strains of mumps vaccine virus strains have shown differences in levels of protection. This study was to identify the temporal trend of incidences of the mumps in Korea and the changes after the introduction of the 2-doses of measles-mumps-rubella vaccination program in the public sector. The objectives are as follows:

First, evaluate the epidemiology of measles, mumps and rubella, and to share a baseline evidence for the future routine and outbreak-response immunization policy.

Second, to analyses the effect of birth cohort exposed to Rubini strain on recent increase of mumps, conduct an age-period-cohort (APC) analysis of gender-specific mumps incidence in Korea from 2001 to 2015.

Third, identify spatial patterns in mumps incidence to give an indication to the geographical risk of the disease in the settings with high MMR vaccination coverage.

Methods:

(1) The data were stored centrally at the National Notifiable Disease Surveillance System (NNDSS), which is operated by Korean Center for Disease Control (KCDC). The NNDSS data was used to calculate the crude incidence of mumps in Korea during 1955-2012, and to explore the changes in epidemiology of mumps between 2001 and 2015. An age-specific incidence per 100,000 population using population data from Korea Statistical Information Service. From internal database acquired from KCDC and Korea Ministry of Food and Drug Safety (MFDS), the major vaccine strains used in Korea in each year were identified.

(2) Incidence of measles, mumps, and rubella cases for birth cohorts were calculated according to vaccination policy as follows: pre catch-up, 1976-1984; catch-up, 1985-1993; keep-up (early), 1994-2002; and keep-up (late), 2003-2011. Pre catch-up (1976-1984) cohort was those who were with limited vaccination coverage of MMR with only one dose provided by the public. Catch-up (1985-1993) cohort was those who were with limited MMR vaccination coverage, but were given the Measles-Rubella (MR) vaccine during the 2001 catch-up campaign.

Early keep-up (1994-2002) cohort was those who were candidates for the keep-up program in the first 8 years (2002-2008), and the late keep-up (2003-2011) were the candidates for the next 8 years (2009-2016).

(3) Age-specific incidence according to gender was calculated for periods and birth cohorts in 3-year blocks to find difference in incidence between the cohorts affected by the Rubini strain. The Poisson age-period-cohort (APC) model was used to estimate the age, period, and cohort effects on secular trend of mumps from 2001-2015.

(4) A geographic weighted regression (GWR) analysis was performed to find demographic predictors of mumps incidence according to district level. The population, density, childhood percentage, and the timely vaccination coverage rate data was derived from the National Statistics database.

Results:

(1) Of the 209,817 cases of mumps reported in Korea between 1955 and 2015, 109,850 (52.4%) were reported between 2001 and 2015. The secular trend of mumps incidence was characterized by a cyclical pattern of spikes at intervals of 5-10 years. Before the introduction of MMR into National Immunization Program in 1980, the average incidence was 11.1 (range 1.7-31.0) cases per 100,000 populations per year for period 1955-

1979.

(2) Between 1995 and 1999, the average numbers of measles and mumps cases were 46 (range: 2-88) and 1,601 (range: 254-2,626), respectively. In 2000 and 2001, an outbreak of measles resulted in a total of 55,707 cases. Following the MR catch-up campaign, the annual reported cases of measles decreased, although there were outbreaks in 2007, 2010, 2013, and 2014 that resulted around 100 cases each year. Between 2001 and 2015, there was constant increase in the number of reported cases of mumps from 1,668 cases to 23,446 cases.

(3) The period effects displayed a similar pattern for both genders, with an upward shift since 2008 with a significantly elevated risk by 2014. In general, the risk of mumps has increased according to birth cohorts in both genders. From 2001-2015, the overall net drifts were 27.67/100,000 (95% CI: 27.5.47-29.90) for males and 27.25/100,000 (95% CI: 24.91-29.65) for females. There were statistically significant cohort and period relative risks and net drifts in both genders.

(4) During low endemic periods, the clusters were mostly confined to Seoul-Incheon-Gyeonggi and Gangwon regions. During high endemic period of 2013-2015, most of the Gwangju-Jeolla regions were with clusters. These regions showed the core “cold spot” clusters consistently during 2004-2006, 2007-2009, and 2010-2012. The result of GWR model to detect

demographic predictor of mumps incidence is summarized in Table 3. The "un-timely vaccination coverage" was a significant predictor of mumps incidence during 2010-2012 period (β : 0.66, P = 0.002). The "proportion of children population" was a predictor during high endemic period of 2013-2015 (β : 2.68, P = 0.001).

Conclusions:

(1) The first study was to address the increasing trend of incidence of mumps in the Republic of Korea for the last decade. The study describes the change in mumps incidence in Korea, which was resulted from different vaccine strains used during past 30 years. The description of age-specific and cohort-specific risk of acquiring mumps has identified the need to strengthen its surveillance in adolescents as well as in younger aged children group. The dynamic in population susceptibility of mumps the study described in this report may provide guidance for the future MMR immunization program.

(2) The second study demonstrates the first result of longitudinal study on the difference in incidence between the three infectious diseases that are combined to form a single vial of vaccine: measles, mumps, and rubella. The key messages of this study are that the incidence of the three diseases could show differential trend according to the choice of vaccine

that was used during catch-up vaccination campaign. The study reports a population study of measles, mumps, and rubella in Korea, which was resulted from MR catch-up vaccination campaign and MMR2 keep-up program used during past 15 years. The description of age-specific and cohort-specific risk of acquiring mumps has identified the need to strengthen its surveillance in adolescents as well as in younger aged children group. For preschool aged children, a timely second dose MMR vaccination should be emphasized, whereas for adolescents and young adults, unvaccinated individuals or those without certain vaccination history should be considered for the catch-up vaccination. The dynamic in population susceptibility of mumps this study described may provide guidance for the future MMR vaccination program.

(3) The third study was to explore the impact of the age, period, and cohort effect on the individual risk of mumps transmission. The study describes a cohort and period-specific risk of acquiring mumps in Korea, and have identified the need to strengthen surveillance in adolescents as well as in younger aged children group. The dynamic in population susceptibility of mumps we described in this report may provide guidance for the future MMR immunization program and the mumps elimination strategies.

(4) In the last study, the intent was to demonstrate the transmission pattern of mumps by space in Republic of Korea during the past 15 years that

might inform public health planning and future vaccination strategies. The study indicates that the rate of mumps incidence according to geographic regions vary by population proportion and neighboring regions, and timeliness of MMR vaccination, suggesting the importance of community-level surveillance and strengthening of vaccination program. Further researches are needed to determine if population structure and non-timely coverage rate are associated with the temporal and spatial variation in other vaccine-preventable disease epidemiology.

Key words: measles-mumps-rubella, National Notifiable Disease Surveillance System, Geographic weighted regression, Age-period-cohort, Korea.

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LIST OF ABBREVIATIONS

APC	Age Period Cohort
EPI	Expanded Program on Immunization
GWR	Geographically Weighted Regression
KCDC	Korean Center for Disease Control and Prevention
LISA	Local Indicators of Spatial Association
MMR	Measles mumps rubella vaccine
MR	Measles rubella vaccine
NNDSS	Nationally Notifiable Disease Surveillance System
WHO	World Health Organization

CHAPTER 1. INTRODUCTION

1-1. Epidemiology of mumps

Mumps is a highly communicable disease characterized by painful swelling of parotid glands. Mumps virus is a member of paramyxovirus family, together with measles and parainfluenza viruses. The usual clinical findings involve pain, tenderness, and swelling in parotid salivary glands. Nonspecific symptoms including low-grade fever, anorexia, malaise, and headache may present several days before the onset of parotitis. Complications such as deafness, encephalitis, and orchitis can occur (Galazka, Robertson et al., 1999). In U.S. before the introduction of vaccine, mumps have posed a large proportion of disease burden among viral encephalitis cases (Azimi, Crablett et al. 1969). The incidence of encephalitis is reported to range from 0.02% to 0.3% among mumps cases (Koskiniemi, Rautonen et al., 1991). In one study, mumps was reported as the etiology for 15% among deaf students (Minja, 1998). In England, morbidity estimation resulted from mumps complications such as orchitis, meningitis, oophoritis and pancreatitis were shown to be substantial (Yung, Ramsay, 2016).

The mumps virus spreads through direct contact with respiratory secretions or saliva or through droplets. Mumps infected persons can transmit the virus for several days before and after onset of parotitis. The mean incubation period is 16 to

18 days, with a range of up to 25 days (Centers for Disease Control and Prevention, 2008). The risk of spreading the virus increases as the contact become longer and closer. Mumps outbreak can occur more frequent in crowded environments, such as prisons, orphanages, school dormitories, and in military recruits (Galazka, Robertson et al., 1999).

Before the introduction of vaccine, mumps was common in childhood usually >100 per 100,000 population based on routine passive surveillance (Levitt, Mahoney, et al., 1970). In the U.S. in the 1960s, the highest incidence occurred during early school years, predominantly in males (Witte, Karchmer, 1968). The epidemic peaked every 2–5 years and those aged 5–9 years consistently being the most affected (Gordon, Kilham, 1949). Before the vaccination program started in 1970s in the developed countries, more than 40-700 cases per 100,000 populations were reported each year (Galazka, Robertson et al., 1999). The basic reproduction number (R_0) of mumps during the prevaccination era was estimated to be around 5-7 (Edmumds, Gay et al., 2000).

1-2. Introduction of mumps vaccine and its public health impact

The earliest stage of mumps vaccine was first developed in 1948, but has only provided an insufficient immunity, and its use was discontinued. The currently used strain of live attenuated mumps vaccine was developed in 1960s (Watson, Hadler et al., 1998). Mumps vaccine is available as single antigen (Japan), combined with measles and rubella vaccines (as MMR, in most part of the world including Korea), or combined with measles, rubella, and varicella vaccine as MMRV (in Europe and U.S.).

The mumps vaccines have proven to be very effective in decreasing the overall incidence and prevalence of disease. In the first effectiveness trials in the 1960s, among 362 vaccinated children and 505 controls, the attack rates 2 and 61 per cent, respectively, resulting an overall protective efficacy of 97% (Hilleman, Weibel et al., 1967). In an outbreak occurred in U.S. in 1982, the vaccine efficacies among vaccinated persons were estimated to be 85%, showing the vaccine is highly effective against outbreak mitigation. The vaccine was then introduced to many developed and developing countries worldwide, as the monovalent form or as combined vaccine with measles and rubella. In countries where a two-dose vaccination schedule was introduced showed more than 99% reduction in mumps incidence, while 88-94% reduction was shown in countries with one-dose schedule and no reduction was shown in countries without mumps vaccine (Galazka, Robertson et al., 1999).

However, the specific efficacy of the vaccines has come into question due to a number of recent cases of vaccine failure in populations that have been vaccinated. There has been an increase in mumps incidence since 1990 in Switzerland, indicating vaccine failure (Strohle, Eggenberger et al. 1997). In one seroprevalence study, the primary vaccine failure rate of mumps vaccine was reported to be more than 10% (Condorelli, Stivala et al., 1998).

Although mumps vaccine failure has not been considered a major public health problem previously, recent mumps outbreaks have led to question the efficacy of the vaccines in the public vaccination program. Since 2000s, the reports on mumps outbreaks have occurred globally. In the U.S., there was an outbreak of mumps causing more than 6,584 people in 2006 (Dayan, Quinlisk et al., 2008). In 2009, an outbreak started in Orthodox Jewish communities in the U.S. resulted in 3,502 cases. In these outbreaks, most affected ones were with prior history of mumps vaccination; therefore, suggest that mumps can be transmitted even in vaccinated people. As is indicated by the resurgence, the vaccines have come under the interest in the public health field for the limited understanding on the evolution of mumps transmission. While existing mumps vaccination strategies are in need be improved and distributed, the public health community should then address the current gap of knowledge in regard to the recent reemergence of the disease.

1-3. Public health implication of the vaccine strains and vaccination programs

To date, different strains of mumps vaccine virus strains have shown differences in levels of protection. The most widely-used strain of mumps vaccine is the Jeryl-Lynn strain. The strain was developed in U.S., and was introduced globally since

1967. The efficacy ranges from 65% (Toscani, Batous et al., 1996) to 81% (Miller, Hill et al., 1995), yet have shown steady decrease in the mumps incidence following its introduction to the community. Another mumps vaccine strain is the Urabe AM9 strain, which was first licensed in Japan. The Urabe vaccine is accepted as the most efficacious among mumps vaccine strains, ranging 76% (Toscani, Batou et al., 1996) to 85% (Miller, Hill et al., 1995) of effectiveness. Overall, the Jeryl-Lynn strain is measured to be slightly less efficacious than the Urabe strain. A clinical trial in Canada has shown the seropositivity of Jeryl-Lynn strain to be 85% while Urabe strain showed 93% (Boulianne, De Serres et al., 1995).

The efficacy data support the use of the Urabe strain; however, there had been reports of post-vaccine aseptic meningitis following its vaccination. The vaccine safety analysis in the United States has shown an indicated risk of aseptic meningitis after Urabe vaccine to be 1 per 3800 vaccinations (Stratton et al., 1994). Despite its high efficacy in preventing mumps, the risk of adverse event has led to the end of use of the Urabe vaccine in many countries.

Another widely-used mumps vaccine was the Rubini strain. This vaccine strain was the most frequently used in Switzerland since 1980s. Since 1990, there have been reports of mumps outbreaks in Switzerland, in particularly among vaccinated children (Zimmermann, Matter et al., 1995). The estimated efficacy of the Rubini mumps vaccines was between 47% and 77%; which was lower than that of measles (91-97%) and rubella (89-97%) vaccines. In one epidemiological study in the schools in Switzerland, the effectiveness of Rubini strain was determined as

12%. Another study done on a kindergarten indicated the vaccine efficacy of 22% (Chamot, Toscani et al., 1995). The increase in mumps cases is different with that of measles and rubella, where there has been a decrease in incidence clearly. It was therefore being concluded that the Rubini strain vaccines have played an important role in the increase in mumps cases since 1990.

Another factor that may have affected the recent increase of mumps is the scope of vaccination programs. In Australia, MMR vaccine was used in public sector since 1989 for the first dose, and in 1994 for the second doses. In 1998, during the Measles Control Campaign (MCC), the catch-up vaccination was offered to those aged between 4 and 16 years. Among 1980s cohort, coverage of mumps vaccine was increasing, but estimated to be less than 70% among children aged less than 5 years. The study suggested that MCC did not target this age group as effectively, and their immune profile showing a partial vaccination (Aratchige, McIntyre et al., 2008).

