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Effectiveness of Non-Pharmaceutical Interventions during COVID-19 pandemic on Influenza using Time-Series Forecasting

코로나19 비약물적 중재가 인플루엔자 발생에 미치는 영향: 시계열 예측을 중심으로

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이 논문을 보건학석사 학위논문으로 제출함

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Abstract

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Coronavirus disease-19(COVID-19) was first identified in Korea during the 2019-20 seasonal influenza epidemic. Social distancing measures, an effective non-pharmaceutical intervention, adopted to mitigate the spread of COVID-19 may have significant impact on influenza activity. This study aims to identify the changes in influenza activity during COVID-19 outbreak and assess the impact level of NPI intensity on influenza transmission.

By comparing 2020-21 and 2021-22 seasonal influenza activity with 2013-19 seasons, it was found that COVID-19 outbreaks and associated NPIs such as use of face mask, school closure or travel restriction may have reduced the influenza incidence by 91%.The SARIMA(Seasonal Autoregressive Integrated Moving Average Model) were used to quantify the effectiveness of NPIs for the transmission of influenza virus. Without NPIs against COVID-19 during influenza epidemic season, ILI rate and positive rate of

influenza virus would likely have remained high during the flu epidemic season, similar to those of previous seasons. This study identified the impact of NPI intensity on transmission of influenza, as the reduction rate increased when the social distancing level was strengthened (Step-by-step daily recovery: 58.10%, Special quarantine measures: 95.12%).

These results suggest evidence for the role of NPIs and personal hygiene behavior in controlling influenza transmission in preparation for future outbreaks, and NPIs intervened against COVID-19 may be useful strategies for prevention and control of influenza epidemic.

Keywords: COVID-19, social distancing, non-pharmaceutical intervention, influenza, SARIMA, time-series forecasting

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Chapter 1. Introduction

1.1 Study Background

The coronavirus disease 2019(COVID-19)—declared pandemic by World Health Organization on March 11, 2020—was first identified in Korea on January 20, 2020. As of November 3, 2022, more than 635 million positive cases have been infected with COVID- 19 worldwide and 25 million in South Korea [1]. Since, there were no treatment and vaccines against the SARS-CoV-2 virus in the early stages of the COVID-19 pandemic, non-pharmaceutical interventions (NPI), were implemented to mitigate its spread and infection. Non-pharmaceutical intervention is actions that people, and communities take apart to slow down the spread of illness.

For example, in South Korea, individual- and community-level NPIs have been implemented in response to the pandemic and social distancing policy has been established. In the early stage of COVID-19, the "Distancing in Daily Life" strategy were implemented [2]. This strategy has been restructured to 3-tiers social distancing system with level 1, level 2 and level 3 on June 28, 2020 after multiple outbreaks occurred near metropolitan area [3]. On November 2020, the system has been reorganized into 5-tiers

(level 1, level 1.5, level 2, level 2.5, level 3) and changed to 4-tiers (level 1, level 2, level 3, and level 4) in July 2021 [4]. Each level includes different actions and public measures of NPI—school closures, administrative order to ban gatherings, travel restrictions, tracing and quarantine, and restriction/cancellation of public and private events, restriction on entertainment facilities (singing room, restaurants, cafes etc.) and many others. NPI regarding personal/individual hygiene were also implemented, such as mandatory use of face masks and ventilation of indoor spaces, use of hand sanitizers, promoting the importance of hand washing and respiratory hygiene and increased education on public etiquette when coughing/sneezing in terms of prevention of COVID-19. As a result, handwashing compliance increased from 74.2% in 2019 to 87.3% in 2020 and 99.9% of the population wear mask on indoor and 99.8% wear mask on outdoor in 2021 [5, 6]. Those individual-, community-, and government-level efforts to follow and establish the NPI played an important role in controlling COVID-19. Previous modeling studies have been proven the effectiveness of NPIs in reducing the spread of the virus and delay the outbreak of COVID-19 [7]. The NPIs used to prevent COVID-19, significant change in the pattern and outbreak of other respiratory diseases such as adenovirus, parainfluenza virus and metapneumovirus were also observed.

Three major changes in respiratory virus have been observed during COVID-19 pandemic: 1) reduction in incidence and hospitalization 2) changes in circulating virus strains and 3) disruption to the seasonality of virus. However, for some respiratory viruses, such as rhinovirus and bocavirus, the incidence has been increased during pandemic. The number of hospital admission with respiratory virus has been declined for both influenza virus and majority of the non-influenza virus such as respiratory syncytial virus, parainfluenza viruses, metapneumovirus and others [8]. Pediatric emergency department visits for respiratory symptoms increased in the beginning of pandemic, however, overall the visits for non-COVID 19 respiratory illness declined during pandemic period [9]. Reduction in cases of acute respiratory illness (ARI) and influenza-like illness (ILI) have been seen [10]. Also, during COVID-19 pandemic, the circulation of respiratory virus in community has been changed too. In Australia, both type of rhinovirus(RSV)—RSV A and RSV B—were co-circulating before the emergence of COVID-19, however, after NPI against COVID-19 was implemented in the community, RSV A were found to be predominant [9,10]. Interestingly, among influenza virus B, Yamagata lineage has not been detected since March 2020 and other subtypes showed less genetic diversity compared to previous season [11]. In northern

hemisphere, 99.8% of reduction in influenza virus were appeared in 2020[11]. On the other hand, the detection rate of human bocavirus and adenovirus maintained and RSV has been increased in 2020[12]. In particular, detection rate of respiratory virus, such as influenza virus, parainfluenza virus, metapneumovirus showed drastic reduction from week 13 in 2020[13]. Especially, the pattern of influenza virus changed a lot and disruption to the seasonality were observed. The number of influenza-like illness per 1000 outpatients also reduced during COVID-19 pandemic compared to previous influenza seasons (Figure 1-1). In 2019-20 season, the flu advisory has been lifted on March 27, which is early compared to other previous seasons. However, from the 2020-21 season, the flu advisory was not issued, which is the first season without the flu advisory since the 2000-01 season—the season when the first flu advisory was issued by Korea Disease Control and Prevention Agency[14].

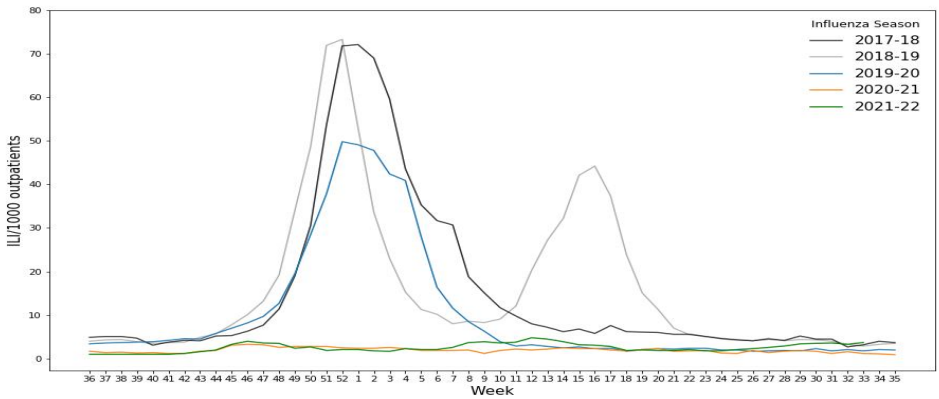

Figure 1-1. Trends on ILI(2017-18~2019-20 season)

*ILI: Influenza-like illness

Influenza and COVID-19 share similar symptom and transmission route. Both have symptoms of fever, cough, sore throat, shortness of breath, runny nose, muscle pain, headache, vomiting and diarrhea [15]. Similar with COVID-19, influenza virus can be transmitted via droplets, aerosol, direct and indirect contacts [16,17]. The reproductive number(R_0)—number of people that one person can transmit virus on average—for influenza virus and COVID-19 known as 1.3~2.4 and 1.4~2.5, respectively [12].

The effectiveness of NPIs in mitigating the spread of viruses differ by characteristics of infectious disease such as transmissibility, latent period and serial interval [18]. The effect of quarantine policy is maximized for fast course disease when the latent period is shorter than incubation period. Also, for the diseases with short duration of infectiousness shows the maximize effect of NPIs [18]. Compared to

COVID-19, influenza virus has a short serial interval—the time of illness onset in the primary case to illness onset in the secondary case[19]— and viral excretion of influenza virus peaks early in the illness [20,21]. The serial interval for influenza virus averages at 2-4 days and the incubation period is 2 days(1-4days), which is shorter than COVID-19; the serial interval of COVID-19 averages 5.2 days, ranged from 4.2 to 7.5 days and the incubation period ranges from 4.8 to 9 days [19]. These features have enabled the rapid spread of influenza, which could limit the impact of quarantine and isolation measures in controlling the spread of virus. Based on this, the assumption has been proposed that NPI will not be effective in controlling influenza outbreak [22]. Therefore, understanding on the role of NPIs for mitigating the spread of influenza virus is necessary. However, there is a lack of research on the effects of NPIs for influenza transmission as the accessibility of NPI implementation in research is very limited due to its high socio-economic cost. Since, NPI is being implemented due to the outbreak of COVID-19, research on the effects of NPIs on other non-COVID-19 disease is essential to reorganize infection prevention and control guidelines.

Concerns about waning immunity of influenza virus have been

raised consistently as population level immunity of influenza virus is developed from prior infection and vaccination [10]. Since the circulation of influenza virus were very low for recent two years and it can reduce the population immunity. Also, this can cause challenges for the selection of vaccine strain since the selection process depends on evaluation of haemagglutinin inhibition antibody titers against circulating virus strains from Northern and Southern hemisphere and it can further reduce the vaccine effectiveness [10].

In consideration of "twin-demic", co-occurrence of influenza and COVID-19, the role of NPIs should be identified in terms of controlling the outbreak of both influenza and COVID-19. To identify the impact of NPIs on influenza, the influenza activity during COVID-19 outbreak will be predicted under a counterfactual scenario without NPI against COVID-19 using time-series forecasting. The predicted value under counterfactual scenario during COVID-19 pandemic is compared to observed value with NPI implementation to further quantify the impact of NPIs on influenza. The findings of this study aim to improve the understanding of role of NPIs on influenza virus and identify the impact of timing and intensity of NPIs to provide the evidence on controlling strategy of influenza virus.

1.2 Literature Review

A literature review was conducted with three specific purposes: 1) to explore the forecasting methodology used in influenza prediction; 2) to find out the relationship between NPIs and patterns of influenza; 3) to explore the research on forecasting influenza activity during COVID-19 outbreak

1.2.1 Methodology of forecasting influenza outbreak

Forecasts of influenza pattern is useful for decision making in preparation for an outbreak. Various approaches on influenza transmission modeling has been applied to the forecasting of seasonal influenza outbreaks [22]. Those modeling approach include compartment models, agent-based models, and time-series models.

The agent-based model (ABM) has been used in influenza modeling [23,24]. ABM is a computational model for agents, a well-defined autonomous decision-making entity [25]. This model assumes that the global behavior emerges due to individual behaviors of the entities by interacting with other entities and their environment based on specific rules [22]. The agent-based model can take account the impact of different interventions and measures including individuals' behavior, however, the contact network are necessary which requires longer development time [26]. The

compartment model, which is also known as mathematical model are one of the widely used forecasting model. Examples are SIR(Susceptible-Infectious-Recovered) model, SEIR(Susceptible-Exposed-Infectious-Recovered model) and V-SEIR (Vaccinated-SEIR) model. The multiple compartments involved in this model can introduce subpopulation, however, the total population should be a fixed and homogeneous population since it cannot capture the difference in contact patterns for different age group and environment [22,27]. Despite these limitations, the compartment model has been widely used in forecasting influenza [28,29]. Due to strong seasonality and periodic change presenting on influenza pattern, time-series models are widely used. ARIMA(Autoregressive Integrated Moving Average) and SARIMA(Seasonal Autoregressive Integrated Moving Average) models are the two most used since these models can reflect the lagged relationship between the time [30-32]. However, the pattern of influenza might be changed between the seasons due to the emergence of new influenza virus subtype, which can be a huge obstacle in terms of time series forecasting.

With these models, various types of influenza related variables and indicators are used to forecast the influenza dynamics. The most widely used data are influenza-like-illness (ILI),

laboratory data including positive rate and detection rate and number of hospital admissions. In the past, google FluTrends data, an estimates of influenza in 25 countries, was also used, however, the program ended since 2015. Recently, neural networks, social-media, internet search query surveillance data are also used with machine learning based forecasting [33-35]. Those forecasting approach predict epidemic trend, the pattern of positive rate, detection rate and ILIs and peak duration.

1.2.2 Non-Pharmaceutical Intervention and Influenza

Many studies on relationship between NPI and respiratory virus outbreak have been conducted even before the COVID-19 pandemic starts. A systematic review and meta-analysis of 21 studies from 2004-2020 provide evidence on protective effect of facial mask on influenza infection (OR=0.55) [36]. Also, NPIs on internal travel restriction delayed the influenza epidemics by one week to two months and international travel restriction delayed the start of epidemic as well as peak point [37].

The NPIs implemented during COVID-19 pandemic may have changed the pattern on respiratory virus. A systematic review of 23 previous publications from 15 different countries found that NPIs

targeted at COVID-19 transmission reduced the spread of influenza virus and have important impact on reducing the mortality and morbidity of influenza.

NPI shortens the duration of an influenza epidemic duration or delays the onset of influenza in community [38]. Each NPIs showed a different effect in terms of reduction in influenza virus. The school closure reduced the risk of influenza epidemic by 43%(IRR=0.57, 95% CI: 0.36-0.96) and canceling public events and restricting internal movements reduced the positive rate of influenza virus by 44%(RPR=0.56, 95% CI: 0.39-0.82) and 41%(RPR=0.59, 95% CI: 0.36-0.96), respectively [38]. Travel restrictions have been implemented in many countries during COVID-19, which has affected the circulation of the influenza virus. Influenza virus A(H3N2) were mainly circulated in Asia and Southeast Asia with region-wide network, which facilitate the spread of strains to other continents including Oceania, Europe, North America, and South America [12]. However, during COVID-19 pandemic, the travel restriction affects this spreading process across countries, which slow down the evolution of influenza virus [10].

1.2.3 Forecasting influenza activity during COVID-19 pandemic

Several studies on forecasting influenza activity during COVID-19 pandemic under counterfactual scenario without COVID-19 targeted NPIs were published to quantify the impact of NPI on respiratory virus. One study quantified the impact of NPI using absolute humidity-driven susceptible-infectious-recovered-susceptible (SIRS) model and found that the influenza activity decreased by 60% in the first week of NPI implementation in the United States and relaxation of NPI would prolong the duration of influenza activity [39]. Using SARIMA (Seasonal-Autoregressive Integrated Moving Average) model, it has been estimated that COVID-19 related NPI reduced the influenza activity by 79.2% in Southern China and 67.2% in United States [40].

1.3 Purpose of Research

This study aimed to identify the changes in outbreak of influenza virus during COVID-19 outbreak and estimate the impact of non-pharmaceutical interventions on activity of influenza virus. The detailed purpose are as follows:

First, changes in influenza virus activity and pattern from 2013-14 season to 2021-22 season will be analyzed to identify the impact of COVID-19 and related NPIs on influenza.

Second, the time series forecasting model will be developed to estimate the outbreak of influenza and positive rate of influenza virus. Using the best-fit model, the incidence of influenza and positive rate of influenza virus from 2020 to 2022 will be estimated under counterfactual scenario without NPI against COVID-19. The predicted value and observed value will be compared to estimate the effectiveness and the impact of timing and intensity of the NPIs implemented during COVID-19 pandemic on influenza. Based on this, the epidemic duration and peak point of influenza virus will be estimated under the scenario without NPIs against COVID-19.

Chapter 2. Methods

2.1 Data Source

2.1.1 Korea Influenza and Respiratory Viruses Surveillance System

Korea Influenza and Respiratory Viruses Surveillance System(KINRESS) is national influenza center established by Korea Disease Control and Prevention Agency(KDCA) to identify the changes on the patterns and incidence of influenza. The goal of this system is to monitor patients and provide information that can be applied in the treatment and prevention on acute respiratory disease and reveal the cause of diseases. KINRESS also perform genetic analysis to determine the cause of outbreak and monitor the emerging of new influenza virus and antiviral resistant flu viruses[41]. It was first launched in 2001 for influenza virus and laboratory surveillance system was established for other acute respiratory infections in 2005. Currently, the target viruses are parainfluenza virus(HPIV), human adenovirus (HAdV), human respiratory syncytial virus (HRSV), human coronavirus (HCoV), human rhinovirus (HRV), human bocavirus (HBoV), and human metapneumovirus(HMPV).

