# A NOVEL APPROACH FOR SEASONAL INFLUENZA SURVEILLANCE IN SOUTH KOREA: DISEASE BURDEN ESTIMATION AND TEMPORAL TRENDS MONITORING.

by
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## *Abstract*

Seasonal influenza is one of the most common infectious diseases with great disease burden. Public health professionals have given many afford to estimate the accurate the disease burden and monitor temporal trends of seasonal influenza. However current influenza surveillance system in South Korea could not provide full functions on disease burden estimation and temporal trends monitoring. There is a need for supporting structure to make robust surveillance.

In aim 1, we aimed to estimate the burden of influenza and its related disease based on billing information from the national health insurance service – national sample cohort. We found that rural area of South Korea has more disease burden compared to the urban area and age under 5 had the highest burden of influenza infection.

In aim 2, we assess the timeliness of influenza epidemiological information from billing system compared to current sentinel surveillance as temporal trends monitoring. We did not observe any delays of influenza out-patients activity compared to current sentinel surveillance in peak time and cross-correlation value comparison. We could not fully apply aberration time comparison since aberration signals highly depended on model sensitivity and specificity and model selection process itself.

In aim 3, we were able to perform influenza temporal trends association analysis by subpopulations. The Seoul Capital Area showed the early signs of influenza activity in peak and cross-correlation time comparison. Age 6 to 15 showed the earlier sign of influenza activity while age over 65 showed the later sing of influenza activity.

We were able to estimate the burden of influenza with different case definitions and provided stratified disease burden as WHO guided. We did not see any delays of influenza out-patient activity

from billing system compared to the current sentinel surveillance. Moreover, we observed potential temporal associations of influenza activity by different subpopulations.

A surveillance system based on solely billing information cannot be perfect by itself. Instead, combinations of surveillance structures with a different source for disease information can be called a robust surveillance system. The surveillance system should have different arrangements with the various data source to make concordance of observation.

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# *Chapter 1 : Introduction*

## *Background of Influenza*

### *The names of influenza*

The origin of term influenza is from Italian *'influentia'* meaning the influence of stars reflects the seasonal trends of disease in a temperate region[1]. As it is described from its name, influenza usually shows its seasonal patterns in a temperate region. Recent studies find out that influenza also shows different patterns based on location, climate, and altitude[2–4]. Nowadays, it is generally considered that it shows single or double peaks annual patterns in a temperate region and irregular patterns in a tropical climate. In a single peak pattern, it usually started its highest activity at the end of the winter and resolved its activity at the beginning of the spring. In the double-peak pattern, it usually showed an earlier peak in the begging of winter, slightly resolved then, showed another peak at the end of the winter. Those double peak patterns can be described due to mutation of unstable influenza strains in the middle of the season.

Influenza viruses, which are causing influenza infection, are classified in four different families: influenza virus A, B, C, and D[5–8]. Influenza A and B are normally considered as a source of the symptomatic human infections. Influenza is named by their virus type, geographical origin, strain number, year of isolation and virus subtypes (mostly for Influenza A only)[5]. Influenza A is one of the common types of influenza circulating as a human pathogen, caused human influenza pandemics in history. One of the most famous influenza A subtype is H1N1 which caused 1919 Spanish flu and also 2009 Swine Flu pandemic[7,9]. H3N2 is also one of the common subtypes which is circulating during the high activity season. Influenza B is not classified as virologic serotypes like influenza A but addressed in two different lineages, Yamagata and Victoria. Since Influenza A and B are the most dominant strains circulating high activity season, those influenza types and subtypes have been included the influenza vaccine to reduce the influenza burden[10]. However, not all influenza types and subtypes are susceptible to human. Most of the known influenza subtypes are only infective to animals; humans are only susceptible to a few subtypes. Sometimes those cross-species – zoonotic influenza infections between animals and human can be a point for mutation of influenza. The mutated influenza strains from cross-species infection could be a potential cause of the pandemic outbreak; public health professionals also need to focus on influenza activity in animals also.

Every year dominant circulating influenzas are changed. The World Health Organization announced the most suspected circulating influenza types each year before the influenza season starts at north and south hemisphere[11]. Traditionally, the trivalent vaccine has H1N1, H3N2, and one of Victoria or Yamagata lineages based on prediction, and the quadrivalent vaccine has H1N1, H3N2 and both of Yamagata and Vitoria. For season 2018-2019, A/Michigan/45/2015 (H1N1)pdm09-like virus, A/Singapore/INFIMH-16-0019/2016 A(H3N2)-like virus, and B/Colorado/06/2017-like (Victoria lineage) virus (updated) were in trivalent vaccines, and B/Phuket/3073/2013-like (Yamagata lineage) were added on top of trivalent vaccines as quadrivalent[12]. For season 2019-2020, Influenza A/Michigan/45/2015 (H1N1)pdm09-like virus, Influenza A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus, and Influenza B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage) are projected for the trivalent vaccines, and Influenza B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage) will be added for the quadrivalent vaccine[13].

## *Epidemiology of Influenza*

One-third of influenza infections are asymptomatic, but common clinical features of influenza are described as acute onset of fever, rhinorrhea, cough and sore throat[14]. There are also other signs or symptoms of influenza such as nasal congestion, sneezing, hoarseness, muscle pains or fatigue[15]. The duration of influenza symptom usually is 3-5 days but sometimes lasted up to 9 days. Total symptoms of influenza typically started on day 1 after inoculation and showed the highest activity at day 3. The peak of body symptoms was observed earlier, at day 2, than total symptoms, and it regressed earlier than other topical symptoms such as respiratory or nasal symptoms[16].

## *Disease burden*

Disease burden of influenza is extensive. Until 2017, the World Health Organization stated the total number of annual death due to influenza was 250,000–500,000[17], and a recent study said the number of death due to influenza ranged from 148,000 to 249,000[18]. In 2018, a new study with an advanced method with current data re-estimated the disease burden and concluded that previous estimation was outdated and underestimated the disease burden[19]. In a new estimation, the number of deaths due to influenza is 300,000-650,000, and the highest mortality was observed in Sub-Saharan African and East Asia regions. Age over 75 showed 10 times higher estimated mortality compared to the general population, and approximately 17% of deaths were observed at age under 5. The influenza 2017-2018 season was predominated by influenza B/Yamagata lineage, showed almost same peak and the onset of its season compared the last year. But influenza prolonged longer compared to the last year in Europe and North America[20,21].

## *Disease burden in South Korea*

Excess mortality due to influenza in South Korea has estimated 2,900 deaths per year, and the burden is highly concentrated in age over 65[22]. And disease burden is varied by time and dominant strains. (H3N2 subtype is highly lethal to older age group). The annual cumulative laboratory-confirmed influenza out-patient cases were 242.8 cases per 100,000 adults, and the laboratory-confirmed influenza admitted-cases were 57.9 cases per 100,000 adults in the 2013-2014 season[23]. For the socioeconomic burden, total medical cost due to influenza out-patient activity was approximately 4.1 million USD in season 2007-2009, and 214.7 USD million in pandemic season, season 2009-2010. The overall socioeconomic cost due to influenza is increasing over time from 42 million USD to 125 million USD[24].

However, there has been a debate on estimating the disease burden of influenza due to difficulties in estimating complications and secondary infections[25]. Influenza can escalate other chronic conditions such as COPD (Chronic-obstruction Pulmonary Disease), asthma, and congestive heart failure. And it is also known as a risk factor for cerebrovascular accident, myocardial infarction, and fetal loss during pregnancy. Moreover, influenza also increased the likelihood of coinfection such as pneumonia and acute lower respiratory infection which also can be occurred without influenza infection.

### *Risk Factor of Influenza infections*

Risk factors for influenza can be used for the vaccination strategy[26–30]. In high-income countries, children age under 6 and older adults are generally considered as a high-risk group based on age. Also, individuals with chronic medical conditions, respiratory disease, such as asthma or chronic obstruction pulmonary disease, cardiovascular disease (coronary artery disease), endocrine disease (diabetes), hepatic disease (liver cirrhosis), renal disease (chronic renal failure) and neurological/neuromuscular disease (Parkinson disease), are considered high risk groups in influenza infection. Lastly, morbid obesity and physical handicaps which reduced respiration functions and individuals with immunosuppressed status due to hematological conditions or HIV infections are also considered target individuals for influenza vaccination.

However, those risk factors are not universal risk factors. A recent study found that those risk factors may act differently depends on the end outcome (common influenza infection, severe influenza infection/influenza mortality) and location (high-income countries, or low- and middle- income countries)[31]. For example, age under 5 has a lower risk compared to the older children (age 6-19) having a severe outcome, intensive care and/or death, in high-income counties. But those young children in low- and middle-income countries more like to have a severe outcome compared to the older children. Pregnant women or people lived with HIV/AIDS also have increased the risk of severe outcome in low-and middle-income countries while the individuals in high-income countries do not. Therefore, it is imperative to identify the population with a high burden of influenza or high risk by different case definitions in different countries.

## *Public Health Surveillance*

### *Definition of surveillance*

Based on definitions of surveillance, there are three significant points in surveillance; a) continuous and systematic collection of data, b) analysis and interpretation of disease with results dissemination, and c) assessment of the distribution of results with actions implementation. The World Health Organization said, "public health surveillance is the continuous, systematic collection, analysis, and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice[32]." The dictionary of epidemiology by Porta also has the same meaning of surveillance in a different language. "Systematic and continuous collection, analysis, and interpretation of data, closely integrated with the timely and coherent dissemination of the results and assessment to those who have the right to know so that action can be taken[33]." However, those three key points of public health surveillance have not fully implemented in national and global surveillance; there is a great need of revising the guidelines and promoting the importance of collections, dissemination, and implementation in public health surveillance[34].

### *Guidelines for surveillance and disease burden estimation of influenza*

After the recent event of global pandemic influenza and discussions of revisions of the guidelines, the World Health Organization released two publications for influenza surveillance and disease burden estimation. Those papers emphases the importance of influenza surveillance and disease burden estimation and presented out practical points in actual implementations[35,36]. The key features are described as the use of age stratification, the use of sentinel validations with representativeness, case definitions for influenza-like-illness and severe acute respiratory illness, defining denominator (in disease burden estimation), and developing seasonal/alert thresholds (in surveillance).

## *Review of Influenza Surveillance System in South Korea*

### *History of influenza surveillance system*

The history of influenza surveillance system in South Korea started in 1997[37]. Even though there was an international influenza network by the World Health Organization in South Korea, there was no stable national influenza surveillance system until 1997. The influenza surveillance was established in 1997 with 71 doctors in 16 different geographical subdivisions. But the actual participation to influenza surveillance was not adequate. Only 70% of the participants reported weekly influenza-like-illness patient at least once, and average weekly report participation was between 30% to 50%. On the other hands, Korea also established virology surveillance to identify the types and subtypes of influenza to calculate the percentage of positive isolations from the specimens.

In 2000, Korean Influenza Surveillance Scheme (KISS) was launched as a revised influenza surveillance network[38]. It had 239 government clinics (described as public health clinics) and 383 private clinics for influenza-like-illness sentinel surveillance and 163 government and 108 private clinics for specimen sites for laboratory surveillance. In this revision, they designed to match the number of participated clinics with population distribution. Even though they aimed to cover 100,000 individuals per one private clinic, it ended with 123,000 individuals. However, the proportion of influenza-like-illness did not match in government and private clinics, and sometimes government clinics reported 0 cases of influenza-like-illness. Even at the time of the pandemic influenza season at the year 2009 – 2010, sentinel influenza surveillance yielded almost the same epidemiological curve compared to the previous season[39]. Then there was another need to a reformation of the influenza surveillance system.

## *Reformation of influenza surveillance system* [39–41].

After historic pandemic influenza 2009, there was another discussion on reformation of the influenza surveillance from the government and academia. As it was noted above, sentinel surveillance did not catch the high pandemic activity in influenza-like-illness and governments clinic and it showed 0 cases occasionally. In the year 2013, there was a second revision of influenza surveillance. Instead of more than 800 governments and private clinics, they selected only 200 clinics, 70 internal medicine, 30 family medicine, and 100 pediatrics, based on the recommendation from the regional doctor's association[42]. The revised surveillance provides four different regional activities based on sentinel sites (Seoul-Gangwon, Chungcheong, Jeolla and Kyungsang), and also provides influenza activity by age group stratification (age 0 to 6, 7-18, 19-49, 50-64, and over 65).

## *Limitations of current surveillance system*

Even though there were two significant revisions of influenza surveillance in South Korea, there are few more aspects that need to be discussed to provide more detailed information on the influenza activity[43]. First, there is a lack of the population representativeness in the sentinel sites. Current 200 sentinel sites are based on recommendation from regional doctors' association (convenient selection), they did not consider any representativeness in the selection process. Moreover, there are 226 minor geographical and political subdivisions in Korea, which is equivalent of county level in the US, but current surveillance system has only 200 sentinels, which means some subdivisions did not have sentinels in their location. Second, there is a lack of geographical stratification. Even though the current sentinel surveillance system provides 4 different geographical regions, those are more like cultural / regional classification, not policy implementable stratification. One of the main points of the surveillance is providing public health interventions based on the results. The second largest in Korea, after the national level, is 17 different geographical subdivisions. Therefore, there is a need to provide influenza activity based on those 17 subdivisions. Third, influenza-likeliness may not display disease intensity correctly in a specific age group. Because the population at risk cannot be defined in the sentinel surveillance, proportion (percentage) of influenza-like-illness compared to the total number of out-patient visit normally used as a metric of disease intensity. However, those proportions may underestimate in the older age group. They do have more medical visits compare to other age groups due to their chronic medical conditions, using a total number of medical visits increase the number of denominators in a proportion calculation which may result decrease the proportion of influenza-like-illness in that age group. Older age is identified as a risk group for influenza infection, more precise monitoring on influenza activity with disease intensity is required. Lastly, there is no information on severe cases of influenza. In a recent guideline from the WHO[35,36], it stated that countries need to focus on not only influenza out-patients (influenza-like-illness), but also severe influenza cases (severe acute respiratory illness). The only available case definition in influenza surveillance in South Korea is influenza-like-illness in outpatient; no other case definitions with severe cases are not available.

## *Study proposal*

We propose to develop an innovative seasonal influenza surveillance system based on disease diagnosis codes in the billing information from National Health Insurance Service-National Sample Cohort (NHIS-NSC). We aim to understand the population distribution of the burden of seasonal influenza in South Korea, validate the timeliness of new approach compared to the current system, and identify the temporal association of influenza activity. The different disease diagnosed codes in the billing information will be able to estimate various range of seasonal influenza burden from influenza out-patients visits to admitted other acute lower respiratory infections. Timeliness validation approach by three different timeliness comparison will ensure the use of a new approach to temporal trends monitoring. Lastly, temporal associations by different geographical subdivisions and age-groups will provide early signals of the beginning of seasonal activity of influenza in South Korea.

### *Specific aim 1*

To estimate the case burden of seasonal influenza and acute respiratory infections in South Korea by applying different case definitions in the National Health Insurance Service. We will use influenza and its related disease diagnosed codes in NHIS-NSC to estimate the burden of seasonal influenza by different geographical subdivisions and age groups.

*Hypotheses: There will be a no difference in the incidence of seasonal influenza by age, income level and geographical location in South Korea year 2007 to 2013.*

### *Specific aim 2*

To assess the timeliness of the proposed approach compared to the current sentinel system in temporal trends monitoring by timeliness validation methods. We will apply peak time comparison, aberration detection time comparisons and maximum cross-correlation values to quantify the time difference. Hence, we can examine the timeliness of new approach and display the potential possibility of use of NHIS-NSC in temporal trends monitoring.

*Hypothesis: There will be no time difference between proposed approach end current sentinel in South Korea year 2010 to 2013.*

### *Specific aim 3*

To evaluate the temporal association of seasonal influenza activity by different geographical levels and age groups in South Korea. We estimate the peak time, aberration detection time and maximum cross-correlation values by different geographical subdivisions and age-groups. Then compare the time difference between subpopulations and the national activity.

*Hypothesis: There will be no time difference of seasonal influenza activity in peak time, aberration time and maximum cross-correlation value comparisons in South Korea year 2010 to 2013.*

*Conceptual framework*

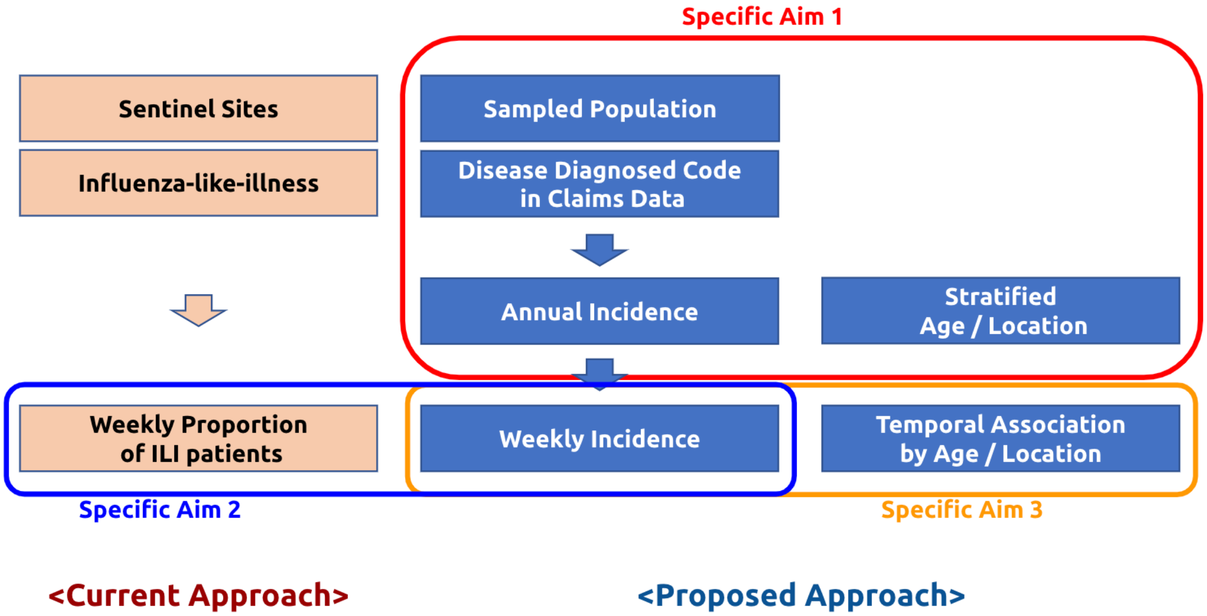


**Figure 1-1. The Conceptual Framework of current influenza sentinel surveillance and proposed surveillance**

Our conceptual framework displays the overall flow of the aims of the proposal. We aim to 1). Estimate the burden of influenza and influenza-like-illness related diseases in Korea using the National Health Insurance Service (National Sample Cohort) by applying different combinations of disease classification codes; 2) Assess the timeliness of new approach to current source by comparing peak comparison, aberration detection comparison, and correlation analysis; and 3). Identify the temporal associations of seasonal influenza activity by different age-groups and geographical subdivisions through timeliness comparison methods

*Organization of the Dissertation*

This dissertation is organized into five chapters: Chapter 1 provides background of influenza and surveillance and limitations of the current influenza surveillance in South Korea; Chapter 2 covers the estimates of influenza case burden using different case definitions by time, geographical subdivision, and age group; Chapter 3 brings the timeliness of new approach compared to the current sentinel system in a view of temporal trends monitoring; Chapter 4 explores the temporal association between different geographical subdivisions and age groups; and Chapter 5 offers executive summaries of each findings, a discussion of the implications of findings into public health practice, and future directions of influenza surveillance from findings.

## *Dataset Description: National Health Insurance Service National Sample Cohort.*

### *The origin of the National Health Insurance Service–National Sample Cohort (NHIS-NSC)*

National Health Insurance Services in South Korea developed a population-based cohort, the National Health Insurance Service–National Sample Cohort (NHIS-NSC) [44,45]. The primary purpose of establishing the cohort was to provide representative information about citizen's use of health insurance, medical expenditures and medical examinations for public health research and health policy development.

South Korea provides universal, national wide, electric, mandatory health insurance since 2000. The results have been the development of a massive information about medical utilization with great interest and availability for researchers. NHIS first provided a population database called 'National Health Information Database (NHID)' containing individual information, demographics and medical treatment data, and eligible individual's insurance status. Due to its large size and lack of confidentiality regarding individual information, NHIS decided to provide a national representative sample database with considerable volume size with a de-identification.

Total 1,025,340 individuals were randomly selected from 2.2% of the total eligible Korean population in 2002. A systematic stratified random sampling process was performed at 1476 strata with age group, sex, eligibility status and income level using proportional allocation by individual's total annual medical expenditures as a target variable. Till 2013, NHIS followed up the original sample cohort with censoring and adding cohort. Individuals who are disqualifying health insurance eligible were eliminated from sample cohort and newborn babies were added annually at 84 different strata by their sex and guardian's income level.

### *Available information from the National Health Insurance Service–National Sample Cohort*

The cohort has four different types of databases. The first database is about individuals' insurance eligibility; the second database is about medical treatment records; the third database is about care provider institution information and the fourth database is about general medical/health examination. In this proposal, we mainly focus on one of the sub-databases of medical treatment database: details of diseases and prescriptions for surveillance method and insurance eligibility database for epidemiological risk profiles. The medical treatment database has four sub-databases; electric medical treatment bills, bill details, details of diseases and details of prescriptions. The insurance eligibility database has 14 different variables; gender, residential area, type of health insurance, a level of income, type and degree of disability register, birth and death, and others.

### *Characteristics of the National Health Insurance Service–National Sample Cohort*

The National Health Insurance Service–National Sample Cohort (NHIS-NSC) has two distinctive characteristics; a representative population-based cohort data and large scale, extensive and stable follow up from national wide health insurance. Representativeness is a major strength due to its application to public health research, health policy development, and public health surveillance. The large sample size with ongoing follow-up process provides enough statistical power to analyze the complex models and overcomes the limitation of cross-sectional data.

However, the literature of cohort profile on NHIS-NSC stated that there are several limitations on NHIS-NSC database. First, information on rare diseases may not be sufficient. NHIS strongly suggest conducting pre-evaluation of a sample size to investigate the rare disease. However seasonal influenza is a common disease, not a rare disease, we expected that we have enough statistical power to conduct surveillance. Second, disease classification code in sub-data: details of diseases may not actual disease status which participant individuals have. The code was created to claim health insurance benefits and services from health care providers. Therefore, we will use different event-based case definitions to estimate seasonal influenza infection.

### *Dataset acquiring process and logistics*

To access NHIS-NSC data, we submitted a research proposal and a confirmation of Institutional Review Board (IRB) review exemption documents from Public Institutional Bioethics Committee (Institutional Review Board) designated by the Ministry of Health and Welfare (South Korea) and Johns Hopkins Bloomberg School of Public Health Academic Affairs to the Review Research Committee of NHIS. By 2015, the NHIS-NSC database contains 156 data files consisting of 13 files for participants' insurance eligibility (1 file), medical treatments (10 files), medical care institutions (1 file) and health examination (1 file). - 12-year cohort between 2002 and 2013. The total size of the cohort file is about 211 gigabytes, and there are 299 million cases of 2002 to 2013 years.

After permission from NHIS, we were only able to access the data from the designated location in South Korea. We downloaded the data of different subunits and separated database, then merged into the final dataset format by including and excluding criteria. After the merging process, the intermediate dataset was reviewed by NHIS, and we could download the de-identified population-level dataset to the personal computer. We only used merged data in the analysis; however, we ensured that any data related to the dissertation is stored on a secure, double password-protected laptop.

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# *Chapter 2 : Burden of seasonal influenza and its associated respiratory disease in South Korea 2006-2013*

## *Abstract*

**Objective** To estimate the burden of seasonal influenza in South Korea and identify the sub-population with the highest burden by age and geographical stratification.

**Participants** Randomly stratified-selected 1,084,673 individuals from the entire South Korean population. Followed from the 36th week of 2006 to 35th week of 2013.

**Methods** We applied 3 different case definitions based on ICD 10 to the national health insurance billing information to estimate the burden of influenza-related medical activity. We also stratified individuals based on age categories and geographical region.

**Results** The annual incidence rate of 'influenza outpatient' were 6.8, 7.7, 8.6, 60.1, 4.9, 9.5, and 3.6 cases per 1000 individuals from 2006 season to 2012 season respectively. The annual incidence rate of admission due to 'pneumonia and influenza' and 'severe acute respiratory illness (SARI)' were 4.3, 4.1, 4.2, 6.1, 6.7, 8.5, and 6.8 and 5.2,5.2, 5.5, 7.6, 8.2, 10.3, and 8.6 cases per 1000 individuals respectively. In the subgroup analysis by age group, age under 5 was the most valuable group for 'influenza outpatients' and in-patient admission due to 'pneumonia and influenza' and 'SARI'. In the subgroup analysis by geographical location, Jeollanamdo, Gyeongsangnamdo, and Gwangju were showed the highest incidence rate of admitted patients due to 'pneumonia and influenza' and 'SARI' for 7 years.

