Mathematical model of transmission dynamics and optimal control strategies for 2009 A/H1N1 influenza in the Republic of Korea

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1. Introduction

During the spring of 2009, the A/H1N1 influenza virus spread rapidly across the globe. As of August 2010, more than 214 countries reported confirmed cases, including over 18,449 deaths (World Health Organization, 2010a,b). The total number of patients of the 2009 A/H1N1 influenza is estimated to be in the range of tens of millions to 200 million (World Health Organization Director-General, 2011). Owing to the mild symptoms and low fatality rate, the 2009 A/H1N1 influenza generated numerous patients throughout the world. Although 2009 A/H1N1 virus that caused the pandemic is now a regular human flu virus and continues seasonally worldwide (Centers for Disease Control and Prevention, 2010), scientists have been warning that another influenza pandemic could strike at any moment (Enserink and Cohen, 2009). Based on past pandemics, the preparedness and response of public health care for an influenza pandemic crisis must be improved. For effective epidemic disease preparedness, it is necessary not only to analyze control strategies on the 2009 A/H1N1 influenza epidemic, but also to establish a new and improved public health care system.

Mathematical modeling is a good tool for analyzing the past intervention strategies and identifying promising new ones. In particular, mathematical modeling quantifies the benefits of abstract and diverse government intervention strategies. Many researchers have devoted their effort to the study of mathematical modeling and intervention strategies for influenza epidemics. Arino et al. (2006) and Arino et al. (2008) considered asymptomatic individuals in the formulation of the Susceptible-Latent-Infected-Asymptomatic-Recovered (SLIAR) model to describe an influenza pandemic, and the basic reproductive number and the final epidemic size were analyzed. The intervention effects with limited antiviral and isolation controls, based on the seven compartment model, were studied by Lee et al. (2010) and it was established that isolation plays an important role especially when antiviral intervention is limited. Chowell et al. (2009) developed a nine compartments model with six age groups and suggested a vaccination strategy for Mexico. Towers and Feng (2009) predicted the A/H1N1 influenza pandemic and assessed the Centers for Disease Control and Prevention (CDC) vaccination campaign using their seasonal SIR model. Qiu and Feng (2010) developed a mathematical model for influenza that considered the drug-sensitive and resistant strains to examine the effect of intervention through antiviral and vaccination strategies. A simple SAIR model for A/H1N1 influenza and a complex model for considering co-infection of A/H1N1 influenza and seasonal flu were studied by Prosper et al. (2011). Optimal control strategies were also suggested in their study. Lee et al. (2012) formulated an age-structured model with age-specific control functions...
and suggested optimal vaccination strategies. Tchuenche et al. (2011) developed a mathematical model with three control functions, vaccine waning, vaccine effectiveness, and treatment effectiveness controls and carried out a sensitivity analysis to determine the important factors of the disease transmission and prevalence. Lee et al. (2013b) studied a seasonal forcing model and an age-structured model and investigated the optimal intervention strategies for influenza outbreaks.

Our work is distinguished from previous works by its use of data on the 2009 A/H1N1 influenza in the Republic of Korea. Using a parameter estimation process, the government’s intervention strategies conducted in 2009 are quantified. Moreover, the quantified values are used as the upperbounds of the optimal control functions, a key idea in optimal control theory. This approach leads to realistic and effective intervention strategies. Using a simple epidemic model without optimal control, we also explore the real-time prediction of the 2009 A/H1N1 influenza epidemic in the Republic of Korea in the early spread. It is possible to use this model as a comparative tool for government intervention strategies. To prevent an influenza epidemic, the timing and amount of vaccine are the most critical issues. In our study, we introduce the optimal control theory to analyze and propose optimal vaccine strategies. Furthermore, the early optimal vaccine strategies with the limited vaccination coverages are discussed.

The remainder of this paper is organized as follows. Section 2 describes the mathematical modeling of A/H1N1 influenza in the Republic of Korea. Parameter estimation and the bootstrap method are discussed in this section. In Section 3, an optimal control framework is presented. We present the real-time prediction of A/H1N1 incidence and suggest optimal intervention strategies in Section 4. Conclusions are presented in the final section.

2. Materials and methods

2.1. Epidemic data

The Korea Centers for Disease Control and Prevention (KCDC) intensified the national public health crisis phase from Atention to Caution on April 27, 2009 after the first detection of an A/H1N1 patient in the Republic of Korea (Lee et al., 2013a). The government then implemented various control policies. Owing to the well-structured public health care system in the Republic of Korea, most influenza patients went to hospitals, and it was mandatory for doctors to report influenza patients to the KCDC (Park and Cho, 2014). This system improved the reliability of the influenza data collected by the Korean government.

Fig. 1 shows the number of daily incidence data in the Republic of Korea from April 27 to December 31, 2009. At the beginning of the epidemic, only cases confirmed by polymerase chain reaction (PCR) among the influenza like illnesses (ILIs) were reported to the KCDC and it took 3–5 days to obtain the PCR result. As the epidemic progressed, the number of ILI patients increased rapidly. On August 20, 2009, the KCDC changed the guideline of the antiviral prescription and the reporting system so that doctors could prescribe antiviral drugs to the ILI patients without a PCR test and were instructed to report the cases who prescribed the antiviral drugs. Therefore, the incidence data indicates that the PCR confirmed cases during Period 1 (April 27–August 19), while the incidence data during Period 2 (August 20–October 14) and Period 3 (October 15–December 31) include all the people who were prescribed antiviral drugs.