Figure 2-1 describe schematic flow of the KINRESS. In cooperation with medical institutions, especially the primary hospitals, Research Institute of Public Health and Environment, Health Department of each province, and Sample Surveillance Medical Institution, KDCA reports surveillance result of respiratory virus every week and monitor the activity. Based on this surveillance system, KDCA issue and lift the flu advisory in accordance with the ILI baseline set each year.

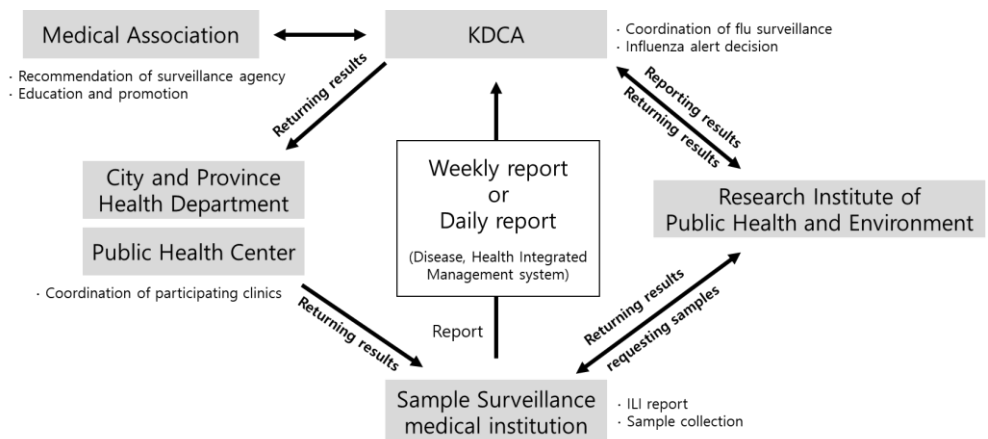

Figure 2-1. Schematic flow chart of the KINRESS

* The number of sentinel sites involve in KINRESS described in Appendix 2

2.1.2 Influenza case surveillance data

Influenza-like illness(ILI) data—provided through KDCA infectious disease website(https://www.kdca.go.kr/npt/)-were used to identify changes of influenza activity occurred during COVID-19

pandemic and predict influenza cases under counterfactual scenario without NPIs against COVID-19 [62]. The ILI defined as the patients with a sudden fever over 38℃ and cough or a sore throat. The ILI/1000 outpatients is a rate of ILI cases among the total number of weekly outpatient patients, which reported on a weekly basis by KDCA result from influenza clinical surveillance. Influenza clinical surveillance sites in South Korea include 199 institutions (2020-21 season) of medical clinics and report patients who have been visited, hospitalized and died with respiratory symptoms to KDCA through weekly report(from April to November) and daily report(from December to April) (Appendix 2).

The ILI data from 2011-12 season to 2021-22 season are used in this research. From 2013-14 season, the KINRESS is reorganized by designating both clinical and laboratory institution as sentinel surveillance sites and the counting methods of ILI case was changed. Therefore, the ILI cases of 2011-12 season and 2012-13 season were re-calculated based on the relationship between old ILI and reorganized ILI in 2013-14 season with following equation:

$$\hat{y}_i = y_i \times \frac{1}{N} \sum_{i=1}^{N} \frac{\hat{x}_i}{x_i}$$

where $\hat{y}_i$ is estimated ILI of previous season before the reorganization of

surveillance system carry out, y_i is the original ILI of previous season, $\hat{x}_i$ is reorganized ILI in 2013−14 season and x_i is the old ILI. In the beginning of 2013−14 season, both old and reorganized ILIs were reported. Thus the average proportion between old(x_i) and reorganized($\hat{x}_i$) ILI are calculated, and further applied to ILI(y_i) of the previous season to estimate reorganized ILI of 2011−12 and 2012−13 season.

2.1.3 Laboratory respiratory virus surveillance data

The virological data from laboratory respiratory virus surveillance are publicly available through "Pathogens & Vector Surveillance Weekly Report" by KDCA(https://www.kdca.go.kr/npt/) and FluNet website (https://www.who.int/tools/flunet). World Health Organization established Global Influenza Surveillance Network and created FluNet, a global web-based tools for influenza virological surveillance by interconnecting National Influenza Centers(NICs) of more than 100 countries. NIC provide virological surveillance result of each country at national level and send representative clinical specimen to WHO for advanced analysis. In South Korea, KDCA report the result of KINRESS to WHO [42]. The total of 63 laboratory institutions, enrolled as 'laboratory monitoring sentinel sites' (2020−21 season), collects respiratory specimen under patient consent

who has been visited clinics with influenza and other respiratory disease having respiratory related symptoms within 3 days of onset [43]. The collected samples are analyzed through multiplex real-time polymerase chain reaction or reverse transcription polymerase chain reaction by the Research Institute of Public Health and Environment. Based on the results, KDCA provide number of positive specimens of eight target acute respiratory virus (HAdV, HPIV, HRSV, IFV, HCoV, HRV, HBoV, HMPV) and its subtypes. In the case of influenza virus(IFV), the number of positive sample for influenza A(H1N1/pdm09), influenza A(H3N2), influenza B(Victoria lineage) and influenza B(Yamagata lineage) are provided respectively (Figure 2-2).

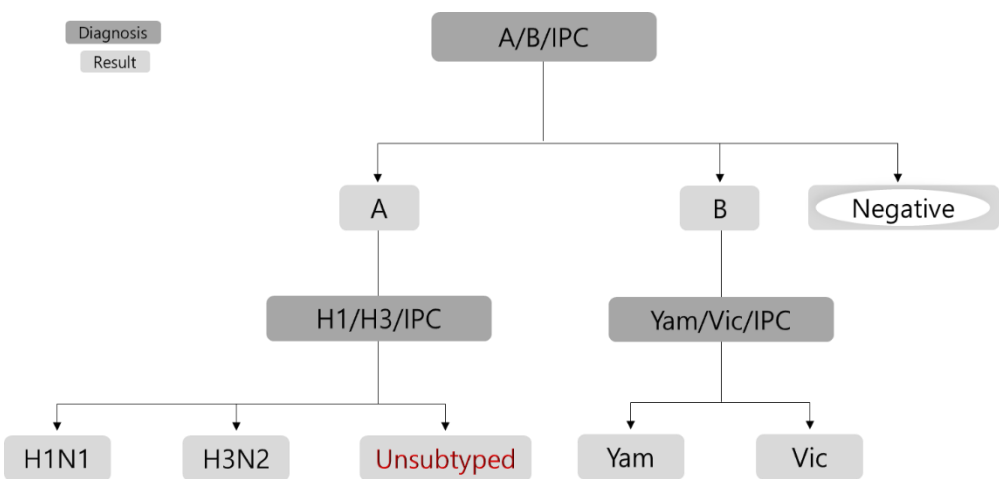

Figure 2-2. Genetic detection flow of influenza virus in KINRESS

For the analysis, the positive rate of IFV and positive rate of IFV A(H1N1/pdm09 and H3N2) are further calculated. In this research, the positive rate of IFV B are not considered since influenza B/Yamagata lineage has not been isolated and detected after COVID-19 emerge [44]. The calculation process is described in Table 2-1.

Table 2-1. Key variables and calculation methods

Variable	Description
Total specimens processed at the laboratory	Number of specimens processed at the laboratory collected with respiratory symptoms
Influenza virus positive rate (IFV positive rate)	Percentage of influenza virus (A H1N1/pdm 09, H3N2, B) among total specimen processed at laboratory $\text{IFV positive rate}(\%) = \frac{\text{Number of detected IFV}}{\text{Total specimens}}$ *IFV: influenza virus include all subtypes (A H1N1/pdm09, A H3N2, B)
Influenza virus A positive rate (IFV A positive rate)	Percentage of influenza virus A (H1N1/pdm 09 and H3N2) among total specimen processed at laboratory $\text{IFV A positive rate}(\%) = \frac{\text{Number of detected IFV A}}{\text{Total specimens}}$ *IFV A: influenza virus A include all subtypes

	(H1N1/pdm09, H3N2)

2.1 Descriptive Analysis

A descriptive analysis was conducted to identify changes in influenza virus activity and patterns from 2013–14 season to 2021–22 season and demonstrate the effectiveness of NPIs targeted for COVID-19 on influenza. The number of detected specimen and the positive rate of influenza virus A(H1N1/pdm09), influenza virus A(H3N2), influenza virus B and total influenza virus of each season were calculated. The comparison of indicators of influenza activity—ILI/1000 outpatients, number of detected IFV, positive rate of IFV—by social distancing period were analyzed. The social distancing period was divided according to the level of social distancing (Appendix 7). The mean difference between 2020 and 2014–19 season, the season before COVID-19 pandemic, were calculated with linear regression after adjusting the seasonality. This process is conducted using R software.

2.2. Time Series

2.2.1 Time series components

A time-series is a ordered set of observation (Xt) recorded through repeated measurements over time t(t=0,1,2,...)[45]. A time series can be categorized into discrete and continuous time series. A discrete time series consists of observation that are taken at distinct time whereas a continuous time series recorded constantly over with some time intervals. For example, the ILI is a discrete time series as the data are recorded in a fixed time intervals, weekly.

A time series is composed of four components: Trend(T_t), Seasonal(S_t), Cycles(C_t), and Residuals(R_t). Trend is a tendency of data that shows long term increase or decrease over time. Seasonal component, also known as seasonality, is a variation that occurs when a time series is affected by annual cycle of the season such as the time of the year or the day of the week [46]. Cyclical component refers to regular or periodic fluctuations that are not in a fixed frequency [47]. Lastly, irregular or residual component is a random fluctuation that are unpredictable with non-repeating pattern.

The four components of time series data can be extracted using various decomposition model. Classical decomposition model is one of the

examples, which assume that the seasonal variation is constant between years. There are two forms of classical decomposition—an additive decomposition and a multiplicative decomposition (Equation 1, 2)[47]. Other than classical decomposition model, STL(Seasonal Trend Decomposition using Loess) model that can treat monthly and quarterly seasonal trends and SEATS(Seasonal Extraction in Arima Time Series) method are widely used. In this research, classical additive decomposition method will be used due to the constant seasonal variation of variables—ILI/1000 outpatients, IFV positive rate and IFV A positive rate. The time series components of each variable identified by decomposition process were used to build time series forecasting model.

Additive model: $$Y(t) = T(t) + S(t) + C(t) + R(t)$$ (Equation 1)

Multiplicative model: $$Y(t) = T(t) \times S(t) \times C(t) \times R(t)$$ (Equation 2)

2.2.2 Stationarity

Stationarity is a random process with a constant mean, variance, and covariance. A stationary time series is one whose properties are independent of the time which the time series is observed [43]. The time series having trend or seasonality are not stationary—as both trend and seasonality affect value at different times. White noise is a stationary random process with zero autocorrelation, zero mean and constant variance. Thus, time series in which white noise appears are stationary. Each autocorrelation of white noise series is expected to be zero, so it can be examined by an Autocorrelation Function(ACF). Autocorrelation is the correlation between lagged values of a time series and measure the linear relationship between an observation at time t and the observation at previous time period, $t-k$. (Equation 3).

$$r_k = \frac{\sum_{t=k+1}^{T}(y_t - \bar{y})\,(y_{t-k} - \bar{y})}{\sum_{t=1}^{T}(y_t - \bar{y})^2} \qquad \text{(Equation 3)}$$

To conduct time series analysis, conversion of non-stationary into stationary is necessary and differencing is one of the most representative methods of this conversion [43]. Differencing can stabilize the mean of a time series and reduce the trend and seasonality by removing changes in the level of time series[46]. The change between consecutive

observations in the original time series occurs with differencing (equation 4) and if the stationary is not appeared after the differencing, a second order differencing can be used as well (equation 5). The second order differencing involve the change in the changes of the original time series data. If the strong seasonality observed in time series, season differencing is needed between observations and previous observation given in the same season (equation 6) [46].

Differencing	$y'_t = y_t - y_{t-1}$	(Equation 4)
Second-order differencing	$y''_t = y'_t - y'_{t-1}$ $= (y_t - y_{t-1}) - (y_{t-1} - y_{t-2})$ $= y_t - 2y_{t-1} + y_{t-2}$	(Equation 5)
Seasonal differencing	$y'_t = y_t - y_{t-m}$	(Equation 6)

*m: the number of seasons

2.2.3 Stationarity test

Stationarity test can determine the need for a differencing. The unit root test is one of the common methods of a statistical hypothesis testing for stationarity, because the process is non-stationary if the autoregressive operator has a unit root. Conducting a unit root test can determine whether a differencing is required[43]. Two common unit root

tests are: Augmented Dickey-Fuller(ADF) test and Kwiatkowski-Phillips-Schmidt-Shin(KPSS) test. The ADF test was created by Dickey and Fuller(1981), an augmented version of the Dickey-Fuller test[48]. The null hypothesis is that unit root is exists in time series observations and if accepted, the time series can be interpreted as non-stationary.

The KPSS test, created by Kwiatkowski, Phillips, Schmidt and Shin (1992), is another type of unit root test. In contrast to ADF test, the null hypothesis is that the data is stationary, and the alternative hypothesis is that the time series is non-stationary. Therefore, the small p-values suggest the needs of differencing of time series to convert it to stationary series.

In this study, ADF and KPSS tests were conducted to determine the need for differencing after confirming the stationarity of the time series observation. Statistical analysis was performed using "fable" package in R software.

2.3 Time Series Forecasting

2.3.1 Seasonal Autoregressive Integrated Moving Average

Seasonal Autoregressive Integrated Moving Average (SARIMA) model was used to forecast the influenza activity and virological trend of IFV. SARIMA is a model that seasonal component is added to Autoregressive Integrated Moving Average Model (ARIMA) and Box and Jenkinson have expanded the ARIMA model to reflect the seasonality [49]. ARIMA model is for non-seasonal and non-stationary data and SARIMA model apply seasonal differencing of appropriate order to remove non-stationarity of time-series data [49]. Due to the strong seasonality of influenza data, the SARIMA model will be used for prediction.

SARIMA model can be written as follows: ARIMA(p,d,q)(P,D,Q)m, where p, d, q is an order of the non-seasonal autoregressive(AR) part, degree of the non-seasonal differencing, and the order of non-seasonal moving average(MA) part, respectively. The P, D, Q each represent the seasonal AR order, degree of the seasonal differencing, and the seasonal MA. The mathematical equation of SARIMA model is given below (equation 7).

$$Y_t = \delta + \frac{\theta_q(B)\Theta_Q B^S}{\emptyset_P(B)\Phi_p(B^s)(1-B)^d(1-B^s)^D}\epsilon_t \qquad \text{(Equation 7)}$$

* Y_t: time-series at t
  δ: constant
  ϵ_t: white noise
  S: seasonal period
  P: order of non-seasonal autoregressive(AR) part
  p: order of seasonal AR part
  D: degree of non-seasonal differencing
  d: degree of seasonal differencing
  Q: order of non-seasonal moving average(MA) part
  q: order of seasonal MA part

2.3.2 SARIMA forecasting

Figure 2-3 describes the process of SARIMA forecasting. The Box-Jenkins method generalized time series forecasting with four steps—Identification, Estimation, Diagnostic checking and Forecasting.

First, the identification process, a time series components were examined through decomposition process. Then autocorrelation function(ACF) and partial autocorrelation function(PACF)—correlation between observations of time series that are separated by time units(k)—analysis carried out to determine the appropriate order of AR and MA parts of the SARIMA model. The ACF plot is used for estimation of MA by determining the proper lagged error terms and the PACF is used in identification of maximum order of AR [49].

Based on this process, the order of each parts of the SARIMA model will be selected. In this research a variation of the Hyndman-Khandakar algorithm will be used[46]. Hyndman-Khandakar algorithm

combines unit-root tests, minimization of the AICc, the sample-size adjusted AIC(Akaike Information Criterion), and MLE(Maximum Likelihood estimation). The first step is estimating number of differences(d) using the KPSS test. The value of p and q are determined using AICc value and the model that shows smallest AICc after differencing will be selected as the optimal model. The AICc is frequently used for model selection and use a model's log-likelihood as a measure of goodness of fit. The optimal model undergoes several variation process of stepwise search to determine if there is a better performance model[46].