**Conclusions** The burden of seasonal influenza was varied by year and also differ from age and geographical location. The temporal and spatial variation of seasonal influenza suggested that monitoring temporal trends seasonal influenza activity by different subpopulation level is needed. Public health preparedness should be implemented to reduce the burden from seasonal influenza on those sub-populations with the high burden.

## *Introduction*

Influenza is a common but a serious re-emerging acute infectious disease with its social and health impact[1]. Even though most of the influenza infections present as asymptomatic infections or mild symptomatic illness[2,3], there are still many numbers of individuals suffer from severe infections and resulted in deaths every year. Previous research suggests that one-fifth of children and one-twentieth of adults in the world experienced symptomatic influenza every year[4,5]. Hospitalization and death due to seasonal influenza mainly occur among people with high-risk factors such as young age, pregnancy, people living with HIV/AIDS, diabetes or hematologic conditions, liver disease or asthma[6–9].

The burden of seasonal influenza illness is tremendous. A recent study re-estimated that severe illness is about 3 to 5 million cases, and the number of deaths is 250,000 to 500,000 events per year globally[5]. The US Centers for Disease Control and Prevention estimated that in the United States during the 2016-17 season, there were 14.5 million medical visits including over 600 000 hospitalizations due to influenza among 30.9 million disease illness[10]. In South Korea, it is estimated that laboratory-confirmed influenza was 97,819 cases, and among them 23.8%, 23,327 cases were hospitalization and 1.3%, 1,249 cases resulted in death in specific adult population in Korea during the 2013-14 season[11].

The World Health Organization emphasized the importance of disease burden estimates through the surveillance system. They said that there is "a need for reliable disease burden estimates to provide a better understanding of the impact of influenza in vulnerable communities and subpopulation."[12] Moreover, it stated that those reliable estimates will be able to governments make evidence-based decisions by allocating health resources and developing strategies to control the transmission of the disease and to reduce the medical and economical burdens.

By the definition, surveillance systems are systematic collection of disease for estimating disease burden and aberration of its activity to increase rapid response to the outbreak [13]. However, the current influenza surveillance system in South Korea could not meet one of those objectives[14,15]. It is hard to estimate actual number of illness in the country. Even though South Korea have been using a proportion of influenzas-like-illness patients as metrics for influenza surveillance, source population in the surveillance are not fully representative from the entire population and we could not define the population at risk precisely. The current influenza surveillance systems in South Korea use convenient sentinel sites or some selected emergency departments in tertiary hospitals. Those sites are useful for administrative convenience and collecting a data but those sentinels could not provide more detailed information on influenza disease burden by age groups or geographical locations due to lack of sample size for stratification.

Therefore, in this paper, we suggest to use newly developed approach to estimate the burden of seasonal in South Korea. We will apply different case definitions based on diagnostic codes through billing information in the national health insurance system. This approach will enable to estimate the burden of seasonal influenza more precisely and can provide stratified disease burden based on age groups and geographical subdivisions.

## *Methods*

We used National Health Information Database (NHID) of the National Health Insurance Service[16]. South Korea has a national-wide, mandatory, universal, single-payer and electronic health insurance system and it covers more than 99% of the population in South Korea. NHID is providing most of Korea residents' (approximately 50 million individuals) insurance eligibility, medical treatment records, provider institution, general medical/health examination.

In this analysis, we mostly focus on two of a sub-database of 'medical treatment database.' We used a section called 'details of diseases' for disease burden estimation and linked 'insurance eligibility database' to estimate burden for epidemiological risk profile. In 'details of the disease,' we integrated individuals' date of medical visit, characteristics of medical visit (outpatient/inpatient), diagnosis codes (based on the Korean Classification Diseases 5 & 6-KCD 5&6), and clinics' information (internal medicine, emergency department, etc.). In 'insurance eligibility,' we merged individuals age, gender and geographical location (ISO 3166-2, the principal subdivisions - provinces or states) to claim data. Due to a large number of individuals and confidentiality issue, we chose stratified random selection from the entire participated from the National Health Information Database. Which resulted in approximately 2% of participants are from the whole eligible Korean residents.

The study population was total 1,084,673 from January 1st, 2006 to December 31st, 2013. We defined a surveillance season year as from current years' 36th week to following years' 35th week. Therefore, we used the billing information from 36th-week of 2006 to 35th-week of 2013 for the general estimation which is relevant from the 2006 influenza season to 2012 influenza season.

We used the Korean Classification Diseases 5 which is a localized version of the International Classification of Disease 10 to estimate the number of seasonal influenza illness. We defined influenza outpatient activity as diagnosis code J09, J10, and J11 in billing information from an outpatient visit with relevant specialties[17,18]. For severe cases of influenza-related illness, we used different combinations of disease diagnosis code which are already discussed by other researchers. We used definitions from influenza (J09-J11) to pneumonia (J12-J18) in admitted patients to correspond to pneumonia and influenza-related admission[19,20]. We also included other acute lower respiratory infections (J20-J22) to account severe acute respiratory illness (SARI) [21,22]. For the base case definition, we only applied those codes to the primary diagnosis code. For extended case definition, we also used those code to secondary diagnosis in billing information. [Figure 2-1]

We observed repeated billing information with the same diagnosis codes from the same individuals for a certain amount of time. If billing was processed from the same individuals from the same institute with the same diagnosis codes within three weeks, we consider those multiple billings were originated by a single illness and included the only first billing information to estimate case burden and exclude the rest of them from estimation.

Even though most of the influenza illness and its related respiratory illness were diagnosed at the general physician, internal medicine, family medicine, pediatrics, emergency department, and otolaryngology, we observed few cases of pneumonia and influenza admission and SARI from other medical departments. Therefore, we primarily used the billing information from General Practitioner (doctors without specialty in Korea), Internal Medicine, Family Medicine, Pediatrics, Emergency Medicine and Otolaryngology.

South Korea declare Se-jong City, which is relevant ISO 3166-2; principal subdivisions, in 2012, July 1st as an administrative capital city of South Korea. Since 2012, July, many counties integrated to Se-jong City from other provinces by multiple time points and the population of Se-jong increased during this transition time[23]. Due to the complex of geographical region dynamics and uncertain population status, we decide to exclude Se-jong City in state-level stratification analysis in this study.

During the 2009-2010 season, South Korea experienced 2009 Pandemic Influenza which expect to have outnumbered influenza out-patient cases in observation. The Korean Center for Disease Control and Prevention's report said that during the 2009 pandemic season, the number of cases is outnumbered 15,000 cases of October 12th, 2009[24]. Therefore, we exclude the 2009 - 2010 season (36th week of 2009 to 35th week of 2010) among influenza out-patient cases in the analysis.

For more detailed information on the case burden of influenza, we stratified our national level estimation into various subpopulation. In the age categories, we follow the World Health Organization guideline[12]. We decide individuals' age in the middle of the seasonal influenza year, which is the last day of December, and categorized them into five different age groups (from 0-5, 5-15,16-50,50-65, and 65 above). Geographical subdivisions follow the lasted 17 geographical and political divisions which were revised in the year 2012 (but excluded Se-jong city). The population at risk is calculated as in the middle of the seasonal influenza year, (the last day of December). To adjust the demographic difference, we used the direct age-standardized method[25]. As the WHO guided, we used a new standard based on the projected 2000 population age distribution[26].

## *Results*

We reviewed total 1,084,673 individuals' billing information from the 2006-07 season to 2012-13 season which is approximately 1,000,000 individuals every year. The number of individuals at age under five slightly increased during the study period while the number of individuals at the age between 5 to 15 and age between 16-50 decreased. However, the number of individuals at the age between 51-65 and over 65 increased almost 25 percent during the study period (Table 2-1).

The number of influenza outpatient ranged from 3,662 cases to 9,666 cases (except pandemic year), which is equivalent 3.6 to 9.5 cases per 1,000 individuals in crude incidence and 4.7 to 13.8 cases per 1,000 individuals in age-standardized incidence. For the pandemic year, the number of influenza outpatient was 59,975, then 60.1 and 78.0 cases per 1,000 individuals in crude and age-standardized incidence.

The number of pneumonia and influenza in-patients (PNIADM)and severe acute respiratory infection (SARI) were 4,265 to 8,547 and 5,502 to 10,365 cases. Crude incidence ranged from 4.1 to 8.5 cases per 1,000 individuals for PNIADM and 5.2 to 10.3 cases per 1,000 individuals for SARI. Age-standardized incidence was 6.0 to 11.9 cases per 1,000 individuals and 7.7 and 14.6 cases per 1,000 individuals respectively.

During the study time, exclude pandemic year, the lowest incidence of influenza outpatient by geographical subdivision level was 1.9 cases per 1,000 individuals (Seoul at season 2012), and the highest incidence of influenza was 16.4 cases per 1,000 individuals (Chungnam at season 2006) in crude. In age-standardized incidence, the lowest was 2.4 (Jeju at season 2012) cases per 1,000 individuals and the highest was 26.2 cases per 1,000 individuals (Ulsan at season 2011). For PNIADM and SARI incidence by subdivision level, the lowest crude incidence was 2.6 cases (Incheon at season 2008, PNIADM) and 3.1 (Incheon at season 2007, SARI) per 1,000 individuals and the highest crude incidence were 18.4 cases (Joennam season 2012, PNIADM and 25.1 (Joennam at season 2012, SARI) per 1,000 individuals. After age-standardized, the lowest incidence was 3.5 cases (Incheon at season 2008) per 1,000 individuals for PNIADM and 4.5 (Incheon at season 2007) cases per 1,000 individuals for SARI. The highest incidence was 25.1 cases (Joennam at season 2012) per 1,000 individuals for PNIADM and 35.4 cases (Joennam at season 2012) per 1,000 individuals for SARI.

In 3-years average age-adjusted annual incidence by subdivision level, Incheon showed the lowest incidence for influenza out-patients, and Seoul showed the lowest incidence for PNIADM and SARI. While JeonBuk showed the highest incidence for influenza out-patients while JeonNam showed the highest incidence for PNIADM and SARI.

In subgroup analysis, we performed the incidence ratio comparison between base case definitions and extended case definitions. Incidence ratio of influenza outpatients case definitions was ranged from 1.15 to 1.31 in over-all age group comparison. But after age stratification, the interval was increased as the lowest ratio was 1.07 (age over 65 at season 2008), and the highest ratio was 2.00 (Age under 5 at season 2006). For PNIADM, the incidence ratio ranged from 1.29 to 1.40 in over-all age group and ranged from 1.19 (Age under 5 at season 2011) to 1.76 (Age over 65 at season 2006) after age-stratification. For

SARI, the ratio started from 1.32 to 1.47 in over-all age group comparison and varied from 1.22 (Age 5-15 at season 2011) to 1.77 (Age over 65 at season 2006) in age-stratification.

## *Discussion*

In this study, we estimated a practice-oriented disease burden based on diagnosis codes in the billing information from the national health insurance system. We were able to calculate population-based cases and incidence rates at the national level and state-level with age stratification and standardization. We observed the different disease incidence rate by age-group and found the unequal distribution of disease by state-level.

We observed a shift in population distribution. Beginning of the study, we have more individuals among age 5-15 then age over 65, but at the end of the study, we have more individuals among age over 65 than age 5-15. Moreover, the number of individuals in the age group 51-65 have increased by 33% during the study period. All of those observations implied that a simple comparison of the case number and crude incidence might not be valid even though the study period was only 7 years.

For annual incidence of influenza out-patient, we observed two seasons with relatively high incidence compare to the other season. First high peak season was on the worldwide pandemic influenza at the year 2009-2010[27]. The second highest incidence was at season 2011 which is not related to pandemic influenza. This could be the results from a mismatch for influenza B and low vaccine efficacy for influenza A, especially H3N, from the 2011-12 season in South Korea or extremally cold weather in January, which is normally considered highly transmitted time of seasonal influenza[28,29]. Base on this result we concluded that the burden of influenza could be different year by year even without pandemic influence, and the magnitude of disease burden could be tripled compared to the regular season.

There were significant changes in the number of diagnoses especially in influenza out-patient by the point of pandemic especially age under 5 and over 65. Before the pandemic, the highest incidence by age group was age over 65, then age 51 and 65. But after the pandemic, the highest incidence was age under 5, then age 6 and 15. To determine the reason for this pattern changes, we compare the ratio between influenza in-patient and influenza outpatient and the ratio between influenza outpatient and pneumonia and influenza outpatient. The ratio between influenza in-patient and influenza outpatient were increased among age under 5 and age over 65 together after the pandemic. But the ratio influenza outpatient and pneumonia and influenza outpatient were increased at the age under 5 and decreased at the age over 65. Moreover, the incidence of PNIADM and SARI were increased after pandemic while the incidence of influenza outpatient was deceased. This implied that age over 65 over-diagnosed as influenza over pneumonia before the pandemic, but that tendency was diminished after 2009 pandemic. The potential cause of these pattern changes in age under 5 could be due to the rise of awareness of influenza among pediatricians and parents of younger children after pandemic influenza.

We observed the difference of disease burden by sex in severe influenza cases. For pneumonia and influenza in-patient, male normally showed higher incidence compared to the female at the age under 5. But after age 5, females showed higher incidence compared to the male until age 50, then flip the relationship again. For SARI, males showed higher incidence at the age of 15, then it flipped until age 50, and flipped again after age 50. The change of incidence between boys and girls at a certain young age followed observations in previous literature[30–32]. Moreover higher incidence of pneumonia and influenza and severe acute respiratory illness among men over age 50 can be explained by risky behaviors of men such as alcoholism and nicotine[33].

We also observed the unequal distribution of disease burden by geographical subdivision stratification. For 3-year-average age-adjusted annual incidence, Jeonbuk showed the 3 times higher influenza out-patient incidence rate compared to Incheon, the lowest subdivision. For PNIADM and SARI, Gwangju and JeonNam showed the highest incidence among 16 states. People normally consider that the highest population density is a risk factor for respiratory infections transmission, but in this analysis, the highest density areas, Seoul and Gyeonggi, actually showed lower incidence compared to the other areas. This can be explained in 2 different ways. First, a crowding as a risk factor from the literature defined as how many people stayed in one single house, or how many children do you have in your family[34–36]. The effective population density is not an aggregate-level calculated from the number of people divided by a size of the area. In this case, the Capital Seoul Area (Seoul, Gyeonggi, and Incheon) has more single families and smaller size of family compared to the other suburban and rural area where have more extended families with a larger family member. This definition of population density in infectious disease, or house crowding, can explain the reason why the Capital Seoul Area showed a lower incidence compared to other geographical subdivision. The other explanation is early initiation of influenza treatment. Since 2009 pandemic influenza, the Ministry of Health and Welfare and the National Health Insurance increased a coverage on the cost of treatment on influenza, such as prescription of oseltamivir with confirmed rapid diagnosis[1,37]. This policy implementation made the early initiation of influenza treatment possible and this implementation mostly happened in politically and economically centered area, the Capital Seoul Area which resulted reduce the transmission of influenza. New policy implementation in large population centered area also can be one of the reasons why those areas have a lower incidence. Moreover, a recent study also supports that a large population is acting like a modulate rather than a driven factor of influenza intensity[38]. On that paper, Tauranga emphasized that rural area needs to more focus on severe influenza cases than mild symptoms with a rapid transmission[39]. We observed that JeonNam and GyeonNam ranked top incidence subdivision in PNIADM and SARI incidence, which can be explained by Tauranga recent paper.

Extended case definition can be used in disease burden estimation also. We performed a sensitivity analysis of base and extended case definitions for FLUOPD, PNIADM, and SARI. The base and extended case ratio was a quite difference year by year before the pandemic but became stable in temporal trends after the pandemic. However, the ratio was not the same through the age group regardless of the pandemic event. This implied us we might use the extend case definition to estimate disease burden more wide definition but cannot just apply one simple multiplier to get extended case definition. Age distribution and disease intensity need to be considered before applying a single multiplier to calculate extended disease burden estimation.

This study has multiple strengths.  First, this study provided original estimates of the number of influenza out-patients and severe cases directly, not as a proportion of cases. Current influenza surveillance system in South Korea and most of influenza surveillance system in the other countries are based on sentinels where we cannot define the population at risk[40]. That sentinel surveillance setting could not provide the number of cases, the incidence of influenza and its related illness. Using systematically sampled population allowed us to estimate the actual population at risk so that we could provide the actual number and the incidence of influenza as a disease burden. This approach will make public health professionals understand the distribution of disease and intensity of disease more precisely and lead them to establish a more informed public health preparedness program.

Second, this study provided estimates of influenza burden by geographical subdivisions and different age categories. Current influenza systems do not have enough sentinels to provide stratified estimates of influenza and its related illness. However, a million of national sample cohort guides to provide the estimates of influenza and its related illness at the subdivision, where different influenza prevention policy can be implemented, and 5 different age categories as the World Health Organization suggested in its guideline[12]. Based on this information, the Korea government could develop revised influenza prevention and control strategy to reduce the burden of influenza. Some geographical subdivision with higher influenza burden needs more intervention to reduce the transmission or outpatient visits through increased vaccination or early initiation of influenza treatment. Free influenza vaccination campaigns in South Korea in age over 65 and under 5 also complied with this analysis.

Lastly, it shows the potential possibility to use billing information as a supportive system for seasonal influenza surveillance. Until recent days, influenza surveillance systems are based on syndromic surveillance methods such as influenza-like illness at the Emergency Department or sentinel sites, proportion and strains of influenza laboratory diagnosis, or mortality rate due to influenza and pneumonia[40]. However, this approach helps us to use billing information to be another pillar of the influenza surveillance system. With nationwide, universal, electric, and mandatory insurance system, we can use billing information as another disease surveillance source.

Still, there are limitations. First, cases in the study were from practice-oriented cases, not actual people who are infected. The individuals in the study who classified as influenza and its related illness were diagnosed persons by the health care facility. Therefore, we could not estimate the number of individuals who developed mild symptoms which don’t need to come to a medical facility or of individuals who cannot come to the medical facility. There is a chance we still underestimate the number of cases and incidence.

Second, disease diagnosed codes are formed for billing purpose, not surveillance purpose. Even though billing information provided a great number and nourished information of individuals, those are constructed for the billing process. Even though the World Health Organization states that the International Statistical Classification of Diseases and Related Health Problems is designed for "standard diagnostic tool for epidemiology, health management, and clinical purposes.", South Korean government and medical doctors used this tool for the billing process. This may lead to seeing us misdiagnosed or miscoded individuals due to insurance eligibility and its coverage. Therefore, there are chances to over or underestimates the burden from the truth. However, practice-oriented disease burden estimation and costs will remain the same.

Third, there is a need for clear definition of disease burden.  In this paper, we used annual cumulative disease cases per 100,000 individuals as a disease burden. However, traditionally disease burden is defined a prevalence of disease in certain population which hard to be applied short cycle infectious disease. Moreover, cases per 100,000 individuals is a relative measurement. Even though, the Capital Seoul Area showed the lowest disease burden in “annual cases per 100,000 individuals”. In a view of total number of influenza patient in the region, the Capital Seoul Area has the greatest disease burden (the largest patients). More clear and precise definition of disease burden in short cycle infectious disease may need to be discussed in future papers.

Lastly, a verification process needs to be done. We used billing information as surveillance source, but it only provided a number and incidence of influenza at year unit. Since surveillance also needs to use the data source to monitor temporal trends of influenza activity, timeliness validation of this approach needs to be done to use of this information in other purposes surveillance such as temporal trends monitoring with aberration detection.

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**Figure 2-1. Case definitions by the International Statistical Classification of Diseases and Related Health Problems 10 / Korean Standard Classification of Diseases-5**

| KCD codes for respiratory infection | Influenza (Out Patient) | Pneumonia and Influenza (In Patient) | SARI: Severe Acute Respiratory Infections (In Patient) |
|---|---|---|---|
| ***Diseases of the respiratory system (J00-J99)*** | | | |
| *J09-J11 Influenza and Pneumonia* | | | |
| *J09-J11 Influenza and Pneumonia* | | | |
| *J09 Influenza due to specific identified influenza virus* | O | O | O |
| *J10 Influenza due to other identified influenza virus* | O | O | O |
| *J11 Influenza, virus not identified* | O | O | O |
| *J12-J18 Pneumonia diagnosis group* | | | |
| *J12 Viral pneumonia, NEC* | | O | O |
| *J13 Pneumonia due to Streptococcus pneumoniae* | | O | O |
| *J14 Pneumonia due to Haemophilus influenza* | | O | O |
| *J15 Bacterial pneumonia, NEC* | | O | O |
| *J16 Pneumonia due to other infectious organisms, NEC* | | O | O |
| *J17 Pneumonia in diseases classified elsewhere* | | O | O |
| *J18 Pneumonia, organism unspecified* | | O | O |
| *J20-J22 Other acute lower respiratory infections* | | | |
| *J20 Acute bronchitis* | | | O |
| *J21 Acute bronchiolitis* | | | O |
| *J22 Unspecified acute lower respiratory infection* | | | O |

**Table 2-1. Study population by age-group during 2006-2013 season**

| | Age Category | 06-07 Season | 07-08 Season | 08-09 Season | 09-10 Season* | 10-11 Season | 11-12 Season | 12-13 Season |
|---|---|---|---|---|---|---|---|---|
| Study Population Number | Age under 5 | 43,592 | 44,229 | 43,437 | 42,673 | 43,206 | 45,355 | 45,906 |
| | Age 5-15 | 138,209 | 134,070 | 125,178 | 118,677 | 111,972 | 105,698 | 101,397 |
| | Age 16-50 | 566,227 | 573,752 | 559,333 | 552,798 | 547,768 | 542,247 | 537,642 |
| | Age 51-65 | 155,432 | 162,841 | 166,183 | 174,384 | 185,650 | 195,805 | 203,153 |
| | Age over 65 | 98,545 | 105,851 | 106,654 | 109,995 | 113,435 | 117,376 | 123,025 |
| | Total | 1,002,005 | 1,020,743 | 1,000,785 | 998,527 | 1,002,031 | 1,006,481 | 1,011,123 |

**Table 2-2. The number of seasonal influenza out-patient, pneumonia and influenza in-patient, and severe acute respiratory illness in South Korea during 2006-2013 season**

| | Age Category | 06-07 Season | 07-08 Season | 08-09 Season | 09-10 Season* | 10-11 Season | 11-12 Season | 12-13 Season |
|---|---|---|---|---|---|---|---|---|
| Influenza Out Patient | Age under 5 | 235 | 359 | 429 | 8,029 | 653 | 2,779 | 777 |
| | Age 5-15 | 436 | 609 | 804 | 20,169 | 1,008 | 2,672 | 785 |
| | Age 16-50 | 2,023 | 2,202 | 2,323 | 25,818 | 2,202 | 2,610 | 1,419 |
| | Age 51-65 | 1,484 | 1,562 | 1,582 | 3,471 | 684 | 932 | 424 |
| | Age over 65 | 2,648 | 3,090 | 3,472 | 2,488 | 367 | 562 | 257 |
| | Total | 6,826 | 7,822 | 8,610 | 59,975 | 4,914 | 9,555 | 3,662 |
| Pneumonia and Influenza In Patient | Age under 5 | 2,062 | 1,967 | 1,979 | 2,700 | 2,769 | 3,535 | 2,910 |
| | Age 5-15 | 635 | 413 | 386 | 891 | 930 | 1,143 | 512 |
| | Age 16-50 | 414 | 415 | 405 | 692 | 713 | 872 | 595 |
| | Age 51-65 | 296 | 338 | 342 | 438 | 572 | 736 | 656 |
| | Age over 65 | 858 | 1,102 | 1,112 | 1,327 | 1,702 | 2,261 | 2,179 |
| | Total | 4,265 | 4,235 | 4,224 | 6,048 | 6,686 | 8,547 | 6,852 |
| SARI In Patient | Age under 5 | 2,621 | 2,626 | 2,690 | 3,568 | 3,597 | 4,504 | 3,934 |
| | Age 5-15 | 730 | 527 | 533 | 1,070 | 1,082 | 1,349 | 688 |
| | Age 16-50 | 548 | 589 | 613 | 920 | 952 | 1,128 | 848 |
| | Age 51-65 | 364 | 407 | 444 | 543 | 707 | 915 | 830 |
| | Age over 65 | 927 | 1,187 | 1,222 | 1,446 | 1,856 | 2,469 | 2,370 |
| | Total | 5,190 | 5,336 | 5,502 | 7,547 | 8,194 | 10,365 | 8,670 |