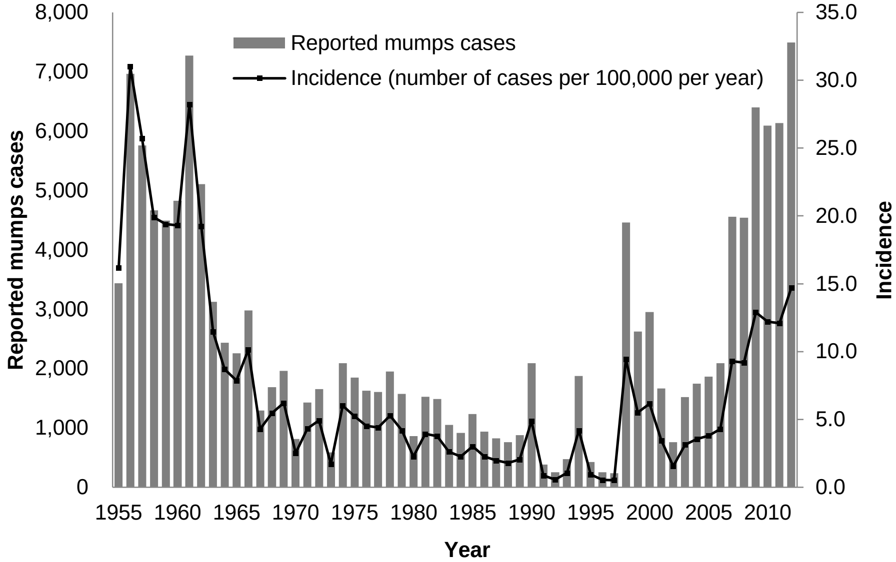
Taking into account for the intrinsic biological properties of vaccine itself and the impact followed by vaccination program, there are lots to address the current research question on the resurgence of mumps in many parts of the world. Yet, most of the scientific questions focus on the association between the vaccines for measles and rubella and their health outcomes, the current situation in regard to mumps warrants a further investigation on its public health implications.

1-4. Vaccination Program and the Epidemiology of Mumps in the Republic of Korea

The vaccination practice was first started in the Republic of Korea in 1882, when the smallpox vaccine was introduced, and in 1895, a legislation that mandates its vaccination was instituted (Lee et al., 2008). In 1949, a total of 18 vaccine-preventable diseases were designated for the production of antiserum against these antigens. Sin 1965, a live attenuated measles vaccine was introduced. In 1980, MMR vaccine became first available, and was included in national immunization program since 1985 (Ki et al., 2003). In 1985, one dose of MMR vaccination given at 15 month of age was partly introduced into National Immunization Program. However, the outbreak of measles in 1989 and 1990 which affected approximately 5,000 cases has prompted the government and academia to take action (The Korean Pediatric Society, 2012). During the outbreak, the peak incidence occurred among young children; therefore, since 1994, the Korean Pediatric Society began to recommend the second dose of MMR vaccination given at six years of age; and the same recommendation was issued by the government three years later (Kim et al., 1995; Yi et al., 1996). The second dose of MMR vaccine was introduced in NIP since 1997; however, vaccination coverage was suboptimal at less than 60% (Lee et al., 2011; Korea Centers for Disease Control and Prevention, 2007). Following the recommendation, the number of reported cases has decreased less than 100 cases annually during the late 1990s; however, an unexpected nationwide outbreak has occurred during 2000-2001 (Korea Centers for Disease Control and Prevention, 2007). The nationwide outbreak of measles resulted 55,707 cases and 7 deaths (Korea Centers for Disease Control and Prevention, 2007). In response, the national measles elimination program was introduced, which included a MR vaccine catch-up vaccination targeting 5.8 million school-aged children (8-15 years) in 2001. Afterwards, two-dose MMR keep-up program through verification of vaccination history at elementary schools (6-7 years) was introduced since 2002.

Following the program, the incidence of measles and rubella has decreased to less than 1 case per millions, allowing the successful elimination (Korea Centers for Disease Control and Prevention, 2007). However, the increase in the incidence of mumps was noted recently (Choi, 2010). Specifically, mumps cases in middle and high school-aged teenagers who have one or two doses vaccination history became increasingly recognized (Kim et al., 2009).

Figure 1-1. Reported cases of mumps to the National Notifiable Disease Surveillance System in the Republic of Korea



Since Rubini strain vaccine was used from 1997 to 2001 in Korea, the increase of mumps incidence in Korea may have been attributable to accumulation of susceptible adolescents who were vaccinated with Rubini strain. Moreover, as mumps tend to cluster geographically where susceptible population reside in close proximity, spatial analyses may bring important insight to detect and predict the incidence patterns of mumps.

A seroprevalence study reported in 2007 showed the difference in seropositivity between Jeryl-Lynn strain vaccinees and Rubini strain vaccinees (Korea Centers for Disease Control and Prevention, 2007). Among 41 Jeryl-Lynn strain vaccinees, 31 (75.6%) were seropositive, whereas among 9 Rubini strain vaccinees, none were seropositive ($P < 0.01$).

1-5. Study Objectives

This study was to identify the temporal trend of incidences of the mumps in Korea and the change after introduction of the MMR 2-doses vaccination program in the public sector. The objectives are as follows:

First, evaluate the epidemiology of mumps in conjunction with measles and rubella, and to share a baseline evidence for the future routine and outbreak-response immunization policy.

Second, to analyses the effect of birth cohort exposed to Rubini strain on recent increase of mumps, conduct an age-period-cohort (APC) analysis of gender-specific mumps incidence in Korea.

Third, identify spatial patterns in mumps incidence to give an indication to the geographical risk of the disease in the settings with high MMR vaccination coverage.

CHAPTER 2. STUDY MATERIALS

2-1. Data sources

Data collected by Korean National Notifiable Disease Surveillance System (NNDSS) from 2001 to 2015, was used to identify the temporal trend of incidences of the mumps in Korea and the change after introduction of the MMR 2-doses vaccination program in the public sector. Incidence was calculated based on population statistics for 2001, 2005, and 2010 obtained from the Korea Statistical Information Service. From internal database acquired from Korea Centers for Disease Control and Prevention (KCDC) and the Ministry of Food and Drug Safety (MFDS), major vaccine strains used in Korea in each year since 1980 was identified.

2-2. Study setting

In Korea, the surveillance of infectious diseases including mumps was first established in 1955 and involved passive reporting of clinically diagnosed cases from public and private health-care sectors. From 1955 to 2000, mumps cases were reported from physicians based on their clinical judgments. Between 2000 and 2001, the case-based surveillance that used a set of case definition for suspected and confirmed mumps cases was introduced, and it became obligatory for all physicians in the country to report the laboratory-confirmed or clinically-suspected mumps cases to the Ministry of Health and Welfare (since 2003, Korea Centers for Disease Control and Prevention, KCDC). Since then, the clinical case definition for diagnosis of mumps have been based on WHO definitions which were adapted for use in Korea: a case with acute onset of unilateral or bilateral tender, self-limiting swelling of the parotid or other salivary gland and without any other apparent cause (World Health Organization, 2003).

The report of the suspected notifiable disease is first recognized by the practitioners in the public and private sectors, in accordance with the Infectious Disease Control and Prevention Act. The reports are made to the regional public health center. Otherwise, the report can be made directly to the centrally operated system owned by KCDC. Once the data are collected, these are reviewed by the local health authorities and also by KCDC public health officers. After the final confirmation by the KCDC, the national report is then published.

Between 1955 and 2000, only yearly reported numbers of suspected mumps cases were recorded. Between 2001 and 2012, data were collected on individual cases using standardized case investigation form, which recorded each patient's demographic and epidemiological data. The data were stored centrally at the NNDSS, which is operated by KCDC.

The study was approved by Seoul National University Institutional Review Board (IRB No. SNU 16-01-050).

CHAPTER 3. REEMERGENCE OF MUMPS IN THE REPUBLIC OF KOREA: DESCRIPTION OF EPIDEMIOLOGIC CHANGES AND VACCINE STRAINS USED

3-1. Background

Mumps is an acute communicable disease of childhood characterized by painful swelling of parotid glands. In the pre-vaccine era, mumps was one of the main causes of viral meningitis in children, but the incidences dropped dramatically after the widespread use of vaccine, mostly in combination with vaccines for measles and rubella (MMR vaccine). Since the establishment of Expanded Program on Immunization in 1974, elimination and control measles and rubella had been largely supported by wide use of measles-rubella (MR) vaccine; however, there had been less attention to the value of control of mumps, and the disease is still one of the leading causes of vaccine-preventable outbreaks in the world today (World Health Organization, 2007).

In the Republic of Korea, MMR vaccine has been introduced since 1980, and was included in the National Immunization Program (NIP) in 1985 (Ki, Park et al., 2003). The vaccination schedule was updated with two MMR doses given at 12-

15 months 4-6 years in 1997; and there was no further change to the vaccination schedule (Lee, Kim et al, 2011). Although two-doses of MMR vaccine have been recommended by NIP in 1997, the two-dose immunization coverage was suboptimal ranging 30-60% (Ki, Kim et al., 2001). There was a large outbreak of measles in 2000-2001, and in response, a catch-up' vaccination campaign using MR vaccine (measles and rubella) was conducted targeting approximately 5.8 million school-aged children (mumps component was excluded). At that time, the government strengthened the two-dose MMR vaccination for all children entering elementary schools to submit certification since 2001 (Centers for Disease Control and Prevention, 2007). Despite this, an unexpected increase in the incidence of mumps among school-aged children was reported in 2001-2002 (Choi, 2010). Moreover, although mumps had been mostly reported from pre-school and elementary school-aged children in the 1990s, it became increasingly recognized among middle and high school-aged teenagers who have one or two doses vaccination history (Kim, Kim et al., 2009). Furthermore, increase in the number of mumps outbreaks within the schools was noted since early 2000s in Korea (Park, Nam et al., 2007).

Between 1980 and 2015, five mumps virus vaccine strains have been used in Korea: Urabe AM9, Hoshino, Jeryl-Lynn, Rubini and RIT4385 strains. The Urabe AM9 and Hoshino strains were used since 1980s until withdrawal in 1999 after their association with increased risk of aseptic meningitis was reported (World Health Organization, 2010). During a two-year interim period between 2000 and

2001, Jeryl-Lynn and Rubini strains were the two main vaccine strains used; however, the Rubini strain was then switched to RIT4385 strain, after the World Health Organization (WHO) recommended not using this strain for NIP because of its low effectiveness (World Health Organization, 2010). From 2002 to 2015, Jeryl-Lynn and RIT4385 have been the only two vaccine strains used in Korea.

Although surveillance on the mumps cases had been conducted continuously since 1955, little is known about the changed epidemiology in population in conjunction with change in major vaccine strains used in Korea. The aim of this report was to evaluate the epidemiology of reported mumps cases according to the changes in the major vaccine strains used in the Korean NIP, and to provide a baseline evidence for the future routine and outbreak-response immunization policy in Korea.

3-2. Methods

Surveillance and case definition

In Korea, the surveillance of infectious diseases including mumps was first established in 1955 and involved passive reporting of clinically diagnosed cases from public and private health-care sectors. From 1955 to 2000, mumps cases were reported from physicians based on their clinical judgments, with or without laboratory confirmation. Between 2000 and 2001, the case-based surveillance that used a set of case definition for suspected and confirmed mumps cases was introduced, and since 2001, it became obligatory for all physicians in the country to report the laboratory-confirmed or clinically-suspected mumps cases to the Ministry of Health and Welfare (since 2003, Korea Centers for Disease Control and Prevention, KCDC). Since then, the clinical case definition for diagnosis of mumps have been based on WHO definitions which were adapted for use in Korea: a case with acute onset of unilateral or bilateral tender, self-limiting swelling of the parotid or other salivary gland and without any other apparent cause (World Health Organization, 2003).

Between 1955 and 2000, only yearly reported numbers of suspected mumps cases were recorded. Between 2001 and 2015, data were collected on individual cases using standardized case investigation form, which recorded each patient's demographic and epidemiological data. The data on individual case's age, sex, social group, season of disease onset, and place of residence were collected; however, we did not have data on vaccination status, vaccine lot numbers, type of vaccine received, and age of vaccination in individual cases. The data were stored centrally at the National Notifiable Disease Surveillance System (NNDSS), which is operated by KCDC. Although the sensitivity of current mumps surveillance had not been assessed previously, one study has previously evaluated the proportion of timely reported cases of mumps Korea, which was found to be 89.7% (Yoo, Park et al., 2009).

Data analysis

First, NNDSS data was used to extrapolate the crude incidence of mumps in Korea during 1955-2015, and to explore the changes in epidemiology of mumps between 2001 and 2015. We calculated age-specific incidence per 100,000 population using population data from Korea Statistical Information Service. From internal database acquired from KCDC and Korea Food and Drug Administration, the major vaccine strains used in Korea in each year since 1980 were identified.

Second, from the NNDSS database, the epidemiology of mumps cases in 2001-2015 was analyzed. Demographic data were analyzed and classified according to the different age groups: <1 year, 1-4 years, 5-9 years, 10-13 years, 14-17 years, and greater than 18 years. The occupations or social groups were classified as: students, military, and employed persons. Predicting that the majority of cases would be school-aged children and adolescents, we attempted to show the seasonal variation by classifying according to school semester system used in Korea: (1) Winter break (January-February), (2) Spring semester (March-June), (3) Summer break (July-August), and (4) Autumn semester (September-December). The place of residence was identified and was classified as: (1) Metropolitan cities and (2) Provinces. Yearly proportion of 5 different age groups (1-4 years, 5-9 years, 10-13 years, 14-17 years, and greater than 18 years) in each year was calculated. Chi-square (χ^2) test was used to assess yearly differences in proportion among different age groups; and $P < 0.05$ was considered statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences software version 16.0 (SPSS Inc., Chicago, IL, USA).

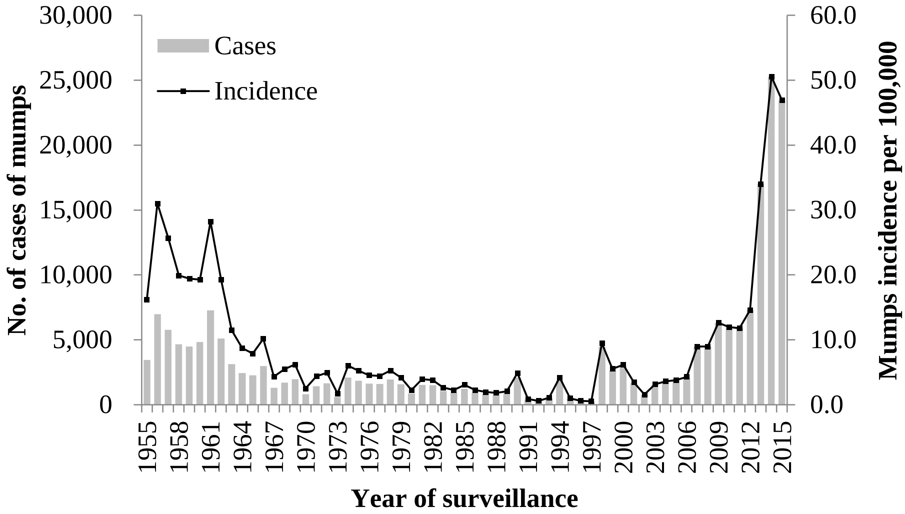
3-3. Result

Crude incidence, 1955-2015

Of the 209,817 cases of mumps reported in Korea between 1955 and 2015, 109,850 (52.4%) were reported between 2001 and 2015 using standardized clinical definition of mumps (Figure 3-1). The secular trend of mumps incidence was characterized by a cyclical pattern of spikes at intervals of about 5-10 years. Before the introduction of MMR into National Immunization Program in 1980, the average incidence was 11.1 (range 1.7-31.0) cases per 100,000 populations per year for period 1955-1979.