The government focused on nonpharmaceutical intervention strategies such as quarantine and isolation of patients during Period 1. As of August 20, the antiviral intervention strategy was implemented more actively. During Period 2, both nonpharmaceutical and antiviral intervention strategies were conducted. About six months after the outbreak onset, the vaccine was approved and the vaccination started. The vaccine strategy was added during Period 3. Table 1 lists the separate time periods and the corresponding policies conducted by the Korean government in 2009.

2.2. SEIAR influenza model

Before we present a model of the 2009 A/H1N1 influenza in the Republic of Korea, a SEIAR influenza model without interventions (uncontrolled model) is described in this subsection. The total population (N) is classified into five subclasses: susceptible (S), latent (E), symptomatic infectious (I), asymptomatic infectious (A), and recovered (R) individuals. The SEIAR model is governed by nonlinear differential equations as follows:

\[
\begin{align*}
\frac{dS}{dt} &= -\beta S \frac{E}{N}, \\
\frac{dE}{dt} &= \beta S \frac{E}{N} - \kappa E, \\
\frac{dI}{dt} &= \eta A - \gamma I, \\
\frac{dA}{dt} &= \eta (1-\rho)E - \delta A, \\
\frac{dR}{dt} &= \alpha I + \gamma A,
\end{align*}
\]

where \(\Lambda = \epsilon E + \eta I + \delta A\).

Since the duration of an influenza epidemic is relatively short, the demographic effect is neglected. The parameter \(\beta^p\) denotes the transmission rate without interventions at which a susceptible individual is infected and becomes a latent individual. Note that A/H1N1 influenza can spread by latent and asymptomatic individuals as well as symptomatic individuals. We set the following infectivity reduction factors: \(\epsilon\) for latency, \(q\) for symptomatic, and \(\delta\) for asymptomatic individuals (0 ≤ \(\epsilon, q, \delta\) ≤ 1). The parameter \(\kappa\) is the progression rate to infectious individuals; therefore, 1/\(\kappa\) implies the average latent period. The constant \(p\) represents the fraction of latent individuals developing symptoms (0 ≤ \(p\) ≤ 1). The parameters \(\alpha\) and \(\eta\) are the recovery rates of infectious and asymptomatic groups, respectively. Since the fatality rate of the 2009 A/H1N1 influenza in the Republic of Korea is estimated to be 16 per 100,000 cases (Kim et al., 2011), the fatality rate is ignored in our study.

<table>
<thead>
<tr>
<th>Intervention policy</th>
<th>Period 1 (April 27–August 19)</th>
<th>Period 2 (August 20–October 18)</th>
<th>Period 3 (October 19–December 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonpharmaceutical</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Antiviral</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Vaccine</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
</tbody>
</table>

Table 1 Three consecutive periods and the corresponding intervention policies.
The basic reproductive number, \( R_0 \), is the number of secondary cases generated by a primary patient over the infectious period in a susceptible population. In general, \( R_0 \) depends on the infectious period, recovery rate, and transmission rate. The \( R_0 \) of the 2009 A/H1N1 influenza in the Republic of Korea is known as 1.6 (Suh et al., 2010; Fraser et al., 2009; Nishiura et al., 2009; White et al., 2009). From our mathematical model (1), the basic reproductive number is derived by the next generation method (Diekmann et al., 1990) as follows:

\[
R_0 = \beta^* \left\{ \frac{\epsilon}{\kappa} + \frac{\delta}{\alpha} (1 - p) - \frac{\delta}{\eta} \right\}.
\]

The uncontrolled transmission rate, \( \beta^* \), can be calculated using the given values of the parameters in (2).

### 2.3. Mathematical model of 2009 A/H1N1 influenza

We have modified the mathematical model developed by Arino et al. (2008) and Chowell et al. (2009) to describe the transmission dynamics for the 2009 A/H1N1 influenza in the Republic of Korea. The total population \( N \) is classified into eight subclasses: susceptible \( S \), latent \( E \), asymptomatic infectious \( A \), symptomatic infectious \( I \), recovered \( R \), ineffectively vaccinated \( U \), effectively vaccinated but still unprotected \( V \), and protected \( P \) individuals. A transition diagram between epidemic groups is shown in Fig. 2.

The uncontrolled transmission rate, \( \beta^* \), in the model (1) is changed to \( \beta \). The parameter \( \beta \) is the controlled transmission rate that includes the nonpharmaceutical intervention factor. The antiviral and vaccination factors are also considered in this model. The antiviral factor is denoted by the parameter \( a \). The parameters \( v \) and \( e \) represent the vaccination rate and efficacy, respectively. Vaccinated individuals progress to protected individuals at a rate of \( \omega \).

In this work, the Korean government’s nonpharmaceutical intervention policies for A/H1N1 influenza, such as securing a budget, quarantine, and the campaign for personnel hygiene, are quantified through a data-fitting process. These nonpharmaceutical policies adopted by the government reduced the transmission rate of influenza. The estimated transmission rate, \( \beta \), includes this reduction effect, while the antiviral factor and the vaccination rate directly indicate the effect of antiviral and vaccine intervention strategies.

