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A Mathematical Model of Hepatitis A Virus Transmission and Its Application for Adult Vaccination Strategy in Korea

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정 성 목

ABSTRACT

A Mathematical Model of Hepatitis A Virus Transmission and Its Application for Adult Vaccination Strategy in Korea

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Despite universal child vaccination programs and mandatory surveillance systems, the incidence rate of Hepatitis A virus (HAV) recently increased rapidly in Republic of Korea (Korea). Previous studies conducted in Korea developed mathematical models of HAV and projected the effectiveness of child vaccination; however, there were no studies done using empirical data upon introduction of the National Immunization Program's child vaccination program. In this study, we proposed an age-structured dynamic model calibrated with recent empirical data, in order to understand the transmission dynamics of HAV infection and evaluate the impact of diverse adult's vaccination strategies as an application of this model.

Although there were some unavoidable assumptions within the model due to lack of underlying information, the projected results fitted well with the empirical data with respect to epidemiology and anti-HAV seroprevalence. Moreover, when compared with the equivalent vaccine coverage, the results indicated that the HAV vaccination for those in their 30s were more effective than that of those in their 20s. Furthermore, when the first dose coverage is greater than 20% and the second dose coverage is at 95%, after a time of eight years, the percentage reduction of notification case is approximately 50%. Sensitivity analysis indicated that the waning rate and proportion of primary vaccine failure could be a fundamental factor in predicting the future epidemic curve of an HAV infection.

The model indicated adult vaccination for 30s can be practical and effective intervention to reduce the burden of HAV in Korea.

Keywords: Hepatitis A, Mathematical model, Transmission dynamics, Adult vaccination

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Chapter 1. INTRODUCTION

1.1 Hepatitis A

Hepatitis A, caused by hepatitis A virus (HAV), is mainly transmitted from person to person by the fecal-to-oral route, either through direct contacts with infected individuals, or indirectly through the ingestion of contaminated foods and water [1]. According to the World Health Organization (WHO), more than 140 million people are infected by HAV worldwide annually. Moreover, the actual number of HAV infections are estimated to be several times higher than the number of reported cases due to under-reporting issues [2]. The presence of symptoms and the severity of HAV infections depend on the age of HAV infected individuals. HAV infection in young children is usually asymptomatic and remains undiagnosed due to the low probability of developing HAV icteric infections [3]. On the other hand, in young adults and adults with acute infections, HAV can lead to severe complications such as, fulminant hepatic failure and hepatocellular carcinoma [4].

Since poor hygiene and low socioeconomic factors may pose an increased risk of HAV infection, the endemicity of HAV vary widely across the globe [5]. North America, Western Europe,

Japan, and Korea are classified to have low endemicity while most countries in South America, Africa, and South Asia are classified to have high endemicity [6, 7]. As majority of children become immune through natural HAV infection in countries with high endemicity, vaccination programs are not recommended by the WHO. On the contrary, WHO strongly recommends and advises the adoption of immunization programs against HAV infection for children aged under 23 months into the national immunization program, upon consideration of vaccination program's cost-effectiveness in countries with low endemicity [8]. Currently, there are no specific curative therapy for HAV except vaccination. Countries with high endemicity are beginning to shift from high to low or intermediate endemicity of HAV, with the aid of improved sanitation and living standards [9]. Thus, HAV vaccination plays an essential and key role in HAV infection control.

1.2 Epidemiological characteristics of hepatitis A in Republic of Korea

In Republic of Korea (Korea), hepatitis A was designated as a Class I national notifiable infectious disease. In addition, the surveillance system also altered from sentinel to mandatory in December 2010. Also, vaccines against HAV infection are now available in Korea, as a two dose course of the HAV child vaccination program for infants 12–23 months old were introduced in the National Immunization Program (NIP) starting May 2015 [10].

In spite all these efforts to control HAV infections, according to the disease web statistics system of Korea Centers for Disease Control and Prevention (KCDC), the reported cases increased steadily from 2012 to 2015, resulting in an increase of more than 1,000. Especially in 2016, the numbers increased dramatically, recording 4,679 cases. Since HAV is known for its low reporting rate, actual cases of HAV infection are expected to be much higher than the reported [11].

Notification cases of HAV in Korea during 2012–2016 (Figure 1) and the age distribution of notified HAV cases from 2012 to 2016 (Figure 2) are as follows.