Since the surveillance was introduced in 1955, the incidence decreased gradually until late 1990s; however, recent surge of incidence was noted after early 2000s.After the introduction into NIP, and the widespread use of Urabe AM09 and Hoshino strains, the average incidence dropped to 2.7 (range 0.5-9.5) cases. During a short period between 2000 and 2001 when Jeryl-Lynn and Rubini strains were used, the incidence was 4.8 (range 3.5-6.2) cases; and since the Rubini strain was switched to RIT4385 strain and Jeryl-Lynn was still used in 2002-2012, the incidence increased to 7.8 (range 1.6-12.6) cases.

Figure 3-1. Mumps incidence in the Republic of Korea, 1955-2015.



* MMR, measles-mumps-rubella vaccine; NIP, national immunization program; MR, measles-rubella vaccine.

Table 3-1 shows the mumps vaccine strains distributed in Korea in the form of MMR from 1997 to 2001. Jeryl-Lynn was imported since 1997, which had low proportion sin 1997 and 1998, however has increased since 1999. Since 2000, Urabe and Hoshino strains were not being imported, and Rubini strain was with the highest proportion in 2001. The difference in local distribution of vaccine strain was not identified.

Table 3-1. Mumps vaccine strains distributed in Korea, 1997-2001 (Adapted from Korea Centers for Disease Control and Prevention, 2005)

	1997		1998		1999		2000		2001	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Jeryl-Lynn/RIT-4385	89584	(11.0)	86810	(6.8)	288080	(23.1)	1401510	(73.1)	1669673	(58.9)
Urabe-AM9	367441	(45.2)	562339	(43.8)	468310	(37.6)	17120	(0.9)	0	(0.0)
Hoshino	316721	(38.9)	566166	(44.0)	339223	(27.2)	49711	(2.6)	46285	(1.6)
Rubini	40000	(4.9)	70000	(5.4)	150000	(12.0)	450000	(23.5)	1120000	(39.5)

Demographic characteristic, 2001-2015

In the period 2001-2015, the Ministry of Health and Welfare reported between 764 and 25,286 cases of mumps per year in Korea, resulting average annual incidence of 7,323 cases-patients (annual incidence range: 1.6-50.6 per 100,000 population per year, Table 3-2). Of 109,850 cases of mumps, 47,951 (43.7%) were aged 17-17 years. 73,339 (66.7%) were males. When classified according to social groups, 68.9% (30,249/43,884) of the cases from 2001 to 2012 were students ($P < 0.05$); however, the proportion had decreased from 76.2% during 2004-2006 to 63.4% during 2010-2012. Seasonal variation according to the school system was observed: more mumps were reported during summer break and spring semester compared to winter break and autumn semester.

Table 3-2. Demographic characteristics of reported mumps cases in Republic of Korea, 2001-2012.

Variables	Years								Total	
	2001-2003		2004-2006		2007-2009		2010-2012			
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total	3,907	-	5,530	-	15,283	-	19,164	-	43,884	-
Age group (yr)										
<1	2	(0.1)	1	(0.0)	12	(0.1)	26	(0.1)	41	(0.1)
1-4	613	(15.7)	582	(10.5)	1,286	(8.4)	2,149	(11.2)	4,630	(10.6)
5-9	1,491	(38.2)	1,415	(25.6)	3,472	(22.7)	4,127	(21.5)	10,505	(23.9)
10-13	1,098	(28.1)	1,515	(27.4)	2,913	(19.1)	3,680	(19.2)	9,206	(21.0)
14-17	550	(14.1)	1,712	(31.0)	6,038	(39.5)	6,217	(32.4)	14,517	(33.1)
≥18	153	(3.9)	305	(5.5)	1,562	(10.2)	2,965	(15.5)	4,985	(11.4)
Sex										
Male	2,461	(63.0)	3,656	(66.1)	10,264	(67.2)	12,879	(67.2)	29,260	(66.7)
Female	1,446	(37.0)	1,874	(33.9)	5,019	(32.8)	6,285	(32.8)	14,624	(33.3)
Social group										
Student	2,658	(68.0)	4,216	(76.2)	11,228	(73.5)	12,147	(63.4)	30,249	(68.9)
Non-student	1,249	(32.0)	1,314	(23.8)	4,055	(26.5)	7,017	(36.6)	13,635	(31.1)
School season*										
Winter break	276	(7.1)	411	(7.4)	926	(6.1)	1,646	(8.6)	3,259	(7.4)
Summer break	624	(16.0)	865	(15.6)	2,632	(17.2)	2,943	(15.4)	7,064	(16.1)
Spring term	1,969	(50.4)	2,294	(41.5)	7,267	(47.5)	7,225	(37.7)	18,755	(42.7)
Autumn term	1,038	(26.6)	1,960	(35.4)	4,458	(29.2)	7,350	(38.4)	14,806	(33.7)

* School season classified as: Winter break (January-February); Summer break (July-August); Spring semester (March-June); and Autumn semester (September-December). Note that social group and school season for 2013-2015 were not assessed.

3-4. Discussion

In this study, the recent increase in incidence of mumps during past 10 years was observed. The overall average incidence of population in the 2000s was measured to have significantly higher incidence than the incidence of population before. This finding may implicate an underachievement of current vaccination strategies regarding controlling of mumps in Korea. Indeed, the finding is consistent with findings elsewhere that describe the differences in vaccine effectiveness among different mumps vaccine strains. In a recent analysis of Cochrane Central Register, effectiveness of mumps vaccine was estimated to be 66% for one dose and 88% for two vaccine doses (Demicheli, Rivetti et al., 2012). The effectiveness of Jeryl-Lynn vaccine strain ranged between 62-95%; and Rubini strain found to be nearly ineffective; whereas Urabe AM9 strain has demonstrated 54-87% of effectiveness (Bonnet, Dutta et al., 2006). However, association of Urabe AM9 strain and the occurrence of aseptic meningitis have led to withdrawal of this vaccine strain from many countries including Korea. Although differences in surveillance methods and vaccination coverage might have affected the recent increase in incident-cases of mumps, there were no major changes in NNDSS and vaccination coverage in Korea between 2001 and 2012; and our findings therefore may suggest that different vaccine strains potentially have affected the difference in mumps incidence in different population. In Korea, the MMR vaccine is given at the public health centers free of charge; therefore, the cost barrier was minimal in Korea.

Furthermore, the effect of cold chain in Korea is not considered heavily since it is tightly regulated by both public health and regulatory agencies.

Since 2002, a two-dose of MMR with Jeryl-Lynn or RIT4385 strains had been chosen in the Korean NIP, even after some doubts in its effectiveness. Therefore, in this circumstance, it becomes very important to assess the change of epidemiology of mumps before and after the changes in the vaccine strains, especially during the transitional periods between late 1990s and early 2000s. After the withdrawal of Urabe AM9/Hoshino strains, the mumps cases have been gradually increased; and subsequently, the age shift of its epidemiology was observed. During the 10 years with Jeryl-Lynn/RIT4385 strains, the crude incidence of mumps has increased from 0.5-1.0 cases per 100,000 populations per year in the mid-1990s to greater than 10 cases during 2010-2012. At the same time, the age distribution of mumps cases shifted to the older age group: most notably, the proportions of middle and high school student-aged teenagers are increasing. This indirectly indicates that the two-doses of MMR vaccine protected younger aged children after the implementation of mandatory vaccination program since 2001, and kept the infection pressure in lower range. This is in line with reports from the Netherlands (Barskey, Schulte et al., 2012), United Kingdom (Pugh, Akinosi et al., 2002), and United States (Greenland, Whelan et al., 2012). When United States experienced the largest mumps outbreak in 2006, the peak age-specific attack shifted from 5-9 years to 18-24 years (Barskey, Glasser 2009). By contrast, in Japan where MMR vaccination has been discontinued, the rightward shift of age distribution was not observed, and most cases remained in age group of 3-7 years (Eshima, Tokumaru et al., 2012).

Furthermore, a potential ‘pocket of immunity’ among individuals was observed in those who did not receive a second dose of MMR vaccine in the 1990s, and was not benefited from ‘measles catch-up’ campaign because MR vaccine was used. It has been postulated in seroepidemiological study that compared measles and mumps: the seropositivity of mumps was lower than that of measles (Kim, Han et al., 2004). This is in line with the report from Australia, where extensive efforts in two-dose MMR vaccination have demonstrated elimination of endemic circulation of measles, but followed by unwanted increase of mumps cases in older age group (Aratchige, McIntyre et al., 2008).

The trend of seroprevalence may provide baseline information on population susceptibility in one community. In United States between 1999-2004, the mumps seropositivity was 90.0% (95% CI, 88.8%-91.1%). Seroprevalence was significantly lower in the 1967-1976 birth cohort (Kutty PK et al., 2010). The recent surge in the U.S. can be partly explained by the insufficient seropositivity of mumps in general population. In Thailand 17 years after the universal vaccination program, the seropositivity rates in children 0-7 years has increased significantly from 45.8% in 2004 to 72.3% in 2014 (Ngaovithunvong V et al., 2016). The trend shows improving serostatus in developing country that had recently adopted mumps vaccination, however still has pocket of immunity due to incomplete vaccinations.

For further insights on population susceptibility of mumps in Korean population, a seroprevalence study should take in place in near future.

Such age shifts of mumps are a result of changes in exposure and inadequacy of immune acquisition, and are a general characteristic of infectious disease epidemiology. In Germany, from 2007 to 2011, the incident rate ratio for children aged under 10 years has decreased by 0.87 (95% CI, 0.86-0.90; P <0.005), whereas the ratio has increased in young adults aged 20-29 years by 1.06 (95% CI, 1.03-1.08; P <0.005; Takla et al., 2013). The recent notification of mumps outbreak in U.S. colleges shows the evident age shift toward older age group (Patel LN et al., 2017). The shift in age may pose higher clinical burden in some diseases (i.e., hepatitis A), but may have lesser impact for the cases of mumps.

These findings are subject to several limitations. First, since the data that was used was from passively reported surveillance system, clinical indications when to report to the KCDC may vary according to the clinicians, clinical settings, and time-specific epidemiology of mumps, therefore may result in underestimation of mumps cases in Korea. Second, the study did not identify the immunization history in individual cases, therefore the association between vaccine strains and occurrence of mumps is speculative, and should be confirmed by case-matched design studies. Third, because the study simplified the frame to capture the major vaccine strain used in each year, the frame is not confirmative, and still there were minor vaccine strains being used in each surveillance years.

Despite these limitations, the data indicate a possibility of suboptimal protection of mumps in population that received Jeryl-Lynn strain. Although the effect of high two-dose MMR coverage may be improve over time as seen in Finland's experience, risk of individual infections and consequent outbreak remain, which highlights the necessity of strengthening of mumps surveillance in school-aged population in Korea. In addition, although further studies are needed for the recommendation to be made, argument on a third-dose MMR in response to mumps outbreak had been made in some countries, which could be also tested in Korea as well (Ogbunanu, Kutty et al., 2012; Nelson, Agunon et al., 2012).

CHAPTER 4. TREND OF MEASLES, MUMPS, AND RUBELLA INCIDENCE FOLLOWING THE MEASLES-RUBELLA CATCH UP VACCINATION IN THE REPUBLIC OF KOREA, 2001

4-1. Background

The incidence of mumps decreased after the introduction of vaccine, mostly administered in combination with vaccines for measles and rubella (MMR vaccine). Since the establishment of Expanded Program on Immunization in 1974, elimination of measles and rubella had been largely supported by the wide use of measles-rubella (MR) vaccine (Cutts, Lessler et al., 2013). However, there had been less attention to the value of control of mumps, and the disease is still one of the leading causes of vaccine-preventable outbreaks in the world today (World Health Organization, 2007).

In the Republic of Korea, MMR vaccine became first available from 1980, and was included in national immunization program since 1985 (Ki, Park et al., 2003). A second dose of MMR vaccine was introduced since 1997; however, vaccination coverage was suboptimal at less than 60% (Lee, Kim et al., 2011; Korea Centers for Disease Control and Prevention, 2007). In 2000-2001, a nationwide outbreak of measles resulted 55,707 cases and 7 deaths (Korea Centers for Disease Control and Prevention, 2007). In response, the national measles elimination program was introduced, which included a MR vaccine catch-up vaccination targeting 5.8 million school-aged children (8-15 years) in 2001. Afterwards, two-dose MMR keep-up program through verification of vaccination history at elementary schools (6-7 years) was introduced since 2002.

Following the program, the incidence of measles and rubella has decreased to less than 1 case per millions, allowing the successful elimination (Korea Centers for Disease Control and Prevention, 2007). However, the increase in the incidence of mumps was noted recently (Choi, 2010). Specifically, mumps cases in middle and high school-aged teenagers who have one or two doses vaccination history became increasingly recognized (Kim, Kim et al., 2009).

Although surveillance on the mumps cases has been conducted continuously, little is known about the changed epidemiology in population in conjunction with the vaccine policy in Korea. The aim of this report was to evaluate the epidemiology of mumps in conjunction with measles and rubella, and to share a baseline evidence for the future routine and outbreak-response immunization policy.

4-2. Methods

The National Notifiable Disease Surveillance System (NNDSS) data was used to describe the trend of measles, mumps, and rubella in Korea after MR catch-up vaccination campaign in 2001. Measles and mumps became notifiable in Korea since 1955, and rubella was included in the system since 2000. Nationwide coverage rate surveyed in 2000, 2008 showed the increase in one dose of MMR vaccination coverage of 90.2% and 98.2%, respectively (Korea Institute for Health and Social Affairs, 2000; Park, Lee et al. 2011). The MMR second dose vaccination coverage was 97.3% in 2012 (Korea Centers for Disease Control and Prevention, 2012).

The crude incidence of measles, mumps, and rubella for 1995-2015 was calculated. Demographic data were analyzed and classified according to the different age groups: 0-4, 5-9, 10-14, 20-24, 25-29, and ≥30. The period of surveillance was classified as follows: 2001, 2002-2006, 2007-2011, and 2012-2015. Incidence of measles, mumps, and rubella cases were calculated according to corresponding birth cohorts as follows: pre catch-up, 1976-1984; catch-up, 1985-1993; keep-up (early), 1994-2002; and keep-up (late), 2003-2011. Pre catch-up (1976-1984) cohort was those who were with presumable limited vaccination coverage of MMR with only one dose provided by the public. Catch-up (1985-1993) cohort was those who were with limited MMR vaccination coverage, but were given the MR vaccine during the 2001 catch-up campaign. Early keep-up (1994-2002) cohort was those who were candidates for the keep-up program in the first 8 years (2002-2008), and the late keep-up (2003-2011) were the candidates for the next 8 years (2009-2016).