**Table 2-3. The annual incidence of seasonal influenza out-patient in South Korea during 2006-2013 season by age and sex.**

| | Age Category | 06-07 Season | 07-08 Season | 08-09 Season | 09-10 Season* | 10-11 Season | 11-12 Season | 12-13 Season |
|---|---|---|---|---|---|---|---|---|
| Influenza Out Patient | Age under 5 | 5.4 (4.7-6.1) | 8.1 (7.3-9) | 9.9 (8.9-10.8) | 188.2 (184.4- | 15.1 (14-16.3) | 61.3 (59.1-63.5) | 16.9 (15.7-18.1) |
| | Age 5-15 | 3.2 (2.9-3.5) | 4.5 (4.2-4.9) | 6.4 (6-6.9) | 169.9 (167.8- | 9 (8.4-9.6) | 25.3 (24.3-26.2) | 7.7 (7.2-8.3) |
| | Age 16-50 | 3.6 (3.4-3.7) | 3.8 (3.7-4) | 4.2 (4-4.3) | 46.7 (46.1-47.3) | 4 (3.9-4.2) | 4.8 (4.6-5) | 2.6 (2.5-2.8) |
| | Age 51-65 | 9.5 (9.1-10) | 9.6 (9.1-10.1) | 9.5 (9.1-10) | 19.9 (19.2-20.6) | 3.7 (3.4-4) | 4.8 (4.5-5.1) | 2.1 (1.9-2.3) |
| | Age over 65 | 26.9 (25.9-27.9) | 29.2 (28.2-30.2) | 32.6 (31.5-33.6) | 22.6 (21.7-23.5) | 3.2 (2.9-3.6) | 4.8 (4.4-5.2) | 2.1 (1.8-2.3) |
| | Crude Overall | 6.8 (6.7-7) | 7.7 (7.5-7.8) | 8.6 (8.4-8.8) | 60.1 (59.6-60.5) | 4.9 (4.8-5) | 9.5 (9.3-9.7) | 3.6 (3.5-3.7) |
| | Age-Adjusted* | 6.3 (6.2-6.5) | 7.1 (7-7.3) | 8.1 (7.9-8.3) | 78 (77.4-78.6) | 5.8 (5.6-6) | 13.8 (13.6-14.1) | 4.7 (4.5-4.9) |
| Influenza Out Patient (male) | Age under 5 | 5.2 (4.3-6.1) | 7.7 (6.6-8.9) | 10.2 (8.9-11.5) | 190.6 (185.5- | 14.7 (13.1-16.3) | 61.2 (58.2-64.3) | 17.3 (15.7-19) |
| | Age 5-15 | 3.1 (2.7-3.5) | 4.4 (3.9-4.9) | 6 (5.4-6.6) | 172.9 (170- | 8.4 (7.6-9.1) | 24.6 (23.3-25.9) | 7.5 (6.7-8.2) |
| | Age 16-50 | 3 (2.8-3.2) | 3.1 (2.9-3.3) | 3.4 (3.2-3.7) | 43.8 (43-44.5) | 3.6 (3.3-3.8) | 4.1 (3.8-4.3) | 2.3 (2.1-2.5) |
| | Age 51-65 | 6.3 (5.8-6.9) | 6.1 (5.6-6.7) | 6.2 (5.7-6.7) | 15.3 (14.4-16.1) | 3 (2.6-3.3) | 3.9 (3.5-4.3) | 1.8 (1.5-2) |
| | Age over 65 | 20.3 (18.9-21.7) | 20.8 (19.5-22.2) | 21.9 (20.5-23.2) | 18.7 (17.5-20) | 2.9 (2.4-3.4) | 4 (3.5-4.6) | 2 (1.6-2.4) |
| | Crude Overall | 5 (4.8-5.2) | 5.5 (5.3-5.7) | 6.1 (5.9-6.3) | 59.1 (58.5-59.8) | 4.4 (4.3-4.6) | 8.9 (8.7-9.2) | 3.4 (3.3-3.6) |
| | Age-Adjusted* | 5.1 (4.8-5.3) | 5.6 (5.4-5.8) | 6.4 (6.2-6.7) | 76.1 (75.2-76.9) | 5.3 (5-5.5) | 13.1 (12.7-13.5) | 4.5 (4.2-4.7) |
| Influenza Out Patient (female) | Age under 5 | 5.6 (4.6-6.6) | 8.5 (7.3-9.8) | 9.5 (8.2-10.9) | 185.5 (180.2- | 15.5 (13.9-17.2) | 61.3 (58.1-64.5) | 16.5 (14.8-18.2) |
| | Age 5-15 | 3.2 (2.8-3.6) | 4.7 (4.1-5.2) | 6.9 (6.2-7.6) | 166.7 (163.6- | 9.7 (8.9-10.5) | 26 (24.6-27.4) | 8 (7.2-8.8) |
| | Age 16-50 | 4.2 (3.9-4.4) | 4.6 (4.3-4.8) | 4.9 (4.6-5.2) | 49.8 (49-50.6) | 4.5 (4.2-4.8) | 5.6 (5.3-5.9) | 3 (2.8-3.2) |
| | Age 51-65 | 12.7 (11.9-13.5) | 13 (12.2-13.8) | 12.8 (12.1-13.6) | 24.6 (23.5-25.6) | 4.4 (4-4.8) | 5.6 (5.1-6.1) | 2.4 (2.1-2.7) |
| | Age over 65 | 31.2 (29.8-32.6) | 34.8 (33.4-36.2) | 39.9 (38.3-41.4) | 25.3 (24.1-26.5) | 3.5 (3-3.9) | 5.3 (4.8-5.9) | 2.2 (1.8-2.5) |
| | Crude Overall | 8.6 (8.4-8.9) | 9.9 (9.6-10.1) | 11.1 (10.8-11.4) | 61 (60.3-61.7) | 5.4 (5.2-5.6) | 10.1 (9.8-10.3) | 3.8 (3.7-4) |
| | Age-Adjusted* | 7.4 (7.2-7.6) | 8.5 (8.2-8.7) | 9.6 (9.3-9.9) | 79.9 (79.1-80.8) | 6.4 (6.1-6.6) | 14.6 (14.2-15) | 5 (4.7-5.2) |

**Table 2-4. The annual incidence of pneumonia and influenza in-patient in South Korea during 2006-2013 season by age and sex.**

| | Age Category | 06-07 Season | 07-08 Season | 08-09 Season | 09-10 Season* | 10-11 Season | 11-12 Season | 12-13 Season |
|---|---|---|---|---|---|---|---|---|
| **Pneumonia and Influenza In Patient** | Age under 5 | 47.3 (45.3-49.3) | 44.5 (42.6-46.4) | 45.6 (43.6-47.5) | 63.3 (61-65.6) | 64.1 (61.8-66.4) | 77.9 (75.5-80.4) | 63.4 (61.2-65.6) |
| | Age 5-15 | 4.6 (4.2-5) | 3.1 (2.8-3.4) | 3.1 (2.8-3.4) | 7.5 (7-8) | 8.3 (7.8-8.8) | 10.8 (10.2-11.4) | 5 (4.6-5.5) |
| | Age 16-50 | 0.7 (0.7-0.8) | 0.7 (0.7-0.8) | 0.7 (0.7-0.8) | 1.3 (1.2-1.3) | 1.3 (1.2-1.4) | 1.6 (1.5-1.7) | 1.1 (1-1.2) |
| | Age 51-65 | 1.9 (1.7-2.1) | 2.1 (1.9-2.3) | 2.1 (1.8-2.3) | 2.5 (2.3-2.7) | 3.1 (2.8-3.3) | 3.8 (3.5-4) | 3.2 (3-3.5) |
| | Age over 65 | 8.7 (8.1-9.3) | 10.4 (9.8-11) | 10.4 (9.8-11) | 12.1 (11.4-12.7) | 15 (14.3-15.7) | 19.3 (18.5-20) | 17.7 (17-18.4) |
| | Crude Overall | 4.3 (4.1-4.4) | 4.1 (4-4.3) | 4.2 (4.1-4.3) | 6.1 (5.9-6.2) | 6.7 (6.5-6.8) | 8.5 (8.3-8.7) | 6.8 (6.6-6.9) |
| | Age-Adjusted* | 6.4 (6.2-6.6) | 6 (5.8-6.2) | 6.1 (5.9-6.3) | 9.1 (8.8-9.3) | 9.6 (9.4-9.9) | 11.9 (11.6-12.2) | 9 (8.7-9.2) |
| **Pneumonia and Influenza In Patient (male)** | Age under 5 | 49.9 (47.1-52.8) | 47.6 (44.9-50.4) | 47.5 (44.8-50.3) | 68 (64.7-71.3) | 65.8 (62.6-69.1) | 81.2 (77.7-84.7) | 64.5 (61.3-67.6) |
| | Age 5-15 | 4.4 (3.9-4.9) | 3.3 (2.8-3.7) | 2.9 (2.5-3.3) | 8.1 (7.4-8.8) | 8.7 (8-9.5) | 10.4 (9.5-11.2) | 5 (4.4-5.6) |
| | Age 16-50 | 0.7 (0.6-0.8) | 0.6 (0.6-0.7) | 0.7 (0.6-0.8) | 1.1 (1-1.2) | 1.2 (1.1-1.3) | 1.3 (1.1-1.4) | 1 (0.9-1.1) |
| | Age 51-65 | 2 (1.7-2.3) | 2.2 (1.8-2.5) | 1.9 (1.6-2.2) | 2.5 (2.2-2.8) | 3.3 (2.9-3.6) | 3.6 (3.2-4) | 3 (2.7-3.4) |
| | Age over 65 | 11.4 (10.4-12.5) | 12.9 (11.9-14) | 14.3 (13.2-15.4) | 15.7 (14.6-16.9) | 18.2 (17-19.4) | 22.6 (21.3-23.9) | 22.2 (21-23.5) |
| | Crude Overall | 4.5 (4.3-4.7) | 4.4 (4.2-4.6) | 4.4 (4.3-4.6) | 6.5 (6.3-6.7) | 6.9 (6.7-7.1) | 8.5 (8.2-8.7) | 6.9 (6.7-7.1) |
| | Age-Adjusted* | 7 (6.7-7.3) | 6.7 (6.4-7) | 6.7 (6.4-7) | 10 (9.6-10.3) | 10.3 (9.9-10.6) | 12.4 (12-12.8) | 9.5 (9.2-9.9) |
| **Pneumonia and Influenza In Patient (female)** | Age under 5 | 44.5 (41.7-47.3) | 41.1 (38.4-43.7) | 43.4 (40.7-46.2) | 58.2 (55-61.4) | 62.2 (59-65.5) | 74.5 (71-78) | 62.3 (59.1-65.4) |
| | Age 5-15 | 4.8 (4.3-5.4) | 2.9 (2.5-3.3) | 3.3 (2.9-3.8) | 6.8 (6.2-7.5) | 7.9 (7.1-8.6) | 11.3 (10.4-12.2) | 5.1 (4.5-5.7) |
| | Age 16-50 | 0.8 (0.7-0.9) | 0.8 (0.7-0.9) | 0.8 (0.7-0.9) | 1.4 (1.3-1.5) | 1.4 (1.3-1.5) | 2 (1.8-2.1) | 1.2 (1.1-1.4) |
| | Age 51-65 | 1.8 (1.5-2.1) | 2 (1.7-2.3) | 2.3 (1.9-2.6) | 2.5 (2.2-2.9) | 2.9 (2.5-3.2) | 3.9 (3.5-4.3) | 3.4 (3.1-3.8) |
| | Age over 65 | 6.9 (6.3-7.6) | 8.7 (8-9.4) | 7.8 (7.1-8.5) | 9.5 (8.8-10.3) | 12.8 (12-13.7) | 16.9 (16-17.9) | 14.5 (13.6-15.4) |
| | Crude Overall | 4 (3.9-4.2) | 3.9 (3.7-4.1) | 4 (3.8-4.2) | 5.6 (5.4-5.8) | 6.4 (6.2-6.7) | 8.5 (8.3-8.8) | 6.6 (6.4-6.9) |
| | Age-Adjusted* | 6.1 (5.8-6.3) | 5.5 (5.3-5.8) | 5.8 (5.5-6.1) | 8.3 (8-8.6) | 9.1 (8.8-9.5) | 11.6 (11.2-12) | 8.6 (8.3-9) |

**Table 2-5. The annual incidence of severe acute respiratory illness in South Korea during 2006-2013 season by age and sex.**

| | Age Category | 06-07 Season | 07-08 Season | 08-09 Season | 09-10 Season* | 10-11 Season | 11-12 Season | 12-13 Season |
|---|---|---|---|---|---|---|---|---|
| Severe Acute Respiratory Illness | Age under 5 | 60.1 (57.9-62.4) | 59.4 (57.2-61.6) | 61.9 (59.7-64.2) | 83.6 (81-86.2) | 83.3 (80.6-85.9) | 99.3 (96.6-102.1) | 85.7 (83.1-88.3) |
| | Age 5-15 | 5.3 (4.9-5.7) | 3.9 (3.6-4.3) | 4.3 (3.9-4.6) | 9 (8.5-9.6) | 9.7 (9.1-10.2) | 12.8 (12.1-13.4) | 6.8 (6.3-7.3) |
| | Age 16-50 | 1 (0.9-1) | 1 (0.9-1.1) | 1.1 (1-1.2) | 1.7 (1.6-1.8) | 1.7 (1.6-1.8) | 2.1 (2-2.2) | 1.6 (1.5-1.7) |
| | Age 51-65 | 2.3 (2.1-2.6) | 2.5 (2.3-2.7) | 2.7 (2.4-2.9) | 3.1 (2.9-3.4) | 3.8 (3.5-4.1) | 4.7 (4.4-5) | 4.1 (3.8-4.4) |
| | Age over 65 | 9.4 (8.8-10) | 11.2 (10.6-11.8) | 11.5 (10.8-12.1) | 13.1 (12.5-13.8) | 16.4 (15.6-17.1) | 21 (20.2-21.9) | 19.3 (18.5-20) |
| | Crude Overall | 5.2 (5-5.3) | 5.2 (5.1-5.4) | 5.5 (5.4-5.6) | 7.6 (7.4-7.7) | 8.2 (8-8.4) | 10.3 (10.1-10.5) | 8.6 (8.4-8.8) |
| | Age-Adjusted* | 8 (7.8-8.2) | 7.7 (7.5-8) | 8.1 (7.9-8.3) | 11.5 (11.3-11.8) | 12 (11.7-12.3) | 14.6 (14.3-14.9) | 11.7 (11.5-12) |
| Severe Acute Respiratory Illness (male) | Age under 5 | 64.4 (61.3-67.6) | 64.1 (60.9-67.2) | 66.3 (63-69.5) | 91.3 (87.5-95.1) | 87.3 (83.6-91) | 105.1 (101-109) | 89.3 (85.7-92.9) |
| | Age 5-15 | 5.1 (4.6-5.6) | 4.2 (3.7-4.7) | 4.2 (3.7-4.6) | 9.7 (9-10.5) | 10 (9.2-10.9) | 12.4 (11.5-13.4) | 6.9 (6.2-7.6) |
| | Age 16-50 | 0.9 (0.7-1) | 0.9 (0.8-1) | 1 (0.8-1.1) | 1.4 (1.3-1.6) | 1.6 (1.4-1.7) | 1.6 (1.5-1.8) | 1.4 (1.2-1.5) |
| | Age 51-65 | 2.4 (2-2.7) | 2.4 (2.1-2.8) | 2.3 (1.9-2.6) | 3 (2.6-3.3) | 3.8 (3.4-4.2) | 4.3 (3.9-4.7) | 3.7 (3.3-4.1) |
| | Age over 65 | 12 (10.9-13) | 13.6 (12.5-14.7) | 15 (13.9-16.2) | 16.6 (15.4-17.8) | 19.4 (18.2-20.7) | 24.2 (22.8-25.5) | 23.5 (22.2-24.9) |
| | Crude Overall | 5.5 (5.2-5.7) | 5.5 (5.3-5.7) | 5.7 (5.5-5.9) | 8.1 (7.8-8.3) | 8.4 (8.2-8.7) | 10.3 (10-10.6) | 8.8 (8.5-9) |
| | Age-Adjusted* | 8.6 (8.3-9) | 8.5 (8.2-8.8) | 8.8 (8.5-9.1) | 12.7 (12.3-13.1) | 12.8 (12.4-13.2) | 15.3 (14.8-15.7) | 12.5 (12.1-12.8) |
| Severe Acute Respiratory Illness (female) | Age under 5 | 55.4 (52.3-58.5) | 54.3 (51.3-57.4) | 57.3 (54.1-60.4) | 75.4 (71.8-79) | 78.9 (75.3-82.6) | 93.2 (89.4-97) | 81.9 (78.3-85.5) |
| | Age 5-15 | 5.5 (4.9-6) | 3.6 (3.1-4.1) | 4.4 (3.8-4.9) | 8.2 (7.5-9) | 9.2 (8.4-10.1) | 13.1 (12.1-14.1) | 6.6 (5.9-7.3) |
| | Age 16-50 | 1.1 (1-1.2) | 1.2 (1-1.3) | 1.2 (1.1-1.4) | 1.9 (1.7-2.1) | 1.9 (1.7-2.1) | 2.5 (2.4-2.7) | 1.8 (1.7-2) |
| | Age 51-65 | 2.3 (2-2.6) | 2.6 (2.2-2.9) | 3.1 (2.7-3.5) | 3.3 (2.9-3.6) | 3.9 (3.5-4.2) | 5.1 (4.6-5.5) | 4.5 (4.1-4.9) |
| | Age over 65 | 7.7 (7-8.4) | 9.6 (8.8-10.4) | 9 (8.3-9.7) | 10.8 (10-11.6) | 14.2 (13.3-15.1) | 18.8 (17.8-19.9) | 16.2 (15.3-17.2) |
| | Crude Overall | 4.9 (4.7-5.1) | 5 (4.8-5.2) | 5.3 (5.1-5.5) | 7 (6.8-7.3) | 7.9 (7.7-8.2) | 10.3 (10-10.6) | 8.4 (8.1-8.6) |
| | Age-Adjusted* | 7.5 (7.2-7.8) | 7.1 (6.8-7.4) | 7.6 (7.3-8) | 10.6 (10.2-10.9) | 11.4 (11-11.7) | 14.2 (13.8-14.6) | 11.2 (10.8-11.6) |

**Table 2-6. Crude and Age-Adjusted Annual Incidence (per 1,000) of seasonal influenza out-patient in South Korea during 2006-2013 season by subdivision level.**

| | | 06-07 Season | 07-08 Season | 08-09 Season | 09-10 Season | 10-11 Season | 11-12 Season | 12-13 Season |
|---|---|---|---|---|---|---|---|---|
| Crude | Seoul | 3.9 (3.6-4.1) | 5.6 (5.3-5.9) | 6.9 (6.6-7.3) | 57.4 (56.4-58.4) | 3.4 (3.1-3.6) | 6.5 (6.1-6.8) | 1.9 (1.7-2.1) |
| | Busan | 5 (4.5-5.5) | 7.7 (7-8.3) | 6.7 (6.1-7.3) | 52.5 (50.9-54.2) | 4.7 (4.2-5.2) | 9.6 (8.9-10.3) | 4.3 (3.8-4.8) |
| | Daegu | 4.2 (3.7-4.8) | 5 (4.4-5.6) | 5.5 (4.9-6.2) | 52 (50.1-54) | 3.5 (2.9-4) | 7.4 (6.6-8.1) | 3 (2.6-3.5) |
| | Incheon | 6.3 (5.7-7) | 6.6 (5.9-7.3) | 7.3 (6.6-8) | 61.8 (59.8-63.8) | 3 (2.5-3.5) | 6.7 (6.1-7.4) | 2.1 (1.7-2.5) |
| | Gwangju | 7.3 (6.3-8.2) | 8.7 (7.6-9.7) | 10 (8.9-11.2) | 66.1 (63.2-69) | 8.1 (7.1-9.1) | 15.4 (14-16.7) | 9.9 (8.8-11.1) |
| | Daejeon | 6.7 (5.7-7.6) | 9.3 (8.2-10.3) | 8.1 (7.1-9.1) | 68.5 (65.6-71.3) | 5.3 (4.4-6.1) | 9.6 (8.5-10.7) | 3 (2.4-3.6) |
| | Ulsan | 5.5 (4.6-6.5) | 9 (7.8-10.2) | 8.9 (7.7-10.1) | 69.8 (66.6-72.9) | 6.8 (5.7-7.8) | 17.7 (16-19.3) | 4.6 (3.8-5.5) |
| | Gyeongi | 4.6 (4.3-4.9) | 6 (5.6-6.3) | 7.4 (7.1-7.7) | 62.7 (61.7-63.7) | 4.2 (4-4.5) | 8.3 (7.9-8.7) | 2.5 (2.3-2.7) |
| | Gangwon | 9 (8-10.1) | 7.3 (6.3-8.3) | 9.5 (8.3-10.6) | 63.6 (60.7-66.5) | 5.8 (4.9-6.6) | 9.7 (8.6-10.9) | 2.9 (2.3-3.5) |
| | ChungBuk | 9.9 (8.8-11) | 10.5 (9.4-11.7) | 11.4 (10.2-12.6) | 65.9 (63.1-68.7) | 7.4 (6.4-8.3) | 11.7 (10.5-12.9) | 4.9 (4.1-5.7) |
| | ChungNam | 16.4 (15.2-17.6) | 13.1 (12-14.3) | 13.3 (12.2-14.4) | 65.4 (63-67.8) | 7.8 (7-8.7) | 15.9 (14.7-17.1) | 6.6 (5.8-7.4) |
| | JeonBuk | 11.1 (10-12.1) | 11.2 (10.1-12.2) | 13.4 (12.2-14.6) | 71.9 (69.2-74.6) | 11 (10-12.1) | 12.7 (11.6-13.8) | 7.9 (7-8.8) |
| | JeonNam | 15.9 (14.7-17.1) | 13.3 (12.2-14.5) | 15.6 (14.4-16.9) | 51.9 (49.6-54.1) | 4 (3.4-4.6) | 8.7 (7.8-9.7) | 4.3 (3.7-5) |
| | GyeonBuk | 9.8 (9-10.7) | 9.3 (8.5-10.1) | 9.9 (9.1-10.8) | 53.1 (51.1-55) | 4.6 (4-5.1) | 9.8 (9-10.7) | 3 (2.5-3.5) |
| | GyeonNam | 8.1 (7.4-8.8) | 9.5 (8.8-10.2) | 10.5 (9.7-11.3) | 61.8 (59.9-63.7) | 6 (5.4-6.6) | 14.7 (13.8-15.7) | 6.5 (5.9-7.1) |
| | Jeju | 13 (10.9-15.1) | 14.7 (12.5-16.9) | 14.1 (11.8-16.3) | 36.7 (33.1-40.3) | 9.7 (7.8-11.5) | 8.9 (7.2-10.7) | 2.1 (1.2-2.9) |
| Age-Adjusted* | Seoul | 4 (3.7-4.3) | 5.6 (5.3-5.9) | 6.9 (6.5-7.3) | 79.1 (77.7-80.5) | 3.8 (3.5-4.2) | 9.7 (9.2-10.3) | 2.5 (2.2-2.7) |
| | Busan | 4.4 (3.9-4.8) | 7.5 (6.8-8.2) | 6.9 (6.3-7.6) | 74.3 (71.9-76.6) | 6.1 (5.4-6.9) | 17 (15.6-18.3) | 6.7 (5.9-7.6) |
| | Daegu | 4.2 (3.6-4.7) | 4.6 (4.1-5.2) | 5.3 (4.7-6) | 68.2 (65.6-70.8) | 4.3 (3.6-4.9) | 11.4 (10.2-12.7) | 4.1 (3.4-4.8) |
| | Incheon | 6.3 (5.6-7) | 6.1 (5.5-6.7) | 6.6 (6-7.3) | 79.6 (77-82.1) | 3.2 (2.7-3.8) | 9.3 (8.3-10.2) | 2.5 (2-2.9) |
| | Gwangju | 7.3 (6.3-8.3) | 8.6 (7.5-9.7) | 9.9 (8.7-11) | 79 (75.6-82.4) | 9.1 (7.9-10.3) | 21.4 (19.4-23.4) | 12.3 (10.8-13.7) |
| | Daejeon | 6.7 (5.8-7.7) | 8.9 (7.8-9.9) | 7.5 (6.5-8.4) | 84.8 (81.3-88.2) | 6.2 (5.1-7.2) | 14 (12.4-15.7) | 4.3 (3.4-5.2) |
| | Ulsan | 5.9 (4.8-6.9) | 9.1 (7.8-10.3) | 9.3 (8-10.6) | 89.1 (85.1-93.1) | 8.4 (7-9.8) | 26.2 (23.7-28.7) | 6.2 (5-7.4) |
| | Gyeongi | 4.8 (4.5-5.1) | 5.8 (5.5-6.1) | 7.2 (6.8-7.5) | 78.5 (77.3-79.7) | 4.7 (4.4-5) | 10.8 (10.3-11.3) | 3 (2.8-3.3) |
| | Gangwon | 6.8 (5.9-7.6) | 5.7 (4.9-6.5) | 7.4 (6.4-8.3) | 83.5 (79.7-87.4) | 7.2 (6-8.4) | 16 (14-18) | 3.7 (2.8-4.5) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ChungBuk | 8.8 (7.7-9.9) | 9.6 (8.5-10.7) | 10.4 (9.2-11.5) | 84.9 (81.3-88.5) | 8.7 (7.5-9.9) | 16.9 (15.1-18.7) | 6.3 (5.2-7.4) |
| ChungNam | 12.4 (11.4-13.5) | 10.9 (9.9-11.9) | 11.6 (10.5-12.7) | 83.7 (80.6-86.7) | 9.4 (8.3-10.4) | 24.1 (22.2-25.9) | 8.6 (7.5-9.7) |
| JeonBuk | 11 (9.9-12.1) | 11.5 (10.4-12.7) | 14.8 (13.4-16.2) | 92.8 (89.3-96.2) | 15.5 (13.9-17.1) | 17.5 (15.8-19.2) | 11.3 (10-12.7) |
| JeonNam | 10.7 (9.8-11.6) | 9.6 (8.8-10.5) | 11.9 (10.9-13) | 63.6 (60.7-66.5) | 4.9 (4-5.7) | 12.3 (10.8-13.7) | 5.4 (4.4-6.3) |
| GyeonBuk | 7 (6.4-7.6) | 7.5 (6.8-8.2) | 7.9 (7.1-8.6) | 70.6 (68-73.2) | 5.7 (4.9-6.5) | 14.9 (13.6-16.3) | 4.2 (3.5-4.9) |
| GyeonNam | 6.9 (6.3-7.5) | 8.6 (7.9-9.3) | 9.8 (9-10.6) | 77.7 (75.3-80) | 7.1 (6.4-7.9) | 21.7 (20.3-23) | 8 (7.2-8.8) |
| Jeju | 10.3 (8.6-11.9) | 12.6 (10.7-14.5) | 11.6 (9.8-13.5) | 43.2 (38.8-47.5) | 8.2 (6.5-9.8) | 9.2 (7.2-11.2) | 2.4 (1.3-3.5) |