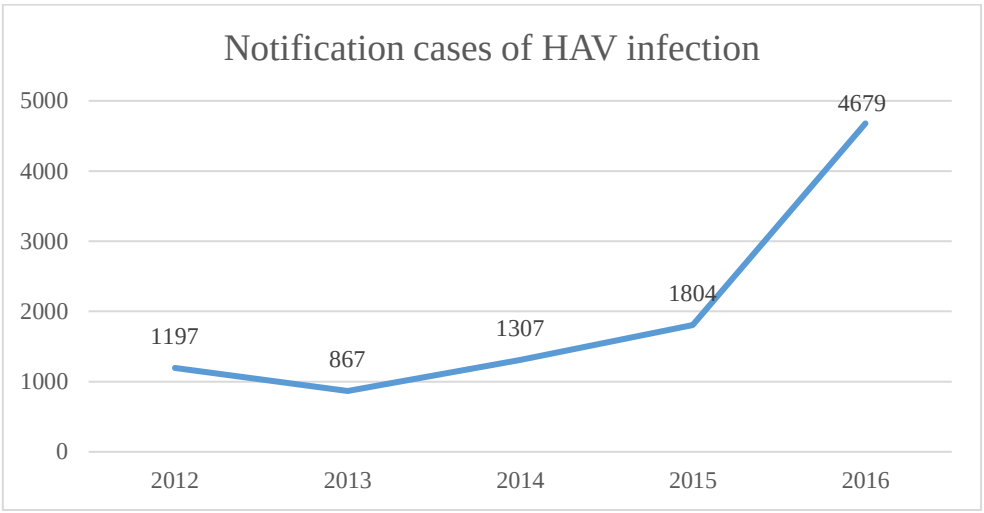


Figure 1. Notification cases of HAV infections in Korea from 2012 to 2016

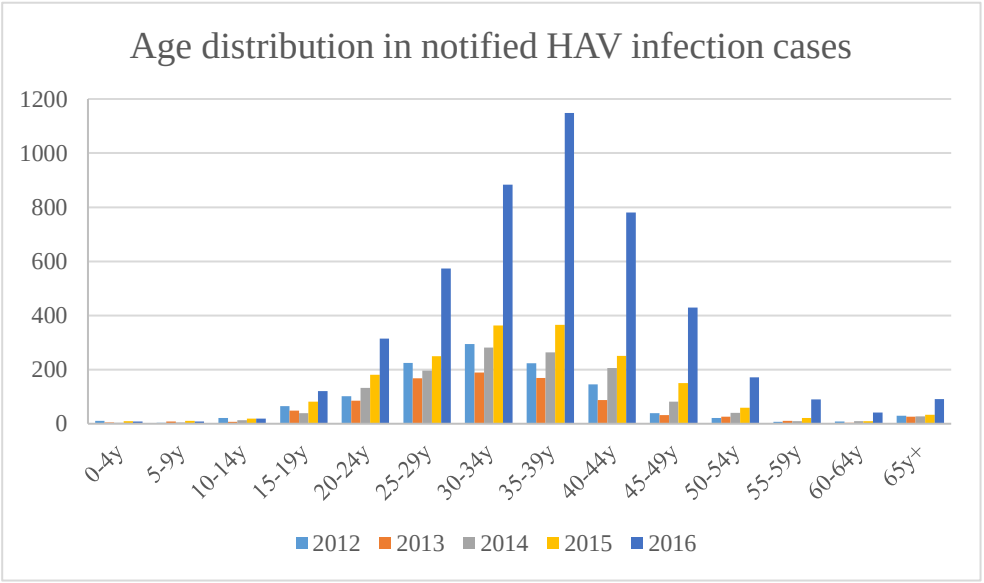


Figure 2. Age distribution of notified HAV infection cases from 2012 to 2016

Furthermore, as HAV cases were reported most frequently by individuals in their 30s followed by 20s and 40s who have higher severity compared to young children, hepatitis A has been considered to be one of the most serious public health problems (Figure 2). Up until the 1980s, most adults had HAV immunity and the seropositivity was estimated to be over 60% in individuals under 20 years of age and 98% in individuals over 40 years old [12].