The transmission model of the 2009 A/H1N1 influenza is then governed by nonlinear differential equations as follows:

\[
\begin{align*}
\frac{dS}{dt} &= -\beta S N - \delta S, \\
\frac{dE}{dt} &= \beta S N + \frac{\kappa}{\epsilon} I N + \frac{\epsilon}{\kappa} E N - \kappa E - \alpha E, \\
\frac{dU}{dt} &= \alpha I + a I - \omega U, \\
\frac{dV}{dt} &= \omega U, \\
\frac{dA}{dt} &= (1 - p) N \alpha E - \eta A, \\
\frac{dI}{dt} &= -\beta I N + \kappa E N - \delta I, \\
\frac{dA}{dt} &= \omega V, \\
\frac{dP}{dt} &= \omega V.
\end{align*}
\]

where \( \Lambda = eE + qI + \delta A \).

Note that if the vaccination \( v \) is not considered in the model, then the terms \( U, V, \) and \( P \) will be eliminated in the system (3). In our model, the antiviral factor is not included in Period 1 and vaccination is not considered in Period 1 and Period 2.

![Fig. 2. Flow chart of the 2009 A/H1N1 influenza model. Note that the antiviral factor is not included in Period 1 and vaccination is not considered in Period 1 and Period 2.](image-url)
not considered in Period 1 and Period 2 according to government’s intervention strategies conducted in 2009. The parameter values are listed in Table 2.

2.4. Parameter estimations

Epidemic parameters are classified into two categories: the first type includes those that describe characteristics of the disease, and the second describes circumstantial effects such as standards of living or government policies. For example, the latent period, $1/\kappa$, is a characteristic of the virus itself. However, the transmission rate ($\beta$), antiviral rate ($\delta$), and vaccination rate ($\nu$) are influenced by social circumstances. For instance, developed countries are equipped with the infrastructure necessary to handle outbreaks and can afford to conduct the required intervention steps. On the other hand, developing countries lack adequate health care facilities. In order to build a reasonable model for a specific country, the parameters $\beta$, $a$, and $\nu$ must be estimated based on the country’s specific circumstances.

Various intervention strategies are quantified through a parameter estimation process. This gives a baseline interpretation of the optimal intervention strategies in Section 3. In our study, the parameters $\beta$, $a$, and $\nu$ are estimated from the cumulative incidence curve of the model, $C(t) = \int_0^t p(xE(\tau))d\tau$, which is fitted to the cumulative incidence data in each period. The least squares fitting, lsqcurvefit in the MATLAB optimization tool box, is used to find the best fitted parameters. The fitted parameters are listed in Table 3. Fig. 3 displays the cumulative cases (red square) and the fitted curve (black solid), $C(t)$, from April 27 to December 31, 2009. The zoomed graph for Period 1 and Period 2 is depicted in the inset of Fig. 3.

There are two possible reasons why the transmission rate, $\beta$, was increased from Period 1 to Period 3. One reason is that the fall semester classes of elementary, middle, and high schools as well as universities begin at the end of August. If we zoom in on the incidence data in Period 2, it is clearly observed that the incidence data is increased rapidly from the end of August (see Fig. 3). The close contacts at school might be one of the main factors for the wide spread of the influenza epidemic. Another possibility is that the incidence data were overdetermined for Period 2 and Period 3 because the number of antiviral prescriptions was used as the incidence data.

2.5. Bootstrap

The bootstrap method, which is a numerical technique for statistical inference, is used to show how accurate estimators are as those of the unknown parameters, $\beta$, $a$, and $\nu$. The basic idea of the bootstrap method is to use the information of resampling data from the observed data. The three parameters are estimated by using the resampling data generated from a Poisson distribution with the mean equal to the observed data. We assume that the observed data are Poisson distributed at a fixed time. This procedure is repeated 1,000 times and the means, standard deviations (S.D.), and 95% confidence intervals (CI) are calculated for each estimation. Fig. 4 shows the distributions of bootstrapping estimations for $\beta$, $a$, and $\nu$. The subscripts of the parameters represent the time period. The means, S.D., and 95% CI are listed in Table 4. A comparison between the bootstrap estimations and the fitted parameters shows the reliability of our estimated parameters.

3. Characteristics of optimal control

In this section, the characterization of optimal control problem is derived through the optimal control theory (Lenhart and Workman, 2007). The controlled state system of the 2009 A/H1N1 influenza in the Republic of Korea is described as follows:

$$
\frac{dS}{dt} = \frac{\beta(t)}{N}A - \nu U(t)S,
$$

$$
\frac{dU}{dt} = \beta(t)\left(\frac{S}{N} + \frac{U}{N}\right)N - \delta E - \nu U(t)I,
$$

$$
\frac{dE}{dt} = (1-p)\nu E - \eta A,
$$

$$
\frac{dA}{dt} = \delta I + \omega V - \eta A,
$$

$$
\frac{dV}{dt} = -\nu(t)\frac{V}{N}A + (1-\nu(t))S - \omega V,
$$

$$
\frac{dP}{dt} = \omega V.
$$

(4)

where $A = eE + qI + \delta A$, and

$$
\beta(t) = \begin{cases} 
\beta^\ast - \nu(t), & \text{if } t \in \text{Period 1,} \\
\beta_2, & \text{if } t \in \text{Period 2,} \\
\beta_3, & \text{if } t \in \text{Period 3.}
\end{cases}
$$