**Table 2-7. Crude and Age-Adjusted Annual Incidence (per 1,000) of pneumonia and influenza in-patient in South Korea during 2006-2013 season by state level.**

| | | 06-07 Season | 07-08 Season | 08-09 Season | 09-10 Season | 10-11 Season | 11-12 Season | 12-13 Season |
|---|---|---|---|---|---|---|---|---|
| Crude | Seoul | 2.8 (2.6-3.1) | 2.7 (2.5-2.9) | 2.8 (2.6-3.1) | 3.5 (3.3-3.8) | 3.7 (3.5-4) | 4.1 (3.8-4.4) | 3.2 (3-3.5) |
| | Busan | 5.2 (4.7-5.7) | 5.1 (4.6-5.6) | 4.3 (3.8-4.7) | 6.8 (6.2-7.4) | 7.3 (6.7-7.9) | 10.3 (9.6-11) | 7.6 (6.9-8.2) |
| | Daegu | 3.5 (3-4.1) | 4 (3.5-4.6) | 3.7 (3.1-4.2) | 5.9 (5.2-6.6) | 5.8 (5.2-6.5) | 8.2 (7.4-9) | 5.6 (4.9-6.2) |
| | Incheon | 2.8 (2.3-3.2) | 2.6 (2.2-3) | 2.6 (2.1-3) | 4.5 (4-5.1) | 5 (4.4-5.6) | 6 (5.3-6.6) | 4.3 (3.8-4.9) |
| | Gwangju | 6.9 (6-7.9) | 6.6 (5.6-7.5) | 7.8 (6.8-8.8) | 11.3 (10.1-12.5) | 13.3 (12-14.7) | 16.1 (14.7-17.5) | 14.9 (13.5-16.2) |
| | Daejeon | 3.8 (3.1-4.5) | 4.2 (3.5-4.9) | 3.6 (3-4.3) | 4.9 (4.1-5.7) | 4.5 (3.7-5.2) | 6.2 (5.3-7.1) | 6.4 (5.5-7.3) |
| | Ulsan | 3.5 (2.7-4.2) | 3.6 (2.9-4.4) | 3.3 (2.6-4) | 5.3 (4.4-6.2) | 7 (5.9-8.1) | 8.9 (7.7-10.1) | 7.5 (6.4-8.6) |
| | Gyeongi | 3.7 (3.4-3.9) | 3.3 (3.1-3.5) | 3.1 (2.9-3.3) | 4.7 (4.4-5) | 4.9 (4.6-5.2) | 5.9 (5.6-6.2) | 4.4 (4.1-4.6) |
| | Gangwon | 4.2 (3.4-4.9) | 4.3 (3.5-5) | 4.1 (3.3-4.8) | 6.3 (5.3-7.2) | 6.9 (5.9-7.9) | 9.7 (8.6-10.8) | 6.7 (5.7-7.6) |
| | ChungBuk | 3.2 (2.6-3.8) | 3.4 (2.8-4.1) | 5 (4.2-5.8) | 6 (5.2-6.9) | 8.3 (7.3-9.3) | 11.6 (10.4-12.8) | 9.4 (8.3-10.5) |
| | ChungNam | 4.3 (3.7-4.9) | 4.5 (3.8-5.1) | 4.8 (4.2-5.5) | 6 (5.2-6.7) | 7.9 (7-8.7) | 10.8 (9.8-11.8) | 8.8 (7.8-9.7) |
| | JeonBuk | 4.7 (4-5.4) | 5.4 (4.7-6.2) | 5.6 (4.8-6.3) | 8 (7.1-8.9) | 8.7 (7.7-9.6) | 10.9 (9.9-12) | 9.8 (8.8-10.8) |
| | JeonNam | 8.1 (7.2-8.9) | 9 (8.1-10) | 8.8 (7.8-9.7) | 14.4 (13.2-15.7) | 14.3 (13.1-15.5) | 18.4 (17.1-19.8) | 16.5 (15.3-17.8) |
| | GyeonBuk | 4.7 (4.1-5.2) | 3.6 (3.1-4.1) | 4.7 (4.1-5.2) | 6.8 (6-7.5) | 7.9 (7.1-8.6) | 10.5 (9.7-11.4) | 7.4 (6.7-8.1) |
| | GyeonNam | 8.1 (7.4-8.8) | 7.9 (7.2-8.6) | 9.2 (8.5-10) | 12 (11.2-12.9) | 12.7 (11.9-13.6) | 16.8 (15.9-17.8) | 14.3 (13.4-15.2) |
| | Jeju | 5.6 (4.3-7) | 7.1 (5.6-8.7) | 4.4 (3.2-5.7) | 6.3 (4.8-7.8) | 10.2 (8.3-12.1) | 9.2 (7.4-11) | 8.2 (6.5-9.9) |
| Age-Adjusted* | Seoul | 4.8 (4.4-5.2) | 4.1 (3.7-4.5) | 4.2 (3.8-4.6) | 5.5 (5-5.9) | 5.9 (5.4-6.3) | 6.1 (5.7-6.6) | 4.3 (4-4.7) |
| | Busan | 10.4 (9.3-11.4) | 9.4 (8.4-10.4) | 7.5 (6.6-8.4) | 11.4 (10.3-12.5) | 12.9 (11.8-14.1) | 18 (16.7-19.4) | 12.7 (11.5-13.8) |
| | Daegu | 5.9 (5.1-6.8) | 6.7 (5.7-7.6) | 6.1 (5.2-7.1) | 9.7 (8.6-10.9) | 9.2 (8.1-10.3) | 12.6 (11.3-13.9) | 8.5 (7.5-9.6) |
| | Incheon | 4.2 (3.4-4.9) | 3.7 (3-4.3) | 3.5 (2.9-4.1) | 6.5 (5.7-7.4) | 7.1 (6.3-8) | 8.3 (7.4-9.2) | 5.3 (4.6-6) |
| | Gwangju | 10 (8.7-11.4) | 9.6 (8.2-11) | 12 (10.4-13.6) | 18.2 (16.3-20.1) | 20.3 (18.4-22.2) | 24.7 (22.7-26.8) | 21.7 (19.8-23.7) |
| | Daejeon | 5.2 (4.2-6.2) | 5.7 (4.7-6.7) | 4.8 (3.9-5.8) | 7 (5.8-8.1) | 6 (4.9-7.1) | 8.2 (7-9.5) | 9.1 (7.8-10.4) |
| | Ulsan | 5.1 (4-6.3) | 4.8 (3.8-5.9) | 4.6 (3.6-5.7) | 7.1 (5.8-8.4) | 10.1 (8.5-11.7) | 13 (11.2-14.8) | 11.2 (9.6-12.9) |
| | Gyeongi | 5.2 (4.8-5.5) | 4.4 (4.1-4.7) | 4.2 (3.9-4.5) | 6.6 (6.2-7) | 6.7 (6.3-7.1) | 7.9 (7.4-8.3) | 5.4 (5.1-5.8) |
| | Gangwon | 5.7 (4.6-6.8) | 5.7 (4.6-6.8) | 5.4 (4.3-6.6) | 9.3 (7.8-10.9) | 8.2 (6.8-9.6) | 12.8 (11.1-14.6) | 7.8 (6.5-9.2) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ChungBuk | 4.5 (3.5-5.5) | 4.5 (3.6-5.4) | 6.5 (5.4-7.6) | 8.5 (7.2-9.9) | 11.7 (10.2-13.2) | 15.9 (14.1-17.6) | 11.2 (9.8-12.6) |
| ChungNam | 5 (4.2-5.9) | 5.6 (4.7-6.5) | 6 (5.1-7) | 7.9 (6.8-8.9) | 9.3 (8.2-10.5) | 13 (11.7-14.3) | 9.3 (8.2-10.4) |
| JeonBuk | 5.5 (4.6-6.4) | 6.7 (5.7-7.7) | 7.1 (6-8.1) | 11.2 (9.8-12.6) | 10.8 (9.5-12.2) | 12.8 (11.4-14.2) | 10.7 (9.4-12) |
| JeonNam | 12.2 (10.8-13.6) | 13.4 (11.9-14.9) | 13.1 (11.6-14.6) | 22.2 (20.3-24.1) | 21.2 (19.3-23.1) | 25.1 (23.1-27.1) | 22.2 (20.3-24.1) |
| GyeonBuk | 7.1 (6.1-8) | 5.4 (4.6-6.2) | 6.7 (5.8-7.7) | 10.2 (9.1-11.3) | 10.5 (9.4-11.6) | 12.8 (11.6-14) | 8.8 (7.8-9.8) |
| GyeonNam | 12.4 (11.3-13.4) | 11.8 (10.8-12.8) | 13.8 (12.6-14.9) | 18.1 (16.8-19.4) | 18.4 (17.1-19.7) | 23.6 (22.2-25) | 19.6 (18.3-20.9) |
| Jeju | 8.2 (6.2-10.3) | 10.8 (8.4-13.1) | 7 (5-9.1) | 8.8 (6.6-11) | 15.4 (12.6-18.3) | 12.7 (10.1-15.2) | 9.8 (7.6-12) |

**Table 2-8. Crude and Age-Adjusted Annual Incidence (per 1,000) of severe acute respiratory illness in South Korea during 2006-2013 season by state level.**

| | | 06-07 Season | 07-08 Season | 08-09 Season | 09-10 Season | 10-11 Season | 11-12 Season | 12-13 Season |
|---|---|---|---|---|---|---|---|---|
| Crude | Seoul | 3.4 (3.2-3.7) | 3.3 (3-3.5) | 3.5 (3.2-3.7) | 4.3 (4-4.6) | 4.3 (4.1-4.6) | 4.9 (4.6-5.2) | 4 (3.8-4.3) |
| | Busan | 6.7 (6.1-7.3) | 6.9 (6.3-7.5) | 6.1 (5.6-6.7) | 9.3 (8.6-10) | 10.4 (9.7-11.1) | 13.6 (12.7-14.4) | 10.4 (9.7-11.2) |
| | Daegu | 4.1 (3.5-4.6) | 5 (4.4-5.7) | 4.7 (4.1-5.3) | 6.9 (6.1-7.6) | 6.9 (6.1-7.6) | 9.7 (8.9-10.6) | 7 (6.3-7.8) |
| | Incheon | 3.5 (3-4) | 3.1 (2.7-3.6) | 3.4 (2.9-3.9) | 5.4 (4.8-6) | 6 (5.3-6.6) | 6.8 (6.1-7.4) | 5.2 (4.6-5.8) |
| | Gwangju | 8.6 (7.5-9.7) | 8.5 (7.4-9.5) | 10.1 (8.9-11.2) | 14.4 (13-15.8) | 16.2 (14.8-17.6) | 19.8 (18.2-21.4) | 18.5 (17-20) |
| | Daejeon | 4.5 (3.8-5.3) | 4.7 (3.9-5.5) | 4.3 (3.6-5) | 5.5 (4.7-6.4) | 5.4 (4.6-6.3) | 6.8 (5.9-7.7) | 7.1 (6.1-8) |
| | Ulsan | 4.3 (3.5-5.2) | 4.4 (3.6-5.2) | 4.2 (3.4-5) | 6.7 (5.7-7.7) | 7.9 (6.7-9) | 10.9 (9.6-12.2) | 9.5 (8.2-10.7) |
| | Gyeongi | 4.4 (4.2-4.7) | 4.1 (3.9-4.4) | 4.2 (3.9-4.4) | 5.7 (5.4-6) | 5.8 (5.5-6.1) | 7 (6.7-7.3) | 5.5 (5.2-5.8) |
| | Gangwon | 4.9 (4.1-5.7) | 5.1 (4.3-5.9) | 5.1 (4.2-5.9) | 7.7 (6.7-8.8) | 8.2 (7.2-9.3) | 11 (9.8-12.2) | 8.7 (7.6-9.8) |
| | ChungBuk | 3.8 (3.1-4.5) | 4.1 (3.4-4.8) | 5.8 (5-6.7) | 7.1 (6.2-8.1) | 9.7 (8.6-10.8) | 13.1 (11.8-14.4) | 10.8 (9.6-11.9) |
| | ChungNam | 5.3 (4.6-6) | 5.4 (4.7-6.1) | 5.8 (5.1-6.6) | 7.2 (6.4-8.1) | 9.4 (8.5-10.4) | 12.7 (11.7-13.8) | 10.2 (9.2-11.2) |
| | JeonBuk | 5.9 (5.1-6.6) | 6.9 (6.1-7.7) | 7.1 (6.2-8) | 10.1 (9-11.1) | 10.8 (9.8-11.9) | 13.7 (12.5-14.9) | 12.7 (11.5-13.8) |
| | JeonNam | 9.9 (8.9-10.8) | 12.2 (11.1-13.3) | 13 (11.8-14.1) | 19.8 (18.4-21.3) | 19.1 (17.7-20.4) | 25.1 (23.6-26.7) | 22.6 (21.1-24.1) |
| | GyeonBuk | 5.4 (4.8-6) | 4.6 (4.1-5.2) | 6.1 (5.4-6.8) | 8.2 (7.4-9) | 9.8 (8.9-10.6) | 12.6 (11.6-13.5) | 9.8 (9-10.6) |
| | GyeonNam | 9.9 (9.1-10.7) | 10.2 (9.4-11) | 11.9 (11.1-12.8) | 15.2 (14.2-16.1) | 15.7 (14.8-16.7) | 20.1 (19.1-21.2) | 17.6 (16.6-18.6) |
| | Jeju | 6.2 (4.8-7.7) | 8.9 (7.1-10.6) | 5.7 (4.3-7.2) | 8 (6.3-9.7) | 11.7 (9.7-13.7) | 11 (9.1-12.9) | 10.4 (8.5-12.3) |
| Age-Adjusted* | Seoul | 6 (5.6-6.5) | 5.2 (4.8-5.6) | 5.3 (4.9-5.7) | 6.9 (6.4-7.4) | 7 (6.5-7.5) | 7.5 (7-8) | 5.8 (5.4-6.2) |
| | Busan | 13.5 (12.3-14.7) | 13.1 (11.9-14.2) | 11.3 (10.2-12.3) | 16.5 (15.2-17.8) | 19.4 (17.9-20.8) | 24.6 (23-26.1) | 18.4 (17.1-19.8) |
| | Daegu | 6.9 (6-7.9) | 8.3 (7.3-9.4) | 7.9 (6.8-8.9) | 11.4 (10.1-12.6) | 11 (9.8-12.2) | 15.1 (13.7-16.5) | 11.2 (10-12.4) |
| | Incheon | 5.2 (4.4-6) | 4.5 (3.8-5.2) | 4.9 (4.2-5.6) | 8.1 (7.2-9.1) | 8.7 (7.7-9.7) | 9.5 (8.5-10.5) | 6.7 (5.9-7.5) |
| | Gwangju | 12.6 (11-14.1) | 12.6 (11-14.1) | 15.3 (13.5-17) | 23.4 (21.3-25.5) | 24.4 (22.3-26.5) | 29.9 (27.7-32.2) | 27 (24.9-29.1) |
| | Daejeon | 6.3 (5.2-7.4) | 6.5 (5.4-7.6) | 6 (4.9-7) | 8 (6.8-9.3) | 7.8 (6.5-9) | 9.3 (8-10.6) | 10.1 (8.7-11.5) |
| | Ulsan | 6.5 (5.2-7.8) | 6 (4.8-7.2) | 5.9 (4.7-7.1) | 9.3 (7.9-10.8) | 11.5 (9.8-13.2) | 16.3 (14.4-18.3) | 14.3 (12.4-16.1) |
| | Gyeongi | 6.4 (6-6.8) | 5.6 (5.3-6) | 5.7 (5.3-6) | 8.1 (7.7-8.5) | 8 (7.5-8.4) | 9.5 (9-9.9) | 7.1 (6.7-7.5) |
| | Gangwon | 6.8 (5.6-8) | 7.1 (5.9-8.4) | 7 (5.7-8.3) | 12.2 (10.4-13.9) | 10.2 (8.7-11.8) | 14.5 (12.7-16.4) | 10.5 (8.9-12) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ChungBuk | 5.5 (4.4-6.6) | 5.4 (4.4-6.5) | 7.9 (6.6-9.2) | 10.4 (8.9-11.9) | 13.9 (12.2-15.5) | 18.1 (16.2-19.9) | 13.2 (11.7-14.7) |
| ChungNam | 6.5 (5.6-7.5) | 7 (6-8) | 7.4 (6.4-8.4) | 9.7 (8.5-10.8) | 11.3 (10.1-12.6) | 15.3 (13.9-16.7) | 11.3 (10.1-12.5) |
| JeonBuk | 7.2 (6.2-8.3) | 8.7 (7.5-9.8) | 9.4 (8.1-10.6) | 14 (12.4-15.5) | 14.1 (12.6-15.6) | 16.5 (14.9-18.1) | 14.4 (12.9-15.9) |
| JeonNam | 14.8 (13.3-16.4) | 18.1 (16.4-19.7) | 19.3 (17.6-21.1) | 30.9 (28.7-33.1) | 28.6 (26.4-30.7) | 35.4 (33.1-37.7) | 31.3 (29.1-33.4) |
| GyeonBuk | 8.4 (7.4-9.5) | 7.2 (6.2-8.1) | 9.1 (8-10.1) | 12.6 (11.3-13.8) | 13.6 (12.3-14.8) | 15.8 (14.4-17.1) | 12.7 (11.5-13.9) |
| GyeonNam | 15.2 (14.1-16.4) | 15.2 (14-16.3) | 17.8 (16.5-19) | 22.9 (21.5-24.3) | 22.7 (21.3-24.1) | 28.3 (26.7-29.8) | 24.2 (22.8-25.6) |
| Jeju | 9.4 (7.2-11.6) | 13.4 (10.8-16) | 9.1 (6.8-11.4) | 11.4 (9-13.9) | 17.4 (14.4-20.4) | 15 (12.3-17.7) | 13.1 (10.5-15.6) |

**Table 2-9. Crude and age-Adjusted recent 3 years Average Annual Incidence*(per 1,000) of seasonal influenza out-patient, pneumonia and influenza in-patient, and severe acute respiratory illness in South Korea during 2010-2012 season by state level.**

| | Influenza Out-Patient | | Pneumonia and Influenza In-patient | | Severe Acute Respiratory Illness | |
|---|---|---|---|---|---|---|
| | **Crude** | **Adjusted** | **Crude** | **Adjusted** | **Crude** | **Adjusted** |
| Seoul | 3.9 (3.8-4.1) | 5.3 (5.1-5.6) | 3.7 (3.5-3.8) | 5.4 (5.2-5.7) | 4.4 (4.3-4.6) | 6.8 (6.5-7) |
| Busan | 6.2 (5.9-6.5) | 9.9 (9.3-10.5) | 8.4 (8-8.8) | 14.6 (13.8-15.3) | 11.5 (11-11.9) | 20.8 (20-21.6) |
| Daegu | 4.6 (4.3-5) | 6.6 (6.1-7.1) | 6.6 (6.1-7) | 10.1 (9.5-10.8) | 7.9 (7.4-8.3) | 12.5 (11.7-13.2) |
| Incheon | 3.9 (3.6-4.2) | 5 (4.6-5.4) | 5.1 (4.8-5.4) | 6.9 (6.5-7.4) | 6 (5.6-6.3) | 8.3 (7.8-8.9) |
| Gwangju | 11.1 (10.4-11.8) | 14.3 (13.3-15.2) | 14.8 (14-15.6) | 22.3 (21.1-23.4) | 18.2 (17.3-19.1) | 27.1 (25.9-28.4) |
| Daejeon | 6 (5.5-6.5) | 8.2 (7.5-8.9) | 5.7 (5.2-6.2) | 7.8 (7.1-8.5) | 6.4 (5.9-7) | 9.1 (8.3-9.8) |
| Ulsan | 9.7 (9-10.4) | 13.5 (12.5-14.6) | 7.8 (7.1-8.4) | 11.5 (10.5-12.4) | 9.4 (8.7-10.1) | 14.1 (13-15.1) |
| Gyeongi | 5 (4.8-5.2) | 6.2 (6-6.4) | 5 (4.9-5.2) | 6.7 (6.4-6.9) | 6.1 (5.9-6.3) | 8.2 (7.9-8.4) |
| Gangwon | 6.1 (5.6-6.7) | 9 (8.1-9.8) | 7.8 (7.2-8.3) | 9.6 (8.7-10.5) | 9.3 (8.7-10) | 11.7 (10.8-12.7) |
| ChungBuk | 8 (7.4-8.6) | 10.6 (9.8-11.5) | 9.8 (9.1-10.4) | 12.9 (12-13.8) | 11.2 (10.5-11.9) | 15 (14.1-16) |
| ChungNam | 10.1 (9.6-10.7) | 14.1 (13.3-14.9) | 9.2 (8.6-9.7) | 10.6 (9.9-11.3) | 10.8 (10.2-11.4) | 12.7 (11.9-13.4) |
| JeonBuk | 10.6 (9.9-11.2) | 14.8 (13.9-15.7) | 9.8 (9.2-10.4) | 11.4 (10.7-12.2) | 12.4 (11.7-13) | 15 (14.1-15.9) |
| JeonNam | 5.7 (5.3-6.1) | 7.5 (6.9-8.1) | 16.4 (15.7-17.2) | 22.8 (21.7-24) | 22.3 (21.4-23.1) | 31.8 (30.5-33.1) |
| GyeonBuk | 5.8 (5.4-6.2) | 8.3 (7.7-8.9) | 8.6 (8.2-9.1) | 10.7 (10.1-11.3) | 10.7 (10.2-11.2) | 14 (13.3-14.7) |
| GyeonNam | 9.1 (8.7-9.5) | 12.2 (11.6-12.8) | 14.6 (14.1-15.2) | 20.6 (19.8-21.3) | 17.8 (17.2-18.4) | 25.1 (24.3-25.9) |
| Jeju | 6.9 (6-7.7) | 6.5 (5.6-7.5) | 9.2 (8.2-10.2) | 12.6 (11.1-14.1) | 11 (9.9-12.2) | 15.2 (13.6-16.8) |

**Table 2-10. Incidence ratio comparison between case definitions and extended case definition**

| | Age Category | 06-07 Season | 07-08 Season | 08-09 Season | 09-10 Season* | 10-11 Season | 11-12 Season | 12-13 Season |
|---|---|---|---|---|---|---|---|---|
| extended influenza out-patient/ influenza out-patient ratio | Age under 5 | 2.00 | 1.50 | 1.44 | 1.23 | 1.37 | 1.28 | 1.29 |
| | Age 5-15 | 1.61 | 1.51 | 1.42 | 1.15 | 1.32 | 1.23 | 1.34 |
| | Age 16-50 | 1.33 | 1.30 | 1.30 | 1.13 | 1.29 | 1.26 | 1.23 |
| | Age 51-65 | 1.19 | 1.21 | 1.15 | 1.17 | 1.31 | 1.28 | 1.23 |
| | Age over 65 | 1.14 | 1.11 | 1.07 | 1.12 | 1.26 | 1.25 | 1.31 |
| | Total | 1.27 | 1.23 | 1.20 | 1.15 | 1.31 | 1.26 | 1.27 |
| extended pneumonia and influenza in-patient / pneumonia and influenza in-patient ratio | Age under 5 | 1.28 | 1.28 | 1.26 | 1.27 | 1.18 | 1.19 | 1.20 |
| | Age 5-15 | 1.24 | 1.34 | 1.29 | 1.16 | 1.14 | 1.13 | 1.19 |
| | Age 16-50 | 1.39 | 1.37 | 1.37 | 1.30 | 1.22 | 1.20 | 1.29 |
| | Age 51-65 | 1.64 | 1.53 | 1.54 | 1.50 | 1.45 | 1.40 | 1.38 |
| | Age over 65 | 1.76 | 1.60 | 1.57 | 1.50 | 1.50 | 1.41 | 1.43 |
| | Total | 1.40 | 1.39 | 1.38 | 1.32 | 1.29 | 1.26 | 1.30 |
| Extended SARI / SARI ratio | Age under 5 | 1.33 | 1.38 | 1.37 | 1.33 | 1.30 | 1.27 | 1.32 |
| | Age 5-15 | 1.33 | 1.50 | 1.50 | 1.24 | 1.24 | 1.22 | 1.45 |
| | Age 16-50 | 1.47 | 1.44 | 1.44 | 1.36 | 1.37 | 1.30 | 1.41 |
| | Age 51-65 | 1.63 | 1.57 | 1.58 | 1.50 | 1.50 | 1.45 | 1.43 |
| | Age over 65 | 1.77 | 1.62 | 1.58 | 1.55 | 1.52 | 1.43 | 1.45 |
| | Total | 1.44 | 1.47 | 1.45 | 1.38 | 1.37 | 1.32 | 1.39 |

**Table 2-11. Incidence Ratio comparison for influenza out-patient diagnosis pattern change**

| | Age Category | 06-07 Season | 07-08 Season | 08-09 Season | 09-10 Season* | 10-11 Season | 11-12 Season | 12-13 Season |
|---|---|---|---|---|---|---|---|---|
| influenza in-patient / influenza out-patient ratio | Age under 5 | 0.12 | 0.10 | 0.10 | 0.04 | 0.13 | 0.15 | 0.27 |
| | Age 5-15 | 0.01 | 0.04 | 0.06 | 0.02 | 0.07 | 0.09 | 0.16 |
| | Age 16-50 | 0.01 | 0.01 | 0.02 | 0.01 | 0.07 | 0.06 | 0.11 |
| | Age 51-65 | 0.00 | 0.01 | 0.01 | 0.03 | 0.07 | 0.08 | 0.14 |
| | Age over 65 | 0.00 | 0.00 | 0.00 | 0.03 | 0.06 | 0.14 | 0.19 |
| | Total | 0.01 | 0.01 | 0.02 | 0.02 | 0.08 | 0.10 | 0.16 |
| influenza out-patient ratio / pneumonia and influenza out-patient | Age under 5 | 0.02 | 0.03 | 0.04 | 0.42 | 0.05 | 0.15 | 0.06 |
| | Age 5-15 | 0.07 | 0.10 | 0.14 | 0.78 | 0.15 | 0.28 | 0.16 |
| | Age 16-50 | 0.26 | 0.26 | 0.29 | 0.81 | 0.25 | 0.25 | 0.18 |
| | Age 51-65 | 0.36 | 0.34 | 0.37 | 0.54 | 0.16 | 0.17 | 0.09 |
| | Age over 65 | 0.51 | 0.48 | 0.51 | 0.45 | 0.09 | 0.11 | 0.06 |
| | Total | 0.19 | 0.21 | 0.24 | 0.68 | 0.13 | 0.19 | 0.11 |

# *Chapter 3 : The use of medical billing information in influenza temporal trends monitoring system: timeliness validation on a new source of surveillance in South Korea*

## *Abstract*

**Objective** To validate the use of billing system as an alternative influenza surveillance data source and compare the timeliness of the epidemiological information from billing system to the current influenza surveillance system in South Korea.