However, the number of adult cases of HAV infection have progressively increased over the last 10 years, reflecting the changing epidemiology due to rapid improvement in sanitation, elevated socioeconomic status, and introduction of HAV vaccines [13]. According to the vaccine coverage surveys conducted by the KCDC using telephone polls, the percentage of individuals inoculated with HAV vaccine within recent three years were estimated to be 23.6% in 1999 but increased to approximately over 80% between 2007 and 2009. Moreover, as the universal child HAV immunization program was designated as a NIP in 2015, over 80% of individuals born after 1997 are expected to show anti-HAV seropositivity. The vaccine coverage data have shown a similar trend when compared with recent studies of anti-HAV seropositivity in children aged under 10, taking into account that waning of vaccine induced immunity (Figure 3).

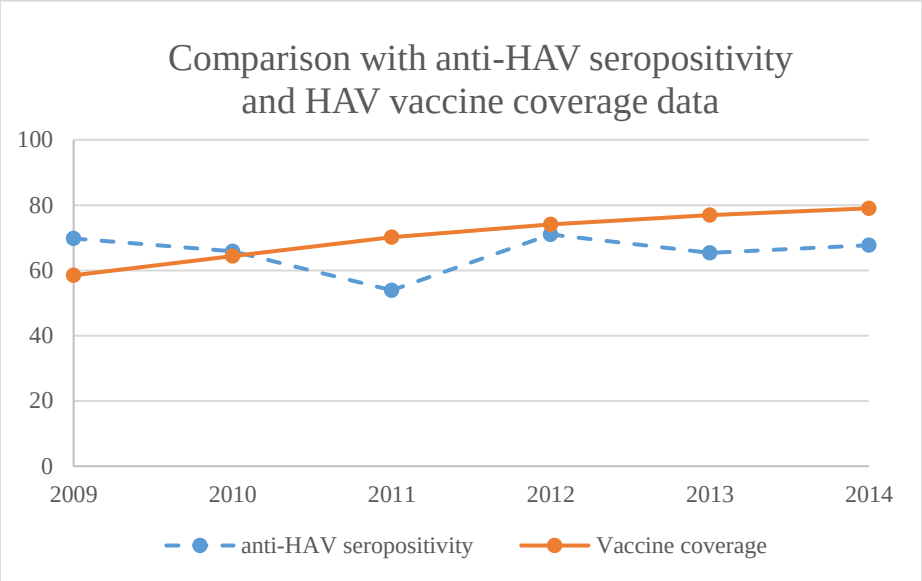


Figure 3. Comparison with anti-HAV seropositivity and HAV vaccine coverage data among children under the age of 10 during 2009-2014

However, as HAV vaccines were first introduced in Korea only in late 1997, along with the endemicity of Korea considered to be low due to improved sanitation, anti-HAV positivity proportion among those in their 20s and 30s, born before 1997, are reported as 20~30% in recent nationwide seropositivity of HAV surveys [12, 14, 15]. Therefore, increasing both the incidence rate of HAV and low seropositivity of anti-HAV of those in their 20s and 30s, imply that catch-up vaccination should be enforced for adult and youths [16]. In 2012, in order to resolve the situation, the Korea Society for Infectious Disease

(KSID) announced its recommendation of adult HAV immunization schedule for 20s and 30s. According to the aforementioned recommendation, adult HAV vaccination is strongly recommended for all individuals in their 20s, regardless of their anti-HAV seropositivity, whereas HAV vaccination is recommended only for anti-HAV seronegative individuals in their 30s [17].

1.3 Previous mathematical modeling researches for hepatitis A vaccination

According to a study done by Thierry V. et al (2006), they developed a VSEIR model of hepatitis A in the United States. The aim of this model was assessing the impact of herd protection resulting from an universal child vaccination program. The model was stratified with 77 age groups and three regions in the United States. [18].

Thierry V. et al (2012) study also developed an age-stratified dynamic transmission model to evaluate the impact of universal child vaccination program in Mexico by using a MVSEIR model. Unlike other previous studies, this model considered the contact pattern between age groups by using a who-acquires-infection-from-whom (WAIFW) contact pattern matrix and under-reporting probability by age groups. Furthermore, the model assumed all infants are protected against HAV infection for nine months by maternal antibodies [19].

Nonetheless, with the recent upsurge of HAV infection cases, to the author's knowledge, only one mathematical modeling study has been conducted in Korea. Ki et al (2008) developed an age-stratified VSEIR model of HAV in Korea to assess the impact of

the child vaccination program. The model used unpublished notification data from 2008 and seroprevalence data from 2009 and also considered age-specific force of infection of HAV[20].