We consider the three time-dependent controls in the controlled system (4). The control $u(t)$ is a nonpharmaceutical control that represents the government’s efforts to reduce the transmission rate. It is also called the social distancing control. In this model, the time-dependent control, $u(t)$, is considered during Period 1 to reduce the uncontrolled transmission rate $\beta^\ast$ which is calculated from the basic reproductive number in (2). By subtracting the data-fitted transmission rate ($\hat{\beta}_1 = 0.5264$) from the uncontrolled transmission rate ($\beta^\ast = 0.533$), the government’s effort to decrease the transmission rate is quantified as $\sigma = 0.0069$. This value is used as an upperbound of the nonpharmaceutical control, $u(t)$. The nonpharmaceutical control includes all policies that are not related to drugs. For example, the quarantine, detection and isolation of infectious people, school closures, cancellation of public events, and campaigns for personnel hygiene are included in $u(t)$. The time-dependent antiviral and vaccine controls are denoted by $u_2(t)$ and $u_3(t)$, respectively. The constant

![Fig. 3. Cumulative incidence data (red square) and its data-fitted curve (black solid) as a function of time. The zoomed graph for Period 1 and Period 2 is shown in the inset of the figure because of the scale difference. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)](image-url)
antiviral and vaccine factors in the model (3) are replaced by the control functions, \( u_2(t) \) and \( u_3(t) \), in model (4), respectively. In 2009, the manufacture and approval of the vaccine for A/H1N1 influenza took approximately 6 months (Lee et al., 2013a). Today, new vaccine manufacturing processes, such as cell culture manufacturing and vectored influenza vaccine, can accomplish vaccine control in less time (Milián and Kamen, 2015). Thus, we will consider the early vaccination strategies in this study. We adjust only the nonpharmaceutical control, \( u_1(t) \), during Period 1, while we use the antiviral control, \( u_2(t) \), and vaccine control, \( u_3(t) \), during Period 2 and Period 3. Since the nonpharmaceutical intervention strategy is challenging to achieve and has high socio-economic cost, we did not apply additional nonpharmaceutical intervention strategies during Period 2 and Period 3.

Our goal is to minimize the number of infectious individuals and the cost of implementing the control measures. The cost is taken to be a nonlinear quadratic function. The objective functional to be minimized is then represented by

\[
J(u_1, u_2, u_3) = \int_{t_0}^{t_f} \left( \frac{B_1}{2} u_1^2(t) + \frac{B_2}{2} u_2^2(t) + \frac{B_3}{2} u_3^2(t) \right) dt
\]

We seek to find optimal controls, \( u_1^*, u_2^*, \) and \( u_3^* \), satisfying

\[
J(u_1^*, u_2^*, u_3^*) = \min \{ J(u_1, u_2, u_3) | u_i(t) \in \Omega, i = 1, 2, 3 \},
\]

where \( \Omega = \Omega_1 \cup \Omega_2 \cup \Omega_3 \), and

\[
\begin{align*}
\Omega_1 &= \{(u_1, u_2, u_3) \in L^2(t_0, t_f) | 0 \leq u_i(t) \leq \sigma, u_2(t) = u_3(t) = 0 \} , \\
\Omega_2 &= \{(u_1, u_2, u_3) \in L^2(t_0, t_f) | 0 \leq u_1(t) \leq \sigma, 0 \leq u_2(t) \leq u_3(t) \leq 0.05 \} , \\
\Omega_3 &= \{(u_1, u_2, u_3) \in L^2(t_0, t_f) | 0 \leq u_1(t) \leq u_2(t) \leq u_3(t) \leq 0.05 \} .
\end{align*}
\]

The parameters \( t_0, t_1, \) and \( t_2 \) indicate the initial times of Period 1, Period 2, and Period 3, respectively. The final time is denoted by \( t_f \). The upperbounds of nonpharmaceutical and antiviral controls are assumed as the corresponding constant control measures. The upperbound of vaccine control is assumed as 0.05 which is less than \( \nu_3 \). Since we will suggest the early vaccination strategy, we cannot use the vaccination rate in Period 3, \( \nu_3 \), as the upperbound of vaccine control during Period 2 and Period 3. The weight constants, \( B_1, B_2, \) and \( B_3 \), balance the infectious individuals and cost terms due to their size and importance. These weight constants might be different for different countries or scenarios. For simplicity, we choose the baseline weight constants as \( B_1 = B_2 = B_3 = 10,000 \).

Pontryagin’s Maximum Principle (Pontryagin, 1987) is used to solve the optimality system. Characteristics of optimal control pro-

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Table 4
Bootstrapping results.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fitted value</th>
<th>Mean</th>
<th>S.D.</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \beta_1 )</td>
<td>0.5264</td>
<td>0.5264</td>
<td>1.6092e−04</td>
<td>(0.5260, 0.5267)</td>
</tr>
<tr>
<td>( \beta_2 )</td>
<td>0.8729</td>
<td>0.8279</td>
<td>1.3342e−04</td>
<td>(0.8277, 0.8282)</td>
</tr>
<tr>
<td>( \beta_3 )</td>
<td>2.6037</td>
<td>2.6032</td>
<td>6.0839e−04</td>
<td>(2.6020, 2.6044)</td>
</tr>
<tr>
<td>( a_2 )</td>
<td>0.4008</td>
<td>0.4008</td>
<td>1.0944e−04</td>
<td>(0.4006, 0.4011)</td>
</tr>
<tr>
<td>( a_3 )</td>
<td>0.7291</td>
<td>0.7287</td>
<td>4.1427e−04</td>
<td>(0.7279, 0.7295)</td>
</tr>
<tr>
<td>( \nu_3 )</td>
<td>0.5684</td>
<td>0.5678</td>
<td>5.9247e−04</td>
<td>(0.5667, 0.5690)</td>
</tr>
</tbody>
</table>

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Fig. 4. Distributions of bootstrapping estimations for \( \beta \), \( a \), and \( \nu \). The subscripts of the
blems, including adjoint system, transversality conditions, and optimality equations, are derived in Appendix.