4-3. Results

Between 1995 and 1999, the average numbers of measles and mumps cases were 46 (range 2-88) and 1,601 (range: 254-2,626), respectively. In 2000 and 2001, an outbreak of measles resulted in a total of 55,707 cases. Following the MR catch-up campaign, the annual reported cases of measles decreased, although there were outbreaks in 2007, 2010, 2013, and 2014 that resulted around 100 cases each year. Between 2001 and 2015, there was constant increase in the number of reported cases of mumps from 1,668 cases to 23,446 cases.

The age distribution of measles, mumps, and rubella cases after the MR catch-up campaign and MMR2 keep-up program are presented in Figure 4-1. The proportion of measles cases in children aged 0- 4 years has increased from 34% in 2001 to 79% in 2007-2011, and has decreased to 47% in 2012-2015. In 2012-2015, there was increase in the proportion of cases aged 15-24 years (33%), compared to that of 13% in 2001. The age distribution of mumps cases has shifted to the older age group. In 2001, 5-9 years aged children accounted for 45% of all cases, whereas in 2012-2015, has decreased to 19%. In 2001, adolescents aged 15-19 years accounted for 6% of all mumps cases, which has increased in 35% in 2012-2015. The proportion of rubella cases in children aged 0-4 years has increased from 20% in 2001 to 43% in 2012–2015.

Figure 4-1. Age distribution of measles, mumps, and rubella cases, following the MR (measles-rubella) catch-up vaccination campaign and MMR2 (two-dose measles-mumps-rubella) keep-up vaccination program in Korea.

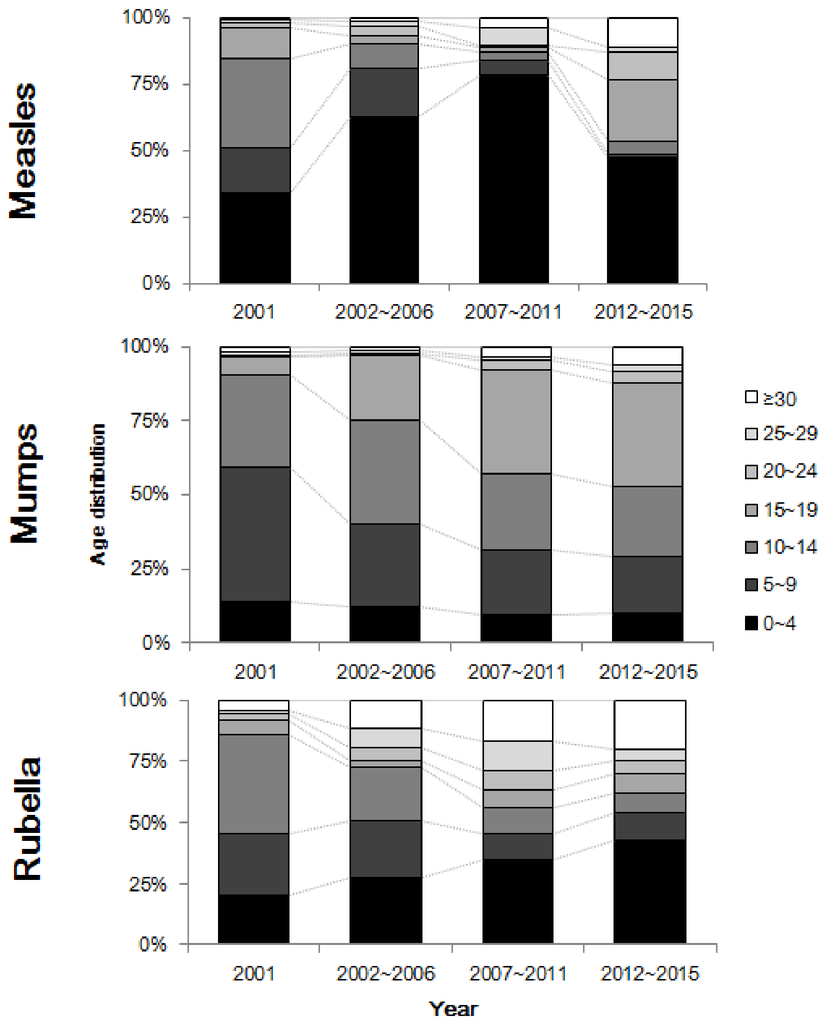


Table 4-1 shows the incidence of measles, mumps, and rubella in Korea by selected birth cohorts. The incidence of measles decreased in all birth cohorts;

however, there were increases in 2007-2011 for late keep-up cohort and in 2012-2015 for early keep-up cohort. In general, the incidence of mumps showed an increase in every birth cohort, however there was decrease in incidence for catch-up cohort from 131 cases in 2007-2011 to 64 cases per 100,000 in 2012-2015. The incidence of rubella showed decreases in catch-up and early keep-up cohorts following MR catch-up vaccination campaign.

Table 4-1. Incidence of measles, mumps, and rubella in Korea, by selected birth cohorts, 2001-2015.

Cohort*	Incidence (per 100,000 person year)			
	2001	2002-2006	2007-2011	2012-2015
Measles				
Late keep-up	-	0.6	1.4	0.6
Early keep-up	158	1.5	1.9	3.3
Catch-up	181	0.3	0.1	0.7
Pre catch-up	19	0.1	0.3	0.8
Mumps				
Late keep-up	-	2	26	530
Early keep-up	12	61	227	696
Catch-up	15	65	131	64
Pre catch-up	1	2	8	28
Rubella				
Late keep-up	-	0.3	0.6	0.6
Early keep-up	0.8	0.5	0.6	0.2
Catch-up	1.1	0.3	0.5	0.1
Pre catch-up	0.1	0.1	0.5	0.2

*MR (measles-rubella) catch-up vaccination was conducted in 2001, and MMR2 (two dose measles-mumps-rubella) keep-up program was initiated since 2001. Birth cohort indicates: pre catch-up, 1976-1984; catch-up, 1985-1993; keep-up (early), 1994-2002; and keep-up (late), 2003-2011

4-4. Discussion

Following the MR catch-up vaccination in 2001, the incidence of measles and rubella decreased, whereas mumps incidence has increased in Korea. From 2001 to 2015, there were gradual increases in mumps incidence for pre catch-up and early keep-up cohorts, whereas the incidence for catch-up cohort has decreased from 131 to 64 annual cases per 100,000 between 2007-2011 and 2012-2015. The decrease of mumps incidence in catch-up cohort could not be attributable to 2001 catch-up vaccination campaign because mumps vaccine was not included in the program. Therefore, sustaining of keep-up program to maintain high two doses MMR vaccination coverage should be emphasized in the current vaccination program.

In an economic analysis to select vaccination strategy in 2001, the two doses MMR keep-up program and catch-up campaign with MR vaccine had higher benefit to cost ratio over catch-up campaign with MMR vaccine (1.27 vs. 1.03) (Bae et al., 2013). In the model, the difference in predicted number of cases and complications of mumps between the two strategies was around 4,000 cases from

2001 to 2020. Between 2002 and 2015, a total of 15,561 cases of mumps were reported among catch-up cohort, which were less than 56,414 cases for early keep-up and 22,259 cases for late keep-up cohorts. Although the trajectory prediction in the model was lower than the actual number of cases, the decision to choose MR vaccine over MMR vaccine for the 2001 catch-up campaign may have less impact on the incidence of mumps in the corresponding cohort. Rather, a worrisome finding in this study is the constant increase of cases in early and late keep-up cohorts.

Among those who were the targets for early keep-up program, there was sharp increase from 61 cases in 2002-2006 to 227 in 2007-2011, then to 696 cases per 100,000 annually in 2012-2015. Our finding may implicate the presence of "pocket of susceptibility" in the early keep-up cohort. Indeed, this finding is consistent with finding in Australia that describes the increase in mumps incidence in birth cohorts who may have not reliably received the second dose of MMR and too young to have had mumps infection (Aratchige, McIntyre et al., 2008). Following the measles control campaign in Australia in 1998, the reported cases of mumps were concentrated among the birth cohort of 1978 to 1982, who had insufficient vaccination coverage of 68%. Although the overall transmission of mumps has been reduced since the introduction of vaccination in Australia, the authors conclude that the accumulation of unvaccinated cohorts over time may have contributed to an increased susceptibility among young adults. The age structure of mumps incidence in Korea is in line with Australia's epidemiology, which reinforces the public health prioritization in young adult population. Various attempts have been introduced to increase the timely second dose MMR vaccination among preschool aged children. In 2011, the Korean NIP began a program of sending text messages for reminder-recalls to improve vaccination coverage (Choe, Yang et al., 2013). The effect of such public health intervention should be conveyed in near future.

It has been postulated in seroepidemiological study that compared measles and mumps: the seropositivity of mumps was lower than that of measles (Kim et al., 2004). This is in line with the report from Australia, where extensive efforts in two-dose MMR vaccination have demonstrated elimination of endemic circulation of measles, but followed by unwanted increase of mumps cases in older age group. The age distribution of mumps cases shifted to the older age group: most notably, the proportions of middle and high school student-aged teenagers are increasing. This indirectly indicates that the two-doses of MMR vaccine protected younger aged children after the implementation of keep-up MMR2 program since 2001, and kept the infection pressure in lower range. This is in line with reports from the Netherlands (Greenland, Whelan et al., 2012), United Kingdom (Pugh, Akinosi et al., 2002), and United States (Barskey, Schulte et al., 2012).

These findings are subject to several limitations. First, since the data used was from passively reported surveillance system, therefore may result in underestimation of reported cases. Second, the study did not identify the immunization history in individual cases, therefore the association between vaccination and increase of mumps is speculative. Despite these limitations, the data indicate a possibility of suboptimal protection of mumps in population with MMR2 keep-up program. Although the effect of high two-dose MMR coverage may be improve over time, risk of individual infections and consequent outbreak remain, which highlights the necessity of strengthening of mumps surveillance in school-aged population in Korea.

Notwithstanding, a review of the past vaccination strategy and its impact on epidemiology of vaccine-preventable diseases is necessary to ensure the functioning of current vaccination program and predict necessity of future. Choice of vaccines in national immunization program warrants careful decision and periodic review of epidemiology of vaccine-preventable diseases. A strong vaccination program that emphasized two-dose MMR vaccination launched in Finland over last 30 years has led to the elimination of mumps from the country since 1997 (Peltola, Jokinen et al., 2008).

CHAPTER 5. INCREASING MUMPS INCIDENCE RATES AMONG CHILDREN AND ADOLESCENTS IN THE RPUBLIC OF KOREA: AGE-PERIOD-COHORT ANALYSIS

5-1. Background

The incidence of reported mumps has increased in many countries since the turn of the century. In the United States, more cases of mumps were reported in 2006 than in any year since 1955 (Barskey, Glasser et al., 2009). An increase has also occurred in France, with more cases reported in 2013 than in the prior two decades (Vyen, Fischer, et al., 2016). The variety of explanations proposed for this resurgence of mumps include inadequate vaccine coverage, mismatch between the genotype of the wild-type and the vaccine virus strains, circulation of other pathogens that can cause parotitis, and the use of ineffective vaccine strain(s) (Sabbe, Vandermeulen, 2016).

The Urabe AM9, Jeryl-Lynn, and Rubini strains mumps vaccine strains have been widely used. The Urabe AM9 and Jeryl-Lynn strains have shown an efficacy of 75.8% (95% CI, 35.6-90.9) and 64.7% (95% CI, 10.6-86.0), respectively (Toscani, Batous et al., 1996). However, the Rubini strain has been ineffective, with efficacy rates from -55.3% (95% CI, -121.8 to -8.8) to 12.4% (95% CI, -102.0% to 62.1%). In 2000 the World Health Organization (WHO) recommended against using not the Rubini strain for public vaccination programs (World Health Organization, 2007).

In Korea, a recent increase of mumps was noted among 10-19-year-old adolescents (Park, Cho, 2014). The Rubini strain vaccine was used from 1997-2000 in Korea. So, we hypothesized that the increase of mumps incidence in Korea can be attributed to the accumulation of susceptible adolescents vaccinated with the Rubini strain.

To understand the effect of the Korean birth cohort immunized with vaccines containing the Rubini strain on the recent increase of mumps in Korea, we performed an age-period-cohort (APC) analysis of gender-specific mumps incidence in Korea from 2001-2015.

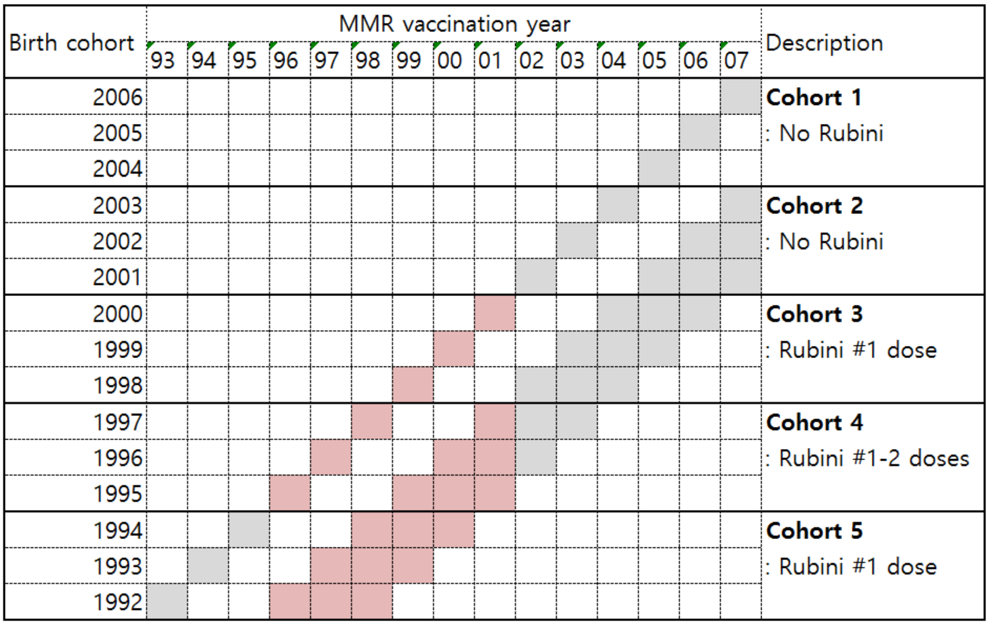
5-2. Methods

Data source

An APC analysis breaks down the time trend in disease incidence into the effect of age, calendar period, and birth cohort. Data on age-specific and gender-specific mumps cases from 2001-2015 were obtained from the National Notifiable Disease Surveillance System (Park, Cho, 2014). Mumps has been a notifiable disease in Korea since 1955. Information on age and gender were included since 2001. No additional policy was made to improve reporting of cases during the period of observation. All physicians are obliged to report laboratory-confirmed or clinically-suspected mumps cases. The clinical case definition for diagnosis of mumps is based on the WHO case definition, which is a case with acute onset of unilateral or bilateral tender, self-limiting swelling of the parotid or other salivary gland and without any other apparent cause (World Health Organization, 2003). We have included all clinical and laboratory confirmed cases for the analysis.