Using the selected model, the number of ILI/1000 outpatient, IFV positive rate and IFV A positive rate will be estimated under counterfactual scenario without NPIs of COVID 19. The Ljung-box test was conducted to check the residual and if the residual is white noise, the forecasting process is carried out by fitting the time series into selected SARIMA model.

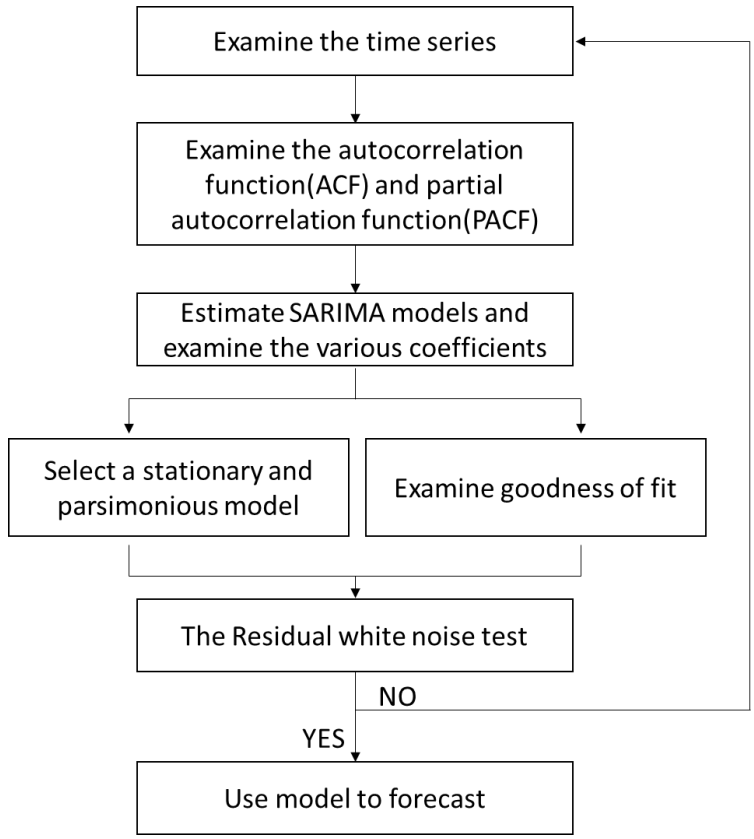

Figure 2-3. Flow of SARIMA forecasting

2.3.3 Forecast performance measure

Evaluation of forecasting accuracy is very important to verify the performance of model in forecasting by comparing training and test datasets. In this research, the training dataset are the time series from 2011-12 season to 2017-18 season and the test datasets are the observations of 2018-19 season. The accuracy of forecasts were determined by various forecast performance measures: the Mean

Absolute Error(MAE) , the Mean Absolute Scaled Error(MASE) and the Root Mean Squared Scaled Error(RMSSE).

The MAE is scale-dependent measures based on average absolute deviation of predicted values from observed [46, 49]. Minimizing the MAE will improve the performance of forecasting. The MASE is scaled error that indicates the effectiveness and accuracy of forecasting with respect to naïve forecast. The RMSSE is the modified form of MASE and is interpreted similarly to MASE. To test the accuracy of the forecasting model, the predicted values were fitted to the actual value of variables.

Chapter 3. Results

3.1 Surveillance of IFV in Korea

3.1.1 Analysis of laboratory respiratory virus surveillance data

Korea Influenza and Respiratory Surveillance System (KINRESS) monitors influenza outbreaks by designating sentinel institutions including clinical laboratory and inpatients sentinel sites. It was first launched in 2001 and reformed from the 2013-14 season.

From 2013-14 season to 2021-22 season, a total of 88,651 specimens were collected and proceed at the laboratory monitoring sentinel sites and the weekly mean number of proceed samples are 189. The average number of proceed samples during pre-NPI period(from 2013-14 season to 2019-20 season) was 215 per week, however, the average weekly number during NPI period(2020-21 and 2021-22 season) declined to 98, a 54% reduction compared to pre-NPI period. The positive rate of influenza virus (IFV) among the proceed samples were also significantly reduced during COVID-19 outbreak. The average annual IFV positive rate in pre-NPI period was 14.33% and it declined to 0.00% and 0.64% in 2020-21 season and 2020-22 season, respectively. This implies that the positive rate of IFV has declined since the initial

implementation of the NPIs strategies against COVID-19.

Figure 3-1 shows the distribution of influenza subtypes from the result of laboratory respiratory virus surveillance data. From 2013-14 season to 2021-22 season, three big patterns were observed: 1)unimodal distribution with co-circulation of IFV subtype A and IFV subtype B, 2)bimodal distribution of IFV subtype A and IFV subtype B 3) predominance of IFV subtype A throughout the flu epidemic period. The influenza season representing a unimodal pattern(2013-14 season, 2015-16 season, 2016-17 season) with one large peak shows the co-circulation of influenza A and B. All three seasons exhibit the same patterns and the distribution of each subtypes are very similar (average IFV A positive rate: 46.84%, average IFV B positive rate: 53.14%)(Table 3-1). The 2016-17 season and 2018-19 season both manifest the bimodal pattern, which IFV A was the predominant subtype of the first peak, followed by the second peak pre-dominated by IFV B. The 2019-20 season, when the COVID-19 first occurred, shows a unique pattern that distinguishes it from other seasons. Unlike other seasons, IFV A was predominant with 95.81% positive rate and IFV B rarely detected. This is expected to be due to the rapid end of flu season with the implementation of NPI for the control of COVID-19.

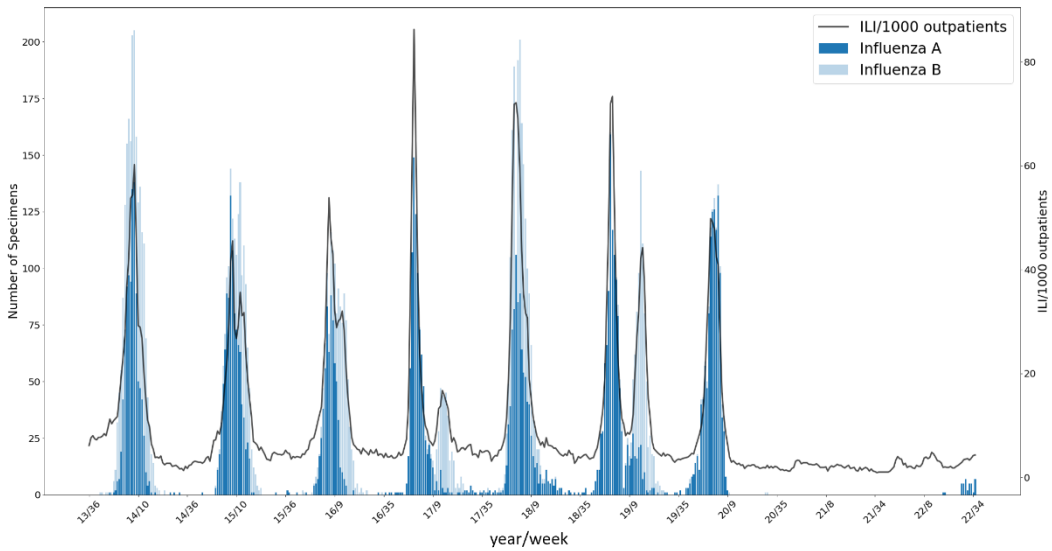

Figure 3-1. Influenza-like illness and laboratory surveillance of influenza virus in Korea, 2013-2022

*ILI: Influenza-like illness

Influenza A: Influenza A H1N1(pdm 09), Influenza A H3N2, Influenza A not subtyped

Influenza B: Influenza B (Victoria), Influenza B (Yamagata), Influenza B not dertermined

Table 3-1. Analysis of laboratory influenza virus surveillance data

Season[1)]	Total specimen	Number of detected specimen (positive rate %)			IFV Total
		IFV A H1N1(pdm09)	IFV A H3N2	IFV B	
2011-2012	14628	1(0.00%)	1950(51.5%)	1834(48.5%)	3785(25.88%)
2012-2013	13951	332(19.48%)	1276(74.88%)	96(5.63%)	1704(12.21%)
2013-2014	12343	346(16.52%)	640(30.56%)	1108(52.91%)	2094(16.97%)
2014-2015	11065	176(10.94%)	836(51.96)	597(37.10%)	1609(14.54%)
2015-2016	10933	582(44.09%)	62(4.70%)	675(51.14%)	1320(12.07)
2016-2017	11526	6(0.50%)	882(72.89%)	322(26.61%)	1210(10.50%)
2017-2018	11989	141(7.00%)	771(38.30%)	1101(54.69%)	2013(16.79%)
2018-2019	11862	760(41.90%)	379(20.89%)	675(37.21%)	1814(15.29%)
2019-2020	8640	825(70.45%)	297(25.36%)	49(4.18%)	1171(13.55%)
2020-2021	4334	0 (0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
2021-2022	5959	0 (0.00%)	38(100.00%)	0(0.00%)	38(0.64%)

1) Influenza season defined as week 36 to week 35 of the following year

3.1.2 Analysis of clinical sentinel surveillance data

The change of influenza-like illness and annual influenza incidence from 2013-14 season to 2021-22 influenza season described in Table 3-2. The duration of flu epidemic continued to increase from 15 weeks in the 2013-14 season to 32 weeks in the 2018-19 season and the issued date of flu advisories were also accelerated. Flu advisories were issued in January for the 2013-14 through 2015-16 seasons, while it issued in November for the 2017-18 and 2018-19 season, the last two seasons before the COVID-19 outbreak. The flu advisories are issue when the case of ILI/1000 outpatients exceed the baseline; ILI baseline determined by calculating mean ILI per 1000 outpatients during non-influenza weeks (the period where influenza virus detection rates remains under 2% for two consecutive weeks) for the most recent three consecutive years and adding two standard deviations [43]. The ILI baseline gradually decreased since 2013-14 season and the baseline in the 2019-20 season was reduced by more than half compared to the 2013-14 season. The week that flu advisory has been issued in 2019-20 season was same with previous season, however, the durations of the epidemic were shortened. The ILI in 2019-20 season remains high until week 4 of 2020 (2021.01.24.), then it gradually decreases and finally dropping

below the baseline (5.8 ILI/1000 outpatients) at week 10(2021.03.07.). The flu advisories were not issued for 2020-21 season and 2021-22 season and ILI remained below baseline throughout the season.

Figure 3-2 compares the trends of ILI/1000 outpatients between 2019 and 2020 by the time social distancing was implemented. In 2019-20 season, the ILI gradually declined after it reach the peak point at week 52. The ILI from the week 1 to week 8 of 2020 was higher than the ILI of the same week in 2019. However, it declined rapidly after week 4, when the first COVID-19 case confirmed in South Korea. Since the week 13 when social distancing was implemented, ILI has remained below 3 until the end of the season.

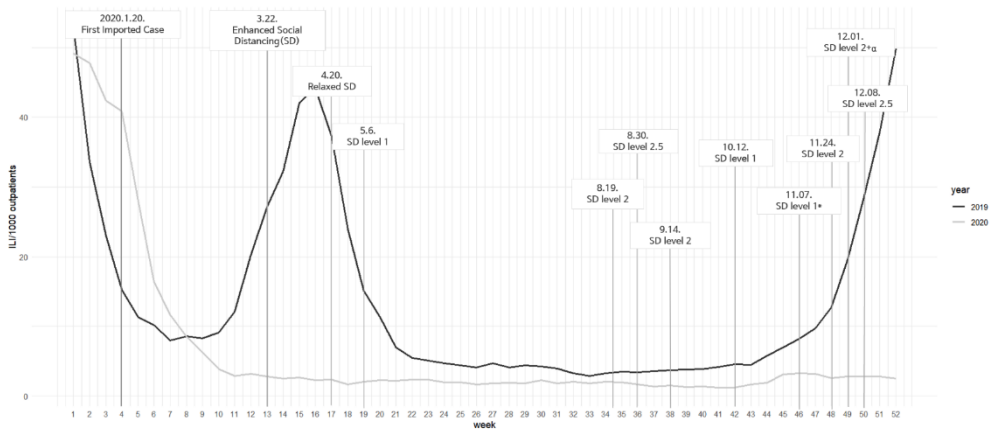

Figure 3-2. Influenza-like Illness and Social Distancing Level in Korea

Table 3-2. Analysis of influenza epidemic based on clinical surveillance data

Season	ILI baseline	Flu advisory issued date (ILI)	Flu advisory lifted date (ILI)	Duration of Epidemics	Peak point (ILI)	
					1st peak	2nd peak
2013-2014	12.1	14.1.2(15.3)	14.5.1.(6.4)	15 weeks	64.3(W7)	-
2014-2015	12.2	15.1.22.(14.0)	15.5.21.(6.2)	17 weeks	45.5(W8)	35.6(W12)
2015-2016	11.3	16.1.14.(12.3)	16.5.27.(6.0)	17 weeks	53.8(W7)	32(W14)
2016-2017	8.9	16.12.8.(13.5)	17.6.2.(6.7)	26 weeks	86.2(W52)	16.7(W14)
2017-2018	6.6	17.12.1.(7.7)	18.5.25.(6.0)	25 weeks	72.1(W1)	-
2018-2019	6.3	18.11.16.(7.8)	19.6.21.(4.7)	32 weeks	73.3(W52)	44.2(W16)
2019-2020	5.9	19.11.15.(7.0)	20.3.27.(3.2)	20 weeks	49.8(W52)	-
2020-2021	5.8	not issued	-	-	-	-
2021-2022	5.8	not issued	-	-	-	-

3.1.3 Changes in influenza incidence during COVID-19 outbreak

Table 3-3 describes the changes in influenza incidence during COVID-19 outbreak. The mean differences and reduction rates of the number of IFV detected and ILI/1000 outpatients by social distancing period in 2020 compared to the average of reference year (2014-15 season ~ 2018-19 season) were analyzed. In the first three weeks of 2020, before the first COVID-19 case confirmed in South Korea, both ILI and IFV positive rates increased by 55.04% from the reference year. The mean difference was 16.48 ILI/1000 outpatients; however, the difference was not significant after adjusting the week effect and IFV positive rate has been increased by 27.68% in 2020. The first COVID-19 case confirmed in week 4. From week 4 to week 10, before the WHO declared a pandemic, both ILI and IFV positive rate decreased significantly to 38.23% and 49.49%, respectively. The mean difference of IFV positive rate between reference year and 2020 were 10.22 ILI/1000 outpatients. After WHO's pandemic declaration in week 11, the Korean government has implemented "enhanced social distancing" from week 13 to week 16. Dramatic reductions were observed in this period(% reduction of ILI: 86.78%, % reduction of IFV positive rate: 100%) and shows statistically significant difference. From week 17 to week 33, "social distancing in daily-life" was implemented and huge

reduction were presented in both ILI and IFV positive rate. However, the mean difference was small since the period(week17~week33) is not included in the general flu epidemic season (Mean Difference of ILI: −3.68 (p−value<0.05), Mean Difference of IFV positive rate:−2.5343 (p−value<0.05)). In the week 48 to the week 52 of 2020, when the level 2 social distancing was implemented, both ILI and IFV positive rate declined significantly, and this period is included in the general flu epidemic period when there was no COVID−19.