We shall now discuss the optimal control strategies with a limited vaccination coverage. Even though our control functions \(u_1(t), u_2(t),\) and \(u_3(t)\) have constant bounds at time \(t\), there is no additional limitation on the total amount of controls during the entire simulation time. While the use of nonpharmaceutical control has no practical limitation on a host population, implementing pharmaceutical control such as vaccine or antiviral strategies depends on its amount reserved by the government. Especially, it is important to consider a limited vaccination coverage. In our study, the limited vaccination coverage is considered as follows:

\[
\int_{t_1}^{t} u_s(t) \frac{S(t)}{N} dt = C. \tag{5}
\]

where \(C\) represents the vaccination coverage. This type of constraint is known as an isoperimetric constraint (Lenhart and Workman, 2007). We introduce one more state variable \(z(t)\) to consider the isoperimetric constraint and it is defined as \(z(t) = \int_{t_1}^{t} u_s(\tau) \frac{S(\tau)}{N} d\tau.\) Hence, the isoperimetric constraint (5) can be rewritten as follows:

\[
\frac{dz(t)}{dt} = u_s(t) \frac{S(t)}{N}, \quad \text{with} \quad z(t_1) = 0 \quad \text{and} \quad z(t) = C.
\]

The optimality system with the isoperimetric constraint (5) is discussed in Appendix. In the results section, we compare optimal control strategies without constraint and one with the isoperimetric constraint.

4. Numerical results

In this section, we first investigate the real-time prediction of infectious transmission during the early period by using the model (3) without pharmaceutical factors \((a = \nu = 0)\). We next propose optimal intervention strategies under various scenarios by using the optimal control theory.

4.1. Real-time prediction of incidence

Mathematical modeling is a simple and useful tool for predicting an infection spread, especially during the early period. Before the antiviral drugs and vaccines are approved, only the nonpharmaceutical intervention strategy is available to reduce the incidence. Thus, at the beginning of an epidemic, it is important to estimate the transmission rate and predict the number of patients. Fig. 5 displays five real-time predictions of daily and cumulative incidence in the left and right columns, respectively. In the five scenarios, the model (3) without pharmaceutical factors \((a = \nu = 0)\) is used for data-fitting during the given period from the outbreak onset (April 27), and then the estimated constants are used to predict infection progress in the following two weeks. For each scenario, the red squares, black solid, and blue dashed curves represent the data, fitted model, and model prediction, respectively. The dotted vertical line indicates the starting time of prediction.

Fig. 5. Real-time prediction of the 2009 A/H1N1 incidence in the five scenarios (a)–(e). The five prediction scenarios are considered every two weeks from 4 weeks to 12 weeks. The red squares, black solid curves, and blue dashed curves represent the data, fitted model, and model prediction, respectively. The dotted vertical line indicates the starting time of prediction. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)
time of the prediction. The relative difference in the cumulative incidence between the data and the prediction, \( \frac{\text{cumulative incidence} - \text{model prediction}}{\text{model prediction}} \times 100 \), is shown as an arrow in the upper right-hand corner in the right column frames.

As we observed in Fig. 5, the cumulative incidences (red squares) are mostly less than the number predicted (blue dashed curves) except in the first scenario (a). The main reason might be the intensive government intervention policies for the relatively small incidence size. We expect that it induced the decrease of the estimate for \( \beta \) during the early stage of the epidemic in scenarios (b)–(e). Note that the diminishing scale of \( \beta \) is very small. In scenario (a), the amount of data is too low for real-time prediction; the number of cumulative incidence during the first 4 weeks is only 10 individuals. During the early period, before the number of infectious individuals became too large, the Korean government conducted good quarantine strategies.

**Fig. 6.** Scenario 1 (early vaccination strategy). Optimal controls and the corresponding state variables are displayed as function of time in the top three and bottom eight frames, respectively. The blue solid curves indicate optimal controls and the corresponding optimal state variables. The black dot-dashed curves show the state variables of data-fitted model. It shows early vaccination is critical to prevent the epidemic. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)
For instance, there was 24-h emergency health care service in public health centers starting June 12 (6 weeks after onset). These early nonpharmaceutical intervention policies helped to decrease the number of incidences. Scenario (b) explored this feature; the relative difference between data and prediction is −44.16%, which could be due to the introduction of this policy. However, scenarios (c) and (d) show relatively good real-time predictions. The shape and magnitude of prediction curves fit the data well. In scenario (e), after 12 weeks, the national public health crisis phase increased from caution to alert. The government introduced the treatment in this period, and then the infectious patient could obtain a prescribed antiviral drug. This action appears to lead to a decline of daily incidence.

4.2. Optimal control strategies

In this section, the optimal control theory is used to find the most effective strategies to minimize the number of infectious individuals while the costs for implementing the controls are kept low under the different scenarios. We especially focus on investigating the effects of starting time and amount of vaccine.