One dose of measles, mumps, and rubella (MMR) vaccination was introduced in the National Immunization Program in 1985 and the second dose since 1995. Vaccination coverage rate of the first dose of MMR remained relatively constant at 95-99% during the surveillance years (Choi, 2010; Choe, Yang et al., 2013). The Rubini strain was used in the National Immunization Program from 1997-2000, and was exposed to birth cohorts from 1992-1994 as their second dose, from 1995-1997 as their first and/or second doses, and from 1998-2000 as their first dose. Between 1997 and 2000, the proportion of Rubini strain among all vaccine strains was around 50% (unpublished data, Korea Centers for Disease Control, Figure 5-1). In Korea, the major vaccine strains used was the Urabe AM9 strain in the 1990s and the Jeryl-Lynn strain beginning in 2000.

Figure 5-1. Birth cohort and the corresponding vaccination schedule and exposure to Rubini vaccine strains.



Statistical analyses

The annual age-standardized incidence per 100,000 populations per year was calculated using population data from the Korea Statistical Information Service and the WHO standard population as the reference. Age-specific incidence according to gender was calculated for periods and birth cohorts in 3-year blocks to find difference in incidence between the aforementioned cohorts affected by the Rubini strain.

Age effects are differences in mumps incidence linked to processes of aging, which include physiologic changes and accumulation of social experiences linked to aging. Period effects are resulted from factor that equally affect all age groups at a particular period of time. In case of mumps, it could arise from the influx of new virus strain that is mismatched with the available vaccine, or immigration from non-immune population. Cohort effects are resulted from the unique experience or exposure of certain birth cohort as they move across time. In this study, we assumed different birth cohorts were affected by the different vaccine strains, thus have different immune profile between the cohorts. We conceptualized the cohort effect as an interaction due to a period effect that is experienced through age-specific to Rubini strain.

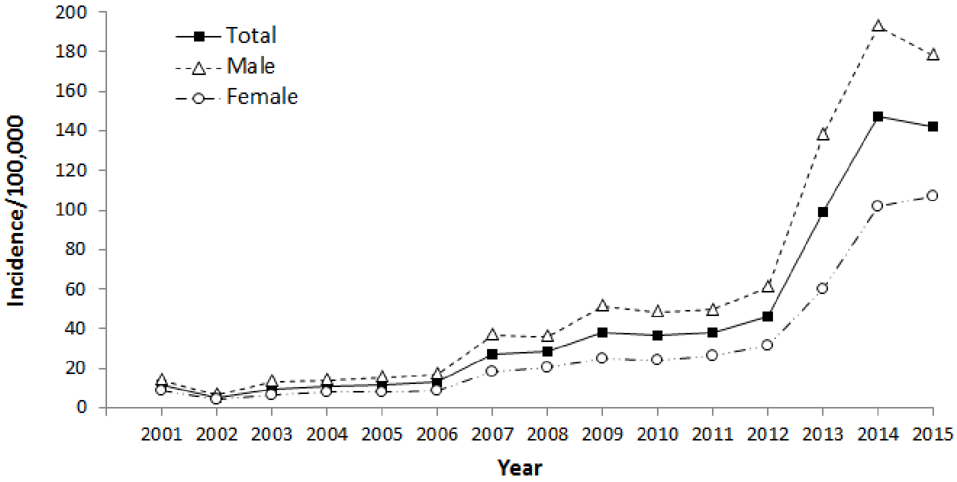
The Poisson APC model was used to estimate the age, period, and cohort effects on secular trend of mumps from 2001-2015. The log age-specific rate λ (a, p) at age a in period p for those born in cohort c = p - a, is as follows: $\log(\lambda(a, p)) = f(a) + g(p) + h(c)$. The age-period model was fit, choosing the year 2001 as the reference period. The log of the fitted values from this model was used as an offset variable in a model of a cohort effect. The cohort effect was used as the residual log rate ratios by cohort.

The APC modeling was performed and the data were analyzed using the R 3.0.2 statistical software and with the Epi 1.1.49 package and the Web Tool developed by the National Cancer Institute (Rosenberg, Check et al., 2014). The Web Tool generates the smoothing longitudinal curve from observed cohort specific age-specific rates. The local drifts are derived from log-linear regression. The relative rates are calculated in given period or birth cohort versus a reference period or cohort. This study was approved by Seoul National University Institutional Review Board (IRB No. SNU 16-01-050).

5-3. Results

The secular trend of mumps incidence is shown in Figure 5-2. Between 2001 and 2005, the annual number of mumps cases reported was around 10 cases per 100,000. From 2006-2010, the incidence increased from 13 cases to 40 cases per 100,000. From 2011-2015, reported mumps incidence increased dramatically to more than 100 cases per 100,000. On average, the annual percent changes were 26.8%, 26.8%, and 26.7% for total, male, and female incidences per 100,000, respectively, which were all significant increases from 2001-2015 (all $P<0.001$). The incidence for males were significantly higher than that of females ($P<0.001$, Wilcoxon signed rank test). The mumps incidence rate was predominant in males during all periods.

Figure 5-2. Age-standardized mumps incidence rate by gender, Republic of Korea, 2001-2015



Incidence rates by gender, age group, and calendar period are shown in Table 5-1. The incidence rate was highest among males aged 15-17 years from 2013-2015, being 508.7 per 100,000 persons.

Table 5-1. Rates of mumps incidence in the Republic of Korea by age, period, and gender, 2001-2015

Gender and age group, years	Mumps incidence per 100,000/year				
	2001-2003	2004-2006	2007-2009	2010-2012	2013-2015
Male					
0-2	3.6	3.5	10.6	18.7	48.7
3-5	14.4	16.4	38.5	67.8	197.6
6-8	17.5	17.5	48.6	68.9	203.0
9-11	15.7	15.1	39.6	50.3	132.3
12-14	15.4	29.8	57.7	80.7	307.9
15-17	9.2	34.3	116.9	122.2	508.7
18-20	0.9	3.4	17.5	28.0	86.5
Female					
0-2	2.6	3.1	9.3	13.7	38.4
3-5	10.2	12.2	31.8	49.9	159.0
6-8	12.3	12.5	34.6	50.9	151.0
9-11	11.2	10.6	25.9	36.9	101.7
12-14	9.5	16.2	28.7	37.0	148.0
15-17	3.0	10.0	39.0	33.8	154.3
18-20	0.6	1.3	8.8	10.8	40.2

Age Effect

The age-specific rates of mumps incidence for males and females across time period is shown in Figure 5-3. In 2001-2003, the mumps incidence was relatively high at age 3-5, then continues to rise with age, with the growth rate gradually slowing down from approximately age 15-17 years. From 2007-2009 the age-specific incidence rate increased steadily in males aged 3-5 years of age, with a surge in cases noted at 15-17 years of age. Both males and females showed increased incidence rates from 2013-2015, with two peaks at preschool age (3-8 years) and adolescent age (15-17 years). As seen in Figs. 5-3 left and right, the incidence of mumps in male was higher than that of female, and the gap was more prominent for adolescents aged 15-17 years.

Figure 5-3. Age-specific mumps incidence for males and females by time period, Republic of Korea, 2001-2015

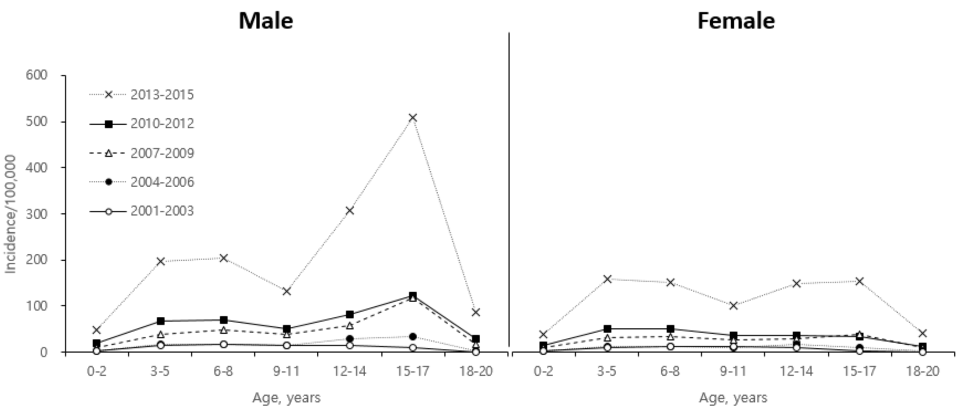
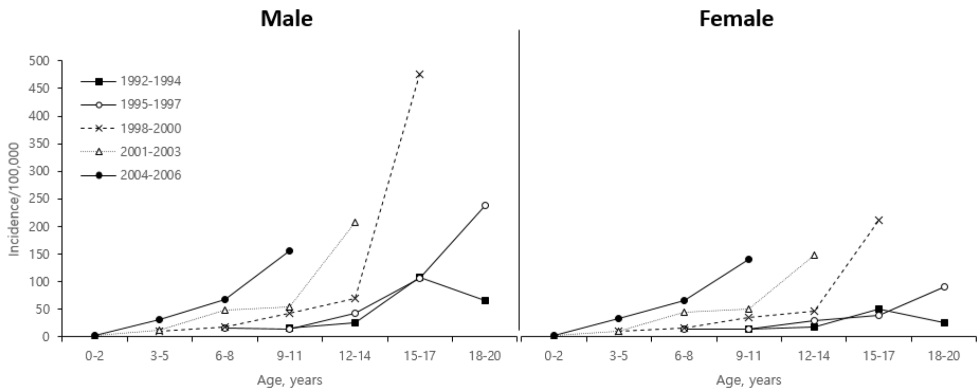


Figure 5-4 presents the age-specific rates across the birth cohorts. Increased incidence during the late teenage period was evident in the 1998-2000 cohort. Age shift towards earlier teenage period was observed across the 2001-2003 and 2004-2006 cohorts. The difference in incidence between male and female was proment for cohort 1998-2000 when they reached age of 15-17 years, in which males were with >450 cases per 100,000 while females were with 150 cases per 100,000. Moreover, male cohort 1995-1997 were with higher incidence compared to female cohort 1995-1997.

Figure 5-4. Age-specific mumps incidence rates for males and females by birth cohort, Republic of Korea, 2001-2015



Period & cohort effect

Figure 5-5 presents the period and cohort effects by gender.. From 2008 to 2014, the mump incidence RR of Korean population increased rapidly, by rate ratio of 7.2. The difference in rate ratio between sexes was not significant. The risk of mumps has increased according to birth cohorts in both genders. From 2001-2015, the overall net drifts were 27.67 (95% CI: 27.5.47-29.90) for males and 27.25 (95% CI: 24.91-29.65) for females. There were statistically significant cohort and period relative risks and net drifts in both genders (Table 2).

Figure 5-5. Period and cohort effects obtained from age-period-cohort analyses for the incidence rates of mumps and the corresponding 95% confidence intervals by gender, Republic of Korea, 2001-2015

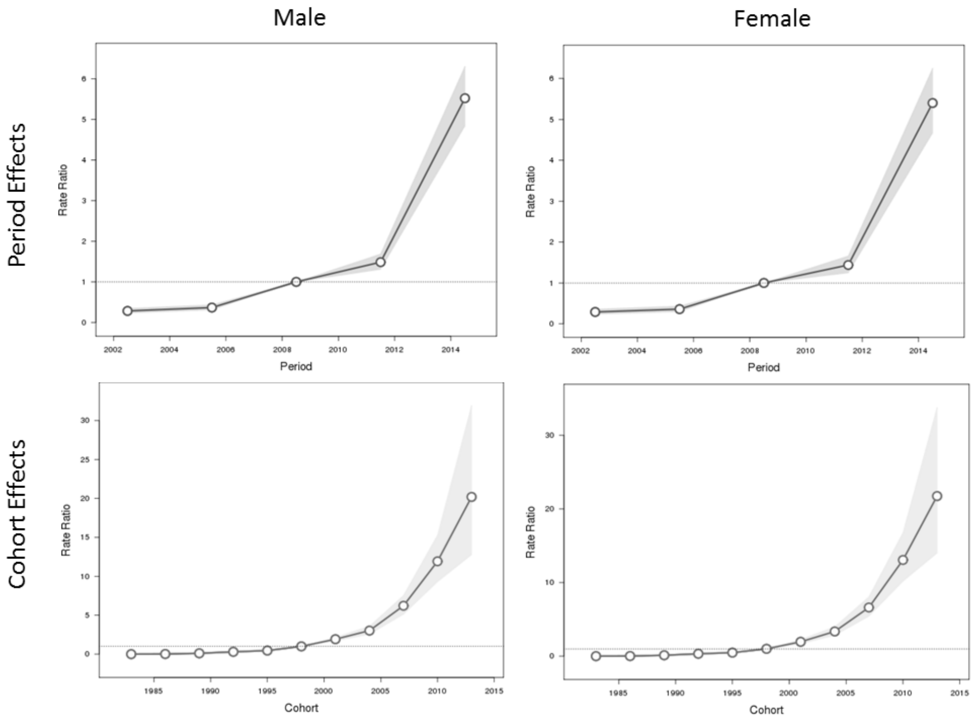


Table 5-2. Wald Chi-Square tests for estimable functions in the APC model

	Male			Female		
	X2	df	P-Value	X2	df	P-Value
NetDrift = 0	761.2	1	<0.001	643.9	1	<0.001
All Period RR = 1	1260.6	4	<0.001	1029.3	4	<0.001
All Cohort RR = 1	1215.8	10	<0.001	981.9	10	<0.001
All Local Drifts = Net Drift	50.8	7	<0.001	28.1	7	<0.001

5-4. Discussion

The increase of mumps may have been affected by birth cohort exposed to Rubini strain (cohort-effect); moreover, there are trend in increased risk in the recent years (period-effect). We measured an increase in incidence after the introduction of Rubini strain to have significantly higher than the incidence of older birth cohort. Our finding may implicate that there is a gap of immunity present in Korea, which have led to the resurgence of mumps, affecting younger (2004-2006 cohort) and older (1995-1997 cohort) population recently. The cohorts of 1998-2000 with increasing incidence over age years were the group that have been potentially exposed to Rubini strain as their first doses of MMR vaccine. The 2004-2006 cohorts were not exposed to Rubini strain, and the 1995-1997 cohorts may have received the Rubini strain as their first or second dose MMR. These groups also have showed increase in incidence over age years, suggesting potential external effect from increased transmissibility in the community.

Indeed, this finding is consistent with findings elsewhere that have used Rubini strain in the public vaccination program. Rubini strain vaccine was exclusively used in Portugal, and the country has experienced a large mumps outbreak in the 1990s (Goncalves et al., 1998). A resurgent outbreak in 2012 revealed that most cases were 11-20 years who have previously received vaccine containing the Rubini strain (Cordeiro et al., 2015). In mid 2000s in Spain, an outbreak investigation on 2,866 mumps clusters showed that 31% of cases occurred in cohorts vaccinated with first or second dose of the Rubini strain (Castilla et al., 2009).