Table 3-3. Comparison of influenza incidence between 2020 and 2014-19 season by social distancing period

No. of Weeks		W1~W3 20.1.1~1.18 Before COVID-19	W4~W10 1.19~2.7 Alert level RED	W11~16 2.8~2.18 Pandemic declared, Enhanced SD	W17~33 2.19~8.15 Relaxed, Daily life, SD1	W34~41 8.16~10.10 SD 2, 2.5	W42~47 10.11~11.21 SD 1	W48~52 11.22~12.31 SD 2, 2.5, 3
ILI/1000 outpatients								
2020	Mean	46.43	16.51	2.73	2.04	1.58	2.40	2.67
	Median	47.80	11.60	2.75	2.00	1.45	2.50	2.70
	IQR	3.35	14.80	0.33	0.50	0.40	1.43	0.28
2014-19	Mean	29.95	26.74	20.68	5.72	3.82	5.38	29.67
	Median	23.05	27.90	19.40	4.70	3.85	4.55	19.20
	IQR	23.20	31.05	17.68	1.78	0.90	2.00	41.00
	% Reduction	-55.04	38.23	86.78	64.32	58.74	55.40	91.01
	mean difference	16.48	-10.22	-17.94	-3.68	-2.24	-2.98	-25.57
	p-value	0.206	0.132	<0.005	<0.005	<0.005	<0.005	<0.05

Number of detected IFV All (A/H1N1, A/H3N2, B)								
2020	Mean	125.00	46.29	0.00	0.12	0.00	0.00	0.00
	Median	126.00	35.00	0.00	0.00	0.00	0.00	0.00
	IQR	6.50	65.50	0.00	0.00	0.00	0.00	0.00
2014−19	Mean	83.22	85.98	68.58	6.22	0.90	6.17	60.32
	Median	79.00	92.50	67.00	2.00	0.50	2.00	50.00
	IQR	55.00	94.50	57.25	5.00	1.00	8.00	99.50
	% Reduction	−50.20	46.16	100.00	98.10	100.00	100.00	100.00
	mean difference	41.78	−39.69	−68.58	−6.10	−0.90	−6.17	−56.72
	p−value	0.204	0.101	<0.005	<0.005	<0.005	0.117	<0.05

IFV Positive Rate								
2020	Mean	40.53	17.58	0.00	0.16	0.00	0.00	0.00
	Median	40.56	15.84	0.00	0.00	0.00	0.00	0.00
	IQR	2.93	26.16	0.00	0.00	0.00	0.00	0.00
2014−19	Mean	31.74	34.81	26.18	2.69	0.45	2.40	20.81
	Median	31.14	39.02	26.89	1.00	0.21	0.83	16.67
	IQR	21.72	38.34	22.10	2.59	0.61	3.08	32.26
	% Reduction	−27.68	49.49	100.00	94.13	99.78	99.96	100.00
	mean difference	8.79	−17.23	−26.18	−2.53	−0.44	−2.40	−19.67
	p−value	0.390	0.0566	<0.005	<0.005	0.0511	0.0981	<0.05

*ILI: Influenza−like illness, IFV: Influenza Virus, IFV Positive Rate: Number of detected IFV/total specimen

% Reduction: (Mean of 2014−19 – Mean of 2020)/(Mean of 2014−19)*100

** W1−3: Before COVID−19, W4−10: alert level RED, W11−16: Pandemic declared, Social Distancing(SD), W16−33: Relaxed SD, Distancing in daily life, Level 1 SD, W34−41: Level 2 SD, W42−47: Level 1,1.5 SD, W48−52: Level 2, 2+a, 2.5 SD

*** Detail summary of social distancing (Appendix 7)

3.2 Time Series Analysis

3.2.1 Characteristics of variables

Table 3-4 provide the summary of time series variables used in forecasting. The forecasted variables are the total number of ILI per 1000 outpatients, positive rates of influenza virus (IFV)and positive rates of influenza virus A.

Table 3-4. Descriptive summary of the variables

Variables	Description	Unit
ILI_TOTAL	Number of influenza-like illness per 1,000 outpatients	/1000 outpatients
PROP IFV	Positive rate of influenza virus include all subtypes (Influenza A(H1N1/pdm 09, H3N2) and Influneza B) Prop IFV=(Number of detection of Influenza all subtypes)/(Total specimen)*100	%
PROP A	Positive rate of influenza A (H1N1/pdm 09, H3N2) Prop_A=(Number of detection of influenza A)/(Total specimen)*100	%

3.2.2 Stationarity Test

The stationarity test was done to build appropriate time series forecasting model. The stationarity was tested with KPSS and ADF test. Both KPSS and ADF test shows the data satisfies stationarity (Table 3-5). The null hypothesis for the KPSS test is that the data is stationary. The high p-value(p-value=0.1) of KPSS test suggest that no differencing is needed for the three variables. The p-value of the ADF test was 0.01, which rejected the null hypothesis, indicating that the stationary time series and it is consistent with the result of the KPSS test. These results suggest that no differencing is needed for this time series.

Table 3-5 Stationarity test results

Variables	KPSS[1] unit root test		ADF[2] test		
	Result	p-value	Lag order	Result	p-value
ILI_TOTAL	0.1519	0.1	7	-5.2538	0.01
PROP IFV	0.0761	0.1	7	-5.4498	0.01
PROP A	0.0744	0.1	7	-5.261	0.01

[1)]KPSS test: Kwiatkowski-Phillips-Schmidt-Shin test

[2)]ADF test: Augmented Dickey-Fuller test

3.2.3 Time series decomposition

The classical additive decomposition were done to identify each time series components—trend, seasonality, cycle and random variation—of variables (Figure3-3, Figure3-4, Figure3-5). Classical decomposition assume that the seasonal component repeats every year[46]. The decomposition result suggests the strong seasonality and irregular trend of the three variables—ILI/1000 outpatients, positive rate of IFV, and positive rate of influenza A.

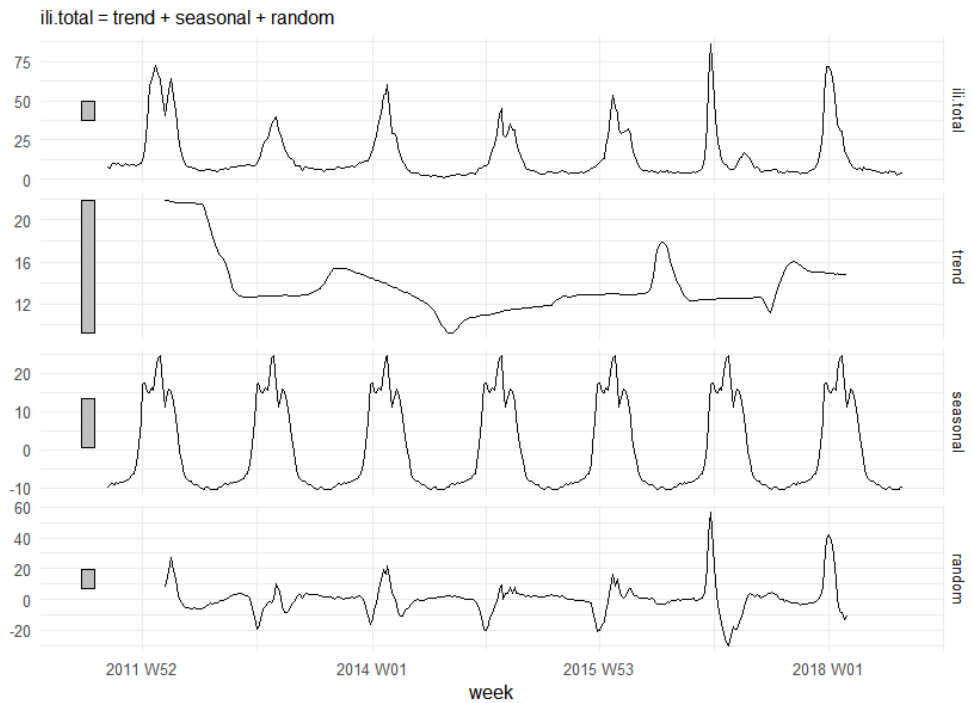

Figure 3-3. Decomposition of ILI/1000 outpatients

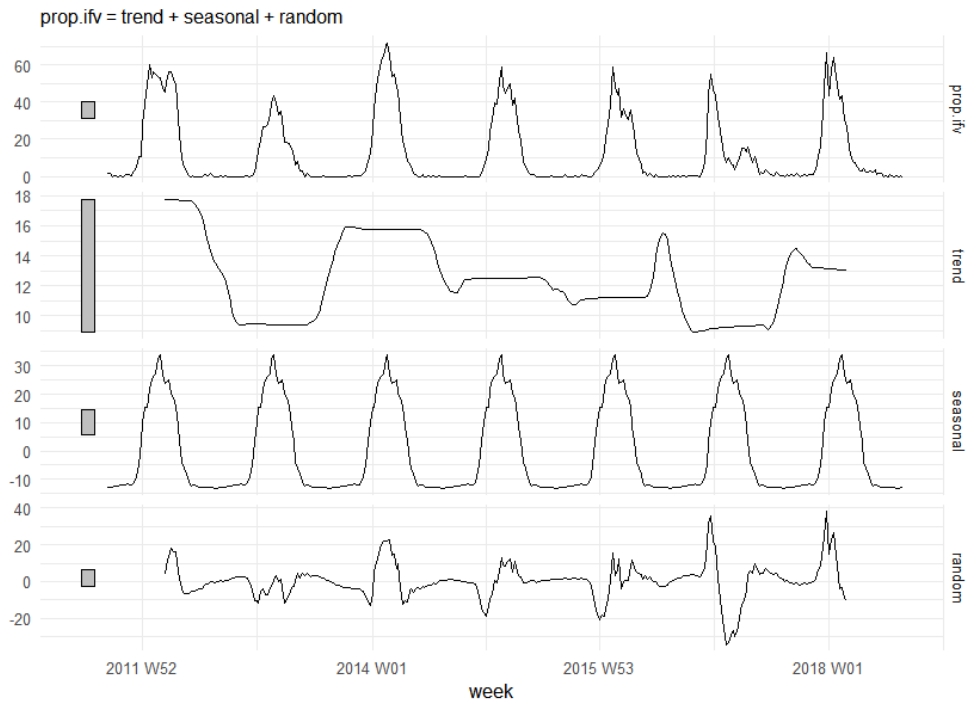

Figure 3-4. Decomposition of positive rate of IFV

Figure 3-5. Decomposition of positive rate of IFV A

3.2.4 Autocorrelation

The ACF(autocorrelation function) and PACF(partial autocorrelation function) were further tested to determine and analyze the characteristics of time series data and identify appropriate order of SARIMA forecasting model. As stated in the 'methods' section, autocorrelation is the correlation between lagged value of a time series and PACF measure the relationship between Y_t and Y_{t-k} after removing the lag effects at lag K. The ACF and PACF graph shows the significant autocorrelation and seasonality (Figure 3-6)

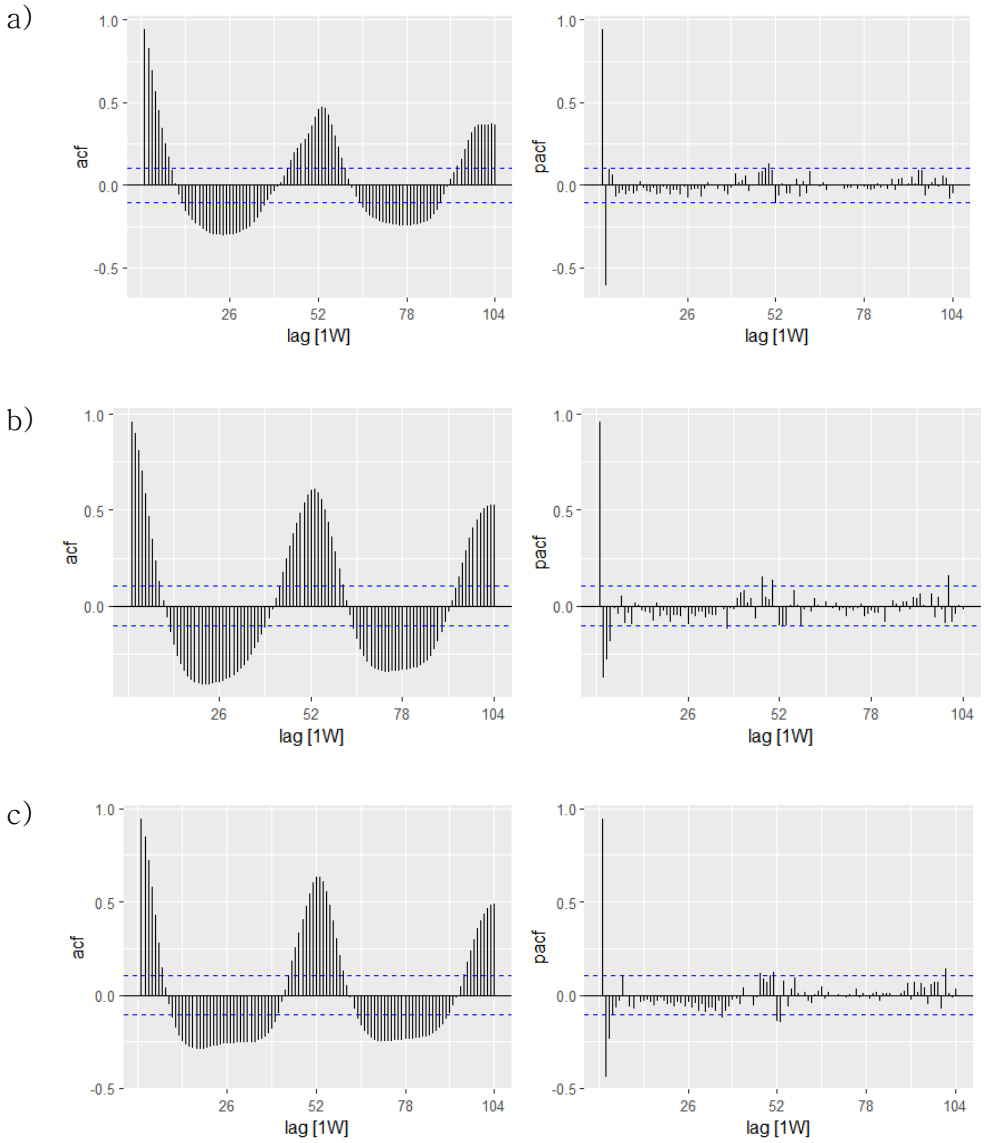

Figure 3-6. ACF and PACF plot

*ACF: Autocorrelation Function

PACF: Partial autocorrelation

a) ACF and PACF of ILI/1000 outpatients

b) ACF and PACF of IFV positive rate

c) ACF and PACF of IFV A positive rate

3.3 Time Series Forecasting

3.3.1 Seasonal Auto-Regressive Integrated Moving Average

Due to strong seasonality in of influenza, SARIMA(Seasonal Auto-Regressive Integrated Moving Average) model was used. To decide the each component of p,d,q,P,D,Q in SARIMA model, the AICc(Akaike's information criterion with correction for small sample size) value of each model are tested. This model will be applied to three different time series data; total number of ILI/1000 outpatients, positive rate of IFV and positive rate of IFV A. The AICc values of all the possible model described in Appendix 3, 4, and 5.

Table 3-6 shows the optimized model parameters that are selected with smallest AICc values of each variables. The model with the smallest AICc values was ARIMA(2,0,2)(1,1,0)[52] for ILI rate, ARIMA(2,0,3)(0,1,1)[52] for positive rate of IFV and ARIMA(2,0,1)(1,1,0)[52] for positive rate of IFV A. The coefficients of selected SARIMA models are provided in Table 3-7.

Table 3-6. Selected SRIMA model

Variables	Selected Model	AICc
ILI cases/1000 outpatient	ARIMA(2,0,2)(1,1,0)[52]	1838.535
Influenza(all) positive Rate	ARIMA(2,0,3)(0,1,1)[52]	1859.892
Influenza A positive rate	ARIMA(2,0,1)(1,1,0)[52]	1738.978

Table 3-7. Selected SRIMA model

IFV positive rate	AR(1)	AR(2)	MA(1)	
Coefficients	1.4009	-0.5495	-0.4172	
Standard Error	0.1179	0.105	0.124	
	MA(2)	MA(3)	SMA(1)	
Coefficients	0.2238	0.2434	-0.5601	
Standard Error	0.0622	0.0846	0.0703	
	log likelihood=-922.76 AIC=1859.53 AICc=1859.89 BIC=1885.75			
IFV A positive rate	AR(1)	AR(2)	MA(1)	SAR(1)
Coefficients	1.7146	-0.8141	-0.665	-0.4458
Standard Error	0.0554	0.0467	0.0809	0.054
	log likelihood=-864.39 AIC=1738.78 AICc=1738.98 BIC=1757.51			
ILI/1000 outpatients	AR(1)	AR(2)	MA(1)	MA(2)	SAR(1)
Coefficients	1.1234	-0.3338	0.2699	0.2312	-0.4366
Standard Error	0.1584	0.1385	0.16	0.0915	0.0566
	log likelihood=-913.13 AIC=1838.26 AICc=1838.54 BIC=1860.74				

The details of the model accuracy assessment are provided in Table 3-8. The mean absolute scaled error (MASE), indication of effectiveness of forecasting algorithm with respect to naïve forecast,

of each fitted models are as follows: ILI total: 0.302; Positive rate of IFV: 0.308; Positive rate of IFV A: 0.390. The MASE value of all variables is less than one, indicating that the model shows better performance compared to naïve method. The residual white noise test was done and the residuals were not distinguishable from white noise series (Appendix 6).