**Participants** 1,021,576 individuals randomly selected from the national health insurance in Korea. Followed from the 36th week of 2010 to 35th week of 2013.

**Methods** Used 6 different case definitions to define influenza activity (3 base case definition and 3 extended). Compared the timeliness of influenza activity captured by those case definitions in billing information. Applied peak time comparison, aberration time comparison, and time-series correlation function to quantify the timeliness.

**Results** For peak time comparison, 'Influenza outpatient' case definition showed average 0-week time difference compared to the current surveillance system. 'Pneumonia and influenza inpatient (PNI-ADM)' and 'Severe acute respiratory illness (SARI)' case definitions showed 1-week late time difference. For time-series correlation, 'Influenza outpatient' showed average 0.33 week earlier activity with average maximum cross-correlation value 0.97, while 'PNI-ADM' and 'SARI' showed 0.67 and 0 week time difference with average maximum cross-correlation 0.75 and 0.75. *For aberration time comparison, each case definition showed an average 1.33, 0.67, and 2.33 week late signals in high sensitivity setting compared to the current system. In high specificity setting, only 'Influenza outpatient' was able to generate signals among various case definitions and it was 0.33 week early in average compared to the current system.*

**Conclusions** We could not see any epidemiologically significant differences between the proposed source and current influenza surveillance system. These findings suggested that we may use billing

information as a surrogate of seasonal influenza activity. Moreover, a million of individuals in new data source will be beneficial to provide more granular influenza activity information through age and geographical stratification.

## *Introduction*

The term influenza originated from Italian, originally from the Latin '*influential'*, reflecting the effect of stars on disease epidemic[1]. As it is shown its name, influenza has shown a tremendous seasonal pattern with two distinctive characteristics in a temperate climate[2,3]. First, it starts its high activity when the temperature is getting low in temperate climate region, which means winter is the beginning time of high seasonal activity at each hemisphere. Second, the actual rise of influenza activities is varied on every year, so we cannot expect the specific time of on set in high seasonal activity.

Monitoring influenza's temporal pattern is not only critical for disease control and prevention and but also essential for pandemic influenza preparedness. Monitoring temporal trends can be explained two different approaches: Observing early aberration signals at the beginning of the high seasonal activity and detecting outnumbered events during the high seasonal activity. Identifying aberration will lead us to prepare hospital infection control action strategy and early initiation of influenza treatment to reduce the hospital/community transmission[4,5]. Moreover, capturing unexpected seasonal activity in temporal trends may give us insight for a pandemic influenza movement[6].

In South Korea, one of the current influenza surveillance systems is outpatient influenza activity monitoring based on 200 sentinels, conveniently selected, with a proportion of influenza-like-illness patient[7–9]. This surveillance approach provides the temporal trends changes over time with a proportion of influenza-like-illness based on total outpatients' medical visits at the national level. However, the intensity of influenza in the current system is a relative measured, as a proportion, which we cannot estimate actual intensity as absolute disease burden. Lack of representativeness and sample size are one of the reasons why this surveillance system could not provide any sub-group information for influenza activity. Moreover, in the World Health Organization influenza surveillance monitoring guideline, it suggested that countries should focus on not only influenza outpatient, but also other serious cases such as pneumonia and influenza admission or severe acute respiratory illness (SARI)[10,11].

There have been some studies on the use of insurance billing information as a direct measure of influenza activity[12–15]. In their approach used combinations of the international classification of disease code (ICD10) to define different case definitions of seasonal influenza. However, those new approaches are not applied to South Korea yet.

Therefore, we proposed the use of billing information and its diagnosis codes as an alternative source of influenza surveillance especially in temporal tends monitoring. We verified our proposed approach with three different timeliness comparison methods to current influenza surveillance. Since South Korea has a universal single-payer health insurance system and all of the information was databased for research purpose, the use of this information could be beneficial to support current influenza surveillance. Moreover, approximately a million individuals in the dataset will be beneficial for subgroup analysis with stratified influenza surveillance.

## *Methods*

In this study, we analyzed the information from the National Health Information Databases (NHID) from the National Health Insurance Service. South Korea provides universal-single payer insurance system to cover most of the Korean population[16]. NHID contains most of the Korean residents' information on medical treatments records with individual characteristics. To use this information for surveillance purpose, we focused on 'detailed of disease section' from 'medical treatment' database and 'insurance eligibility' database. We merged individuals' characteristics, such as age, location, to diagnosis codes in billing information which contained in 'detailed of disease section.' In billing information, we integrated date of medical procedure, medical procedure type (outpatient/inpatient), diagnosis codes (based on the Korean Classification Diseases 5 & 6, KCD 5 & 6)[17], and doctors' specialty information (internal medicine, emergency department, etc.).

To remove the confidentiality issues with individual matching information, we performed stratified random selection based on geographical location and age group. Even though we reduce our sample size, we still maintained the representativeness of our samples with enough number of individuals in one million individual's observation (2% of the entire population). The total study period was defined from 36th week of 2010 to 35th week of 2013, and a total number of participants in this study was total 1,021,576 individuals based on time period. Each influenza season was defined from current years' 36th week to next years' 35th week to account the seasonality of influenza.

There were two exclusion criteria in this study. First, we excluded multiple medical visits with the same diagnostic codes. In billing information, there are a certain amount of multiple medical visits in a short amount of time with the same disease diagnosis codes. (For example, age 3 toddler visited pediatrics 4 times during a month with Influenza due to unidentified influenza virus with other respiratory manifestations (J11.1)). In this case, we considered these multiple events are due to single disease episode. We excluded other medical visits which followed from first medical visits with the same diagnosis code within 28 days. Second, we excluded billing information from the institutions where do not focus on primary care. There were some billing information contains other respiratory illness from non-primary care departments such as orthopedics or general surgeon departments. Since those specialties are not primarily deal with acute respiratory illness, we decided that that information is not relevant to monitor temporal trends of seasonal influenza. Thus, we excluded billing information from non-primary care department, only counted information from a general physician, internal medicine, family medicine, pediatrics, emergency department, and otolaryngology.

To capture various clinical patterns of seasonal influenza, we used the International Statistical Classification of Diseases and Related Health Problems (ICD) and outpatient/inpatient status to define 3 different base case definitions. First, Influenza outpatient (FLU-OPD). This case definition followed individuals who visit the outpatient clinical setting with a confirmatory diagnosis of influenza. Therefore, we defined influenza outpatient as individuals who visited an outpatient facility with a primary diagnosis code with influenza illness (J09, J10, and J11) in their primary billing information[13,18]. Second, Pneumonia and influenza in-patients (PNI-ADM). This definition is corresponding with admitted individuals due to pneumonia and influenza[19,20]. To capture those individuals, we looked up primary diagnosis with influenza and pneumonia (J12-J18) codes in their billing information. Third, severe acute respiratory illness (SARI). This case definition includes admitted other acute lower respiratory illness on top of pneumonia and influenza. We extended our case definition from influenza and pneumonia to other acute lower respiratory illness (J20-22) in primary diagnosis code in admitted patients[12,14]. We also extended our case definition from primary only to primary and secondary diagnosis code, to increase the sensitivity of those definitions.

There has been the use of different metrics to validate the timeliness of two different surveillance sources. In this study we followed the three most common timeliness validation approaches to quantify temporal difference; peak time comparison, cross-correlation, and aberration time comparison[21–28].

In peak time comparison, we calculated the weekly proportion of influenza-like-illness or weekly incidence of case definitions and chose the epidemiological week with the highest value in each surveillance year. Then we determined the time difference between proposed and reference surveillance source. For cross-correlation, we transformed each source's epidemiological curve into a time-series format then computed time lags to the maximum correlation. We considered the time lag with the value of the greatest number as the time variation.

At the aberration time comparison, we applied the Early Aberration Reporting System (EARS)'s signal detection algorithms, developed by the United States Centers for Disease

Control and Preventions, to generate the signals at the beginning of the high seasonal activity[29,30]. We ran different EARS's algorithms, C1, C2 and C3 with various thresholds and signal counting approaches to acquire highly sensitive model and highly specified model. To generate the signals from any suspected aberration activities and gain the signals as early possible, we modified the EARS model to have high sensitivity. In high sensitivity model, we defined the first signal from the C3 algorithm in surveillance year an aberration signal. To reduce false positive and produce the only effective signal from relevant activity, we adjusted the EARS model to have a high specificity. In high specificity model, we determined the first two consecutive signals from C1 algorithm within surveillance year as an aberration signal.

We noted the epidemiological week with the first week of aberration signal from reference and each case definition. Again, we examined the time difference between the reference ad proposed surveillance source.

## *Results*

We followed up total 1,021,576 individuals for 156 weeks, from the 36th week of the year 2010 to 35th week of the year 2013. The minimum value of the proportion of influenza-like-illness patient from South Korea sentinel influenza surveillance system were 1.6, 1.5 and 1.6 percentages in season 2010, 2011, and 2012 and the maximum proportion were 23.9, 23.1 and 12.7. The lowest weekly incidence of influenza out-patient were 0.9, 0.3 and 0.3 cases per 100,000 individuals from NHIS-NSC respectively, and the highest weekly incidence of influenza out-patient were 84.7, 87.4 and 39.7 cases per 100,000 individuals. The lowest weekly incidence of pneumonia and influenza in-patient were 5.59, 7.55 and 6.23 cases per 100,000 individuals and the highest weekly incidence were 26.05, 25.83, and 22.5 cases per 100,000 individuals. For SARI, the lowest weekly incidence was 8.2, 9.3 and 8.9 cases per 100,000 individuals and the highest were 32.9, 30.1 and 27.8 cases per 100,000 individuals respectively. The relative proportion from the lowest week to highest week at each surveillance year were 14.9, 15,4 and 7.9 for influenza-like-illness. For relative incidence at each surveillance year were 94.3, 292.0 and 133.7 for influenza out-patients, 4.7, 3.4 and 3.6 for PNI-ADM and 4.0, 3.2, and 3.1 for SARI. (Figure 3-1)

The peak week from proportion of influenza-like-illness and weekly incidence of FLU-OPD, PNI-ADM, and SARI with base and extended case definition ranged from 52th week of 2010 to 1st week of 2011 for 2010 season, from 6th week of 2012 to 8th week of 2012 for 2011 season, and from 8th week of 2013 to 9th week of to 2012 season. The time difference between current influenza surveillance to proposed surveillance approach with each case definitions was one week early (season 2012 with influenza outpatient base and extended case definitions) to 2 weeks late (season 2011 with PNI-ADM and SARI base case definition only). The recent 3 years average time difference were 1 week late with PNI-ADMI and SARI case definition and 0 for other case definitions. (Table 3-1 and Table 3-2.)

The highest maximum cross-correlation value by reference and each case definition was 0.986 at 2012 season with extended influenza out-patients case definition. The lowest maximum cross-correlation value was 0.666 at 2010 season with extended pneumonia and influenza inpatient. The recent 3 years average maximum cross-correlation values from each case definitions were 0.974 and 0.976 for influenza outpatient base and extended case definitions. For PNI-ADM and SARI, the 3 years average maximum cross-correlation values were 0.748 and 0.755 for base case definition and 0.748 and 0.758 for extended case definitions. (Table 3-3 and Table 3-4.)

The time lag in maximum cross-correlation value ranged one week early (-1 week) to 2 weeks later (+2 week). The recent 3 years average maximum cross-correlation value were -0.33 for influenza out-patients base and extended case definitions and 0.67 for PNI-ADM base and extended case definitions and SARI extended case definition. And 0 for SARI base case definition.

The first week of aberration signal with high sensitivity setting was 37th week to 41st week of 2010 for 2010 season, 36th week to 38th week of 2011 for 2011 season, and 37th to 44th week of 2012 for 2012 season. The recent 3 years average time different by the first week of aberration signal with high sensitivity setting were 1.33, 0.67 and 2.33 weeks for FLU-OPD, PNI-ADM, and SARI with base case definition and 0.00, 3.00 and 3.33 weeks with extended case definition. (Table 3-5, Table 3-6, and Figure 3-2)

The first week of aberration signal with high specificity setting was 49th week to 50th week of 2010 for 2010 season, 1st week of 2012 and 2013 for 2011 and 2012 season. We could not detect any aberration signals in PNI-ADM and SARI case definitions with high specificity setting. Influenza out-patients base and extended case definitions generate signals 1 week earlier (-1 week) than reference source at season 2010 only. At season 2011 and 2012, the reference source and influenza out-outpatients case definitions generated the signals at the same week. (Table 3-7, Table 3-8, and Figure 3-2)

### *Discussion*

In this paper, we compared the timeliness of newly proposed surveillance source, billing information from the national health insurance system. We used three different timeliness validation approaches and did not observe any significant delays of influenza activities in peak time and cross-correlation methods. There were some delays of signals or no signals in aberration time comparison with different sensitivity specificity setting which led us more discussions on the use of aberration time comparison in timeliness validation approaches.

Weekly incidence of influenza out-patients reflected actual fluctuation of disease dynamics and showed the exact ratio of disease intensity by time. The unit of influenza-like-illness is proportion, which means the number of influenza-like-illness patients divided by the total number of outpatients in a week. Since it is a proportion, the epidemiological curves from this case definition could not show actual disease intensity[31,32]. Sometimes the intensity of the disease, which is the high number of ILI patients, were diluted due to a large number of denominators in proportion calculation. For example, the proportion of influenza-like-illness can be smaller due to a sheer number of other events in denominator due to chronic disease in a specific age group. However, weekly incidence calculated from NHIS-NSC provided a direct disease trend from the sampled population. This implied that the epidemiological curves from billing information are a more accurate measure. Moreover, the proportion ratio of influenza-like-illness from the lowest week to the largest weeks were 7.9 to 15.4 compared to 94.3 to

292.0. Therefore, we may interpret that the actual disease intensity changes were larger in influenza out-patients than the changes measured by sentinel surveillance.

We did not find a lack of timeliness in temporal trends from influenza out-patients case definitions compared to the temporal trends from current sentinel surveillance in peak time and cross-correlation comparison methods. Base and extended influenza out-patients case definitions showed a week early to a week later temporal trends by influenza season year in the two methods. Moreover, the maximum correlation values are higher than 95% all the time. We may conclude that the use of influenza out-patients will give the same temporal trends in perspectives of peak time and cross-correlation functions compared to the current sentinel surveillance.

While the epidemiological curve from PNI-ADM and SARI incidence followed little delayed in timeliness compared to the influenza-like-illness. In peak time comparison, base case definitions showed zero to two weeks the temporal trends each year. The natural history of influenza normally started with influenza-related symptoms, out-patients medical visited, then admitted due to severe cases[33]. The one to two weeks of delays in peak time is not because of lack of timeliness, is more likely due to the natural history of the disease itself. The value of 3 years average maximum cross-correlation was lower than the values from influenza out-patients. PNI-ADM and SARI showed higher weekly incidence than influenza out-patients in non-influenza peak season. Those observations indicated that there are also other factors in temporal trends in pneumonia and influenza in-patients and SARI than influenza infection only.

We observed signals in September with significant time delays aberrational time comparison, especially in high sensitivity setting. There were little increased of influenza activity at the beginning of September, and the lowest incidences were observed during the summer, July and August. Based on lower incidence for reference week in signal detection algorithms and a small amount of increased after school openings with high sensitivity model setting resulted generated the signals in September[34,35]. However, those signals were not directly related to the actual aberration in December and January. Therefore, we consider those signals as false positive. In high specificity setting, we could not observe the signals from PNI-ADM and SARI case definitions. Since PNI-ADM and SARI temporal trends did not show typical annual attends in epidemiological curves, the specificity model could not generate the signals.

As stated from other literature aberration comparison is not an optimal approach to compare the timeliness of two different sources[21]. It really depends on the model, model's direction (sensitivity and specificity) and priors, reference observations to build the signal detection algorithm in the model, based on previous outbreak information[30]. Aberration time is more depends on model selection process rather than actual timeliness of surveillance source and can be different by optimization of the signal detection algorithm.

There are 3 public health implication points based on this study. The epidemiological curve from the use of billing information can give a direct disease intensity as weekly incidence which will not be affected by other disease incidences, which easily can be observed in the proportion of influenza-like-illness setting. Public health professionals can estimate the actual number of patients in high activity season and set up a health emergency plan more precisely. Moreover, about a million individuals in the sampled cohort could provide stratified information for further detailed surveillance.

Importantly, we did not observe any significant time delays especially influenza out-patients activity compared to the current sentinel observations in peak time, and cross-correlation function approaches. We will observe the same peak and almost the same patterns of epidemiological curves in the proposed approach. Furthermore, there has been a use of electronic real-time 'drug utilized review (DUR)' service in drug overuse surveillance in South Korea, there is a possibility to develop a real-time influenza surveillance system with the same approach.

Lastly, this approach could provide other influenza-related diseases such as Pneumonia and Influenza inpatient and Severe Acute Respiratory Illness. Current influenza surveillance system provides a proportion of influenza-like-illness, percentage of the influenza-positive rate from specimens and the strains of positive specimens. Providing temporal trends of severe influenza cases can be beneficial to understand the natural history of influenza in South Korea, moreover to set up a projection of future public health preparedness for influenza-related admissions.

However, few more things need to addressed. Current comparison is only based on 3 years observation after the pandemic season. 3 years of observation may not be enough to make a strong conclusion of the new approach to influenza surveillance. Including more years with recent information could be beneficial to establish strong evidence to support the use of new approaches.

Moreover, those approaches are based on a retrospective study. Even though we did not observe any delays in two timeliness comparison approach, those are based on data which are already collected. When we apply this approach in the real world, we may observe administrative lacks due to billing process in the insurance system, and then we may catch the disease information a few weeks later than current surveillance system. Therefore, a new real-time technical structure such as real-time 'drug utilized review (DUR)' service in South Korea and monitoring and evaluation need to be considered as a set of surveillance system when the new surveillance approach is introduced.