The period effect also indicate that mumps is clearly not a disease only of adolescents who may have been previously immunized with a vaccine containing the Rubini strain. Nearly one-third of the affected individuals during 2013-2015 were 3-8 years of age. This may indicate insufficient effectiveness of the current vaccination program against outbreak of mumps in Korea. In countries in which a two-dose mumps vaccination program was implemented to their public program, and so which covered a substantial proportion of the target population, there has been a shift in higher risk for mumps to other age groups. When the United States experienced a large mumps outbreak in 2006, the peak age-specific attack shifted from 5-9 years to 18-24 years (Barskey, Schulte et al., 2012). In Germany in 2007-2011, a significant increasing incidence trend among 20-29-year-old individuals suggested an age-shift over time (Takla, Wichmann et al., 2013). As in many other infectious diseases, introduction of vaccine into routine childhood immunization may have shifted the pool of susceptible population to older age cohorts who either had not received the vaccine or were exposed to natural infection. Moreover, difference in vaccination coverage and vaccine strains may have affected the shift in the age and also another surge in the younger age group. By contrast, in Japan where mumps vaccination has been discontinued since 1993, most mumps cases remained in age group of 3-7 years (Eshima, Tokumaru et al., 2012). A strong vaccination program in Finland that includes two-dose mumps vaccination has led to the elimination of mumps from the country since 1997 (Peltola, Jokinen, et al., 2008). In addition to the strengthening of two-dose vaccination in Korea, other potential cause of recent increases in the younger age group should be investigated further.

In this study, we found the highest incidence among cohort with potential exposure to Rubini strain, and moreover the differences between the cohorts that have received one or two doses (1995-1997) of MMR vaccine as Rubini strain. To date, the difference in vaccine efficacy between different strains according to vaccination timing (primary vs. secondary) for mumps vaccine is not clearly understood. In Germany, children aged 15 years with different primary vaccines received were boosted with the Rubini vaccines (Gassner et al., 1995). Regardless of the vaccine strains they were given on the primary doses, the booster dose with Rubini strain did not demonstrate an adequate immune response. The diminishing of seroprotection by the Rubini strain vaccine was confirmed by serological findings that showed seropositivity of decreasing from 72.4% to 25.6% in five years in for mumps in children below 5 years (Liew et al., 2010). Our observation of earlier increase of incidence among secondary dose group (1998-2000) compared to primary dose group (1992-1994) is not clearly understood, but other factors such as earlier exposure to the heavy force of infection of mumps circulating in the community driven by the 1998-2000 cohort should be investigated in the future. Moreover, difference between Urabe strain and Jeryl-Lynn strains, the possible additional dose that were distributed during each cohort's window period for timely vaccination.

The greatest impact on mumps incidence was shown especially during the surge years in the late 2000s. The severity and incidence is generally higher in males in most viral illnesses. Although vaccination rates similar in both genders (Choe YJ et al., 2012), the incidence of mumps is significantly higher in males. Surveillance from the United Kingdom from 1975-1981 revealed nearly twice as many laboratory mumps cases in males than in females, with more reports of complications like pancreatitis, myocarditis, and orchitis (Galbraith, Young et al., 1984). In contrast, in Japan from 2000-2009, the male-to-female ratio for mumps by age group showed a male predominance from age 0-14, which changed to female predominance from age 15-19 and 20 years and older (Eshima, Tokumaru et al., 2012). These findings may have been affected by the difference in degree of disease presentation between sexes, which could have led to difference in the likelihood of a diagnosis of mumps. Additional reports of mumps outbreak show higher incidence in males. As with measles vaccination, females show higher and more persistent antibody titers and may therefore be less susceptible to infection (Dominguez A et al., 2006). If the catch-up vaccination take place only in adult male population, decreased gender-specific immunity in female may result in less chance of conferring vertical transfer of immunity to fetus, thus pose additional burden to the pediatric population. Additional study to investigate the benefit of catch-up vaccination in both genders should be take place in near future. In males, mumps complication such as epididymo-orchitis can occur in as much as 30%, whereas in females, oophoritis develops in only 5% (Hviid A, et al., 2008). Less typical complications of mumps, such as meningitis and encephalitis, also occur more frequently in males. Relating these gender-specific differences in disease outcome to distinct immune responses is problematic in the absence of relevant data, however may pose under-reporting in female mumps cases with minor symptoms, therefore may have posed the disproportionate incidence between genders (Hill K, et al., 1995).

These findings are subject to several limitations. First, since the data used was from a passively reported surveillance system, clinical indications when to report to the government may vary according to the clinical settings, and so may result in underestimation of mumps cases. Secondly, the differences in surveillance sensitivity and vaccine coverage may have affected the change in reported cases of mumps. As the data did not distinguish between clinical cases and laboratory confirmed cases, the seasons which were affected by other pathogen that may have caused similar clinical presentation could have affected the result. Thirdly, vaccination history in individual cases were not identified, therefore the association between vaccine strains and occurrence of mumps we postulate is speculative and should be later confirmed by case-matched design studies. Lastly, there could be other plausible explanations for the increase in mumps incidence, such as geographical occurrence of local outbreaks, which may independently affect the other populations regardless of vaccine-exposed cohorts. Difference in vaccine strains before and after the Rubini strain may have affected the difference in the incidence.

Despite these limitations, the data indicate a possibility of suboptimal protection of mumps in Koreans who may have received Rubini strain. Although the effect of high two-dose vaccine coverage should improve over time, risk of individual infections and consequent outbreak remain. Strengthening of mumps surveillance in school-aged population should be a priority. There had been no major changes in reporting system and vaccine coverage in Korea between 2001 and 2015; therefore, our findings may suggest that the cohort who may have received vaccine containing Rubini strain potentially have affected the change in mumps incidence. However, even if the cohort that was exposed to Rubini may have played a key role in driving overall re-emergence of mumps in the country, there may be other factors not discussed in this study. These other potential causes, such as surveillance bias, misclassification or over-diagnosis, and viral immune escape, should be investigated in the Korean context as well (Barskey, Juieng et al., 2013; Santak, Lang-Balija et al., 2013).

This study showed a significant period effect (late 2000s) in increase of the mumps cases. Higher RRs were observed after the late 2000s, especially males who were born between 1998 and 2000, showing significant cohort effect. The increased mumps incidence rate in the 2000s may be related to low levels of herd protection, owing to insufficient population immunity posed by Rubini strain. In late 1990s and early 2000s, 50% of Korean born toddlers were vaccinated with such vaccine strain. This study showed the importance of establishing data on seroprevalence in these age group. There was a lesser cohort effect for persons born before 1995, who may have well passed the typical biological age that is vulnerable to mumps infection. The possible increased risk of infection with the mumps virus may have influenced a greater repercussion on incidence due to the non-existence of effective protective measures.

CHAPTER 6. SPATIAL DISTRIBUTION OF MUMPS IN REPUBLIC OF KOREA, 2001-2015: IDENTIFYING CLUSTERS AND POPULATIONS AT RISK

6-1. Background

The mumps incidence decreased dramatically after the widespread use of vaccine, mostly in combination with vaccines for measles and rubella (MMR vaccine). Mumps vaccination has been used globally during several decades, but the disease is still one of the leading pathogen among vaccine-preventable outbreaks in the world today (Galazka, Robertson et al., 1999). More recently, mumps resurgence was noted in many countries despite high 2-dose MMR vaccination coverage (Dayan, Quinlisk et al., 2008). Suggested causes of resurgence vary by country and region, but there are evidences that insufficient vaccine efficacy, mismatch between vaccine and circulating virus, and intense social contacts may have contributed to the mumps outbreaks (Cordeiro, Ferreira et al., 2015; Gouma, Sane, et al., 2014; Braeye, Linina et al., 2014).

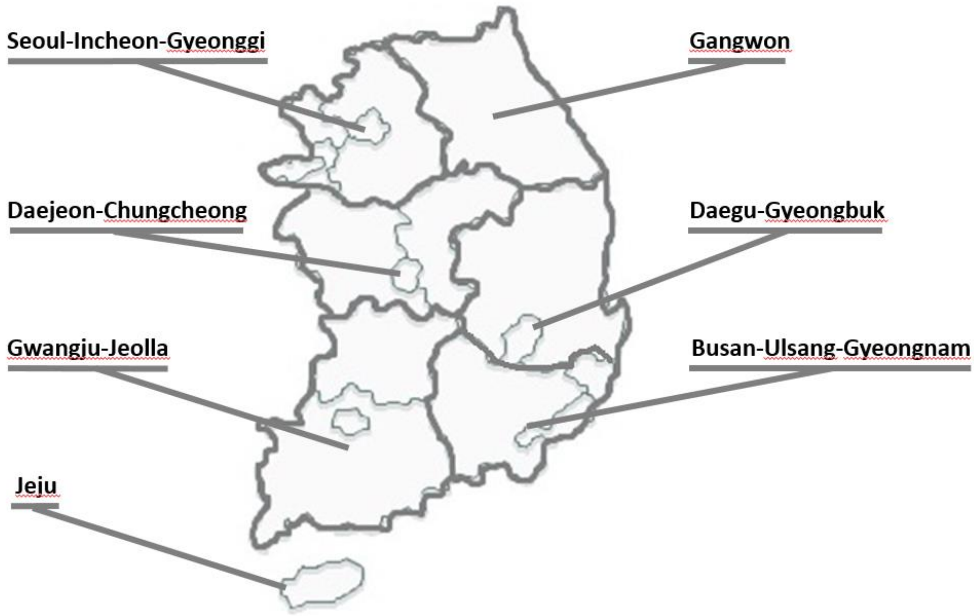
In Republic of Korea, MMR vaccine has been included in National Immunization Program (NIP) since 1985 (Choi, 2010). The vaccination schedule was updated with two MMR doses given at 12-15 months and 4-6 years in 1997. Following that, reported mumps cases decreased from 5,000-8,000 cases annually to less than 2,000 cases per year (Park, 2015). In 2000s, however, the resurgence of mumps was noted primarily among school-aged children and adolescents.

The geographic differences in outbreak during the 2000s resurgence have not been assessed previously. As mumps tend to cluster geographically where susceptible population reside in close proximity, spatial analyses may bring important insight to detect and predict the incidence patterns of mumps. In this study, we sought to understand spatial patterns in mumps incidence to give an indication to the geographical risk of the disease in the settings with high MMR vaccination coverage.

6-2. Methods

Republic of Korea occupies around 100,032 square kilometers, with population of approximately 50.2 million in 2013. It is divided into 16 provinces (si-do), which are subdivided into 252 districts (si-gun-gu). We grouped the provincial level according to their geographical proximities: Seoul-Incheon-Gyeonggi (northwest); Daejeon-Chungcheong (midwest); Gwangju-Jeolla (southwest); Gangwon (northeast); Daegu-Gyeongbuk (mideast); and Busan-Gyeongnam (southeast) (Figure 6-1).

Figure 6-1. Map of grouped provinces, Republic of Korea.



Number of reported mumps cases was collected at district level from the National Notifiable Disease Surveillance System, from 2001 to 2015. The data cover population distribution by age, sex, and the date of disease onset. The address field contained in the dataset was used to locate the geographical region of occurrence. We used data from census to calculate the annual incidence rate. Indirect standardization was used to control for age.

We classified the 15 years of the surveillance period into three periods according to the level of endemicity: low endemicity (2001-2003 and 2004-2006; $<$ 20 cases per 100,000 per year), intermediate endemicity (2007-2009 and 2010-2012; 20-59 cases per 100,000 per year), and high endemicity (2013-2015; $\geq$ 60 cases per 100,000 per year). We grouped the 12 months of the year into four seasons according to academic calendar system in Republic of Korea: Winter Break (January − February), the 1st Semester (March − July), Summer Break (August), and the 2nd Semester (September – December).

We used GeoDa software (version 1.8, The University of Chicago, IL, USA) to investigate for mumps clusters by spatial analyses. To visualize the difference in age adjusted incidence between districts, we have divided into seven color scales. A geographic weighted regression (GWR) analysis was performed to find demographic predictors of mumps incidence according to district level. GWR is a local regression model which generates parameters disaggregated by the spatial units. Mumps is a communicable disease with basic reproduction rate of 5-7, therefore each individual events of mumps are not independent. Moreover, each individual outbreak or clusters of mumps in defined geographic area are dependent to the adjacent or closely connected area. We set the GWR to provide a local model of variables including vaccination timeliness and population structure to understand the cluster incidence of mumps. Total population size, population density, percentage of children (age 0 – 19 years), and timely vaccination rate of MMR vaccines (12-15 months and 4-6 years, surveyed in 2005-2012) were tested for correlations to the higher incidence rate of mumps in corresponding district.

The population, density, childhood percentage, and the timely vaccination coverage rate data was derived from the National Statistics and National Immunization Program database. The current vaccination schedule recommends the administration of one dose of MMR by age 12-15 months and an additional dose at 4-6 years. Therefore, the defined non-timely vaccination coverage was not receiving of the recommended number of doses of MMR doses by age of 15 months and 6 years.

To examine if incidence is clustered into specific regions, we have performed spatial autocorrelation analysis using Moran's Index. To find the "hot spots" (high values next to high, HH), and "cold spots" (low values next to low, LL), local indicators of spatial association (LISA) analysis was performed.

6-3. Results

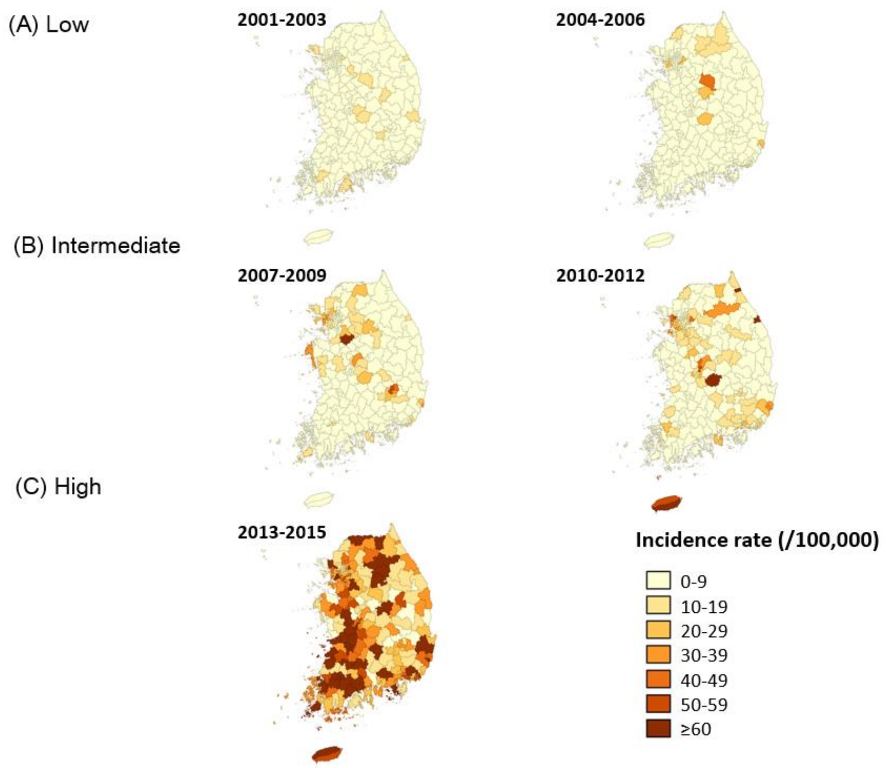
For the low endemic periods of 2001-2003 and 2004-2006, the total numbers of cases were 3,950 and 5,696 cases, respectively (Table 6-1). The reported cases has increased during intermediate endemic periods of 2007-2009 and 2010-2012 by 15,498 and 19,723 cases, and during high endemic period of 2013-2015, the total reported number was 65,758 cases. Around half of cases were reported from Seoul-Incheon-Gyeonggi area during low and intermediate endemic period, whereas during high endemic period of 2013-2015, around 45% of cases were reported from Gwangju-Jeolla and Busan-Ulsan-Gyeongnam areas. Change in the seasonal variation in the number of cases was apparent, with proportion of cases occurring during the second semester (September – December) has increased from 26.8% in 2001-2003 to 40.1% in 2013-2015.