Table 3-8. Accuracy test of selected SARIMA forecasting model

Variables	Selected Model	RMSSE	MAE	MASE
ILI total	(2,0,2) (1,1,0) [52]	0.309	2.08	0.302
IFV positive rate	(2,0,3) (0,1,1) [52]	0.313	2.21	0.308
IFV A positive rate	(2,0,1) (1,1,0) [52]	0.370	1.73	0.390

* RMSSE: Root Mean Squared Scaled Error

MAE: Mean Absolute Error

MASE: Mean Absolute Scaled Error

3.3.2 Prediction result

To estimate impact of NPI on influenza incidence, the forecasting of ILI/1000 outpatients, positive rate of IFV and positive rate of IFV A was generated under counterfactual scenario without NPIs against COVID-19. Figure 3-7 shows the fitted and predicted curve for each variable. As the accuracy test result of forecasting model performance suggests, the fitted value of the model explains the observed value well.

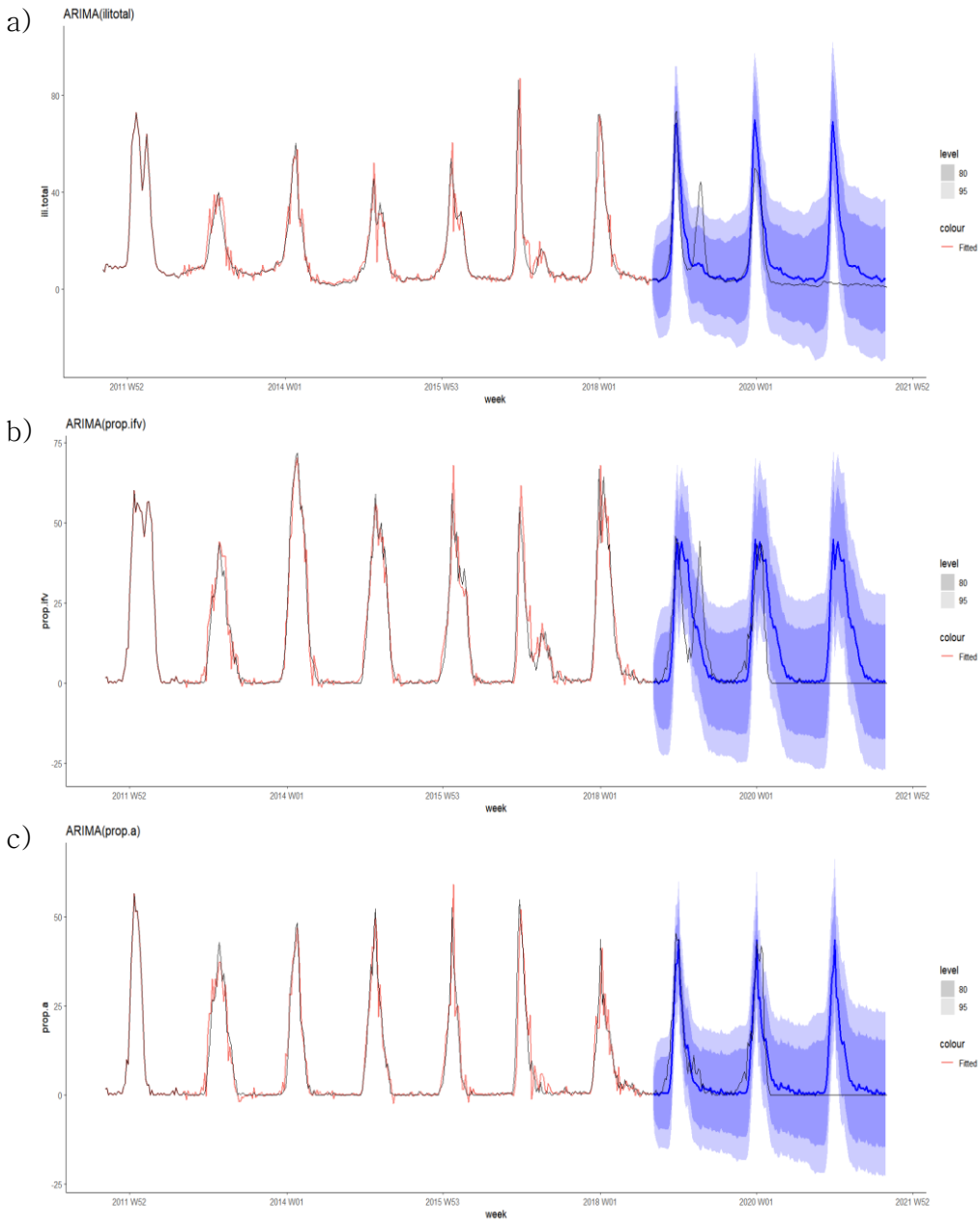

Figure 3-7. Fitting result of SARIMA model

*Red line indicates fitted value, blue line indicates predicted and black line is observed

a) Forecast of ILI/1000 outpatients

b) Forecast of IFV positive rate

c) Forecast of IFV A positive rate

The predicted value of ILI/1000 outpatients, positive rate of IFV and positive rate of IFV A under counterfactual scenario are shown in Figure 3-8. The significant differences were observed between predicted value and real-world observed value during the period that NPI was implemented for the control of COVID-19. In South Korea, various social distancing measure were implemented throughout the COVID-19 outbreak. Each level of social distancing intervenes different types of measures and the difference between predicted value and observed value were varied by the level of social distancing. This result suggests that timing and intensity of the NPIs have an impact on influenza activity. If the COVID-19 did not occur and NPI had not been implemented, the ILI case/1000 outpatients, positive rate of IFV and positive rate of IFV A will maintain the similar trend that last for recent 8 seasons (2011-12 season to 2018-19 season).

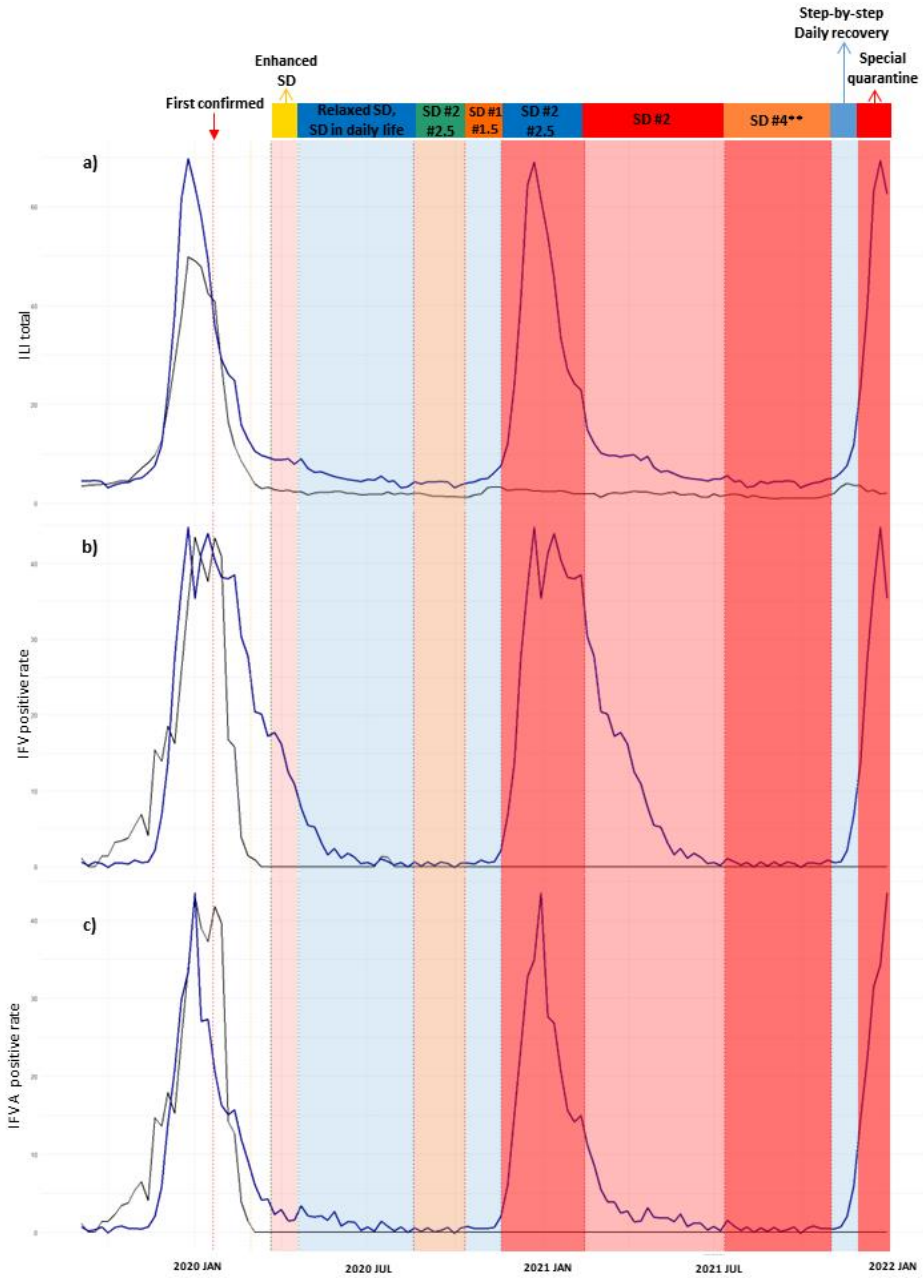

Figure 3-8. Forecasting result (2019 W35~2021 W52)

*Black line: observed ILI , Blue line: Forecasted ILI

**Timeline of social distancing in South Korea are presented on Appendix 7

a) Forecasts of ILI/1000 outpatients

b) Forecasts of IFV positive rate

c) Forecasts of IFV A positive rate

Using the best-fit SARIMA model, the characteristics of influenza seasonal epidemic in 2020 and 2021 were estimated under counterfactual scenario without NPI for COVID-19 and compared with the observed value (Table 3-9). Before the COVID-19 outbreak, 2014-15 to 2018-19 season, the ILI rate (ILI/1000 outpatients) were 13.91 on average and the positive rate of IFV and IFV A were 12.92% and 7.60%, respectively. A similar trend was observed from 36th week of 2019 to 4th week of 2020, when COVID-19 confirmed case first occurred; the ILI rate was 16.11, positive rate of IFV was 14.03% and positive rate of IFV A was 7.21%. However, after the emergence of COVID-19, the significant differences were observed between real-world and predicted value of three variables. From the week 5 of 2020—the week after COVID-19 emerge—to the end of 2020, the reduction rate of ILI/1000 outpatients, positive rate of IFV and positive rate of IFV A were 71.80%, 73.94% and 83.33%, respectively. Throughout the 2021, ILI/1000 outpatients were reduced by 87.2% compared to predicted value under counterfactual scenario without NPIs against COVID-19 and both the positive rate of IFV and IFV A reduced by 99.9%.

Table 3-9. Comparison between observed and predicted ILI incidence under counterfactual scenario

	Before COVID-19		After COVID-19					
	2014-19	2019-20 (2019 W36~ 2020 W4)	2020 (2020 W5[1)]~2020 W52)			2021		
	Observed	Observed	Observed	Predicted	Change %	Observed	Predicted	Change %
ILI Total	13.91	16.11	3.45	12.22	71.80	1.90	14.78	87.12
Positive rate of IFV (%)	12.92	14.03	1.68	10.09	73.94	0.0014	11.93	99.99
Positive rate of IFV A (%)	7.60	7.21	1.47	5.63	83.33	0.0014	6.95	99.98

*Observed value is the average value of the base period

*Predicted is value under counterfactual scenario without NPI

2014-19: 2014 W36~2019 W35

2019: 2019 W1~2019 W52

2020: 2020 W5~2020 W52

1) 2020 W5: The first week after COVID-19 emerge

2021: 2021 W1~2021 W52

IFV: Influenza Virus, IFV A: Influenza Virus A(H1N1/pdm09 and H3N2)

Change %=(Predicted-Observed)/Predicted * 100

3.3.3 Forecasting duration of flu epidemic and peak point

Duration of flu epidemics and peak points are estimated based on forecasting result of ILI/1000 outpatients (Table 3-10). The duration of flu epidemics defined as the number of weeks between the week that flu advisory issued and lifted. The issue and lift of the flu advisory is determined by KDCA and its medical expert's association based on ILI cases.

The ILI baseline of 2019-20 season was 5.9. The observed duration of flu epidemic was 20 weeks (week 46 of 2019~week 13 of 2020), however, the flu epidemic is expected to end at week 25 under the counterfactual scenario. This suggest that NPIs targeted COVID-19 has shortened the epidemic. Also, the peak point occurs in week 52 during 2019-20 season with 49.8 ILI/1000 outpatients. However, under counterfactual scenario, the peak point expected to occur at week 1 with 64.06 ILI/1000 outpatients. There were no flu epidemics in the 2020-21 season and 2021-22 season as the flu advisory has not been issued. Under counterfactual scenario, the duration of epidemics expected to be 31 weeks for both 2020-21 and 2021-22 season (2020-21 season: week 47 of 2020 to week 25 of 2021, 2021-22 season: week 46 of 2021 to week 24 of 2022). The estimated peak point is 64.33 at week 51 of 2020-21 season

and 69.37 at week 52 of 2021-22 season. This is similar to the previous seasons before the pandemic of COVID-19.

Table 3-10. Summary of forecasted influenza epidemic

	Season	ILI baseline	Duration of Epidemics*	Peak point (ILI)
observed	2018-19	6.3	32 weeks (W46~W25)	73.3(W52)
	2019-20	5.9	20 weeks (W46~W13)	49.8(W52)
predicted	2019-20	5.9	32 weeks (W46~W25)	64.06(W1)
	2020-21	5.8	31 weeks (W47~W25)	64.33(W51)
	2021-22	5.8	31 weeks (W46~W24)	69.37(W52)

3.3.4 Impact of NPI on influenza-like illness

Table 3-11 and Figure 3-9 describes the percent changes of ILI/1000 outpatients between predicted and observed value in 2020-2021 by the timing of NPI period. The most changed occur in week 48 to week 52 in 2021 and week 48 and week 6 in 2020-21 season. From week 48 of 2020 to week 6 of 2021, the observed ILI decreased by 93.83% compared to predicted value under counterfactual scenario. During this period, social distancing level 2 and 2.5 were implemented due to 3rd wave, Christmas, and New Year's Day. Therefore, the strong public health measures such as banning private gatherings were implemented. In addition, from week 48 to week 52 of 2021—when social distancing was strengthened compared to the previous season— the ILI has declined by 95.12%. On the other hand, the rate of change was low during period when social distancing was eased. For example, the period during which the 'social distancing level 1(week 42~week 47, 2020)' or 'step-by step daily recovery (week 44~week47, 2021)' was implemented, the observed ILI rate decreased by only 55.06% and 58.10%, respectively compared to the forecasted value. This indicates the significant role of the intensity and timing of the NPIs on influenza transmission.