However, this model was developed using data before both the mandatory surveillance system and universal child HAV immunization program was implemented in Korea. Also, this model did not consider contact pattern between age-group in transmission of HAV. Moreover, it assumed a homogeneous mixing pattern, which is used as a fundamental factor of person-to-person transmission in our study.

Although the low anti-HAV seropostivity among those in their 20s and 30s and the necessity of catch-up adult vaccination are emphasized in many recent published researches, mathematical modeling studies or cost-effectiveness studies on adult vaccination programs have not been yet conducted in Korea.

Therefore, the purpose of this present study is to develop a mathematical model to understand the transmission dynamics of HAV by using recent mandatory surveillance data, including the period after the HAV vaccination was introduced as an NIP. Likewise, through the developed model, this study intended to assess the impact of universal adult vaccination and draw out the best adult vaccination strategy.

Chapter 2. METHODS

2.1 Modeling steps and data used

The main steps to set the mathematical model of transmission dynamics of HAV in Korea and the key data inputs used in the model are as follows.

First, we estimated the demographic model parameters by using the population, the number of deaths, estimated future population data stratified by one-year age groups, by calendar month periods and monthly new births data from KOSTAT (Statistics Korea). As aging takes place continuously over time in the developed model, the model is fully dynamic from 2012 to 2016 and assumed a fixed death rate from 2016 to 2030 due to lack of actual population data.

Secondly, we estimated the parameters of the transmission model by manually calibrating the dynamics model outcomes to age-specific annual notification data from 2012 to 2016 obtained from KCDC. As HAV infection has no seasonality, monthly notification cases were assumed to be uniformized within the same year. Only contact probability per age group, transmission probability per contact, and under-reporting probability per age

were estimated, not parameters related with no natural history of HAV.

Thirdly, we used the model with the best fitted parameters to project the dynamics of HAV infections in Korea from 2017 to 2030. Those outcomes are the age-specific force of infection and incidence rates of HAV over time. Furthermore, we also compared the age-specific incidence cases per year between two vaccination strategies (with child vaccination only, and with child and adult vaccination). As the model is deterministic, there are no confidence intervals provided in the model.

Lastly, one-way sensitivity analysis was conducted, focusing on the variation of incidence cases by changing the parameters related to vaccination including waning in vaccine protection, and proportion of vaccine failure.

2.2 Demography

The hepatitis A model was stratified into 1,081 monthly age groups (0 month–1 month, 1 month–2 months, etc., up to 1,080 months) to account for the age–dependent risk of infection being symptomatic in HAV. Furthermore, it also accounted for the dynamics over time of new births, death rates, and number of population by age groups by using KOSTAT data.

However, as age–stratified population data obtained from KOSTAT (Statistics Korea) has shown an increased number of population within the same cohort caused by late registration of birth, we modified the demographic parameters using empirical data. The demographic model was constructed based on population data by 1–year age groups on January 2012 and estimated the population for next month by using the number of monthly deaths and new births data from 2012 to 2016. After 2017, we used KOSTAT projection data on number of new births and assumed that the monthly death rates by age groups of 2016 remain constant till 2030 due to lack of empirical data. Compared to total number of mid–year population and estimated future population obtained from KOSTAT, the differences between empirical data and modelled data were less than three percent.

2.3 Natural history of hepatitis A

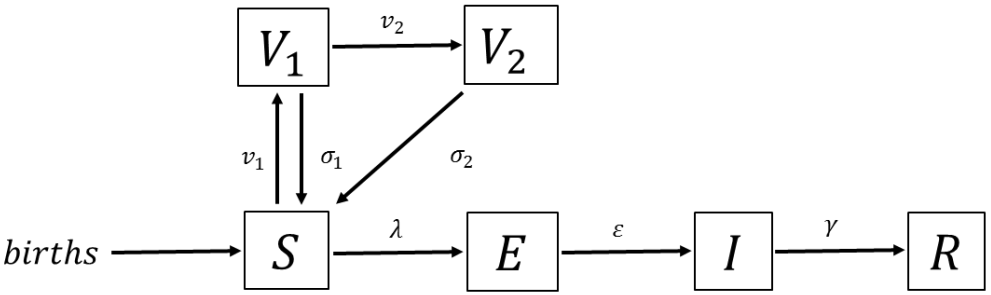
A VSEIR deterministic, compartmental, and age-stratified dynamic transmission model (Figure 3) was developed for dynamics of hepatitis A in Korea.