Table 6-1. Characteristics of mumps cases during the three periods in the Republic of Korea: low (2001-2003 & 2004-2006), intermediate (2007-2009 & 2010-2012), and high endemicity (2013-2015)

Variable	2001-2003		2004-2006		2007-2009		2010-2012		2013-2015	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Total cases	3,950		5,696		15,498		19,723		65,758	
Age group (years)										
0-5	897	(22.7)	895	(15.7)	1,928	(12.4)	3,136	(15.9)	9,304	(14.1)
6-11	1,819	(46.1)	1,721	(30.2)	4,153	(26.8)	4,895	(24.8)	12,504	(19.0)
12-14	717	(18.2)	1,471	(25.8)	2,799	(18.1)	3,537	(17.9)	12,105	(18.4)
15-17	361	(9.1)	1,298	(22.8)	5,033	(32.5)	5,117	(25.9)	20,036	(30.5)
≥18	156	(3.9)	311	(5.5)	1,585	(10.2)	3,038	(15.4)	11,809	(18.0)
Gender										
Female	1,463	(37.0)	1,915	(33.6)	5,081	(32.8)	6,486	(32.9)	22,281	(33.9)
Male	2,487	(63.0)	3,781	(66.4)	10,417	(67.2)	13,237	(67.1)	43,477	(66.1)
Geographic area										
Seoul-Gyeonggi	2,076	(52.6)	3,196	(56.1)	8,169	(52.7)	9,487	(48.1)	21,659	(32.9)
Daejeon-Chungcheong	336	(8.5)	621	(10.9)	1,046	(6.7)	2,506	(12.7)	5,935	(9.0)
Gwangju-Jeolla	469	(11.9)	191	(3.4)	680	(4.4)	974	(4.9)	16,467	(25.0)
Gangwon	150	(3.8)	321	(5.6)	537	(3.5)	823	(4.2)	2,309	(3.5)
Daegu-Gyeongbuk	451	(11.4)	504	(8.8)	3,668	(23.7)	1,268	(6.4)	4,492	(6.8)
Busan-Gyeongnam	327	(8.3)	768	(13.5)	1,319	(8.5)	3,471	(17.6)	13,694	(20.8)
Jeju	141	(3.6)	95	(1.7)	79	(0.5)	1,194	(6.1)	1,202	(1.8)
Seasonality										
Winter Break (Jan-Feb)	316	(8.0)	408	(7.2)	970	(6.3)	1,703	(8.6)	6,725	(10.2)
1st Semester (Mar-Jul)	2,357	(59.7)	2,903	(51.0)	9,003	(58.1)	9,152	(46.4)	28,220	(42.9)
Summer Break (Aug)	220	(5.6)	349	(6.1)	931	(6.0)	1,291	(6.5)	4,176	(6.4)
2nd Semester (Sep-Dec)	1,057	(26.8)	2,026	(35.6)	4,594	(29.6)	7,577	(38.4)	26,337	(40.1)

Figure 6-2 showed variation in mumps incidence rates of districts according to surveillance years. During low endemic periods of 2001-2003 and 2004-2006, there were sporadic regional distributions of outbreak in the central and northern part of the country. During intermediate endemic periods of 2007-2009 and 2010-2012, the increase of incidence was noted across the country from Seoul-Incheon-Gyeonggi region to Busan-Ulsan-Gyeongnam region. During high endemic period of 2013-2015, a nationwide high incidence of mumps was noted especially concentrated in Gwangju-Jeolla and Busan-Ulsan-Gyeongnam regions that reported more than 60/100,000 cases per year.

Figure 6-2. Incidence rate per 100,000/year of mumps during the three periods in the Republic of Korea: low (2001-2003 & 2004-2006), intermediate (2007-2009 & 2010-2012), and high endemicity (2013-2015)



There was a clear pattern for the mumps cluster shown through global spatial autocorrelation analysis (Table 6-2). A significant autocorrelation was found within the mumps incidence in four surveillance periods of 2004-2006, 2007-2009, 2010-2012, and 2013-2015.

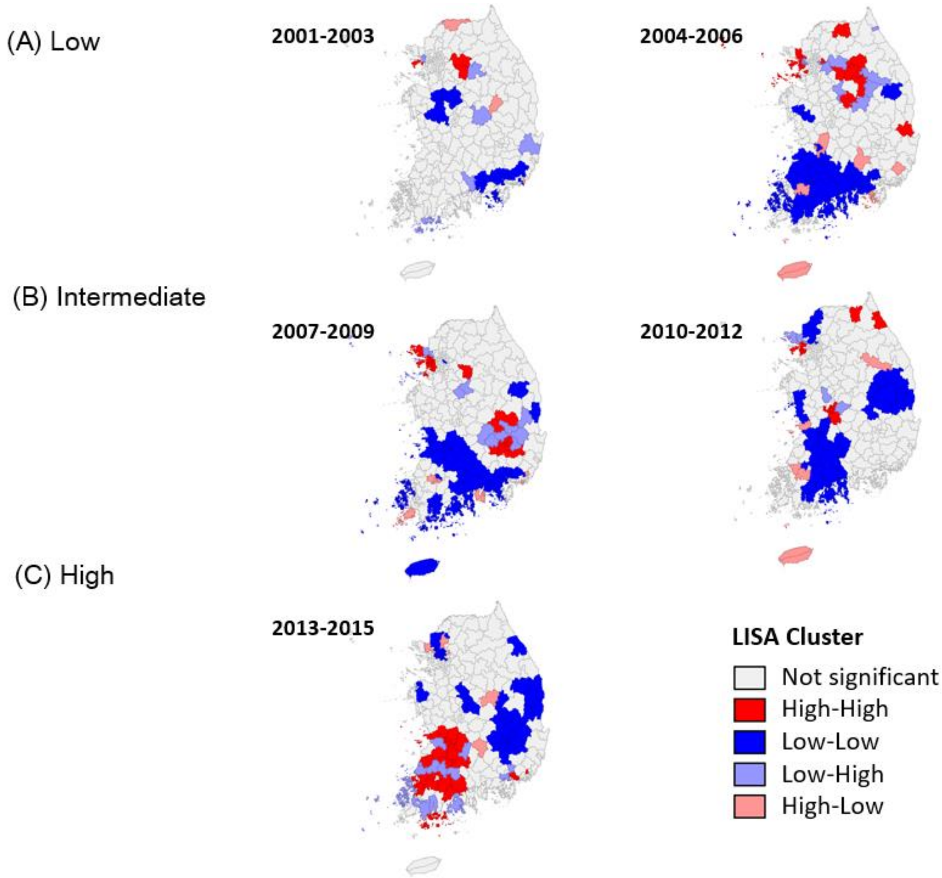
Table 6-2. Global spatial autocorrelation analysis of mumps incidence in the Republic of Korea, 2001-2015

	Moran's I	Z	*P*
2001-2003	-0.008	-0.144	0.462
2004-2006	0.200	5.755	<0.001
2007-2009	0.483	13.745	<0.001
2010-2012	0.122	3.583	0.003
2013-2015	0.240	7.003	<0.001

Map showing the dynamics of clustering are summarized in Figure 6-3. During low endemic periods, the HH clusters were mostly confined to Seoul-Incheon-Gyeonggi and Gangwon regions. During high endemic period of 2013-2015, most of the Gwangju-Jeolla regions were with HL or HH clusters. These regions showed the core “clod spot” clusters consistently during 2004-2006, 2007-2009, and 2010-2012.

The result of GWR model to detect demographic predictor of mumps incidence is summarized in Table 3. The “un-timely vaccination coverage” was a significant predictor of mumps incidence during 2010-2012 period (Coeff. 0.656910, P = 0.00201). The “proportion of children population” was a predictor during high endemic period of 2013-2015 (Coeff. 2.6784700, P = 0.00065).

Figure 6-3. Cluster map of mumps incidence during the three periods in the Republic of Korea: low (2001-2003 & 2004-2006), intermediate (2007-2009 & 2010-2012), and high endemicity (2013-2015)



* Hot spots, marked with red color, are the regions where prevalence of self and neighboring regions were all high; cold spots, marked with blue color, are the regions where prevalence of self and neighboring regions were all low

6-4. Discussion

In this study, we have demonstrated that there were clusters in mumps incidence across the different geographical regions in Republic of Korea, which may have been affected by the untimely vaccination and the regional proportion of childhood population. Our spatial scan statistic identified that during the intermediate and high endemic period, the regions with lower degree of timely MMR vaccination and higher proportion of childhood population was significantly susceptible to mumps incidence.

The adequate level of herd protection is attained by the MMR vaccination coverage which can result in outbreak in small clusters without widespread transmission of the mumps. As the MMR vaccination coverage becomes close to the level for herd protection in Republic of Korea by 98.3% in 2012, small changes may become important (Choe, Yang et al., 2013). Timeliness of MMR vaccination is of great significance in such circumstances. In a survey conducted in United States in 2000, only 73.2% of children have received at least 1 dose of MMR at recommended age (Luman, McCauley et al., 2002). Extending the survey up to 2002, there were geographical differences in timeliness of MMR vaccination across the country (Luman, Barker, McCauley, 2005). In 2005 mumps outbreak in U.S., some of severely affected states were with lower timely MMR vaccination coverage rate compared to national average of 74.1% (S.E., 0.3): Illinois (73.4%), Iowa (69.3%), Kansas (73.7%), Minnesota (73.5%), Missouri (77.0%), Nebraska

(70.7%), South Dakota (66.4%), and Wisconsin (70.1%) (Luman, Barker et al., 2005). A survey that assessed 753 Korean children in 2007 showed that parental unawareness of necessity for vaccination and its schedule was amongst the most important factor for non-timely administration of MMR vaccine (Jeong, Park, et al., 2011). Although there are other possibilities for the recent increase of mumps with geographic clusters, improving heterogeneity in the timely receipt of MMR vaccine may induce a better herd protection in the community which will then affect the mumps incidence at the national level as well.

As the age structures within the community vary, the districts with high childhood population showed vulnerability to mumps outbreak during high endemic period in Republic of Korea. The population age structure and composition were known to affect the disease transmission and vaccine impact in various levels. The changes to a population's demographic structure may affect the spread of disease through change in the patterns of household and the community contacts (Omran, 1971). During the pandemic influenza A/H1N1 outbreak in 2009, a Canadian modelling study suggested the difference in age distribution of the population and pre-existing immunity level will affect the disproportionate transmission of the disease (Geard, Glass et al., 2015). As many reports suggest shift in age distribution of mumps in countries with high MMR vaccination coverage rate, the regional population age structure may pose vulnerability to mumps outbreak over time (Takla, Wichmann et al., 2013).

We also found out that Gwangju-Jeolla area, where the cluster analysis showed LL during low and intermediate endemicity during 2004-2012, has dramatically changed to HH and LH across the region. Previously, it has been suggested that resurgence in pertussis incidence may be due to less chance of natural immune boosting (Lavine, King et al., 2011). This has not been demonstrated in case of mumps, however from our data, it is plausible that the diminished outbreaks for 10 years may have led to accumulation of vulnerable susceptible in southwestern area, and then turned into the "hot spot" during the high endemic period in 2013-2015. Although our analysis has not fully elucidated the role of population immunity on the geographic difference in mumps incidence, it may suggest that immune waning and susceptibility to mumps may be important determinant of outbreak dynamic.

There may be other factors that influence the current increased incidence of mumps in Korea as well as globally. The increased interest in the potential effect of weather variability and mumps has been documented in the previous studies (Onozuka et al., 2011). One study in Japan has performed a time-series analysis to assess the relationship with weather variability and incidence of mumps. The study calculated that the mumps incidence has increased by 7.5% for every 1℃ increase in temperature and by 1.4% for every 1% increase in humidity. Another study from Czech Republic has demonstrated that mumps was not associated with warmer and drier weather (Hubalek, 2005). We have found that the factors such as societal and population immunity may have influenced the geographic cluster and subsequent outbreak in Korea. As the effect of climate on the difference in mumps incidence is not clearly understood yet, the weather variability should be taken into account for adjusting on the regional mumps epidemiology in the future researches.

There are several limitations to our study. The observed clusters may have been overestimated or underestimated because the data was derived from passively reported surveillance, which cannot exclude the possibility of biased reporting of the cases. Mumps cases can be missed by surveillance, or other viral or bacterial pathogen may present the symptoms that resemble those of mumps. Further, the vaccination factors related to mumps incidence have not been well demonstrated because of unavailability of vaccination coverage data at individual level. Moreover, it was our assumption to assess the population density as a whole, which in turn, may not be translated directly into the social contact rate among the high risk group of students. It is unclear to what extent the relations between pulation density and the contact matrix can be generalized across the different geographical areas. To address this limitation, a prospective population-based survey of epidemiologically relevant social contact patterns in Korean students need to be in place.

Despite the limitations, our data has certain strengths. This is the first attempt to conduct exploratory data analysis on transmission of mumps according to time and space from a country with population of approximately 50 million with relatively strong vaccination system. During the surveillance period, there were no significant changes in mumps surveillance system and vaccination coverage rates.

Moreover, our data shows that there is a clear correlation between the quality of vaccination program and the population structure and the incidence of mumps. For pathogens directly transmitted from person-to-person such as mumps, disease outbreak may cluster in geographic place where the susceptible population is large and dense. Timely and adequate vaccination coverage may interrupt these processes over large geographic areas. In this study, the cluster pattern of mumps was modeled using disease surveillance, timely vaccination coverage, and population structure. In the future study, the best model for mumps outbreak prediction could be identified by combining population and surveillance data as predictor variables based on our study result. The annual report on timely vaccination coverage data by geographic area will support that insufficient population immunity may be associated with mumps incidence and epidemic transmission.