Table 3-11. Comparison between observed ILI and predicted ILI under counterfactual scenario by NPI period

		2020						2021			
	No of Weeks	W4~10	W11~16	W17~33	W34~41	W42~47	W48~6	W7~27	W28~43	W44~47	W48~52
		20.1.19 ~2.7	2.8~2.18	2.19~8.15	8.16~10.10	10.11~11.21	20.11.22~ 21.2.13	2.14~7.10	7.11~10.30	10.31~11.27	11.28~12.31
ILI Observed	Mean	16.5	2.7	2.0	1.6	2.4	2.5	1.9	1.3	3.2	2.5
	Median	11.6	2.8	2.0	1.5	2.5	2.5	1.9	1.2	3.5	2.4
	IQR	14.8	0.3	0.5	0.4	1.4	0.3	0.4	0.6	0.7	0.6
ILI Predicted	Mean	22.2	8.9	5.3	4.1	5.3	39.9	7.8	4.2	7.7	51.7
	Median	24.9	8.9	4.8	4.3	4.9	37.1	7.3	4.4	6.9	62.5
	IQR	13.2	0.4	1.4	0.4	1.4	31.7	4.6	0.5	2.8	23.4
ILI Change %[1)]		25.55	69.34	61.18	61.34	55.06	93.83	75.66	70.23	58.10	95.12
Average COVID-19 case[2)]		1,108	490	316	1,103	1,132	4,439	4,141	12,419	20,424	39,460

* W1-3: Before COVID-19, W4-10: First case confirmed, alert level RED, W11-16: Pandemic declared, Social Distancing(SD), W16-33: Relaxed SD, Distancing in daily life, Level 1 SD, W34-41: Level 2 SD, W42-47: Level 1,1.5 SD, W48-6: Level 2, 2+a, 2.5 SD, W7-27: Level 2 SD, W28-43: Level 4 SD, W44-47: Step-by-step daily recovery, W48-52: Special quarantine measure

** Detail summary of social distancing(Appendix 7)

[1)]ILI Change %=(Predicted-Observed)/Predicted *100

[2)]Average COVID-19 case: Average number of COVID-19 newly confirmed COVID-19 case in South Korea

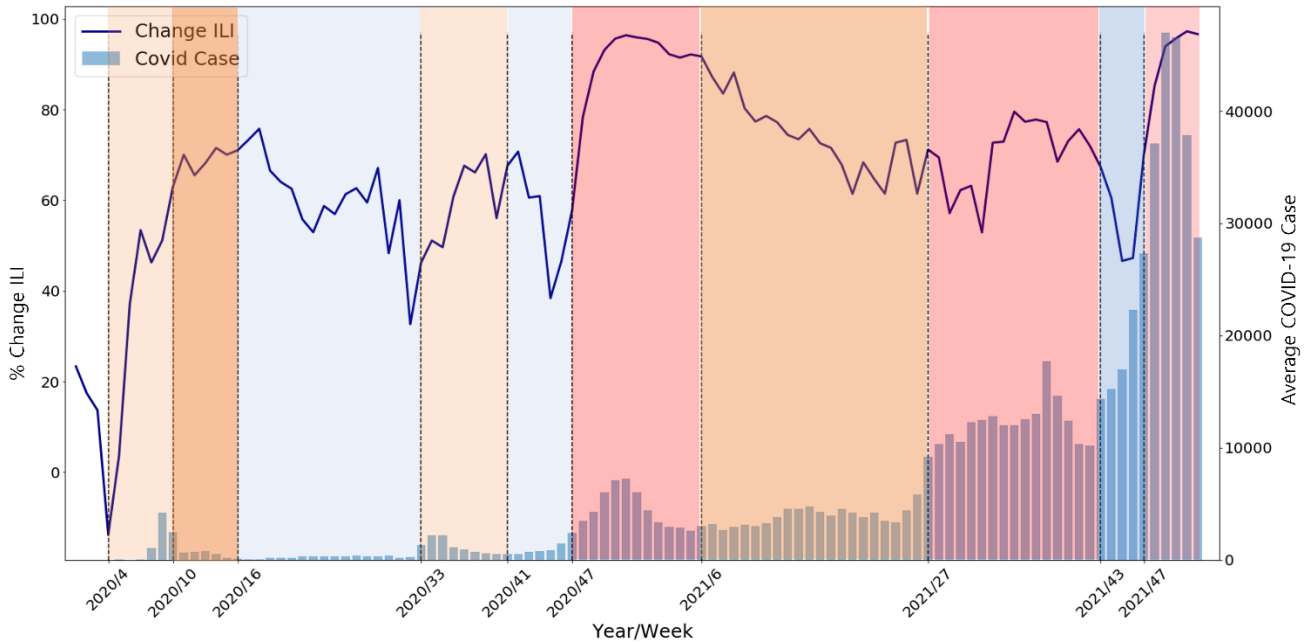

Figure 3-9. Comparison between % changed ILI and average COVID-19 cases

* W1-3: Before COVID-19, W4-10: First case confirmed, alert level RED, W11-16: Pandemic declared, Social Distancing(SD), W16-33: Relaxed SD, Distancing in daily life, Level 1 SD, W34-41: Level 2 SD, W42-47: Level 1,1.5 SD, W48-6: Level 2, 2+a, 2.5 SD, W7-27: Level 2 SD, W28-43: Level 4 SD, W44-47: Step-by-step daily recovery, W48-52: Special quarantine measure

** Detail summary of social distancing(Appendix 7)

***ILI Change %=(Predicted-Observed)/Predicted *100

**** Average COVID-19 case: Average number of COVID-19 newly confirmed COVID-19 case in South Korea

Chapter 4. Discussions

Non-pharmaceutical intervention to mitigate the spread of COVID-19 could have affected the transmission and circulation of influenza virus in community. This study aimed to identify the impact of NPIs for the control of COVID-19 on influenza. The characteristic of each season's influenza patterns was analyzed and time series forecasting were conducted to quantify the impact of NPIs on substantial decrease in influenza activity.

The study depicted the changes in influenza patterns and the difference in reduction rate according to the social distancing policies during the COVID-19 pandemic. The positive rate of IFV and its subtypes were considerably lower during COVID-19 outbreak compared to the previous seasons. In addition, in 2020-21 season, IFV specimens were not detected and none of the IFV B was detected after the emergence of SARS-CoV-2 in South Korea. This has been occurred in other countries and both Nextstrain and Flunet last reported influenza B/Yamagata lineage virus in March 2020 [10, 50]. Compared to the 2013-14 to 2018-19 season, the positive rate of IFV and IFV A decreased by 58.11% and 99.02%, respectively. Accordingly, the 2019-20 season showed a different virological

pattern than before, with the lowest IFV B positive rate ever. The virological pattern can be divided into two; co-circulation of IFV A and B in whole flu epidemic or predomination of IFV A followed by predomination of IFV B in second peak. The unique pattern that can be observed in 2019-20 season may be the impact of NPIs. The early stages of COVID-19 outbreak, which is from week 9, are the periods corresponding to the normal flu epidemic. The NPIs against COVID-19 may have inhibited the emergence and the spread of IFV B in the community. School closure can also explain this unusual pattern of IFV B, as the IFV B circulates more actively among children [51]. The analysis of clinical sentinel surveillance data suggests the huge reduction on ILI case, epidemic duration, and ILI peak point. During COVID-19 outbreak (2020-21, 2021-22 season), flu advisories has not been issued since the ILI cases did not reach the baseline (5.8 ILI/1000 outpatients). In 2019-20 season, the flu advisory was issued on November 15, 2019, before the emergence of COVID-19, similar to the 2018-19 season and the ILI peaked at week 52 with 49.8 ILI/1000 outpatients. The ILI cases at peak point is relatively low number compared to the previous seasons; the peak point in 2018-19 season was 73.3 ILI/1000 outpatients and 72.1 ILI/1000 outpatients in 2017-18 season. This might be due to

early lift of flu advisories since in 2019–20 season, the flu advisory lifted as early as 12 weeks earlier compared to the previous season. The changes in IFV positive rate and ILI cases between 2020 and the previous seasons were identified. As a result, the largest reduction of ILI cases occurred at week 48–week 52(% reduction: 91.01%, mean difference: −25.57) and week 11–week 16 (% reduction: 86.78%, mean difference: −17.94). In 2020, the 'enhanced social distancing' was implemented from week 12 to week 16 after the pandemic declaration in week 11. Also, level 2 social distancing was implemented from week 48 to week 52 and the ban on private gathering of 5 or more people was the major measures.

The time–series forecasting was conducted to estimate the influenza activity during COVID–19 outbreak under counterfactual scenario without NPI against COVID–19. The model accurately predicted the ILI cases/1000 outpatients, positive rate of IFV and IFV A during 2011–18 season. Consistency between the observed and predicted value indicated a reliability of these model in estimating the influenza activity. According to the prediction, if NPI had not been implemented during COVID–19 outbreak, the influenza activity would have remained high throughout the entire season, as shown in Figure 3–8. The NPI has been reduced the ILI cases by 56.17% in 2020 and

87.12% in 2021. Also, a large decreases were observed in both the positive rate of IFV and IFV subtype A during the COVID-19 outbreak. This implies the prevention role of NPI for the control of influenza. The characteristics of flu epidemics under the counterfactual scenario has been also examined. The result showed that the level of peak and incidence rate are differ by season, however, the flu epidemic duration and timing of peak points are turned out to be similar. The percent change between observed ILI rates and predicted under counterfactual scenario were analyzed by the timing of NPI implementation. As a result, the ILI has been decreased by 95.12% compared to the counterfactual scenario during week 48 to week 52 in 2021, when the social distancing was most strengthened. The large difference between the observed and predicted value highlights the role of NPI in mitigating the activity of influenza virus.

These results suggest the effectiveness of NPIs against COVID-19 on influenza activity. The NPIs that were implemented from the beginning of the COVID-19 outbreak such as hand hygiene, mask wearing, respiratory etiquette and staying home with respiratory symptoms played a big role in terms of the spread of influenza virus. The impact of mask wearing on influenza has been

proven in previous studies, and it has delayed a pandemic influenza by reducing the reproduction number [52]. Influenza viruses can be transmitted through droplet, aerosols (droplet nuclei) and contact transmission. The use of facial masks can act as a barrier not only to droplet transmission but also to hand-to-face contact transmission since the facial mask covers both the mouth and nose [53]. The hand hygiene may also be important in controlling influenza activity and transmission. According to previous study, maintenance of hand hygiene and use of face mask reduced the infection risk by 27% (RR: 0.78, 95% CI 0.60-0,89) [54]. Previous research suggests the significant impact of promotion on handwashing on reduction of transmission [55]. However, further research is needed as the role of handwashing is highly controversial in terms of mitigating the respiratory virus infection [56]. The recent survey on changes in personal hygiene behavior during COVID-19 outbreak revealed the improvement in the awareness of the importance of personal hygiene and the hand/respiratory hygiene compliance [57]. This may have affected the spread of influenza during COVID-19 outbreak. On the other hand, even in the period that social distancing was relaxed for a while, there was no significant increases in influenza case or IFV specimen. This suggests the potential effects of NPIs other than

physical distancing between individuals. For example, travel restriction would have had a significant impact on the transmission of influenza virus. Many countries have been restricted the travel to overseas to prevent the spread of COVID-19. In South Korea, travel restriction has been implemented to some countries, including China. In some cases, the entry was possible through special entry procedures only with the government permission. The 14 days self-quarantine was mandatory for all arrivals including both residents and foreigners. As a result, the number of travelers has decreased by more than 60% [58]. The incubation period of IFV is 2 days and even if an overseas entrant is infected with IFV, it may not be contagious due to 14 days quarantine process, which can reduce the IFV cases. Previous research has found that the travel restriction delay the transmission of influenza and have profound impact on timing of the peak of epidemics, delaying the spread by 2-19 weeks [59]. Not only the travel restriction, but also the other travel -related NPIs may affect the influenza activity such as border closure and screening travelers. Border closures reduced the influenza mortality and delayed the importation of IFV from 3 to 30 months and screening travelers also had significant impact on import delays [59]. The school closure may have important role in terms of reducing influenza

incidence during COVID-19 outbreak. Implementing school closure before and after the peak point of influenza has been reduced the overall flu epidemic duration with delaying the peak [60]. The previous study evaluated the effect of school closure duration on flu epidemic [61]. In South Korea, school closure was implemented in the first semester, the beginning of the COVID-19 outbreak and even after school opened in May, the school open were restricted depending on the situation.

Previous studies on the effect of NPI on respiratory infectious disease other than influenza have shown that the impact of NPIs targeted for COVID-19 are different by the virus. The weekly positive rate and the number of hospitalizations of rhinovirus increased during COVID-19 outbreak and the observed incidence was much higher than predicted under counterfactual scenario [14]. The circulation of adenovirus and respiratory enteroviruses decreased during COVID-19 NPI period, however, the levels persisted even when the NPIs were strengthened [10]. The difference of the impact of NPIs on types of respiratory infectious disease are due to the characteristics and the pathogenesis of each virus [10]. However, significant reduction on influenza virus activity were shown in most of the previous research during COVID-19

outbreak, suggesting the impact of NPIs on mitigating the transmission of IFV [10].

There are limitations to the study. First the decrease in ILI case might be due to decrease in visit of medical institution. From the beginning of COVID-19 outbreak, people with respiratory symptoms were recommended to go clinics exclusively treating respiratory diseases and restricted to visit other medical clinics. This may have reduced the number of outpatients and thus the actual number of patients infected with IFV may have been underestimated. Second, the laboratory respiratory surveillance data does not represent the total number of IFV cases in South Korea. Since only samples from patients who have visited designated institutions are tested, there may be an unconfirmed IFV. Finally, the SARIMA forecasting model used in this study did not consider the positive rate of IFV B. Also, the scenario did not consider the possibility of an emergence of new influenza subtype, which may not reflect the real-world situation. However, assuming that the pattern of influenza activity has been maintained so far, this forecasting model well depict.

Influenza has been reported to cause significant socioeconomic cost due to its high mortality and morbidity. Several studies in South Korea have confirmed higher mortality rate among

the population aged 65 and older compared to other age groups [63, 64]. Hong et al. used negative binomial regression model to estimate influenza-associated mortality in Korea during 2009-2016 season and IFV A H3N2 showed highest influenza-associated mortality including all-cause, respiratory, and circulatory deaths among IFV subtypes [64]. The older population, aged over 65, were more vulnerable to influenza and the IFV A H1N1-associated mortality rate was higher in the population aged under 65 [64]. Influenza can cause high burden of illness as it can lead to severe symptoms, hospitalization, and death. The influenza-associated excess death during influenza season was approximately 2,300 to 5,300 per year on average [63]. Therefore, to reduce the socioeconomic cost and the burden of disease, the management of the spread of virus and early detection of the flu epidemic is necessary.

Recently, concerns regarding 'twin-demics'(dual epidemics) of influenza and COVID-19 have been continuously raised. The rapid public health response on influenza is very important. This research gives important policy implication of involving NPIs in terms of controlling influenza. There was significant reduction in ILI cases, positive rate of IFV and IFV A compared to the prediction value under counterfactual scenario in 2020 and 2021, which suggest the role of

social distancing and public health measures such as use of face mask, hand washing, school closure and travel restriction. The intensity and timing of the NPIs also showed remarkable changes on influenza transmission. The early detection of flu epidemic has significant impact on clinicians' awareness of the influenza epidemic, which can lead to various preparations before issuing the flu advisory and it can reduce the burden of illness. Also, the promotion on influenza vaccination and personal hygiene can be made before the flu epidemic occurs.

The immunity may have changed during COVID-19 outbreak since the influenza virus has not been circulated in community for recent two years and the vaccination rate was lower than the previous year. This can cause tremendous risk if the flu epidemic emerges in community. In addition, the challenges on vaccine strain selection have been continuously raised as low number of IFV subtype have been detected in the past two years. These uncertainty on future seasonal influenza emphasize the importance of the research on the effect of public health measures on influenza transmission.

Evidence from our studies improves the understanding of role of non-pharmaceutical interventions on influenza, however, since

some NPIs often come with a high socioeconomic cost, the effectiveness of each NPIs should be evaluated.

Chapter 5. Conclusion

Non-pharmaceutical interventions for the control of COVID-19 have affected the transmission of influenza virus and other respiratory diseases. The social distancing, an effective NPI to reduce the level of SARS-CoV-2 transmission, and personal behavior changes reduced the influenza activity in South Korea. Timing and the intensity of the NPIs was associated with the decreases in influenza activity during COVID-19 outbreak. The early detection and proper management of influenza are necessary due to its high mortality and hospitalization among high-risk group. Evidence from our study improves the understanding of the effectiveness of NPIs against influenza virus. Further studies are needed to evaluate the effectiveness of each NPIs, as some NPIs carry high socioeconomic cost and may not be feasible to the pubic or government for the control of influenza.

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국문 초록

코로나19 비약물적 중재가 인플루엔자 발생에 미치는 영향: 시계열 예측을 중심으로

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2019-2020 절기 인플루엔자 유행기간인 2020년 1월 20일 국내 코로나19 첫 확진자가 발생하였다. 지역사회 내 전파를 최소화하고자 사회적 거리두기, 개인위생 강화 등 여러 비약물적 중재가 시행되었으며 코로나19 외 인플루엔자를 포함한 여러 호흡기 감염병의 발생 양상에 큰 영향을 미친 것으로 알려졌다. 이에 본 연구에서는 코로나19 발생 이후 인플루엔자 발생 양상을 도출하고 인플루엔자 전파에서의 비약물적 중재의 효과를 확인하였다.