Lastly, the use of other timeliness comparison methods needs to be considered. In this study, we applied three different approaches and used two of them to make a conclusion of the timeliness of a new data source. There were three different metrics in terms of influenza activity monitoring over time; average epidemic curve, seasonal threshold, alert threshold. Those two methods used to make a conclusion are based on only average epidemiological curve perspectives. Since there were two more perspectives in influenza activity motioning, other advanced approaches need to be developed and applied to verify the timeliness of new data source

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**Figure 3-1. Proportion of influenza-like-illness and weekly incidence of influenza out-patient, pneumonia and influenza in-patient, and severe acute respiratory illness with base case definitions in South Korea during influenza season 2010 to 2012**

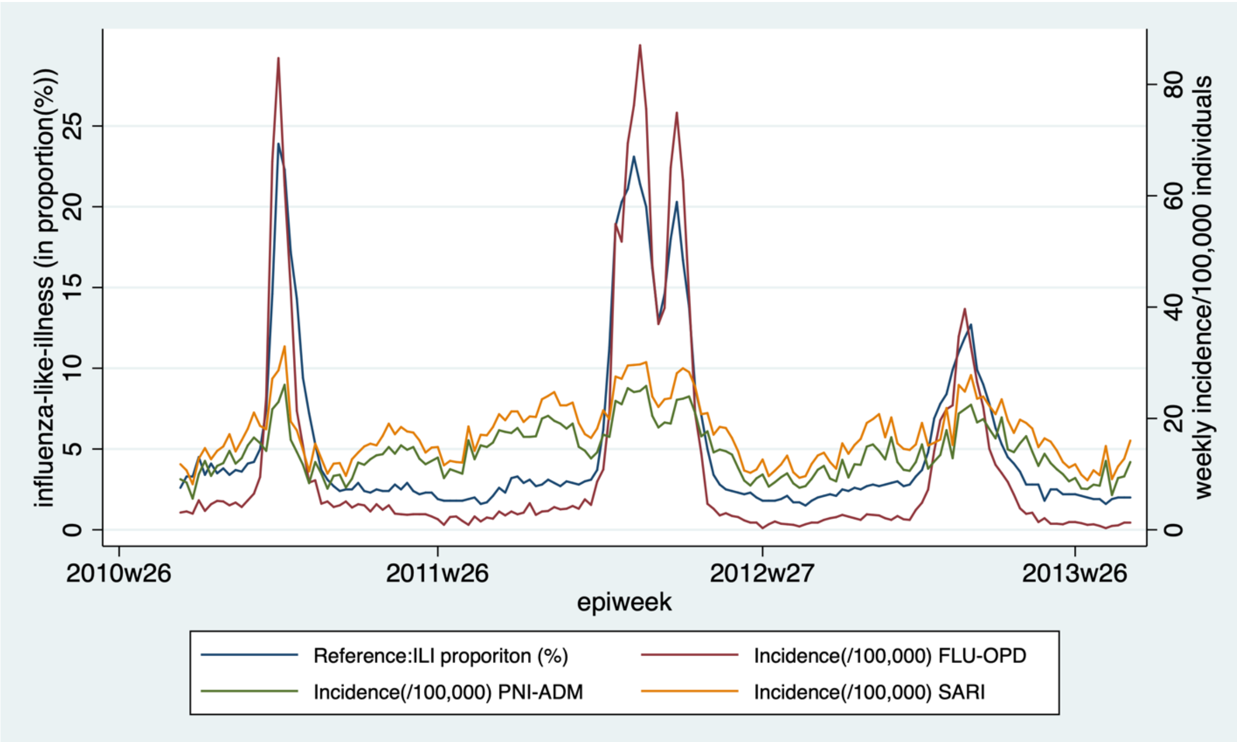



**Figure 3-2. Proportion of influenza-like-illness and weekly incidence of influenza out-patient, pneumonia and influenza in-patient, and severe acute respiratory illness with extended case definitions in South Korea during influenza season 2010 to 2012**

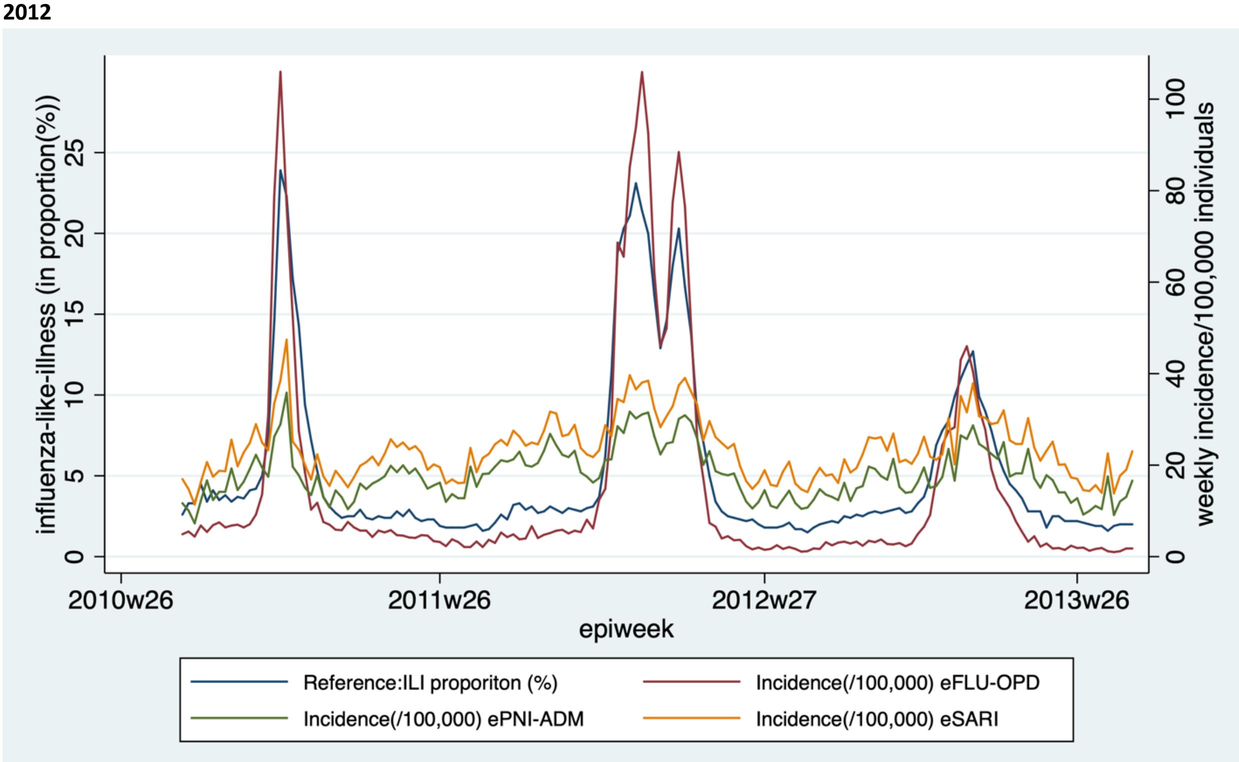


**Table 3-1. Peak week of influenza-like-illness and influenza out-patient, pneumonia and influenza in-patient, and severe acute respiratory illness in South Korea during influenza season 2010 to 2012**

| | PEAK WEEK by EPIWEEK | | | | | | |
|---|---|---|---|---|---|---|---|
| | **Reference** | **FLUOPD** | **PNIADM** | **SARI** | **eFLUOPD** | **ePNIADM** | **eSARI** |
| **10** | 2010w52 | 2010w52 | 2011w1 | 2011w1 | 2010w52 | 2011w1 | 2011w1 |
| **11** | 2012w6 | 2012w7 | 2012w8 | 2012w8 | 2012w7 | 2012w5 | 2012w5 |
| **12** | 2013w9 | 2013w8 | 2013w9 | 2013w9 | 2013w8 | 2013w9 | 2013w9 |

**Table 3-2. Peak week difference between proportion of influenza-like-illness and weekly incidence of influenza out-patient, pneumonia and influenza in-patient, and severe acute respiratory illness in South Korea during influenza season 2010 to 2012**

| | PEAK WEEK DIFFENCE | | | | | | |
|---|---|---|---|---|---|---|---|
| | Reference | FLUOPD | PNIADM | SARI | eFLUOPD | ePNIADM | eSARI |
| **10** | | 0 | 1 | 1 | 0 | 1 | 1 |
| **11** | | 1 | 2 | 2 | 1 | -1 | -1 |
| **12** | | -1 | 0 | 0 | -1 | 0 | 0 |
| **Mean** | | 0.00 | 1.00 | 1.00 | 0.00 | 0.00 | 0.00 |

**Table 3-3. The maximum cross-correlation value between proportion of influenza-like-illness and weekly incidence of influenza out-patient, pneumonia and influenza in-patient, and severe acute respiratory illness in South Korea during influenza season 2010 to 2012.**

| | The MAXIMUM CROSS-CORRELATION VALUE | | | | | | |
|---|---|---|---|---|---|---|---|
| | Reference | FLUOPD | PNIADM | SARI | eFLUOPD | ePNIADM | eSARI |
| **10** | | 0.958 | 0.676 | 0.729 | 0.957 | 0.666 | 0.715 |
| **11** | | 0.982 | 0.768 | 0.766 | 0.985 | 0.797 | 0.817 |
| **12** | | 0.982 | 0.801 | 0.770 | 0.986 | 0.782 | 0.743 |
| **Mean** | | 0.974 | 0.748 | 0.755 | 0.976 | 0.748 | 0.758 |

**Table 3-4. The time lag in maximum cross-correlation value between proportion of influenza-like-illness and weekly incidence of influenza out-patient, pneumonia and influenza in-patient, and severe acute respiratory illness in South Korea during influenza season 2010 to 2012.**

| | The TIME LAG in MAXIMUM CROSS-CORRELATION VALUE | | | | | | |
|---|---|---|---|---|---|---|---|
| | Reference | FLUOPD | PNIADM | SARI | eFLUOPD | ePNIADM | eSARI |
| **10** | | -1 | -1 | -1 | -1 | 0 | 0 |
| **11** | | 0 | 1 | 0 | 0 | 1 | 1 |
| **12** | | 0 | 2 | 1 | 0 | 1 | 1 |
| **Mean** | | -0.33 | 0.67 | 0.00 | -0.33 | 0.67 | 0.67 |

**Table 3-5. The first week of aberration signals by The Early Aberration Reporting System (EARS) with high sensitivity setting from influenza-like-illness and influenza out-patient, pneumonia and influenza in-patient, and severe acute respiratory illness in South Korea during influenza season 2010 to 2012.**

| | The FIRST WEEK of ABERRATION SIGNAL with HIGH SENSITIVITY | | | | | | |
|---|---|---|---|---|---|---|---|
| | Reference | FLUOPD | PNIADM | SARI | eFLUOPD | ePNIADM | eSARI |
| **10** | 2010w37 | 2010w39 | 2010w40 | 2010w40 | 2010w38 | 2010w40 | 2010w41 |
| **11** | 2011w36 | 2011w38 | 2011w36 | 2011w36 | 2011w36 | 2011w36 | 2011w36 |
| **12** | 2012w38 | 2012w38 | 2012w37 | 2012w42 | 2012w37 | 2012w44 | 2012w44 |

**Table 3-6. The time difference on first week of aberration signals by The Early Aberration Reporting System (EARS) with high sensitivity setting from influenza-like-illness and influenza out-patient, pneumonia and influenza in-patient, and severe acute respiratory illness in South Korea during influenza season 2010 to 2012.**

| | The TIME DIFFERENT of FIRST WEEK of ABERRATION SIGNAL with HIGH SENSITIVITY | | | | | | |
|---|---|---|---|---|---|---|---|
| | Reference | FLUOPD | PNIADM | SARI | eFLUOPD | ePNIADM | eSARI |
| **10** | | 2 | 3 | 3 | 1 | 3 | 4 |
| **11** | | 2 | 0 | 0 | 0 | 0 | 0 |
| **12** | | 0 | -1 | 4 | -1 | 6 | 6 |
| **Mean** | | 1.33 | 0.67 | 2.33 | 0.00 | 3.00 | 3.33 |

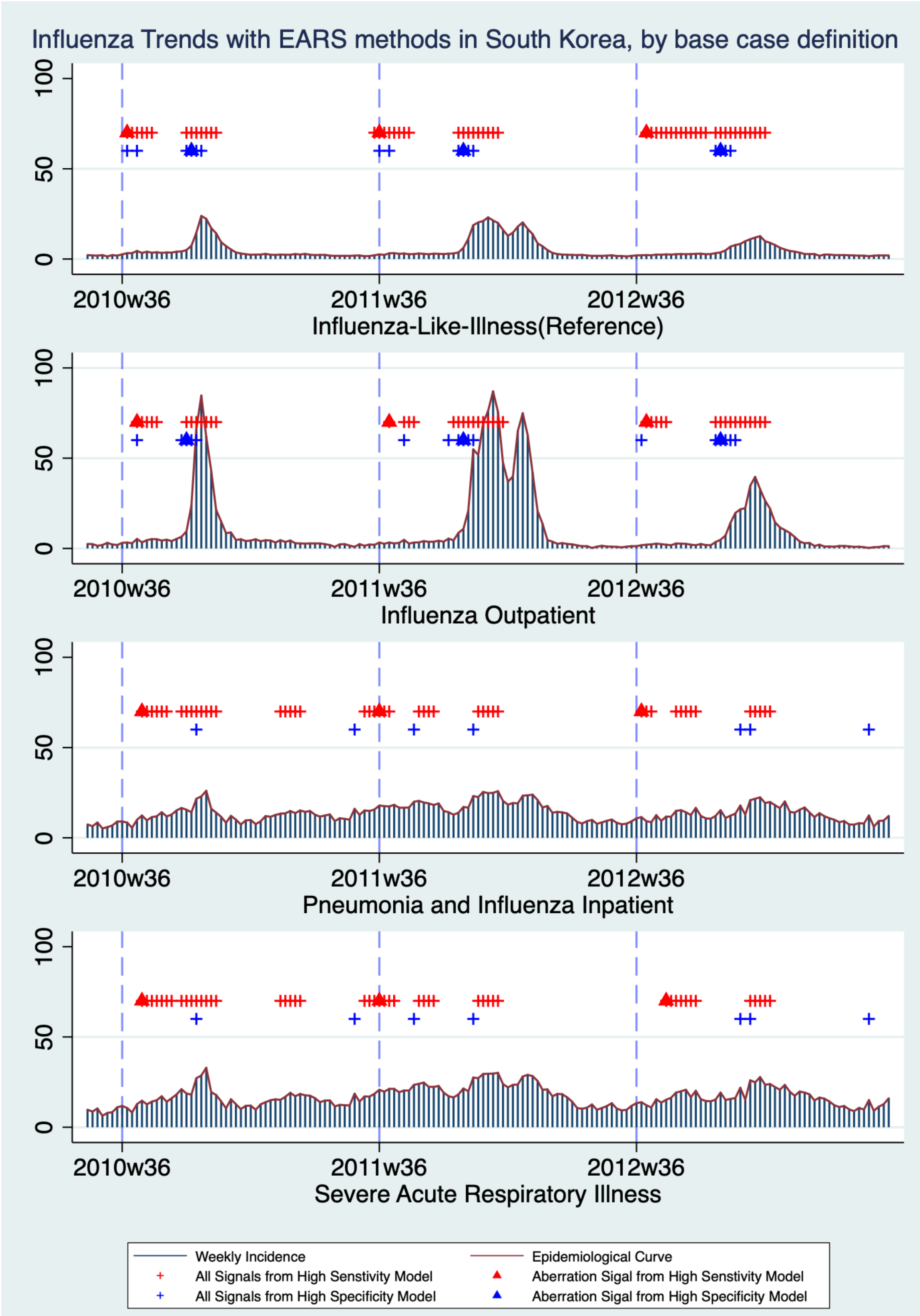
**Table 3-7. The first week of aberration signals by the Early Aberration Reporting System (EARS) with high specificity setting from influenza-like-illness and influenza out-patient, pneumonia and influenza in-patient, and severe acute respiratory illness in South Korea during influenza season 2010 to 2012.**

| | The FIRST WEEK of ABERRATION SIGNAL with HIGH SPECIFICITY | | | | | | |
|---|---|---|---|---|---|---|---|
| | Reference | FLUOPD | PNIADM | SARI | eFLUOPD | ePNIADM | eSARI |
| **10** | 2010w50 | 2010w49 | n/a | n/a | 2010w49 | n/a | n/a |
| **11** | 2012w1 | 2012w1 | n/a | n/a | 2012w1 | n/a | n/a |
| **12** | 2013w1 | 2013w1 | n/a | n/a | 2013w1 | n/a | n/a |

**Table 3-8. The time difference on first week of aberration signals by the Early Aberration Reporting System (EARS) with high specificity setting from influenza-like-illness and influenza out-patient, pneumonia and influenza in-patient, and severe acute respiratory illness in South Korea during influenza season 2010 to 2012.**

| | The TIME DIFFERENT of FIRST WEEK of ABERRATION SIGNAL with HIGH SPECIFICITY | | | | | | |
|---|---|---|---|---|---|---|---|
| | Reference | FLUOPD | PNIADM | SARI | eFLUOPD | ePNIADM | eSARI |
| **10** | | -1 | n/a | n/a | -1 | n/a | n/a |
| **11** | | 0 | n/a | n/a | 0 | n/a | n/a |
| **12** | | 0 | n/a | n/a | 0 | n/a | n/a |
| **Mean** | | -0.33 | | | -0.33 | | |

**Figure 3-3. Application of the Early Aberration Reporting System (EARS) with high sensitivity/high specificity setting to reference and proposed surveillance source with different case definitions.**



*Chapter 4 : The comparison of seasonal influenza trends in South Korea 2010-2013: temporal association of influenza activity by different geographical locations and age groups*

## *Abstract*

**Objective** To evaluate the temporal association of seasonal influenza activity by different geographical subdivisions and age groups in South Korea 2010-2013.

**Participants** Randomly sampled residents, 1,021,576 who lived in South Korea from 36th weeks 2010 to 35th weeks of 2013.

**Methods** Influenza case was defined by influenza-related diagnosis in the national insurance billing information. We applied 3 different timeliness validation methods (peak time comparison, aberration time comparison, and time-series correlation) to 16 different subdivisions and 5 different age groups to national observation and measured time difference.

**Results** For a peak time comparison, time difference by geographical subdivision ranged from -4 weeks to 7 weeks and by age group ranged from -2 to 6 weeks. For time-series correlation, time lag ranged from -1 to 3 weeks in geographical comparison and was -1 week to 1 week in age group comparison. For aberration time comparison with high specificity model, time difference of the first aberration signal was from 0 to 7 weeks in geographical subdivision and was -12 weeks to 3 weeks in age group analysis.

**Conclusions** Seoul Capital Area showed an earlier sign of influenza activity by peak time and correlation. Age between 6 to 15 showed a prior peak and time lag to national observation after accounting double peak phenomenon and age over 65 showed the later sign of influenza. Public health professionals and subdivision governments should focus those subpopulations for an early sign of national level influenza activity.

## *Introduction*

Influenza is one of the most common infectious diseases in the world and has the largest burden of disease in mortality and morbidity[1,2]. Influenza virus has distinctive patterns of transmission with symptom development by temperature and humidity in the temperate region[3,4]. It is commonly known as '*seasonal*' influenza due to its annual activity pattern in temperate climate region[5]. Even though it usually develops its seasonal activity at the beginning of the winter on each hemisphere, the exact time of aberration is different year by year and by distinct sub-population[6].

There have been many studies to monitor temporal trends of influenza by region and age group. Traditionally it is known that influenza showed different activity by region, altitude, and climate[4]. Researchers in the United States identified that influenza aberration at school children in Washington DC preceded the sign of influenza activity compare to the sentinel sites in Atlanta[7]. Recent studies on influenza confirmed cases in Mexico identified that influenza outpatient peak differed by state level and influenza activity from some states could be a predictor for the national-level influenza outbreak activity[8,9].

However, there is no study conducted in South Korea to understand the influenza temporal trends by different geographical subdivision or different age group. South Korea once had an influenza surveillance system with stratified influenza-like-illness proportion reporting by 4 different regions, but no temporal association investigation was conducted[10]. After revision of sentinel surveillance, Korea Centers for Disease Control and Preventions started providing the influenza-like-illness proportion by different age group in their public reports, but no information on temporal association between age group was presented[11]. Moreover, due to the small sample size and lack of the representativeness from the sentinel sites, the current surveillance system cannot provide influenza activity by political subdivision level, which is the second largest unit of policy implementation after national level[12].

Importantly, the influenza-like-illness proportion cannot present exact disease temporal trends due to the large proportion of chronic disease in the denominator, especially in the elderly age group.

Monitoring temporal trends of influenza and its related disease by different sub-population is beneficial to decrease the transmission in population and establish a set of public health preparedness. By identifying the first group who showed the aberration of influenza activity, we could set up vaccination strategy to reduce the starts at the population or will could target that population for early initiation of treatment to reduce transmission of influenza at the beginning of the season[13–16]. Through understanding temporal associations between communities and disease intensity, we could use those serial patterns in population as a tool of early aberration alert system. Moreover, assessing the disease dynamics by disease intensity, we could prepare the peak of severe cases which help us to establish public health preparedness.

Therefore, we propose a study to compare temporal trends of influenza by geographical subdivision and age group. This approach will help us to capture the difference of seasonal influenza activity by each state or provinces and age group and also understand the temporal association between those subpopulations. Importantly, identifying subpopulation who start the influenza activity first will guide us to set up public health preparedness by considering those subpopulations as an early signal from national-wide influenza activity.

## *Method*

The study population was defined individuals who lived in South Korea from the 36th week of 2010 to 35th week of 2013 (which is corresponded influenza surveillance year from 2010 to 2012) from the National Health Insurance Service-National Same Cohort[17]. We used the national health insurance data sharing program to assess the data. The National Sample Cohort provides nationally representative individuals with stratified random sampling process based on age, sex, eligibility of the insurance and income level[18].

We used one of the commonly used case definitions to determine influenza activity in the surveillance by other researchers[19,20]. Influenza activity is considered any influenza-specific diagnostic code (J09-J11) in primary diagnosis code in billing information without a repeated visit in 30 days at primary outpatient health care facilities only. Based on this case definition, we calculated the number of cases by epidemiological week with geographical subdivisions and age-group. We used the mid-year population by each surveillance year as the population at risk. The number of individuals by each population on the last day of the year used as a denominator to calculate the weekly incidence of influenza.

We followed timeliness validation approaches to quantify temporal associations[21–28]. We applied three different methods to present time difference; peak time comparison, cross-correlation, and aberration time comparison. For peak time comparison, we calculated the week of the highest number in influenza activity and compared the time of between two groups. In cross-correlation, we transformed observations into time series format and calculated the correlation values with different time lags. We counted the time lag with maximum correlation value as the time difference. At the aberration time comparison, we adopted the early aberration reporting system (EARS) developed by the United States Centers for Disease Control and Preventions[29,30]. We modified EARS's signal algorithms to adjust the sensitivity and specificity of the model. We defined the first signal from the C3 algorithm as an aberration signal in high sensitivity setting to focus on generating signals from any suspicious activity. In contrast, we defined the two consecutive signals from C1 algorithm as an aberration signal in high specificity setting to reduce the false positive from the signals based on non-seasonal influenza activity. Finally, we tabulated the first week of aberration signals from each population and calculated the time difference by two different sensitivity setting.

To describe the temporal association of seasonal influenza activity, we stratified our comparison in two different strata, geographical subdivision and age group. We applied the ISO 3166-2 published by the international organization for standardization into geographic location to make 16 different subdivisions, which is commonly known as state-level or province-level[31]. However, we had to exclude Se-Jong Special Self-governing City due to rapid population changes since it was newly established during the study period[32]. We followed the Global Epidemiological Surveillance Standards for Influenza by the World Health Organization to process age-grouping[33]. Due to the confidentiality of individuals in the data sharing program, we could not calculate the exact age at the time medical visit. Therefore, we used the middle-year age during the surveillance year as a reference and merged two youngest age group 0-2 year and 2-5 year as one group age under 5. At last, we used 5 different major age grouping for analysis: age under 5 years, 5 to 15 years, 15 to 50 years, 50 to 65 years, and over 65 years.

## *Results*

At the national level, the peak week of influenza activity was the 52nd week of 2010, 7th week of 2012, and 8th week of 2013 for 2010, 2011 and 2012 influenza season. In state-level comparison, the peak week of influenza ranged from 51st week of 2010 to 2nd week of 2011, from 6th of 2011 to 13th week of 2012, and from 4th week of 2012 to 11th week of 2013 respectively. (Table 4-1 and Figure 4-1)

The time difference of geographical subdivision level compared to the national level by peak level comparison ranged from 4 weeks early (-4 week, Seoul and Jeju 2012 season) to 6 weeks late (+6 week, Daejeon 2011 season). For three years average, Seoul showed two weeks of early peak week while ChungBuk showed 2 weeks of later peak compared to the national peak. (Table 4-2)

For cross-correlation value comparison in geographical subdivision comparison, the maximum cross-correlation value ranged from 0.750 (Daejeon season 2011) to 0.990 (GyeonNam season 2010). For three years average, Busan showed the highest value as 0.979, and Jeju showed the lowest value as 0.780. (Table 4-3)

For the time difference measured by time lag with maximum cross-correlation value were one week early (-1 week) to 3 weeks late (+3 week). Three years average time lag was -0.33 week from Seoul and Gangwon, and 1 week late for JeonBuk. (Table 4-4)

The first week of aberration signal from high sensitivity model was 39th week of 2010, 38th week of 2011 and 38th week of 2012 at national level, and from 36th week to 50th week for 2010 season, 37th week to next year's 1st week for season 2011 and 36th week to 50th week for season 2010. The time difference of the first week of aberration signal from high sensitivity model was -3 weeks (Seoul 2010 season) early to 15 weeks late (Ulsan 2011 season). For three years average, ChungNam showed the least late time difference as 0.67 week while Ulsan showed the most time difference by 11 weeks of later signals. In 2012 season, we could not detect the aberration signal from Jeju based on high sensitivity model definition. (Table 4-5 and 4-6).

The 49th week of 2010, 1st week of 2012 and 2013 were the first week of aberration signal from high specificity model. The range of the first week by geographical subdivision was from 50th week to 52nd week of 2010, 2nd week to 5th week of 2012, and 2nd week of 2012 to 8th week of 2013 for 2010, 2011 and 2012 season. In subdivision level time different comparison, Daejeon showed the least time difference compared to the national level, Jeju showed the most time difference as 4-week later signal. However, we could not detect 14 aberration signals based on the high specificity model case definition. (Table 4-7 and 4-8).

In age group temporal association analysis, the peak week of influenza activity by age group was 51st week of 2010 to 1st week of 2011 for 2010 season, 5th week to 13th week of 2012 for 2011 season, and 7th week to 8th week of 2013 for 2012 season. The time difference by peak time comparison was -2 weeks (Age under 5 in season 2011) to 6 weeks (Age 6-15 in season 2011). For three average, Age under 5 showed the earlier peak (- 0.67 week), and Age 6-15 showed 1.67 week later peak compared to the overall national peak. (Table 9, 10 and Figure 4-2)

The maximum cross-correlation value ranged from 0.859 (Age over 65 in 2011 season) to 0.998 (Age 16-50 in 2010 season) for 3 years. The 3 years average maximum cross-correlation value by age group was 0.897 (Age over 65) to 0.986 (Age 16-50). The time difference measured by the time lag with maximum cross-correlation value was -1 week to 1 week, and -0.33 week early in Age 6-15 group and 0.67 week late in Age-under-5 group in 3 years average. (Table 4-11 and 4-12)

The first week of aberration signals with high sensitivity model was the 36th week to 41st week for 2010 season, 36th week to 52nd week for 2011 season, and 38th week to next year's 2nd week for 2012 season. The time difference from each age group compared to the overall national signal were 3 weeks early (-3 weeks, Age 51-65 in 2010 season) to 16 weeks late (+16 weeks, Age over 65 in 2012 season). In three years average, Age 6-15 showed the -1 week earliest signal but Age under 5 showed 6 weeks last signal compared to the reference. (Table 4-13, 4-14, and Figure 4-3)

In high specificity setting model, the first week of aberration signal was 37th week to 52nd week in 2010 season, 2nd week to 3rd week of next year's in 2011 season, and 3rd to 4th week of the following year's in 2012 season. The time difference was -12 weeks earlier (Age 6-15 in 2010 season) to 3 weeks later (Age 51-65 in 2010 season and Age 6-15 in 2012 season). In 3 year-average, Age under showed -2.33 week of early signal and Ager 51-65 showed 2.5 weeks of the late signal. However, in the high specificity model, we could not generate the eligible signals based on case definition in Age over 65, and Age 51 – 65 at the year of 2012 (Table 4-15 and 4-16)

## *Discussion*

There were early peaks in the area of Seoul Capital Area; Seoul, Gyeonggi, and Incheon. Those subdivision areas are located in the north-west of South Korea and highly populated area. There are two potential causes of this phenomenon. A recent study from the Science mentioned that the large population needs to be considered as an epicenter of influenza activity[34,35]. Since the Seoul Capital Area contributes 50% of the entire population, we may think the Seoul Capital Area is an epicenter for South Korea.