4.2.1. Scenario 1: Early vaccination strategy

Due to the improved manufacturing system of vaccine, we could suggest the early vaccination strategy. Recall that we apply only nonpharmaceutical control, $u_1(t)$, during Period 1, while we use antiviral control, $u_2(t)$, and vaccine control, $u_3(t)$, during Period 2 and Period 3. Note that the vaccine policy is applied only to Period 3 in the model (3) (see also Table 3). The constant data-fitted transmission rates, $\beta_2 = 0.82792$ and $\beta_3 = 2.6037$, are used in Period 2 and Period 3, respectively.

Fig. 6 depicts the optimal controls and the corresponding state variables in the top three and the bottom eight frames, respectively. In the bottom eight frames, the state variables from the data-fitted model and optimal solution are represented by black dot-dashed and blue solid curves, respectively. Note that the upperbounds of nonpharmaceutical and antiviral control are set as the corresponding estimated parameters and the upperbound of vaccine control is assumed as 0.05. During Period 1, the optimal nonpharmaceutical control, $u_1(t)$, is taken as its maximum, $\sigma$, because only nonpharmaceutical intervention is accessible. During Period 2 and Period 3, the antiviral control function, $u_2(t)$, is used much less than the data-fitted constant for antiviral use: $a_2=0.4008$ for Period 2 and $a_3=0.7294$ for Period 3. Both antiviral and vaccine control are used at their maximum for the beginning of the control periods and the controls decreased as time passed. The usage of antiviral control is increased slightly at the beginning of Period 3, since the transmission rate in Period 3 is much higher than that in Period 2. While antiviral control is used steadily during Period 2 and Period 3, vaccine control is used at its maximum until 200 days and decreased thereafter. Early vaccine control, $u_3(t)$, could reduce the number of susceptible individuals from Period 2. The fewer the number of individuals that are exposed and infected under the same transmission rate, the less is the antiviral control used. Compared to the curves of infectious individuals in 2009 (black dot-dashed line), the peak of infectious individuals has almost disappeared in the optimally controlled case. Fig. 6 shows that the optimal control strategy of early vaccination works well to eliminate the influenza epidemic. It suggests that vaccine control is more meaningful if implemented earlier.

4.2.2. Scenario 2: Limited early vaccination strategies

In reality, there exists a limited amount of vaccines. In this section, the isoperimetric constraint is used to reflect the vaccine limitation. Furthermore, the starting day of vaccination is important as well as the total vaccine usages. We investigated the impact of the vaccination coverages and timing of using optimal vaccine strategies. All three optimal controls are applied under the same conditions as in Scenario 1 except that the amount of vaccine is limited.

Fig. 7 depicts a contour map of the cumulative incidences on a log-10 scale under the optimal control strategies as a function of vaccination coverage and timing. The black thick curve indicates the cumulative incidence of the 2009 A/H1N1 influenza. We found that the cumulative incidence significantly decreases if the vaccination control with the higher vaccination coverage is implemented earlier. Given a fixed number of cumulative cases to be achieved the sooner vaccination begins the fewer individuals need to be vaccinated. If vaccination control starts 115 days after the outbreak, about 62% vaccination coverage is needed for the cumulative incidence in 2009. Even though the vaccination coverage is over 85%, the cumulative incidence cannot be reduced as much as the default one (black solid curve) when the vaccination timing is significantly delayed as in the case of a delay of 155 days. This implies that if the vaccination control is implemented earlier, the impact of an influenza epidemic can be mitigated with less vaccination coverage. If the vaccination coverage is increased from 60% to 65%, the cumulative incidence considerably increases. On the other hand, if the vaccination coverage is increased from 85% to 90%, the
changes of the cumulative incidences are relatively small. This indicates that the marginal efficiency of vaccine control is decreasing.

Fig. 8 shows 12 case studies from the contour map (Fig. 7). In Fig. 8, the optimal antiviral control, optimal vaccine controls, and the corresponding cumulative incidences under different vaccination coverages and timings are displayed in the left, middle, and right columns, respectively. The black solid, blue dotted, and red dot-dashed curves indicate optimal solutions when vaccination starts at 115 days, 135 days, and 155 days after the outbreak onset, respectively. Four vaccination coverages for the isoperimetric constraint, *C* = 60%, 70%, 80%, and 90%, are considered. Note that the optimal nonpharmaceutical controls are not displayed because these used at their maximum during Period 1 for all cases. Fig. 8 shows that early vaccine control leads to a significant decrease of cumulative incidence in spite of low vaccination coverage. If the amount of available vaccine is reduced from the top to bottom frames, the antiviral controls are used to a greater extent. These indicate that early vaccination plays a significant role and antiviral therapy is most important when the vaccination rate is low.

5. Conclusions

A dynamic transmission model for the 2009 A/H1N1 influenza epidemic in the Republic of Korea based on incidence data reported by KCDC was developed in this work. The model was constructed for three consecutive periods from April 27 to December 31, 2009. Since the data included the effects of interventions conducted by the Korean government in 2009, we estimated the relative reduction of transmission rate, $\sigma$, by subtracting data-fitted parameters from the uncontrolled transmission rate. In our study, this quantified reduced transmission rate was used as the upperbound of the nonpharmaceutical control during the early stage of outbreak (Period 1) in the study of optimal control strategies. This is a new approach to suggest optimal control strategies with the a realistic upperbound of control.