코로나19가 발생하기 이전인 2013-2019 절기와 2020-2022 절기의 인플루엔자 의사환자분율 및 인플루엔자 병원체 검출률을 비교한 결과 마스크 착용, 등교 중지, 출입국 제한 등 비약물적 중재가 시행된 시기에 인플루엔자 의사환자가 91% 감소한 것으로 나타났다. 사회적

거리두기의 단계가 인플루엔자 전파에 미치는 영향을 확인하기 위해 SARIMA 모델을 이용한 예측 모형을 구축하였다. 그 결과 코로나19의 비약물적 중재가 시행되지 않았을 경우 2020-2022 인플루엔자 유행은 전 절기와 비슷한 수준을 유지할 것으로 확인되었다. 또한, 사회적 거리두기 단계가 강화될 때 의사환자 감소율이 증가하는 것으로 나타났다 (단계적 일상회복 단계: 58.10%, 2021년 연말 특별 방역대책: 95.12%).

본 연구에서는 코로나19 시기에 강화된 개인위생과 비약물적 중재가 인플루엔자 발생 감소에 미치는 영향을 확인하였으며 이로써 본 연구 결과는 향후 인플루엔자 유행에 대비한 예방 및 관리 정책의 근거를 제시한다.

주요어: 코로나19, 사회적 거리두기, 비약물적 중재, 인플루엔자, SARIMA, 시계열 예측

학번: 2021-21267

Appendix

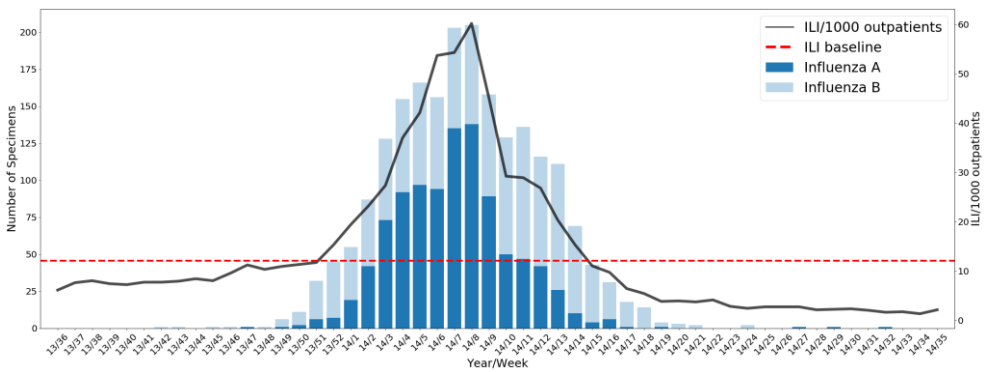
Appendix 1. The number of detected influenza virus and the influenza-like illness rates of the 2013-14 season to 2021-22 season

*Dark blue bar: Number of specimens of influenza A

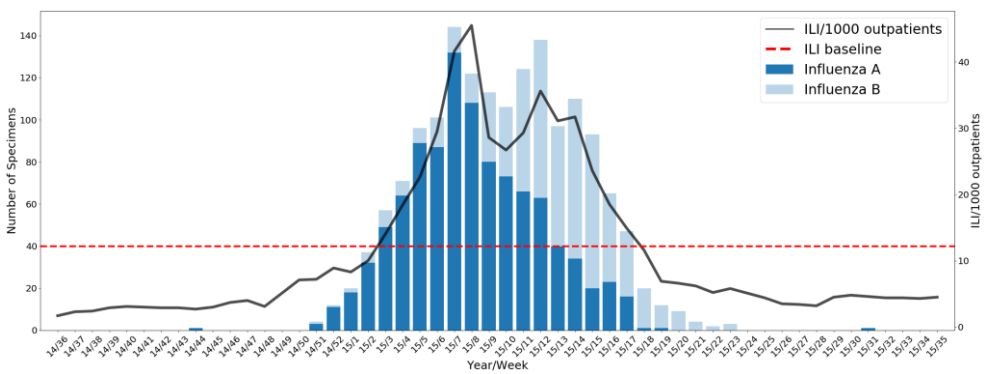
Light blue bar: Number of specimens of influenza B

Red line: ILI-base line(differ by each year)

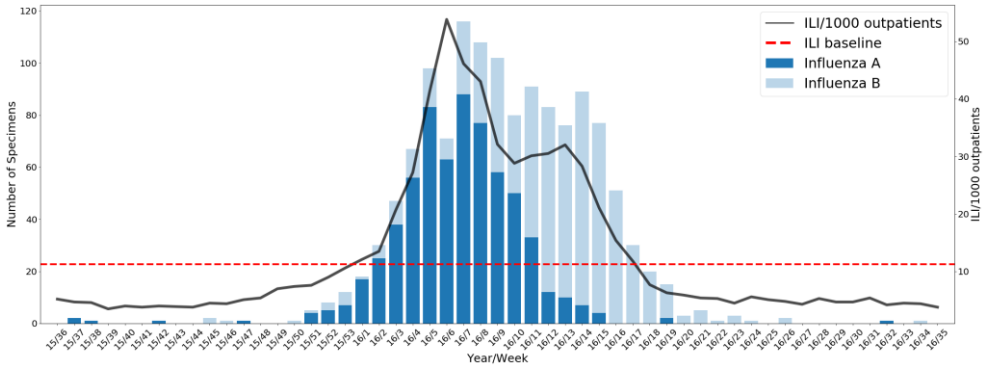
Black line: ILI rates (ILI case/1000 outpatients)



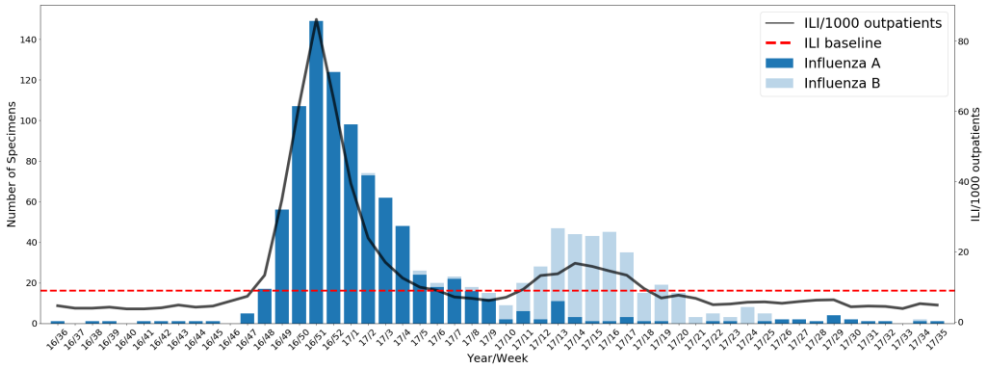
2013-2014 influenza season



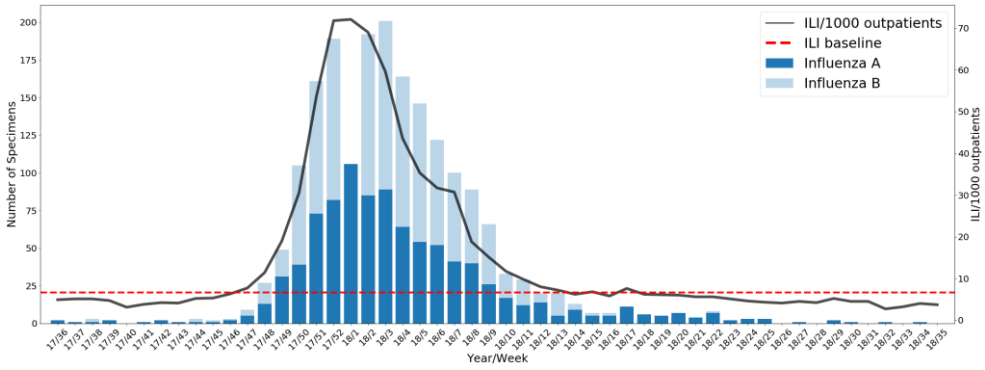
2014-2015 influenza season



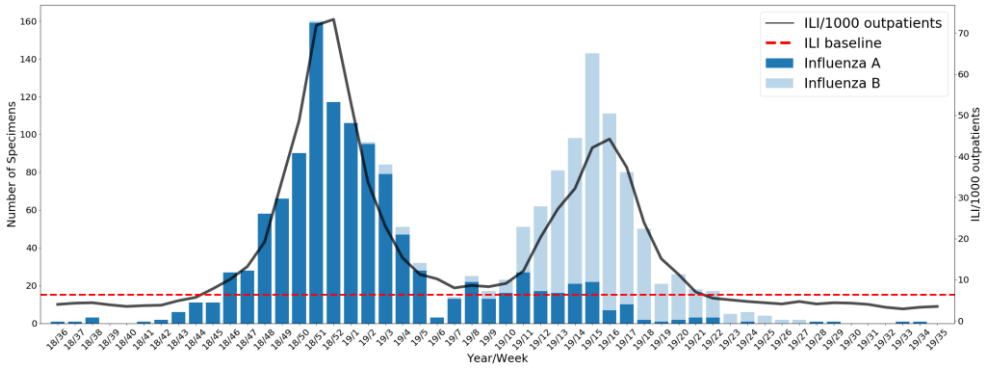
2015–2016 influenza season



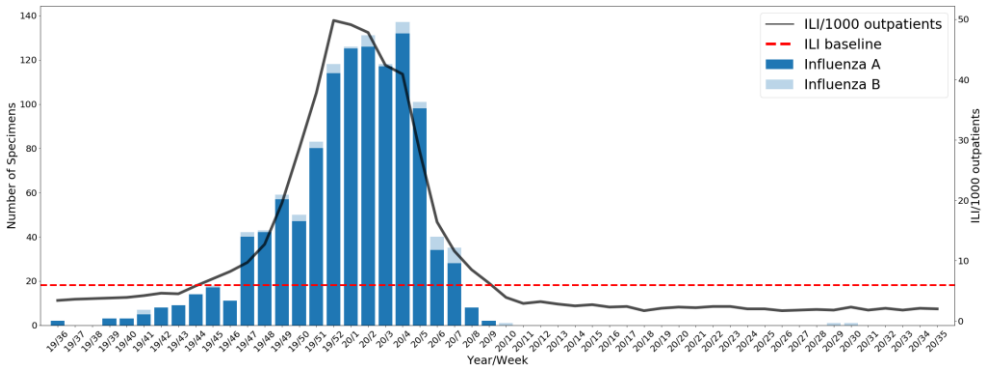
2016–2017 influenza season



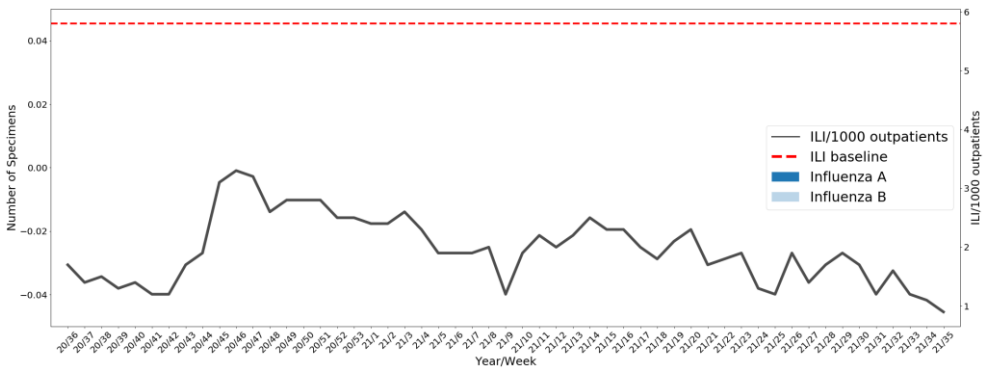
2017–2018 influenza season



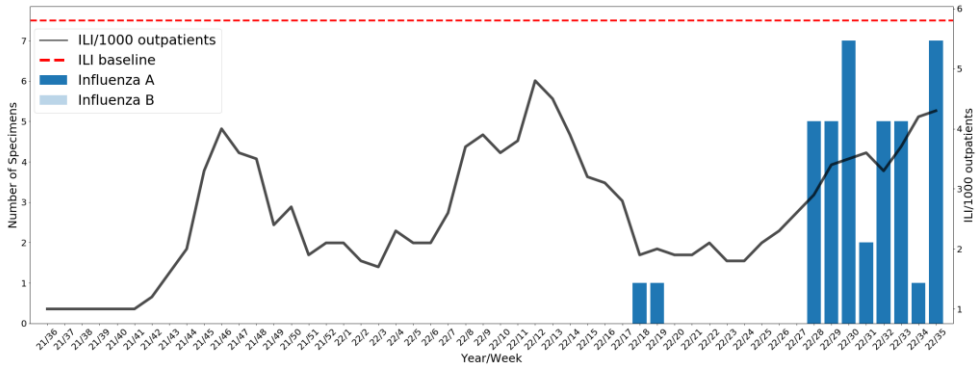
2018–2019 influenza season



2019–2020 influenza season



2020–2021 influenza season



2021−2022 influenza season

Appendix 2. KINRESS sentinel sites (2020–21 season)

Region	ILI sentinel sites	Laboratory monitoring sentinel sites	Inpatient monitoring sentinel sites
Total	199	63	219
Seoul	37	6	43
Busan	11	4	18
Daegu	10	3	8
Incheon	11	4	14
Gwangju	7	3	5
Daejeon	6	2	8
Ulsan	6	3	2
Sejong	2	2	1
Gyeonggi	43	7	43
Gangwon	6	3	8
Chungbuk	6	3	9
Chungnam	6	4	9
Jeonbuk	8	4	10
Jeonnam	8	4	9
Gyeongbuk	13	3	13
Gyeongnam	14	4	12
Jeju	5	4	7

Appendix 3. Selecting Best Model for ILI/1000 outpatients

Model	AICc
ARIMA (0,0,0) (0,1,0) [52] with drift	4878.186
ARIMA (0,0,0) (1,1,0) [52]	4794.621
ARIMA (0,0,0) (1,1,0) [52] with drift	4796.511
ARIMA (0,0,1) (0,1,1) [52] with drift	4534.526
ARIMA (0,0,1) (1,1,0) [52]	4498.464
ARIMA (0,0,2) (0,1,1) [52]	4351.486
ARIMA (0,0,2) (1,1,0) [52]	4324.5
ARIMA (0,0,3) (0,1,0) [52]	4308.146
ARIMA (0,0,3) (0,1,1) [52]	4262.614
ARIMA (0,0,3) (0,1,1) [52] with drift	4261.414
ARIMA (0,0,3) (1,1,0) [52]	4258.548
ARIMA (0,0,4) (0,1,0) [52]	4279.432
ARIMA (0,0,4) (0,1,1) [52]	4221.903
ARIMA (0,0,4) (1,1,0) [52]	4222.907
ARIMA (1,0,0) (0,1,0) [52]	4370.846
ARIMA (1,0,0) (0,1,0) [52] with drift	4372.752
ARIMA (1,0,0) (1,1,0) [52]	4316.943
ARIMA (1,0,0) (1,1,0) [52] with drift	4318.97
ARIMA (1,0,1) (0,1,0) [52]	4295.617
ARIMA (1,0,1) (0,1,1) [52]	4236.156
ARIMA (1,0,1) (1,1,0) [52]	4244.362
ARIMA (1,0,1) (1,1,0) [52] with drift	4246.397
ARIMA (1,0,2) (0,1,0) [52]	4262.955
ARIMA (1,0,2) (0,1,1) [52]	4199.456
ARIMA (1,0,2) (0,1,1) [52]	Inf
ARIMA (1,0,2) (0,1,1) [52] with drift	Inf
ARIMA (1,0,2) (0,1,2) [52]	Inf
ARIMA (1,0,2) (1,1,0) [52]	4212.912
ARIMA (1,0,2) (1,1,0) [52] with drift	4214.952
ARIMA (1,0,2) (1,1,1) [52]	Inf
ARIMA (1,0,3) (0,1,0) [52]	4261.168
ARIMA (1,0,3) (0,1,0) [52] with drift	4262.921