Moreover, previous studies in other countries suggested that the seasonality of influenza patterns is more like depends on the transmission of specific strains from the tropical region[36,37]. South Korea does not have any land border, the most common way come in and out of the country is through the air flight or major port. Incheon, connected Seoul with land boarder, has the largest airport in South Korea and major harbor ports connected with China. The origin of influenza activity can be imported from international travelers entering South Korea through Seoul Capital Area.

There are some odd delays of influenza peak in season 2011. Those observations are due to double peak patterns in influenza activity[12,38]. Not like 2010 and 2012, season 2011 showed the double peak pattern. In double-peak season, the first peak is usually the more prominent peak than the second peak. However, some geographical locations develop more prominent peaks in their second wave. The time difference in 2011 is due to the double-peak phenomenon, not time difference.

Seoul, Gyeonggi-do, and Busan showed the highest value in 3 years average at the maximum cross-correlation comparison. It is more like the population contribution from those subdivisions to the nation is large enough to show the strong cross-correlation. At the same time, Jeju showed 75% of cross-correlation value which is the lowest in the states.  The reason why Jeju showed different pattern could be considered that because Jeju is an island apart from mainland South Korea. However, Jeju is the smallest subdivision unit among 16 states. Moreover, due to the small participants after stratified sampling process, we frequently observed 0 cases per week in Jeju. Therefore, it is not clear Jeju island has unique patterns of influenza activity, or it is due to lack of the observation in time series analysis, we need to give extra caution on interpreting the cross-correlation values, especially when we have different population contribution to the nation from each subdivision.

Even though we could not make any definite conclusion about the temporal association in age group comparison, there are two directions about the temporal association. Age under 5 and 6 to 15 showed the early development of influenza activity, and age over 65 showed little delayed activity of influenza compared to the overall population.

Age over 65 showed late development of influenza in peak time and cross-correlation comparison. There are two potential explanations for this. First, this can be due to actual disease transmission dynamic; we have the first transmission in young people, then later transmission in older people[23]. A second potential explanation is about access to health. Compared to younger people, older people did not recognize their symptom until it developed as severe cases[35]. So, they came to the clinic a few days (or a week) later compare to the younger people even though they have the same time of infected. We need more studies to understand the phenomenon whether later influenza activity in older people is due to actual disease dynamics or social factors related to access to health.

Age 6-15 showed early sings in aberration time comparison. Those signals in high sensitivity setting at the age group 5-15 are due to in school openings in September[39,40]. Even though in timeliness comparison approach, we consider these signals as false positive for influenza high activity, these signals are important as situation awareness for the potential beginning point of influenza outbreak and can be used a key for pandemic preparedness

This study has strength with implication point. This approach showed the possibility of use of billing information in stratified influenza surveillance, especially in temporal trends monitoring. Current influenza surveillance used sentinel surveillance with influenza-like-illness with little or no stratification on a specific population. In this study, we used billing information as surveillance source and stratified influenza activity by different geographical subdivision and age group as world health organization suggested. Moreover, the current health insurance system with real-time Drug Utilization Review (DUR) gives direction to establish real-time influenza surveillance based on billing information shortly.

Moreover, based on this analysis, we could specify a potential target population to monitor influenza activity. Even though we did not have enough observation years to build a particular direction of the temporal association between subpopulation, there is a trend of influenza activity by different geographical location and different age group. With more years of observation to support this direction, we could find a key location or/and age group as a beginning point of influenza activity in South Korea. Enhancing vaccination strategy, early massive initiation of treatment, and campaigns to reduce the transmission in hospital and community in key population will be an essential public health preparedness plan to reduce the burden and intensity of influenza in the future.

However, there are a few limitations when we need to consider the use of this study. First, we only have 3 years of observation in this study. Some of the findings showed the clear direction of the temporal association; most of the observations did not show the clear direction of association in the limited study period. We need to include more years in a future study to find out concordance patterns of association in long term observation.

Second, national level observation is probably not sufficiently independent from subpopulation observations. We used one of the most common ways to validate the timeliness of two different data source. However, in aim 3, our data comparison was conducted by geographical subdivision level or age-group to the national average which made of those subpopulations. For example, Seoul Capital Area contributes 50% of the entire Korean population. Therefore, their maximum cross-correlation value should be high in comparison. The peak observed in Seoul Capital Area contributions 50% of peak in national peak due to population size. Therefore, comparing the temporal trends association to the nation observation may give us bias result. However, there is no clear standard or guideline to analyze the subpopulation level trends. More studies on methods development on temporal trends analysis are needed to provide precise estimation about those associations.

Finally, the use of aberration detection algorithm in temporal trends comparison gives more information on model validity rather than temporal associations by population. As it was discussed previous literature, aberration signals from influenza activity highly depend on a model setting with sensitivity and specificity or model selection process itself[21,30]. We have more and early signals in high sensitivity setting, but those can be easily considered as false positive. Sometimes we could not generate aberration signals based on our case definition in high specificity setting. If we used the other model, instead of EARS, we may see the same results based on model sensitivity and specificity. Most of the signal generating algorithms are based on previous years or weeks observation in that data source, which means there is no universal signal generating algorithms which can be applied easily in all different dataset. Therefore, it is appropriate to use aberration signals comparison as a supplementary approach in temporal trends association instead of the main methods to validate the association.

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**Figure 4-1. Weekly incidence of influenza out in South Korea and other 16 different states during influenza season 2010 to 2012**

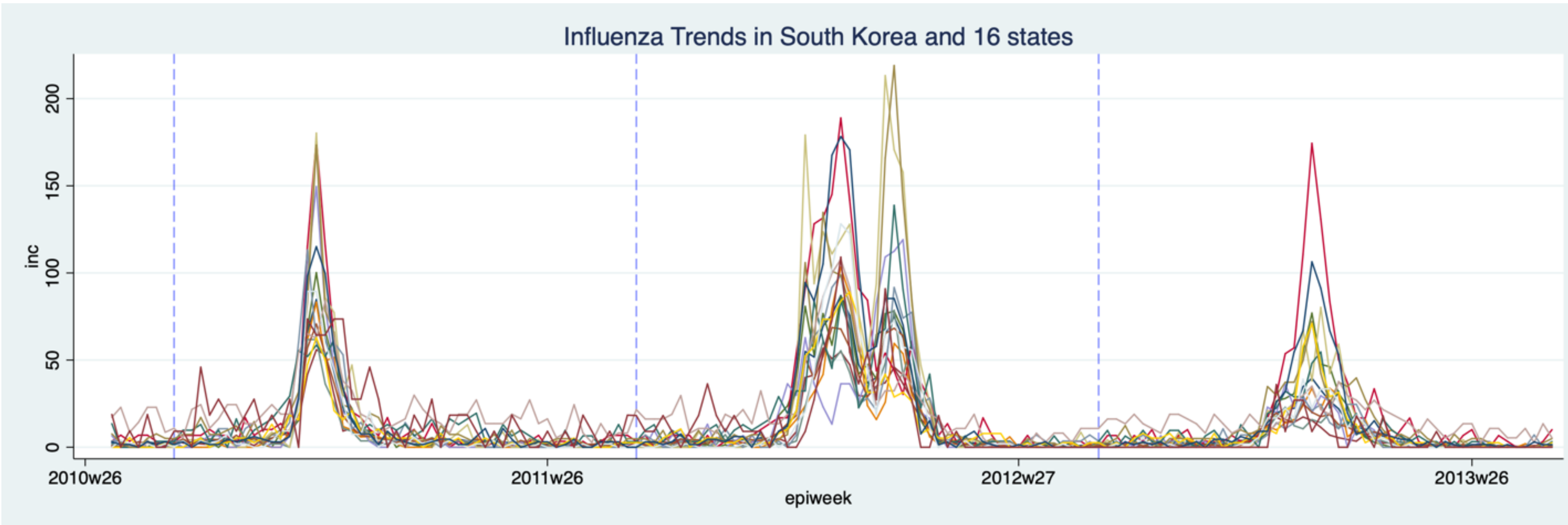


**Table 4-1. Peak week of influenza out-patient in South Korea and other 16 different states during influenza season 2010 to 2012**

| PEAK WEEK by EPIWEEK | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Nation** | **Seoul** | **Busan** | **Daegu** | **Incheon** | **Gwangju** | **Daejeon** | **Ulsan** | **Jeju** |
| **10** | 2010w52 | 2010w52 | 2010w52 | 2010w52 | 2010w51 | 2010w52 | 2010w52 | 2010w52 | 2010w51 |
| **11** | 2012w7 | 2012w5 | 2012w7 | 2012w7 | 2012w13 | 2012w7 | 2012w14 | 2012w12 | 2012w7 |
| **12** | 2013w8 | 2013w4 | 2013w8 | 2013w8 | 2013w5 | 2013w8 | 2013w5 | 2013w9 | 2013w4 |
| | | **Gyeongi** | **Gangwon** | **Chung-Buk** | **Chung-Nam** | **Jeon-Buk** | **Jeon-Nam** | **Gyeon-Buk** | **Gyeon-Nam** |
| **10** | | 2010w52 | 2010w51 | 2011w2 | 2010w52 | 2011w1 | 2010w52 | 2010w51 | 2010w52 |
| **11** | | 2012w6 | 2012w7 | 2012w13 | 2012w13 | 2012w7 | 2012w8 | 2012w7 | 2012w7 |
| **12** | | 2013w7 | 2013w7 | 2013w9 | 2013w8 | 2013w11 | 2013w8 | 2013w7 | 2013w8 |

**Table 4-2. Peak week difference of influenza out-patient between South Korea and other 16 different states during influenza season 2010 to 2012**

| PEAK WEEK DIFFENCE | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Nation** | **Seoul** | **Busan** | **Daegu** | **Incheon** | **Gwangju** | **Daejeon** | **Ulsan** | **Jeju** |
| **10** | | 0 | 0 | 0 | -1 | 0 | 0 | 0 | -1 |
| **11** | | -2 | 0 | 0 | 6 | 0 | 7 | 5 | 0 |
| **12** | | -4 | 0 | 0 | -3 | 0 | -3 | 1 | -4 |
| | | **Gyeongi** | **Gangwon** | **Chung-Buk** | **Chung-Nam** | **Jeon-Buk** | **Jeon-Nam** | **Gyeon-Buk** | **Gyeon-Nam** |
| **10** | | 0 | -1 | 2 | 0 | 1 | 0 | -1 | 0 |
| **11** | | -1 | 0 | 6 | 6 | 0 | 1 | 0 | 0 |
| **12** | | -1 | -1 | 1 | 0 | 3 | 0 | -1 | 0 |

**Table 4-3. The maximum cross-correlation value of influenza out-patient in South Korea and other 16 different states during influenza season 2010 to 2012.**

| The MAXIMUM CROSS-CORRELATION VALUE | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Nation** | **Seoul** | **Busan** | **Daegu** | **Incheon** | **Gwangju** | **Daejeon** | **Ulsan** | **Jeju** |
| **10** | | 0.985 | 0.989 | 0.985 | 0.975 | 0.983 | 0.982 | 0.966 | 0.768 |
| **11** | | 0.987 | 0.975 | 0.927 | 0.938 | 0.895 | 0.750 | 0.936 | 0.835 |
| **12** | | 0.936 | 0.972 | 0.914 | 0.870 | 0.943 | 0.885 | 0.905 | 0.737 |
| | | **Gyeongi** | **Gangwon** | **Chung-Buk** | **Chung-Nam** | **Jeon-Buk** | **Jeon-Nam** | **Gyeon-Buk** | **Gyeon-Nam** |
| **10** | | 0.998 | 0.914 | 0.862 | 0.961 | 0.879 | 0.962 | 0.981 | 0.990 |
| **11** | | 0.990 | 0.943 | 0.884 | 0.913 | 0.880 | 0.921 | 0.944 | 0.954 |
| **12** | | 0.956 | 0.830 | 0.918 | 0.938 | 0.772 | 0.938 | 0.945 | 0.956 |

**Table 4-4. The time lag in maximum cross-correlation value of influenza out-patient in South Korea and other 16 different states during influenza season 2010 to 2012.**

| The TIME LAG in MAXIMUM CROSS-CORRELATION VALUE | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Nation** | **Seoul** | **Busan** | **Daegu** | **Incheon** | **Gwangju** | **Daejeon** | **Ulsan** | **Jeju** |
| **10** | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| **11** | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **12** | | -1 | 0 | 0 | 0 | 0 | 0 | 0 | -1 |
| | | **Gyeongi** | **Gangwon** | **Chung-Buk** | **Chung-Nam** | **Jeon-Buk** | **Jeon-Nam** | **Gyeon-Buk** | **Gyeon-Nam** |
| **10** | | 0 | -1 | 0 | 0 | 0 | 0 | 0 | 0 |
| **11** | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **12** | | 0 | 0 | 0 | 0 | 3 | 0 | 0 | 0 |

**Table 4-5. The first week of aberration signals in influenza out-patient by the Early Aberration Reporting System (EARS) with high sensitivity setting in South Korea and other 16 different states during influenza season 2010 to 2012.**

| The FIRST WEEK of ABERRATION SIGNAL with HIGH SENSTIVITY | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Nation** | **Seoul** | **Busan** | **Daegu** | **Incheon** | **Gwangju** | **Daejeon** | **Ulsan** | **Jeju** |
| **10** | 2010w39 | 2010w36 | 2010w44 | 2010w49 | 2010w39 | 2010w44 | 2010w41 | 2010w50 | 2010w39 |
| **11** | 2011w38 | 2011w47 | 2011w49 | 2011w38 | 2011w46 | 2011w36 | 2011w52 | 2012w1 | 2011w44 |
| **12** | 2012w38 | 2012w39 | 2012w46 | 2012w40 | 2012w38 | 2012w38 | 2012w41 | 2012w45 | |
| | | **Gyeongi** | **Gangwon** | **Chung-Buk** | **Chung-Nam** | **Jeon-Buk** | **Jeon-Nam** | **Gyeon-Buk** | **Gyeon-Nam** |
| **10** | | 2010w39 | 2010w41 | 2010w39 | 2010w39 | 2010w50 | 2010w47 | 2010w42 | 2010w44 |
| **11** | | 2011w42 | 2011w37 | 2011w52 | 2011w39 | 2011w41 | 2011w40 | 2011w51 | 2011w41 |
| **12** | | 2012w40 | 2012w50 | 2012w37 | 2012w39 | 2012w36 | 2012w41 | 2012w41 | 2012w50 |

**Table 4-6. The time difference on first week of aberration signals in influenza out-patient by the Early Aberration Reporting System (EARS) with high sensitivity setting in South Korea and other 16 different states during influenza season 2010 to 2012.**

| The TIME DIFFERENT of FIRST WEEK of ABERRATION SIGNAL with HIGH SENSTIVITY | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Nation** | **Seoul** | **Busan** | **Daegu** | **Incheon** | **Gwangju** | **Daejeon** | **Ulsan** | **Jeju** |
| **10** | | -3 | 5 | 10 | 0 | 5 | 2 | 11 | 0 |
| **11** | | 9 | 11 | 0 | 8 | -2 | 14 | 15 | 6 |
| **12** | | 1 | 8 | 2 | 0 | 0 | 3 | 7 | |
| | | **Gyeongi** | **Gangwon** | **Chung-Buk** | **Chung-Nam** | **Jeon-Buk** | **Jeon-Nam** | **Gyeon-Buk** | **Gyeon-Nam** |
| **10** | | 0 | 2 | 0 | 0 | 11 | 8 | 3 | 5 |
| **11** | | 4 | -1 | 14 | 1 | 3 | 2 | 13 | 3 |
| **12** | | 2 | 12 | -1 | 1 | -2 | 3 | 3 | 12 |

**Table 4-7. The first week of aberration signals in influenza out-patient by the Early Aberration Reporting System (EARS) with high specificity setting in South Korea and other 16 different states during influenza season 2010 to 2012.**

| The FIRST WEEK of ABERRATION SIGNAL with HIGH SPECIFICITY | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Nation | Seoul | Busan | Daegu | Incheon | Gwangju | Daejeon | Ulsan | Jeju |
| 10 | 2010w49 | 2010w50 | 2010w52 | 2010w50 | 2010w51 | 2010w51 | 2010w51 | 2010w51 | |
| 11 | 2012w1 | 2012w3 | 2012w1 | 2012w2 | 2012w4 | 2012w3 | 2012w1 | 2012w3 | 2012w5 |
| 12 | 2013w1 | | 2013w3 | 2013w8 | 2013w1 | 2013w4 | | | |
| | | Gyeongi | Gangwon | Chung-Buk | Chung-Nam | Jeon-Buk | Jeon-Nam | Gyeon-Buk | Gyeon-Nam |
| 10 | | 2010w51 | 2010w51 | | 2010w51 | | 2010w52 | 2010w51 | 2010w51 |
| 11 | | 2012w1 | 2012w4 | | 2012w3 | 2012w4 | 2012w3 | 2012w3 | 2012w3 |
| 12 | | 2013w2 | | | | | | 2013w3 | |

**Table 4-8. The time difference on first week of aberration signals in influenza out-patient by the Early Aberration Reporting System (EARS) with high specificity setting in South Korea and other 16 different states during influenza season 2010 to 2012.**

| The FIRST WEEK of ABERRATION SIGNAL with HIGH SPECIFICITY | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Nation | Seoul | Busan | Daegu | Incheon | Gwangju | Daejeon | Ulsan | Jeju |
| 10 | | 1 | 3 | 1 | 2 | 2 | 2 | 2 | |
| 11 | | 2 | 0 | 1 | 3 | 2 | 0 | 2 | 4 |
| 12 | | | 2 | 7 | 0 | 3 | | | |
| | | Gyeongi | Gangwon | Chung-Buk | Chung-Nam | Jeon-Buk | Jeon-Nam | Gyeon-Buk | Gyeon-Nam |
| 10 | | 2 | 2 | | 2 | | 3 | 2 | 2 |
| 11 | | 0 | 3 | | 2 | 3 | 2 | 2 | 2 |
| 12 | | 1 | | | | | | 2 | |

**Figure 4-2. Weekly incidence of influenza out in South Korea and 5 different age group during influenza season 2010 to 2012**

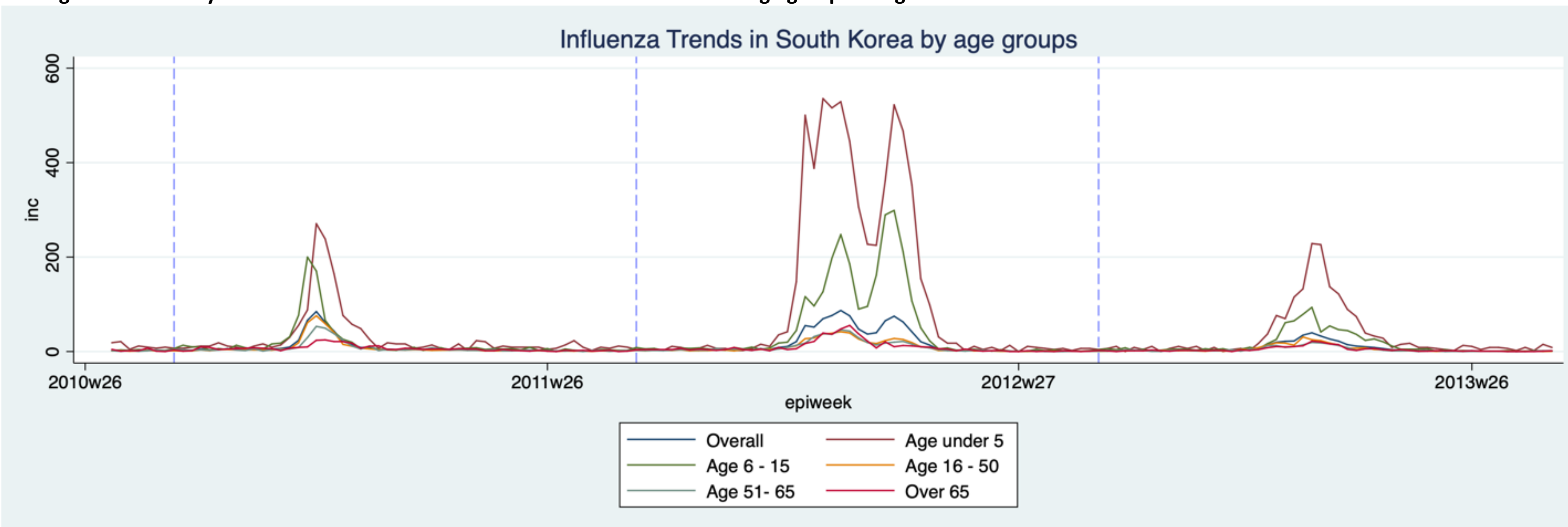


**Table 4-9. Peak week of influenza out-patient in South Korea and 5 different age group during influenza season 2010 to 2012**

| | PEAK WEEK by EPIWEEK | | | | | |
|---|---|---|---|---|---|---|
| | **Reference** | **Age under 5** | **Age 6-15** | **Age 16-50** | **Age 51-65** | **Age over 65** |
| **10** | 2010w52 | 2010w52 | 2010w51 | 2010w52 | 2010w52 | 2011w1 |
| **11** | 2012w7 | 2012w5 | 2012w13 | 2012w7 | 2012w7 | 2012w8 |
| **12** | 2013w8 | 2013w8 | 2013w8 | 2013w7 | 2013w8 | 2013w8 |

**Table 4-10. Peak week difference of influenza out-patient between South Korea and 5 different age group during influenza season 2010 to 2012**

| | PEAK WEEK DIFFENCE | | | | | |
|---|---|---|---|---|---|---|
| | **Reference** | **Age under 5** | **Age 6-15** | **Age 16-50** | **Age 51-65** | **Age over 65** |
| **10** | | 0 | -1 | 0 | 0 | 1 |
| **11** | | -2 | 6 | 0 | 0 | 1 |
| **12** | | 0 | 0 | -1 | 0 | 0 |

**Table 4-11. The maximum cross-correlation value of influenza out-patient in South Korea and 5 different age group during influenza season 2010 to 2012.**

| | The MAXIMUM CROSS-CORRELATION VALUE | | | | | |
|---|---|---|---|---|---|---|
| | **Reference** | **Age under 5** | **Age 6-15** | **Age 16-50** | **Age 51-65** | **Age over 65** |
| **10** | | 0.955 | 0.942 | 0.998 | 0.958 | 0.876 |
| **11** | | 0.985 | 0.946 | 0.984 | 0.941 | 0.859 |
| **12** | | 0.964 | 0.948 | 0.976 | 0.956 | 0.955 |

**Table 4-12. The time lag in maximum cross-correlation value of influenza out-patient South Korea and 5 different age group during influenza season 2010 to 2012.**

| | The TIME LAG in MAXIMUM CROSS-CORRELATION VALUE | | | | | |
|---|---|---|---|---|---|---|
| | **Reference** | **Age under 5** | **Age 6-15** | **Age 16-50** | **Age 51-65** | **Age over 65** |
| **10** | | 1 | -1 | 0 | 1 | 1 |
| **11** | | 0 | 0 | 0 | 0 | 0 |
| **12** | | 1 | 0 | 0 | 0 | 0 |

**Table 4-13. The first week of aberration signals in influenza out-patient by the Early Aberration Reporting System (EARS) with high sensitivity setting in South Korea and 5 different age group during influenza season 2010 to 2012.**

| | The FIRST WEEK of ABERRATION SIGNAL with HIGH SENSITIVITY | | | | | |
|---|---|---|---|---|---|---|
| | **Reference** | **Age under 5** | **Age 6-15** | **Age 16-50** | **Age 51-65** | **Age over 65** |
| **10** | 2010w39 | 2010w41 | 2010w37 | 2010w39 | 2010w36 | 2010w39 |
| **11** | 2011w38 | 2011w52 | 2011w36 | 2011w36 | 2011w41 | 2011w37 |
| **12** | 2012w38 | 2012w40 | 2012w39 | 2012w38 | 2012w38 | 2013w2 |