We investigated the real-time prediction of transmission during the early epidemic period by using the model without pharmaceutical factors. Surprisingly, the model made a relatively good real-time prediction, especially in scenarios (c) and (d) (see Fig. 5), which show predictions for the two week periods: 8 weeks and 10 weeks after the onset. Fig. 5 also suggests that the Korean government did a good job on the quarantine strategy during the early period before the amount of infectious individuals became too large. We explored the SEIAR model...
without considering the pharmaceutical intervention and provided a qualitatively good prediction during the early stage of the epidemic.

Optimal control theory was applied to our model over the entire period, which includes nonpharmaceutical, antiviral, and vaccine policies. One very important factor in epidemic prevention is vaccination. We investigated the effects of timing and vaccine coverage on the cumulative incidence. Since new vaccine manufacturing systems could provide vaccines in a time less than 6 months from the outbreak (Milián and Kamen, 2015), we applied the vaccine strategy from 115 days after the onset in our study. The results showed that an early optimal vaccine strategy is critical to eliminate the epidemic (see Fig. 6). Further, the results show good agreement with the result of previous studies on the benefits of early vaccination and nonpharmaceutical intervention for the influenza A epidemic (Khazeni et al., 2014). Since the amount of vaccine is limited in reality, we considered the limited optimal vaccine strategy using the isoperimetric constraint. Under the same vaccination coverage, the cumulative incidence increased significantly with delaying vaccination time. Even if the vaccination coverage is high, the epidemic can occur when the vaccination timing is too late (see Fig. 7). Our results imply that the timing of vaccination is significant to prevent the epidemic. In our study, there remains some uncertainty because of data inconsistency. After government policy changed, the test confirming PCR was not conducted on all ILI patients. Thus, seasonal flu patients might have been included in the 2009 A/H1N1 influenza incidence. This indicates that the transmission rate might be underestimated. Additionally, even though the vaccine data were also collected by the government, it is difficult to estimate the number of vaccinated individuals in 2009 because the vaccination policy was changed frequently. With more detailed data, vaccine control strategies could be improved. Despite these limitations, this study gives some insight on intervention strategies that could be used for new emerging infectious diseases in the Republic of Korea.

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Appendix

From Pontryagin’s Maximum Principle (Pontryagin, 1987), optimal controls should satisfy the necessary conditions. Pontryagin’s Maximum Principle changes (4) into problem that minimize pointwise a Hamiltonian $H$, with respect to the control.

$$\frac{d}{ dt}H = I(t) + \sum_{i=1}^{3} B_i u_i^2(t) + \sum_{i=1}^{8} \lambda_i g_i,$$

where $g_i$ is the right hand side of the differential equation of the $i$th state variable. Applying Pontryagin’s Maximum Principle, we obtain

Theorem 1. There exist optimal controls $u_i^*(t)$, $u_j^*(t)$, and $u_k^*(t)$ minimizing the objective functional $J(u_i(t), u_j(t), u_k(t))$ over $\Omega = \Omega_1 \cup \Omega_2 \cup \Omega_3$, where $\Omega_1 = \{ (u_1, u_2, u_3) \in L^1(\xi_0, \tau_1) \mid 0 \leq u_1(t) \leq \sigma, u_2(t) = u_3(t) = 0 \}$, $\Omega_2 = \{ (u_1, u_2, u_3) \in L^1(\xi_0, \tau_2) \mid u_1(t) = 0, 0 \leq u_2(t) \leq a_2, 0 \leq u_3(t) \leq 0.05 \}$, $\Omega_3 = \{ (u_1, u_2, u_3) \in L^1(\xi_0, \tau_3) \mid u_1(t) = 0, 0 \leq u_2(t) \leq a_2, 0 \leq u_3(t) \leq 0.05 \}.$

Given these optimal solutions, there exist adjoint variables, $\lambda_i(t)$, ..., $\lambda_8(t)$, which satisfy

$$\frac{d}{ dt} \lambda_i(t) = \lambda_i(0)(t) + \lambda_i(1)(1-e)u_i(t) - \lambda_i(t),$$

$$\frac{d}{ dt} \lambda_1(t) = \lambda_1(0)(t) + \lambda_1(1)(1-e)u_1(t) - \lambda_1(t),$$

$$\frac{d}{ dt} \lambda_2(t) = -1 + \lambda_2(t),$$

$$\frac{d}{ dt} \lambda_3(t) = \lambda_3(0)(t) + \lambda_3(1)(1-e)u_3(t) - \lambda_3(t),$$

$$\frac{d}{ dt} \lambda_4(t) = \lambda_4(0)(t) + \lambda_4(1)(1-e)u_4(t) - \lambda_4(t),$$

$$\frac{d}{ dt} \lambda_5(t) = \lambda_5(0)(t) + \lambda_5(1)(1-e)u_5(t) - \lambda_5(t),$$

$$\frac{d}{ dt} \lambda_6(t) = \lambda_6(0)(t) + \lambda_6(1)(1-e)u_6(t) - \lambda_6(t),$$

$$\frac{d}{ dt} \lambda_7(t) = \lambda_7(0)(t) + \lambda_7(1)(1-e)u_7(t) - \lambda_7(t),$$

$$\frac{d}{ dt} \lambda_8(t) = \lambda_8(0)(t) + \lambda_8(1)(1-e)u_8(t) - \lambda_8(t),$$

with transversality conditions $\lambda_i(\tau_f) = 0,$ for $i = 1, \ldots, 8$.