ARIMA(1,0,3)(0,1,1)[52]	4196.86
ARIMA(1,0,3)(0,1,1)[52]	Inf
ARIMA(1,0,3)(0,1,1)[52] with drift	Inf
ARIMA(1,0,3)(0,1,2)[52]	Inf
ARIMA(1,0,3)(1,1,0)[52]	4212.706
ARIMA(1,0,3)(1,1,0)[52] with drift	4214.757
ARIMA(1,0,3)(1,1,1)[52]	Inf
ARIMA(1,0,4)(0,1,0)[52]	4263.246
ARIMA(1,0,4)(0,1,0)[52] with drift	4265.014
ARIMA(1,0,4)(0,1,1)[52]	4197.664
ARIMA(1,0,4)(0,1,1)[52]	Inf
ARIMA(1,0,4)(0,1,1)[52] with drift	4198.674
ARIMA(1,0,4)(0,1,1)[52] with drift	Inf
ARIMA(1,0,4)(1,1,0)[52]	4212.179
ARIMA(1,0,4)(1,1,0)[52] with drift	4214.236
ARIMA(1,0,5)(0,1,0)[52]	4265.03
ARIMA(2,0,1)(0,1,0)[52]	4267.891
ARIMA(2,0,1)(0,1,1)[52]	4199.975
ARIMA(2,0,1)(0,1,1)[52]	Inf
ARIMA(2,0,1)(0,1,1)[52] with drift	4200.41
ARIMA(2,0,1)(0,1,1)[52] with drift	Inf
ARIMA(2,0,1)(0,1,2)[52]	4201.857
ARIMA(2,0,1)(0,1,2)[52]	Inf
ARIMA(2,0,1)(1,1,1)[52]	Inf
ARIMA(2,0,2)(0,1,0)[52]	4262.409
ARIMA(2,0,2)(0,1,0)[52] with drift	4264.067
ARIMA(2,0,2)(0,1,1)[52]	4196.074
ARIMA(2,0,2)(0,1,1)[52]	Inf
ARIMA(2,0,2)(0,1,1)[52] with drift	4196.78
ARIMA(2,0,2)(0,1,1)[52] with drift	Inf
ARIMA(2,0,2)(0,1,2)[52]	Inf
ARIMA(2,0,2)(0,1,2)[52] with drift	Inf
ARIMA(2,0,2)(1,1,0)[52]	4210.865
ARIMA(2,0,2)(1,1,0)[52]	1838.535
ARIMA(2,0,2)(1,1,1)[52]	Inf

ARIMA(2,0,2)(1,1,1)[52] with drift	Inf
ARIMA(2,0,3)(0,1,0)[52]	4264.082
ARIMA(2,0,3)(0,1,1)[52]	4198.151
ARIMA(2,0,3)(0,1,1)[52]	Inf
ARIMA(2,0,3)(0,1,1)[52] with drift	4198.843
ARIMA(2,0,3)(0,1,1)[52] with drift	Inf
ARIMA(2,0,4)(0,1,0)[52]	4266.001
ARIMA(3,0,1)(0,1,1)[52]	4201.78
ARIMA(3,0,1)(0,1,1)[52]	Inf
ARIMA(3,0,2)(0,1,0)[52]	4264.847
ARIMA(3,0,2)(0,1,1)[52]	4198.023
ARIMA(3,0,2)(0,1,1)[52]	Inf
ARIMA(3,0,2)(0,1,1)[52] with drift	4198.849
ARIMA(3,0,2)(0,1,1)[52] with drift	Inf

Appendix 4. Selecting Best Model for positive rate of IFV

Model	AICc
ARIMA(0,0,0)(0,1,0)[52] with drift	4926.051
ARIMA(0,0,0)(1,1,0)[52]	4868.715
ARIMA(0,0,0)(1,1,0)[52] with drift	4870.728
ARIMA(0,0,1)(0,1,1)[52] with drift	4585.977
ARIMA(0,0,1)(1,1,0)[52]	4589.561
ARIMA(0,0,2)(1,1,0)[52]	4496.821
ARIMA(0,0,3)(0,1,1)[52]	Inf
ARIMA(0,0,3)(1,1,0)[52]	4399.356
ARIMA(0,0,4)(0,1,0)[52]	4403.406
ARIMA(0,0,4)(0,1,1)[52]	Inf
ARIMA(0,0,4)(0,1,1)[52] with drift	Inf
ARIMA(0,0,4)(1,1,0)[52]	4373.745
ARIMA(0,0,5)(0,1,1)[52]	4308.014
ARIMA(1,0,0)(0,1,0)[52]	4385.59
ARIMA(1,0,0)(0,1,0)[52] with drift	4387.577
ARIMA(1,0,0)(1,1,0)[52]	4352.9
ARIMA(1,0,0)(1,1,0)[52] with drift	4354.953
ARIMA(1,0,1)(0,1,0)[52]	4382.659
ARIMA(1,0,1)(1,1,0)[52]	4348.263
ARIMA(1,0,1)(1,1,0)[52] with drift	4350.329
ARIMA(1,0,2)(0,1,0)[52]	4378.038
ARIMA(1,0,2)(0,1,1)[52]	Inf
ARIMA(1,0,2)(1,1,0)[52]	4339.503
ARIMA(1,0,2)(1,1,0)[52] with drift	4341.581
ARIMA(1,0,3)(0,1,0)[52]	4340.232
ARIMA(1,0,3)(0,1,1)[52]	4283.559
ARIMA(1,0,3)(0,1,1)[52] with drift	4285.166
ARIMA(1,0,3)(0,1,2)[52]	Inf
ARIMA(1,0,3)(1,1,0)[52]	4313.255
ARIMA(1,0,3)(1,1,0)[52] with drift	4315.348
ARIMA(1,0,3)(1,1,1)[52]	Inf
ARIMA(1,0,4)(0,1,0)[52]	4339.184
ARIMA(1,0,4)(0,1,0)[52] with drift	4341.176
ARIMA(1,0,4)(0,1,1)[52]	4283.179
ARIMA(1,0,4)(0,1,1)[52] with drift	4284.781
ARIMA(1,0,4)(1,1,0)[52]	4311.975
ARIMA(1,0,4)(1,1,0)[52] with drift	4314.081
ARIMA(1,0,5)(0,1,0)[52]	4337.06
ARIMA(2,0,2)(0,1,0)[52]	4348.981

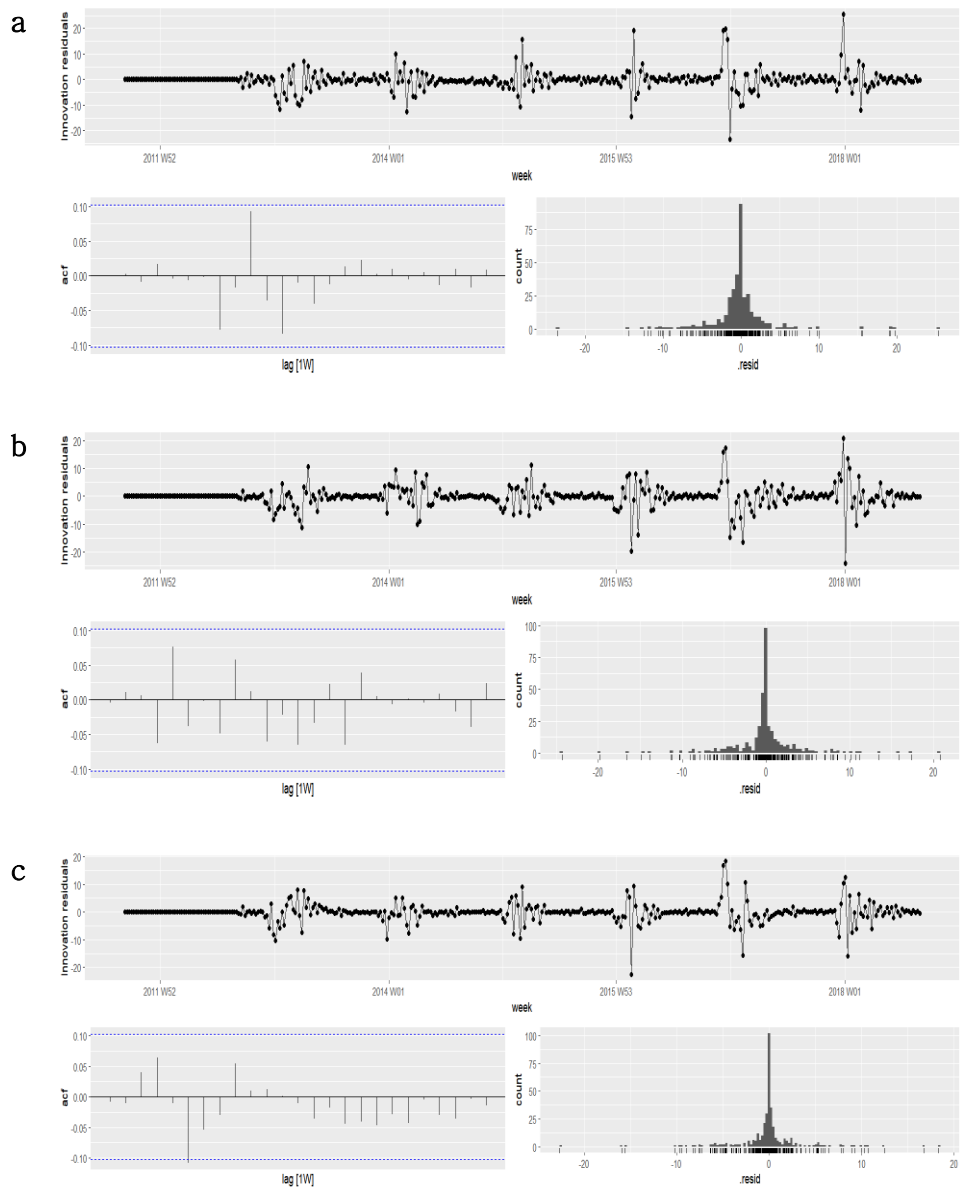
ARIMA(2,0,2)(0,1,1)[52]	Inf
ARIMA(2,0,2)(0,1,1)[52] with drift	Inf
ARIMA(2,0,2)(0,1,2)[52]	Inf
ARIMA(2,0,2)(1,1,1)[52]	Inf
ARIMA(2,0,2)(1,1,1)[52] with drift	Inf
ARIMA(2,0,3)(0,1,0)[52]	4336.033
ARIMA(2,0,3)(0,1,0)[52] with drift	4337.996
ARIMA(2,0,3)(0,1,1)[52]	4276.174
ARIMA(2,0,3)(0,1,1)[52]	1859.892
ARIMA(2,0,3)(0,1,1)[52] with drift	4277.451
ARIMA(2,0,3)(1,1,0)[52]	4304.724
ARIMA(2,0,4)(0,1,0)[52]	4337.274
ARIMA(3,0,2)(0,1,1)[52]	Inf
ARIMA(3,0,3)(0,1,0)[52]	4337.463

Appendix 5. Selecting Best Model for positive rate of IFV A

Model	AICc
ARIMA(0,0,0)(0,1,0)[52] with drift	4417.613
ARIMA(0,0,1)(0,1,1)[52] with drift	4113.879
ARIMA(1,0,0)(1,1,0)[52] with drift	3914.875
ARIMA(1,0,0)(1,1,1)[52]	Inf
ARIMA(1,0,1)(0,1,1)[52]	3893.143
ARIMA(1,0,1)(1,1,0)[52]	3892.948
ARIMA(1,0,1)(1,1,1)[52]	Inf
ARIMA(1,0,1)(1,1,1)[52] with drift	Inf
ARIMA(1,0,1)(1,1,2)[52]	Inf
ARIMA(1,0,1)(2,1,1)[52]	3934.613
ARIMA(1,0,2)(1,1,1)[52]	3870.372
ARIMA(1,0,2)(1,1,1)[52] with drift	3872
ARIMA(2,0,0)(0,1,1)[52]	3880.142
ARIMA(2,0,0)(1,1,0)[52]	3884.168
ARIMA(2,0,0)(1,1,1)[52]	3869.793
ARIMA(2,0,0)(1,1,1)[52] with drift	3871.299
ARIMA(2,0,0)(1,1,2)[52]	Inf
ARIMA(2,0,0)(2,1,1)[52]	3923.839
ARIMA(2,0,1)(0,1,0)[52]	3917.753
ARIMA(2,0,1)(0,1,1)[52]	3853.616
ARIMA(2,0,1)(0,1,1)[52]	Inf
ARIMA(2,0,1)(0,1,1)[52] with drift	3854.62
ARIMA(2,0,1)(0,1,1)[52] with drift	Inf
ARIMA(2,0,1)(0,1,2)[52]	Inf
ARIMA(2,0,1)(1,1,0)[52]	3862.934
ARIMA(2,0,1)(1,1,0)[52]	1738.978
ARIMA(2,0,1)(1,1,0)[52] with drift	3864.025
ARIMA(2,0,1)(1,1,1)[52]	3847.94
ARIMA(2,0,1)(1,1,1)[52]	Inf
ARIMA(2,0,1)(1,1,1)[52] with drift	3848.086
ARIMA(2,0,1)(1,1,1)[52] with drift	Inf
ARIMA(2,0,1)(1,1,2)[52]	Inf
ARIMA(2,0,1)(1,1,2)[52] with drift	Inf
ARIMA(2,0,1)(2,1,0)[52]	3903.366
ARIMA(2,0,1)(2,1,1)[52]	Inf
ARIMA(2,0,1)(2,1,1)[52] with drift	Inf
ARIMA(2,0,2)(0,1,1)[52]	3854.678
ARIMA(2,0,2)(0,1,1)[52]	Inf
ARIMA(2,0,2)(0,1,1)[52] with drift	3855.8

ARIMA(2,0,2)(0,1,1)[52] with drift	Inf
ARIMA(2,0,2)(1,1,0)[52]	3864.967
ARIMA(2,0,2)(1,1,0)[52] with drift	3866.102
ARIMA(2,0,2)(1,1,1)[52]	3849.421
ARIMA(2,0,2)(1,1,1)[52]	Inf
ARIMA(2,0,2)(1,1,1)[52] with drift	3849.773
ARIMA(2,0,2)(1,1,1)[52] with drift	Inf
ARIMA(3,0,0)(1,1,1)[52]	3857.43
ARIMA(3,0,0)(1,1,1)[52]	Inf
ARIMA(3,0,1)(0,1,1)[52]	3855.908
ARIMA(3,0,1)(0,1,1)[52]	Inf
ARIMA(3,0,1)(1,1,0)[52]	3866.205
ARIMA(3,0,1)(1,1,1)[52]	3850.658
ARIMA(3,0,1)(1,1,1)[52]	Inf
ARIMA(3,0,1)(1,1,1)[52] with drift	3851.065
ARIMA(3,0,1)(1,1,1)[52] with drift	Inf

Appendix 6. Residual analysis of SARIMA model



*a) ILI case/1000 outpatients

b) Positive rate of IFV

c) Positive rate of IFV A

* Dashed line indicate the 95% confidence interval

Appendix 7. Social distancing levels by period(2020-2021)

Period	Week	Social Distancing Level
2020.01.20.	W4	First imported COVID-19 case confirmed in South Korea Alert level raised to yellow
2020.02.23.	W9	Alert level raised to Red
2020.02.29. ~03.21	W9~W12	Social Distancing[1)]
2020.03.11.	W11	WHO declared COVID-19 a pandemic
2020.03.22. ~04.19	W13~W16	Enhanced Social Distancing[1)]
2020.04.20. ~05.05	W17~W18	Relaxed Social Distancing[1)]
2020.05.06. ~08.18.	W19~W33	Distancing in Daily Life[1)] and Level 1 Social Distancing[2)]
2020.08.19. ~8.29.	W34~W35	Level 2 Social Distancing[2)3)]
2020.08.30. ~9.13.	W36~W37	Level 2.5 Social Distancing
2020.09.14. ~10.11.	W38~W41	Level 2 Social Distancing * 9.28.~10.10.: Holiday special quarantine:
2020.10.12. ~11.6.	W42~W45	Level 1 Social Distancing

2020.11.07. ~11.18.	W46~W47	Level 1 Social Distancing[4]
2020.11.19. ~11.23.	W47~W48	Level 1.5 Social Distancing (special quarantine for National Exam for University)
2020.11.24. ~11.30.	W48~W49	Level 2 Social Distancing
2020.12.01. ~12.07.	W49	Level 2+a Social Distancing
2020.12.08. ~21.02.14.	W50~W6	Level 2.5 Social Distancing *Private gathering restricted
2021.02.15. ~07.11	W7~W27	Level 2 Social Distancing
2021.07.12. ~10.31.	W28~W43	Level 4 Social Distancing[5] *9.13.~9.26.: Holiday special quarantine
2021.11.01. ~11.28.	W44~W47	Step-by Step Daily recovery
2021.11.29. ~12.31.	W48~W52	Special quarantine measure

1) Social Distancing policy divided into 3 steps

2) 2020.06.28: Social Distancing policy reformed to 3 tiers(Level 1, 2, 3)

3) Only metropolitan area

4) 2020.11.07: Social Distancing reformed to 5 tiers(Level 1, 1.5, 2, 2.5, 3)

5) 2021.07.12.: Social Distancing reformed to 4 tiers(Level 1, 2, 3, 4)