CHAPTER 7. OVERALL DISCUSSION AND CONCLUSION

7-1. Reemergence of mumps in Republic of Korea

The study was to address the temporal trend of incidence of mumps in Korea for the last decade. The study describes the change in mumps incidence in Korea, which was resulted from different vaccine strains used during past 30 years. The description of age-specific and cohort-specific risk of acquiring mumps has identified the need to strengthen its surveillance in adolescents as well as in younger aged children group. The dynamic in population susceptibility of mumps the study described in this report may provide guidance for the future MMR immunization program.

7-2. Trend of measles, mumps, and rubella incidence following the measles-rubella catch-up vaccination in the Republic of Korea, 2001

The second study demonstrates the first result of longitudinal study on the difference in incidence between the three infectious diseases that are combined in a single form of vaccine: measles, mumps, and rubella. The key messages of this study are that the incidence of the three diseases could show differential trend according to the choice of vaccine that was used during catch-up vaccination campaign. The study reports a population study of measles, mumps, and rubella in Korea, which was resulted from MR catch-up vaccination campaign and MMR2 keep-up program used during past 15 years. The description of age-specific and cohort-specific risk of acquiring mumps has identified the need to strengthen its surveillance in adolescents as well as in younger aged children group. For preschool aged children, a timely second dose MMR vaccination should be emphasized, whereas for adolescents and young adults, unvaccinated individuals or those without certain vaccination history should be considered for the catch-up vaccination. The dynamic in population susceptibility of mumps this study described may provide guidance for the future MMR vaccination program.

7-3. Increasing mumps incidence rates among children and adolescents in the Republic of Korea: Age-period-cohort analysis

The study was to explore the impact of the age, period, and cohort effect on the individual risk of mumps transmission. The study describes a cohort and period-specific risk of acquiring mumps in Korea, and have identified the need to strengthen surveillance in adolescents as well as in younger aged children group. The increase of mumps may have been affected by birth cohort exposed to Rubini strain (cohort-effect); moreover, there are trend in increased risk in the recent years (period-effect). Our finding may implicate that there is a gap of immunity present in Korea, which have led to the resurgence of mumps, affecting younger (2004-2006 cohort) and older (1995-1997 cohort) population recently. The cohorts of 1998-2000 with increasing incidence over age years were the group that have been potentially exposed to Rubini strain as their first or second, or even both doses of MMR vaccine. The 2004-2006 cohorts were not exposed to Rubini strain, and the 1995-1997 cohorts may have received the Rubini strain as their second dose MMR. These groups also have showed increase in incidence over age years, suggesting potential external effect from increased transmissibility in the community. The dynamic in population susceptibility of mumps we described in this report may provide guidance for the future MMR immunization program and the mumps elimination strategies.

7-4. Spatial distribution of mumps in the Republic of Korea, 2001-2015: identifying clusters and population at risk

In this study, the intend to demonstrate the transmission pattern of mumps by space in Republic of Korea during the past 15 years that might inform public health planning and future vaccination strategies. The study indicates that the rate of mumps incidence according to geographic regions vary by population proportion and neighboring regions, and timeliness of MMR vaccination, suggesting the importance of community-level surveillance and strengthening of vaccination program. Further researches are needed to determine if population structure and non-timely coverage rate are associated with the temporal and spatial variation in other vaccine-preventable disease epidemiology.

7-5. Implications for mumps vaccination policy and future researches

Nowadays in Korea, mumps is clearly not a disease of only the young children, and recently more than half of the affected individuals are aged greater than 14 years old. In addition, our data shows that males were generally more affected than females, which is not dissimilar to epidemiology of mumps in other countries. Based on the recent immunization coverage rate of Korea with 92.4-97.5%, we assume that most of the cases are immunized with one or more dose of MMR vaccine, hence milder and insignificant symptoms are expected in the future. This stresses the importance of follow-up seroepidemiological study when estimating the actual burden of mumps in Korea. However, the effects of second-dose MMR vaccination to compensate primary vaccine failures should be carefully considered when validating the laboratory measures to diagnose a case of mumps. A strong vaccination program that emphasized two-dose MMR vaccination launched in Finland over last 30 years has led to the elimination of mumps from the country since 1997. Therefore, in situation of Korea, further strengthening and continuing of two-dose MMR vaccination is of importance.

The potential recipients of Rubini strains, most notably 1998-2000 cohorts have entered their late teenage or early twenties of their life course. The mandatory military service which result around 650,000 personnel in the year 2010, may pose threat to the transmission and subsequent outbreak of mumps in Korean army. The seroprevalence of mumps among Korean soldiers was 81.1% in 2010 (Park et al., 2012). Since 2012, the Korean military recruit camp provides additional dose of MMR vaccine to those with no evidence of second dose of vaccine. This policy was set as a temporary single-dose MMR program without antibody testing for new recruits until recruits born after 1995 who had received 2-dose MMR vaccines join the military (Heo et al. 2015). However, our data suggest that the cohort who have received the Rubini vaccine, irrespective of their number of vaccines received, are susceptible to mumps transmission and outbreak. Therefore, to suggest a more effective and evidence-driven vaccination strategy, a prospective cross-sectional seroprevalence study among general population, and more specifically, military recruits is necessary.

In 2017, the Ministry of Education has issued a vaccination guideline for students entering dormitories to have confirmed vaccination history for 2-doses of MMR vaccines. The direction of such policy is agreeable based on the result of study that mumps is clearly a disease among students aged upper-teens who may reside in dormitories in high schools and colleges. Given the possibility of decline of population immunity for the cohort that have received either doses of Rubini strains, an additional study to demonstrate the population immunity among student-aged group will be needed to reinforce the need of a third-dose MMR vaccination that prevents cluster outbreak of mumps in the schools.

In conclusion, there is still a considerable incidence of mumps in Korea, potentially affected by the vaccination program, vaccine strain used, and the shift in age of the affected population. Based on the study result, additional effort to monitor the population immune status should be warranted for consideration of a third dose MMR vaccination on defined susceptible population such as military recruits, students, and dormitory residents. If any pocket of immunity is found during serosurveillance study, the respective age group should be considered for the catch-up vaccination with MMR vaccine. Through continuous monitoring and evaluation of vaccination policies against mumps using national surveillance system, we could develop more effective approaches for more effective control and prevention of mumps transmission in the Republic of Korea.

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국문 초록

연구 제목: 국가필수예방접종 프로그램이 유행성 이하선염 발생에 미친 영향: 국가 감염병 감시체계 자료 연구

연구 배경:

유행성 이하선염은 전 세계적으로 발생하는 전염력이 높은 급성 호흡기 바이러스 질환으로써 임상적으로 비화농성 이하선염으로 나타나며 일부에서 감염 시 무균성 뇌수막염, 고환염, 췌장염 등의 합병증이 동반될 수 있다. 전파력은 비교적 강한 편으로 인플루엔자나 풍진보다 높고, 홍역이나 수두보다는 약한 정도이다. 감염된 비말 핵이나 타액과의 직접 접촉으로 전파되며 주로 늦겨울에서 봄에 유행을 한다.

백신은 유행성 이하선염을 예방하고 관리하기 위한 가장 효과적인 공중보건학적 중재수단이다. 1945 년에 유행성 이하선염 바이러스가 처음 분리된 수년 후부터 백신이 개발되어 사용되어 왔으며 1980 년부터는 주로 홍역과 풍진 백신이 추가된 MMR(Measles, Mumps, Rubella) 혼합백신 형태로 사용되고 있다. 유행성 이하선염 백신은 야생주 바이러스의 병원성을 약화시킨 약독화 백신주 바이러스 형태로 생산되며 공정 과정과 약독화 백신주 간의 특성에 따른 백신의 효능과 안전성의 다양한 차이가 나타난다. 과거부터 전세계적으로 크게 3 가지의 주요 유행성

이하선염 백신주들이 사용되었다. 그 중 Urabe 주 및 Jeryl-Lynn 주 백신은 비교적 양호한 수준의 효능 및 효과를 보여주었다. 또 다른 백신주는 Rubini 주 백신이다. 1986 년 스위스에서 개발되어 유럽을 중심으로 사용되었고 우리나라에는 1995 년 허가되어 1996 년부터 유통이 시작되었고 2000 년부터 2001 년까지 특히 보건소를 중심으로 널리 사용되었다. 하지만 1990 년대 국외에서 Rubini 주 백신의 효과가 -55.3~12.4%로 낮다는 연구들이 보고되면서 세계보건기구에서는 2001 년 11 월 Rubini 주 백신을 국가 예방접종 프로그램에서 제외하도록 권고하였으며, 우리나라도 2002 년 5 월부터 Rubini 주 백신의 사용을 중단하였다.

우리나라는 2000~2001 년 52,897 명의 홍역 환자가 발생하는 대유행에 대응하여 7~15 세 소아 청소년 약 580 만명에게 유행성 이하선염 백신주가 제외된 홍역-풍진(Measles, Rubella; MR) 백신 일제 예방접종 사업을 시행하였다. 이후 국가홍역퇴치 5 개년 사업을 수립, 추진하였고 생후 12-15 개월 MMR 1 차접종 이후 생후 4-6 세 MMR 2 차 접종 여부를 초등학교 입학 시 확인하도록 하는 MRM 2 차 접종 확인 사업을 수행하면서 2005 년 세계보건기구의 홍역퇴치 기준인 인구 백만 명 당 홍역 확진 환자 1 명 이하에 부합하기까지 홍역 발생이 감소하였다. 반면 같은 기간, 유행성 이하선염의 보고 건수는 2001 년 1,668 명에서 2005 년

1,863 으로 감소하지 않았으며 이후 지속적으로 증가하여 2010 년 6,094 명, 그리고 2014 년 25,286 명으로 크게 증가하였다.

유행성 이하선염은 기초재생산수(basic reproduction number)가 7-10 수준의 대단히 전파력이 높은 감염병 중 하나며 인구의 예방접종률이 90% 이상 유지를 하여도 밀접 접촉이 잦은 학교 및 군대에서의 국지적 유행이 우려되는 감염병이다. 불충분한 백신의 효과 및 역학적 특성으로 인해 우리나라와 같이 높은 수준의 MMR 백신 접종률을 유지하는 국가에서도 유행성 이하선염의 유행이 지속적으로 보고되고 있다. 이와 같이 우리나라에서도 유행성 이하선염에 대한 중요성이 점차 증가하고 있으나 향후 유행성 이하선염의 발생에 백신이 미치는 영향을 예측하는 자료는 제한적이며 또한 발생 추세와 증가의 원인, 그리고 백신 전략에 대한 연구 또한 부족하다. 따라서 본 연구에서는 최근까지 우리나라에 유행성 이하선염이 증가하고 있는 역학적 특성을 파악하고 그 원인으로 영향을 미칠 수 있는 연령, 코호트, 기간 효과를 평가하며 지역적 요인에 따른 공간 군집을 탐색하고자 한다. 이를 통해 우리나라 유행성 이하선염 예방 및 관리를 위한 가장 효과적인 예방접종 정책 대안을 산출한다.

연구 방법

본 연구는 보건복지부 질병관리본부의 감염병 감시자료에서 2001 – 2015 국내 유행성 이하선염 보고 자료를 추출하여 이들 중 역학적 정보를 분석한다. 각 케이스를 연령과 지역으로 구분한 후 연령-기간-코호트 효과 분석한다. 그리고 유행성 이하선염의 전파를 근거로 한 질병 지도화 및 군집 탐색을 통해 유행성 이하선염의 예방접종 정책 대안을 마련을 위한 근거를 추가한다.

연구 결과

(1) 2001년부터 2015년까지 유행성 이하선염은 지속적으로 유의한 증가 추세를 보였다. 연령별 발생률은 5~9세에서 13~17세로 높은 연령층으로 이동하는 추세를 보였다.

(2) 2001년 전국적으로 시행되었던 홍역-풍진 백신(MR vaccine)의 일제예방접종 이후 홍역 및 풍진 발생은 연간 10~200례 미만의 낮은 수준으로 유지되었으나 유행성 이하선염의 경우 연간 20,000례 이상 보고되었다. 일제 예방접종 대상 코호트 및 초기의 예방접종 확인사업 대상 코호트에서의 유행성 이하선염의 발생이 유의하게 높았다.

(3) 연령과 코호트 요인을 보정하고 각 년도의 효과를 고려할 경

우 1998-2000년 출생 코호트에서 유의하게 10대 후반기에 유행성 이하선염 발생이 높았으며 2012-2014년 기간 효과가 관찰되었다.

(4) 유행성 이하선염의 발생이 높았던 시기, 전국적으로 유의한 군집현상이 관찰되었으며 이는 MMR 백신의 적기접종률과 기초단체 별 소아 인구 분율과 연관이 있는 것으로 나타났다.

결론 및 공중보건학적 대응방안 제안

2000 년대 이후 유행성 이하선염의 연도별 발생이 지속적으로 증가하였고 유의한 기간 효과 및 코호트 효과가 관찰되었다. 유행성 이하선염 발생 증가의 원인으로서는 (1) 2001 년 이후 MMR 2 차접종 확인 사업 초기의 추가적인 예방이 제공되지 않은 불충분한 유행성 이하선염의 관리; (2) 1990 년대 말 불충분한 효능을 갖는 Rubini 주 백신이 사용되었던 시기의 접종 대상이었던 출생 코호트의 누적; 그리고 (3) 낮은 지역 적기접종률 및 높은 소아인구 분율을 갖는 지역에서의 군집 형성에 의한 것으로 분석되었다.

현재 1995 년생이 군대에 입대할 때까지 MMR 을 추가 접종하는 프로그램을 운영하고 있으나 본 연구결과를 근거로 Rubini 주 백신에 노출되었을 수 있는 2000 년생들이 입대할 때까지 예방접종 사업이

유지되어야 하는 것으로 분석되었다. 기숙사 입사생, 또는 유행성 이하선염이 유행하는 학교의 학생들을 대상으로 하는 추가 예방접종을 제안하며 후속 연구로 단면적 혈청역학조사를 연도별 또는 격년으로 시행하는 면역도의 시계열적 평가가 필요하다. 마지막으로 유행이 생길 수 있는 지역을 예측할 수 있는지에 대해서도 본 연구에서 구축한 모형을 통해 연도별 지역별 적기접종률 데이터를 입력하여 해당 연도의 유행 위험을 예측할 수 있을 것이다.

본 연구는 국가 감염병 감시체계에 기반한 예방접종 대상 감염병 관리 평가를 위한 기초연구로서 유행성 이하선염 백신 정책 및 백신주와 관련한 감염병 역학에 대한 근거자료를 제공하며 향후 예방접종 대상 감염병 관리 정책을 위한 기초 자료로써 사용될 수 있을 것이다.

주요어: 유행성 이하선염, 볼거리, 백신, MMR, 연령-기간-코호트 효과

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