Furthermore,

$$u_1^*(t) = \min \left( u_{i_{\max}}(t), \max \left( 0, (\lambda_2 - \lambda_3) \sigma + (\lambda_2 - \lambda_3) \sigma + (\lambda_2 - \lambda_3) V \right) \right)$$

$$u_2^*(t) = \min \left( u_{i_{\max}}(t), \max \left( 0, (\lambda_2 - \lambda_3) \sigma \right) \right),$$

$$u_3^*(t) = \min \left( u_{i_{\max}}(t), \max \left( 0, (\lambda_2 - \lambda_3) \sigma \right) \right),$$

where $u_{i_{\max}}(t), u_{i_{\max}}(t), u_{i_{\max}}(t)$ indicate the period-dependent upperbounds of control.

Proof. The existence of optimal controls $u_1^*(t)$, $u_2^*(t)$, and $u_3^*(t)$ such that $J(u_1^*(t), u_2^*(t), u_3^*(t)) = \min \Omega(\xi_0, \tau_1)$ with state system (4) is
given by the convexity of the objective functional integrand. By using Pontryagin’s Maximum Principle (Pontryagin, 1987), the adjoint equations and transversality conditions are obtained. Differentiation of Hamiltonian $H$ with respect to the state variable gives the following system:

$$
\frac{d\lambda_0}{dt} = -\frac{dH}{dt}, \quad \frac{d\lambda_1}{dt} = -\frac{dH}{dt}, \quad \frac{d\lambda_2}{dt} = -\frac{dH}{dt}, \quad \frac{d\lambda_3}{dt} = -\frac{dH}{dt}, \quad \frac{d\lambda_4}{dt} = -\frac{dH}{dt},
$$

with $\lambda_i(t_f) = 0$ for $i = 1, \ldots, 8$.

Optimal controls $u_1^*(t)$, $u_2^*(t)$, and $u_3^*(t)$ are derived using the following optimality conditions:

$$
\frac{dH}{du_{1i}} = B_1 u_1 + ((1-\lambda_2) S + (\lambda_2 - \lambda_3) U + (\lambda_3 - \lambda_4) V) \frac{\partial}{\partial u_{1i}} = 0,
$$

$$
\frac{dH}{du_{2i}} = B_2 u_2 + (1-\lambda_2) \frac{\partial}{\partial u_{2i}} = 0,
$$

$$
\frac{dH}{du_{3i}} = B_3 u_3 + (-\lambda_1 + \lambda_4 (1-e) - \lambda_7 e) S \frac{\partial}{\partial u_{3i}} = 0,
$$

at $u_1^*(t)$, $u_2^*(t)$, and $u_3^*(t)$ on the set (7). On this set

$$
\begin{align*}
\frac{dH}{du_{1i}} &= ((\lambda_3 - \lambda_4) U + (\lambda_3 - \lambda_4) V) \frac{\partial}{\partial u_{1i}} = 0, \\
\frac{dH}{du_{2i}} &= (\lambda_3 - \lambda_4) \frac{\partial}{\partial u_{2i}} = 0, \\
\frac{dH}{du_{3i}} &= (\lambda_3 - \lambda_4 (1-e) - \lambda_7 e) \frac{\partial}{\partial u_{3i}} = 0.
\end{align*}
$$

Taking into account the bounds on controls, we obtain the characterization of $u_1^*(t)$, $u_2^*(t)$, and $u_3^*(t)$ in (8).

The forward–backward sweep method is used to solve the optimality system with the initial conditions for the state variables and the transversality conditions for the adjoint system. The state equations are solved forward in time and the adjoint system is solved backward in time with initial guesses of control functions. The controls are updated using a convex combination of the previous controls and the optimality equations from the current state and adjoint variables. The iteration is repeated until convergence occurs (Lenhart and Workman, 2007).

For Scenario 2 (limited early vaccination strategy), the 9th state variable from the isoperimetric constraint, $z(t)$, is added, and the Hamiltonian $H$ is changed as follows:

$$
H = \lambda_0 \left( I(t) + \sum_{i=1}^{3} B_i u_{1i}^2(t) \right) + \sum_{i=1}^{8} \lambda_i \dot{S} + \lambda_9 \dot{g}.
$$

With the same process of Theorem 1, $z(t)$, we have one more adjoint equation,

$$
\frac{d\lambda_9}{dt} = -\frac{dH}{d\lambda_9}.
$$

Then, the optimal control $u_3^*(t)$ is changed as follows:

$$
\begin{align*}
\frac{dH}{du_{3i}} &= (\lambda_2 - \lambda_4 (1-e) - \lambda_7 e - \frac{\lambda_6}{N}) S \frac{\partial}{\partial u_{3i}} = 0.
\end{align*}
$$

In this problem, there is one state variable with the additional fixed endpoint ($z(t_f) = C$) to consider the isoperimetric constraint which results in the loss of the terminal condition for the corresponding adjoint variable. The adapted forward–backward sweep method with the multiplier of the integrand of the objective functional, $\lambda_9$, equal to 1 is used in our study. The main idea of the adapted forward–backward sweep method is to guess a value for the missing terminal condition and use a root finding method to converge an appropriate value to satisfy the fixed-end condition of an artificial state variable. Thus, by using this algorithm, we could find optimal controls satisfying the new necessary conditions which involve with not a fixed terminal condition for the adjoint variable, but the fixed endpoint of the state variable.

References