**Table 4-14. The time difference on first week of aberration signals in influenza out-patient by the Early Aberration Reporting System (EARS) with high sensitivity setting in South Korea and 5 different age group during influenza season 2010 to 2012.**

| | The TIME DIFFERENT of FIRST WEEK of ABERRATION SIGNAL with HIGH SENSITIVITY | | | | | |
|---|---|---|---|---|---|---|
| | **Reference** | **Age under 5** | **Age 6-15** | **Age 16-50** | **Age 51-65** | **Age over 65** |
| **10** | | 2 | -2 | 0 | -3 | 0 |
| **11** | | 14 | -2 | -2 | 3 | -1 |
| **12** | | 2 | 1 | 0 | 0 | 16 |

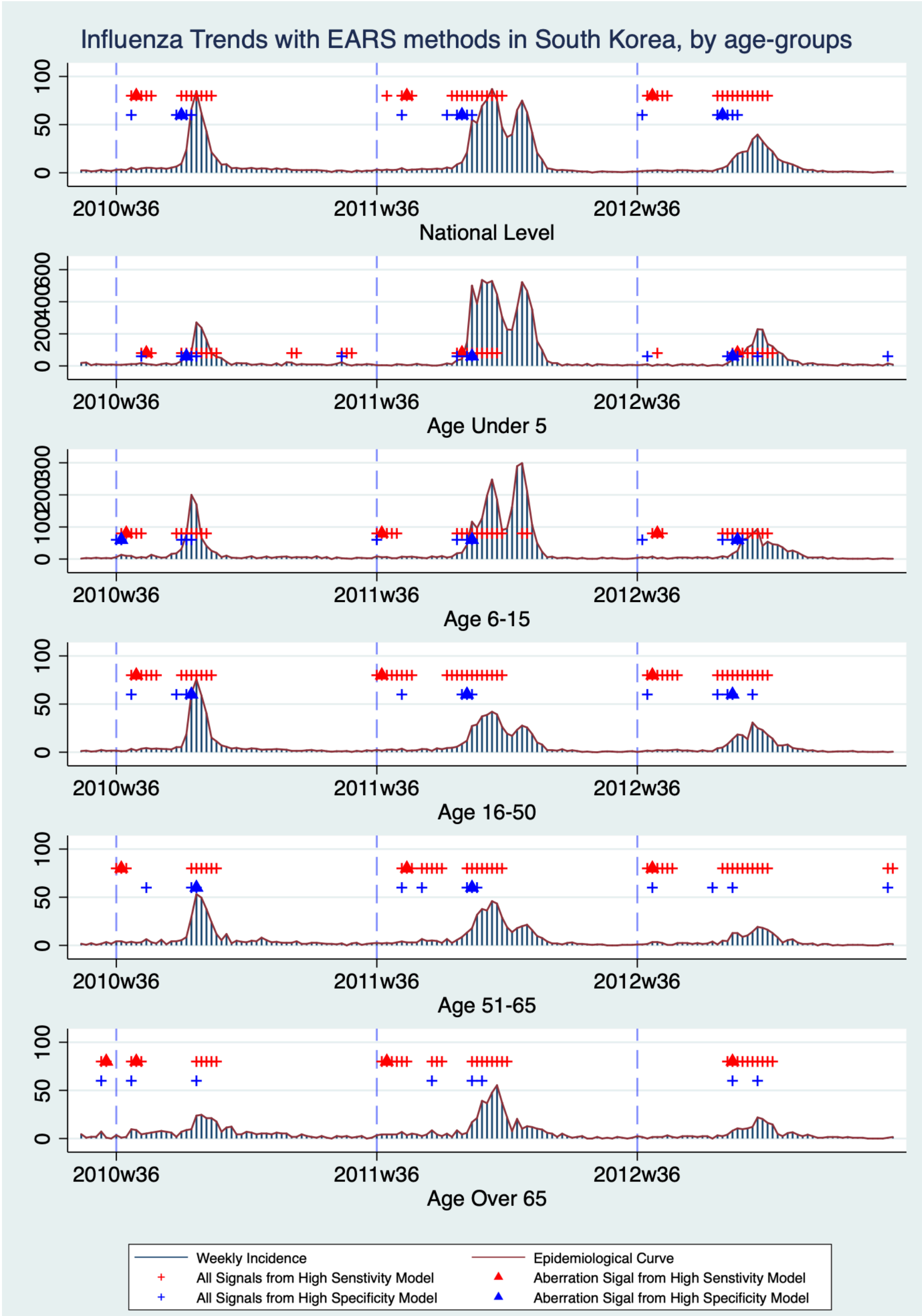
**Table 4-15. The first week of aberration signals in influenza out-patient by the Early Aberration Reporting System (EARS) with high specificity setting in South Korea and 5 different age group during influenza season 2010 to 2012.**

| | The FIRST WEEK of ABERRATION SIGNAL with HIGH SPECIFICITY | | | | | |
|---|---|---|---|---|---|---|
| | **Reference** | **Age under 5** | **Age 6-15** | **Age 16-50** | **Age 51-65** | **Age over 65** |
| **10** | 2010w49 | 2010w50 | 2010w37 | 2010w51 | 2010w52 | |
| **11** | 2012w1 | 2012w3 | 2012w3 | 2012w2 | 2012w3 | |
| **12** | 2013w1 | 2013w3 | 2013w4 | 2013w3 | | |

**Table 4-16. The time difference on first week of aberration signals in influenza out-patient by the Early Aberration Reporting System (EARS) with high specificity setting in South Korea and 5 different age group during influenza season 2010 to 2012.**

| | The TIME DIFFERENT of FIRST WEEK of ABERRATION SIGNAL with HIGH SPECIFICITY | | | | | |
|---|---|---|---|---|---|---|
| | **Reference** | **Age under 5** | **Age 6-15** | **Age 16-50** | **Age 51-65** | **Age over 65** |
| **10** | | 1 | -12 | 2 | 3 | |
| **11** | | 2 | 2 | 1 | 2 | |
| **12** | | 2 | 3 | 2 | | |

**Figure 4-3. Application of the Early Aberration Reporting System (EARS) with high sensitivity/high specificity setting in South Korea and 5 different age group during influenza season 2010 to 2012.**



# *Chapter 5 : Key findings, implications, and future directions*

## *Summary of findings*

We proposed the use of billing information as surveillance source in disease burden estimation and temporal trends monitoring. We were able to estimate the burden of influenza with different case definition and provided stratified disease burden as WHO guided. We did not see any delays of influenza out-patient activity drawn from billing information compared to the current sentinel surveillance. Moreover, we observed potential temporal associations of influenza activity by different subpopulation. Aberration time comparison was not sufficient to compare timeliness validation between two different sources neither investigate temporal associations between different subpopulation.

## *Summary of aim 1*

In chapter 2 (aim1), we aimed to estimate the burden of influenza and its related disease based on billing information. We applied three different case definitions based on disease codes in primary and secondary diagnosis to calculate the annual disease burden, then stratified by geographical subdivisions and age-group. We found an unequal distribution of disease burden by geographical subdivisions and different disease burden by different age group. There was a pattern change of diagnosis of seasonal influenza out-patients especially age under 5 and over 65 by the time of 2009 pandemic influenza.

The unequal distribution of influenza burden by geographical subdivision could be due to population crowding and early initiation of influenza treatment in an urban area. Different disease burden by different age group supported current government influenza vaccination system. Lastly, we showed the possibility of use of billing information in surveillance, especially disease burden estimation, and temporal trends monitoring.

### *Summary of aim 2*

In chapter 3 (aim 2), we validate the timeliness of epidemiological curves drawn from billing information compared to current sentinel surveillance as temporal trends monitoring. We estimated weekly incidences of influenza out-patients, pneumonia and influenza in-patients, and severe acute respiratory illness. We applied peak time, cross-correlation values, and aberration time comparison as a timeliness validation method. We did not observe any delays of influenza out-patients activity compared to current sentinel surveillance in peak time and cross-correlation value comparison. There was a week of delay in pneumonia and influenza in-patients and severe acute respiratory illness, but it was more likely due to the natural history of disease rather than actually delays in surveillance. We could not use aberration time comparison since aberration signals highly depended on model sensitivity and specificity and model selection process itself.

### *Summary of aim 3*

In chapter 4 (aim 3), we were able to perform influenza out-patient temporal trends association analysis by subpopulations. We applied timeliness validation methods to quantify differences of influenza activity by different geographical subdivision and age group. The Seoul Capital Area showed the early signs of influenza activity in peak and cross-correlation time comparison. Age 6 to 15 showed the early sign of influenza activity while age over 65 showed the later sing of influenza activity. As we addressed in chapter 3, the aberration time comparison was not ideal to quantify the time difference. The aberration signals were highly sensitive by model setting and model itself rather than epidemiological curves earliness.

## *Public Health Implications*

### *Use of billing information as surveillance source*

Traditionally influenza surveillance systems are based on selective sentinels to aggregate the information from the population or participated laboratory to see more specific information on subtypes and positive rate from the specimens[1]. There has been the use of billing information as surveillance source[2], but those approaches could not fully apply to general influenza surveillance since there were limitations to define the population at risk in the study or community. However, in this study, we could apply billing information as a direct measure of disease burden and temporal trends monitoring since South Korea established a national wide, mandatory, universal, single-payer electric insurance system.

Use of billing information could provide direct influenza burden by medical seeking behavior. Current influenza surveillance system and disease burden estimations in South Korea applied a complex statistical model to estimate the burden of influenza through sentinels or selective tertiary hospitals[3,4]. Even though they calculated the disease burden, those were still estimations from models, not direct measure. By applying peer-reviewed relevant case definitions of seasonal influenza, we were able to calculate the number of medical visits due to influenza illness and could provide the absolute number of influenza-related medical seeking behavior without a complex statistical model

Use of billing information with representative sampling can provide a direct measure of influenza intensity instead of relative disease intensity drawn from proportion influenza-like-illness. One of the limitations of current influenza surveillance is a relative measure of disease intensity. For example, a recent influenza report stated that age over 65 showed the lowest proportion influenza-like-illness among all age group[5]. However, based on our analysis in annual incidence and weekly epidemiological curve figures, that is not true. Because age over 65 has a high number of medical visits due to their chronic conditions which increased the number in the denominator in proportion calculation. With universal coverage of health insurance system and stratified sampling process from the entire population, we could easily define a population at risk and did provide weekly incidence of influenza, direct measure of disease.

Use of billing information with representative sampling and a large number of participants could be used stratified surveillance by geographical subdivisions and age group. After revision of influenza surveillance 2013, current surveillance system used 200 sentinels, 100 for adult (70 internal medicine, 30 family medicine), 100 for pediatrics[3]. However, those are not representative sentinels from each geographical subdivision (such as state/province or city/country) and 200 sentinels were not enough to provide sufficient information by geographical subdivision and age group surveillance information. The proposed approach in this dissertation used a million of individuals every year to estimate the disease burden and monitor temporal trends of seasonal influenza. Therefore, we could provide the influenza disease burden by different subpopulation, monitor temporal trends by subpopulation, and investigate the temporal association of influenza activity by subpopulation.

### *Stratified surveillance*

Stratified disease burden estimation can be used in a revising vaccine strategy, medical resource allocation and identifying epidemiology of influenza. Current influenza burden estimation could not provide stratified disease burden estimation based on geographical subdivision and different age group. Therefore, general assumptions for vaccine strategy and medical resource allocation were equal distribution of disease. However, with stratified disease burden estimation, there is a chance to identify high disease burden subpopulation based on geographical region and age group. Public health practitioners would revise vaccine strategy and medical resource allocation. Moreover, stratified disease burden estimation could provide more information on the epidemiology of influenza. Until recent years, population size was considered as a driven factor for influenza transmission. However, based on recent publication with more specified information in influenza activity[6], we know that population size is more act like modulator than a driven factor for transmission. Stratified disease burden estimation can be a base-data structure to investigate more about the epidemiology of influenza.

Finding temporal trends association in influenza activity could be a key to reducing the transmission of influenza by understanding the disease dynamics of influenza. It was almost impossible to get entire populations disease behavior and knowledge about disease dynamics. In this dissertation, we were able to estimate the weekly incidence of influenza by geographical subdivision and age group with different case definitions. Based on those stratified temporal trends monitoring, we found out the possible temporal association of influenza activity by geographical subdivision and age group. Those subpopulations with early influenza activity could be a key population to prevent and control influenza activity. Providing intensive vaccination and providing early initiation of influenza treatment may reduce early influenza transmission in those population, which may reduce the entire population's influenza activity.

## *Future directions*

We need to add more recent years of observation to make a clear direction of temporal associations. In the begging of the study, we aimed to analysis 7 years of observation. However, there was a change of influenza diagnosis patterns by the time of the pandemic outbreak, we only used 3 years of observation to analysis the temporal association of influenza. 3 years of observation is not enough to provide clear direction to establish policy development and revising strategy. Adding more observations with recent findings need to be done provide clear directions of temporal association.

We need to implement a new approach in the surveillance system and monitor and evaluate the results. There has been a lot of new approaches and published papers in public health surveillance, but most of them did not actually implement to the public health practice until now [7]or even when they are implemented, it is hard to see any post monitoring and evaluations on those new approaches[8]. After other studies with extending observation, implementing this approach as another pillar of the influenza surveillance system needs to be prioritized. Moreover, providing monitoring and evaluation system need to be accompanied when this approach is actually applied.

## *Final conclusion*

In this dissertation, we were able to estimate the burden of influenza more directly. Influenza out-patient activity drawn from billing information did not show any delays in timeliness compared to the current influenza sentinel surveillance. Lastly, there was potential temporal trends association by geographical subdivision and age group.

A surveillance system based on solely billing information never be perfect. Instead, other surveillance structures with surveillance with information can be a more stable surveillance system. The surveillance system should have different structures with the different data source to make concordance of observation.

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CURRICULUM VITAE of

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Hojoon Lee was born 31st December, 1985 in Incheon, South Korea

## Educational Background

**August 2019 *(Expected)*** **Doctor of Public Health** **Baltimore, USA**

Department of Epidemiology
Bloomberg School of Public Health, Johns Hopkins University

**May 2016** **Master of Public Health** **Baltimore, USA**

Bloomberg School of Public Health, Johns Hopkins University
*Concentration: Epidemiological & Biostatistical Methods for Public Health & Clinical Research*

**Feb 2011** **Doctor of Medicine** **Seoul, Korea**

Department of Medicine / Department of Pre-Medicine
College of Medicine, Hanyang University
Doctor of Medicine is the first medical professional degree in South Korea

## Public Health Professional Experience

**2015-Present** **Graduate Researcher** **Baltimore, USA**

Department of Epidemiology
Bloomberg School of Public Health, Johns Hopkins University

Doctoral Dissertation
*'A Novel Approach for Seasonal Influenza Surveillance in South Korea: Early warning methodology and timeliness validation of new data source'*

- Developed the dissertation proposal and its aims (12-page NIH R01 grant format) and presented the proposal in public, at the department Friday seminar.
- Received Doctoral Thesis Research Fund ($4,700) from the department as an independent student investigator
- Arranged the institutional review board process in South Korea as a primary investigator and successfully completed the IRB process
- Analyzing 1 million peoples' medical claims to understand the distribution of the burden of seasonal influenza and to identify the signals from the highest seasonal activity in South Korea

MPH Capstone
*'Application of early aberration reporting system (EARS) to seasonal influenza weekly reports in Mexico (2007-2014)'*

- Conducted early aberration reporting system to Mexico weekly influenza reports and classified 3 different algorithms' signals from 32 states to describe the temporal trends
- Awarded MPH CAPSTONE AWARD (10 awards out of more than 450 MPH students)

MPH Practicum
*'An exploratory study to examine the effectiveness of community-based Ebola virus disease prevention and management strategies in Bo District, Sierra Leone'*

- Designed a case-control study with a representative random sampling process and formulated questionnaires related to Ebola virus disease prevention and management strategies
- Assisted the institutional review board application at Johns Hopkins University and in Sierra Leone.

**Research Assistant** **Baltimore, USA**

Department of Epidemiology
Bloomberg School of Public Health, Johns Hopkins University

Global Public Health Observatory
- Identified review articles on the geographic information system to identify health inequity and inequality in the urban population
- Organized literature review on temporal and spatial-temporal signal detection algorithms in public health surveillance

Translational Epidemiology Task Force
- Systemized meta-narrative scoping review for 55 articles on translational epidemiology and suggested 5 key priorities about translational epidemiology
- Wrote a manuscript on translational epidemiology and its implications as first author (under review process)

Infectious Disease Dynamics
- Screened more than 2,000 cholera articles, and reviewed and extracted outbreak data from 302 articles
- Summarized outbreak information and tabulated number of cases or deaths by given information from the articles

**2013-2015** **Project Leader / Team Manager** **Seoul, Korea**

Resource Development Team / Public Health Doctor System Supporting Team
Korea Health Promotion Foundation

- Performed active sample surveillance of human resources at twenty sentinel clinics in eight different states; evaluating public health doctors' role in each clinic and comparing the number of patients per physician
- Suggested a policy memo to the Ministry of Health and Welfare for practical allocation of about 3881 public health doctors to 1776 locations in 226 rural counties.

Korea Health Promotion is an affiliate of the Ministry of Health and Welfare
Public health doctor is a form of an alternative military service

**2012-2015** **Contributing Writer - Monthly Medical Magazine** **Seoul, Korea**

Section: research trend sharing
MAMA: Monthly Archive of Medical Academics, Korean Doctor's Weekly

- Explored newly published international medical articles every month
- Summarized into Korean on a section 'Research Trend Sharing'
- Contributed total **36 issues (3 years)**

*Korean Doctor's Weekly is a medical newspaper publisher in South Korea*
*MAMA is a monthly medical magazine published by Korean Doctor's Weekly*

**2014** **Consultant / Data Analyst** **Kishapu, Tanzania**

Tanzania Mother and Child Health Care Program Proposal Survey, Good Neighbors Tanzania

- Collaborated with local program director on health facilities and health care provider reinforcement in Kishapu District
- Analysed and demonstrated an epidemiological study on maternal health and health care provider using statistical analysis (/w STATA)

Good Neighbors is an international NGO based on South Korea

**2012-2013** **Director / Physician** **Gangjin, Korea**

Sinjeon Health Sub-Center, Gangjin County Government

- Administered the Korean national vaccination program for children and elderlies
- Provided primary health care and medical check-ups for new-born babies and elderlies
- Supplied house-call visit for physically disabled people

Sinjeon Health Sub-Center is a branch office of local government health care center

**2011** **Physician** **Kaphunga, Swaziland**

Won-Kwang Kaphunga Clinic, F.A.C.: Future for African Children

- Provided primary health care and HIV/AIDS patient care
- Distributed patient's education program for HIV/AIDS prevention
- Facilitated medical outreaches to rural areas of Swaziland; Matsana and Sithobela

Future for African Children is a South African and Swaziland NGO

**2011** **Field Consultant / Primary Data Collector** **Niamey, Niger**

Niger Meningitis Vaccination Program, International Vaccination Institute

- Assisted Niger meningitis vaccination program in the region of Niamey, Maradi, and Dakoro
- Collected primary vaccination data from local health department

**2011** **Intern** **Bonn, Germany**

World Health Organization, European Centre for Environment and Health

- Attributed WHO/ECEH publications
· World Health Organization. *National profile of occupational health system in Finland*. Copenhagen: WHO Regional Office for Europe; 2012
· World Health Organization. *Country profile of occupational health system in Germany*. Copenhagen: WHO Regional Office for Europe; 2012
- Conducted a systematic literature review for a project on *'Housing and Health Guidelines'*
- Provided 2400 publication abstracts discussing housing conditions and health effects for in-depth analysis and categorization to the WHO project secretariat

## Teaching Experience

**2018** **Classroom Instruction** **Baltimore, USA**

Bloomberg School of Public Health, Johns Hopkins University
Department of Epidemiology

- *2018 Epidemiology 340.601 – Principles of Epidemiology (1 lecture on Review for the Final Exam)*
- *2018 Epidemiology 340.721 – Epidemiologic Inference in Public Health I (2 lectures on Review for the Midterm and Final Exam)*

**2016-Present** **Teaching Assistant** **Baltimore, USA**

Bloomberg School of Public Health, Johns Hopkins University
Department of Epidemiology

- *2019 Epidemiology 340.722 Epidemiologic Inference in Public Health II*
- **2019 Epidemiology 340.769 Professional Epidemiology Methods*
- **2018 Epidemiology 340.770 Public Health Surveillance*
- **2018 Epidemiology 340.601 Epidemiologic Inference in Public Health I*
- **2018 Epidemiology 340.601 Principles of Epidemiology*
- *2018 Epidemiology 340.722 Epidemiologic Inference in Public Health II*
- *2018 Epidemiology 340.993 Special Studies in Advanced Public Health Surveillance*
- **2018 Epidemiology 340.769 Professional Epidemiology Methods*
- **2017 Epidemiology 340.770 Public Health Surveillance*
- *2017 Epidemiology 340.721 Epidemiologic Inference in Public Health I*
- *2017 Epidemiology 340.993 Special Studies in Advanced Public Health Surveillance*

**As a lead TA*

Department of Biostatistics

- *2018 Biostatistics 140.622 Statistical Methods in Public Health II*
- *2018 Biostatistics 140.621  Statistical Methods in Public Health I*
- *2017 Biostatistics 140.622 Statistical Methods in Public Health II*
- *2017 Biostatistics 140.621  Statistical Methods in Public Health I*
- *2017 Biostatistics 140.624 Statistical Methods in Public Health IV*
- *2017 Biostatistics 140.623 Statistical Methods in Public Health III*
- *2016 Biostatistics 140.622 Statistical Methods in Public Health II*
- *2016 Biostatistics 140.621  Statistical Methods in Public Health I*

Master of Public Health Program

- *2017 Master of Public Health Program Capstone*
- *2018 Master of Public Health Program Capstone*

## Publications

### First Author

Michael Windle,* **Hojoon D. Lee**,* Sarah Cherng, Catherine R. Lesko, Colleen Hanrahan, John W. Jackson, Mara McAdams DeMarco, Stephan Ehrhardt, Stefan D. Baral, Gypsyamber D'Souza, David W. Dowdy "*From Epidemiological Knowledge to Improved Health: A Vision for Translational Epidemiology. Am J Epidemiol. 2019 Mar 30. pii: kwz085. doi: 10.1093/aje/kwz085.*

### Book - Co Translator

Nancy Krieger. *Epidemiology and the People's Health: Theory and Context*,  NY, New York: Oxford University Press; 2011 *(2018 Published in Korean)*

- Co-translators: KIM Eun-mi, KIM Yu-mi, **LEE Hojoon**, LEE Hwa-young, PYO Junhee, SHIN Sang-su, SHIN Young-jeon

### Official Document - Acknowledgement

World Health Organization. *National profile of occupational health system in Finland*. Copenhagen: WHO Regional Office for Europe; 2012

World Health Organization. *Country profile of occupational health system in Germany*. Copenhagen: WHO Regional Office for Europe; 2012

### Abstract

**Lee HJ**, Castillo-Salgado C.  *"Comparison of seasonal influenza trends: timeliness validation of state outbreak reports in Mexico 2007-2014."*

- Oral presentation at International Meeting on Emerging Diseases and Surveillance  2018, Vienna, Austria • November 9-12, 2018
- Poster presentation at  Society for Epidemiologic Research 51th Annual Meeting, Baltimore, MD, June 19-22, 2018.

**Lee HJ**, Castillo-Salgado C.  *"Application of Early Aberration Reporting System (EARS) to Seasonal Influenza Weekly Reports in Mexico (2007-2014)."*

- Poster presentation at International Meeting on Emerging Diseases and Surveillance  2018 -, Vienna, Austria • November 9-12, 2018

## Awards

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|---|---|---|
| **2018** | **The Alexander Langmuir Teaching Assistantship in Professional Epidemiology**<br>Department of Epidemiology<br>Bloomberg School of Public Health, Johns Hopkins University | **Baltimore, USA** |
| **2018** | **Abe Lilienfeld Scholarship Fund**<br>Department of Epidemiology<br>Bloomberg School of Public Health, Johns Hopkins University | **Baltimore, USA** |
| **2018** | **Doctoral Thesis Research Fund**<br>Department of Epidemiology<br>Bloomberg School of Public Health, Johns Hopkins University | **Baltimore, USA** |
| **2017** | **The Leon Gordis Teaching Assistantship in Professional Epidemiology / Leon Gordis Centennial Scholarship**<br>Department of Epidemiology<br>Bloomberg School of Public Health, Johns Hopkins University | **Baltimore, USA** |
| **2016** | **The Dyar Memorial Fund**<br>Department of Epidemiology<br>Bloomberg School of Public Health, Johns Hopkins University | **Baltimore, USA** |
| **2016** | **Master of Public Health Capstone Award**<br>Master of Public Health Capstone Committee<br>Bloomberg School of Public Health, Johns Hopkins University | **Baltimore, USA** |

## Licensure and Skills

**Korean Medical License (2011)** **Seoul, Korea**

**Computational Skills**

STATA / R / ArcGIS / QGIS / Microsoft Office: Word, Excel, PowerPoint

**Language Skills**

Korean / English
Fluency in Reading, Writing, Speaking and Listening

French
Basic notions of Speaking and Listening