The model accounted for infection status of HAV, vaccination status by dose, and age. Therefore, individuals in the model flowed continuously between six compartments when their infection status changed, and as they grew older, or when vaccinated in this model. Compartments composed in the model were defined as follows; Susceptible, Exposed, Infected, Recovered, Vaccinated after first dose, Vaccinated after second dose.

There were some assumptions on the natural history of HAV in this model. As exposed compartment defined latency, individuals in the exposed states were assumed to be infected, but non-infectious. The time an individual spent in an exposed and infected state were assumed to be 30 days in this model. Though some previous studies used the latent period and infectious period of HAV as 14 days and 21 days, respectively; however, if models with monthly time step assumed infectious period to be less than 30 days, it can cause negative values in each compartment. Also, according to the guideline of management of

hepatitis A from the KCDC, as the maximum of latent period of HAV is 50 days and highly contagious period of HAV is from two weeks before or one week after symptom onset, latent period and infectious period can be calculated to be approximately 30 days [21]. Furthermore, since HAV has been believed to have an only single serotype, individuals who recovered from a natural HAV infection was assumed to get lifelong immunity.

Differential equations and schematic diagram of hepatitis A model (Figure 4) in Korea are as follows.



$$\frac{dV_1}{dt} = v_1 S - (\mu + \sigma_1 + v_2)V_1$$

$$\frac{dV_2}{dt} = v_2 V_1 - (\mu + \sigma_2)V_2$$

$$\frac{dS}{dt} = bN + \sigma_1 V_1 + \sigma_2 V_2 - (\lambda + \mu + v_1)S$$

$$\frac{dE}{dt} = \lambda(S + (1 - \eta_1)V_1 + (1 - \eta_2)V_2) - (\varepsilon + \mu)E$$

$$\frac{dI}{dt} = \varepsilon E - (\gamma + \mu)I$$

$$\frac{dR}{dt} = \gamma I - \mu R$$

Figure 4. Differential equations and schematic diagram of hepatitis A model in Korea

2.4 Transmission

The model included only person-to-person transmission, which is the most important risk in countries with low endemicity, like Korea. Theoretically, the transmission of HAV from contaminated food and water is feasible, but it is ignored in the present model. This is because that nowadays, the possibility that people become infected by HAV from contaminated food and water is quite low due to improved sanitation and living standards. Also, according to Park (2009), the most common source of HAV infection in Korea is estimated as the fecal-to-oral transmission through contacts between person, which usually occurs at home. In addition, the cause of HAV infection was hardly determined in 40~50% of HAV cases [22].

The component of the force of infection at time t, $\lambda_{i,t}$, caused by person-to-person transmission in this model depended on the transmission probability per contact and contact probabilities between age groups as described below.

$$\lambda_{i,t} = \sum_{j=1}^{1081} c_{ij} \times q_j \times \frac{I_{j,t-1}}{N_{j,t-1}}$$

In the formula above, where I_j means the sum of HAV infectious individuals in the jth age group at time t-1, and N_j means the

sum of total population in the jth age group at time t−1. q_j is the transmission probability per contact in the jth age group and c_{ij} indicates an effective physical contact rate between ith and jth age groups. In Korea, contact pattern between age groups and transmission probability of HAV per contact A have not been yet studied. Therefore, in the absence of data, contact rate was assumed by using POLYMOD contact pattern matrix (Finland contact pattern matrix was used among contact pattern matrices of eight European countries) with multiplier and assumed a fixed person−to−person transmission probability per contact of the mean susceptible risk of HAV infection.

As HAV infection has a highly low probability of developing icteric infection, most cases go undiagnosed in young children. Thus, the model also accounted for age−specific risk of symptomatic HAV cases in infected individuals to consider different under−reporting probability in young children below 10 years old.

2.5 Impact of hepatitis A vaccination

In this model, universal child immunization program with the two doses currently in progress was taken into account. In the model, child vaccination program administered at 12−23 months of age (first dose) and 6−18 months after the first dose (second doses) was assumed. The vaccine effectiveness by dose were assumed to be an all−or−none protection against HAV infection in 97% of vaccinated individuals after the first dose and 99%, after the second dose. The present model was modelled as vaccinated individuals with the ineffective vaccination were still in the vaccinated compartment, but was able to become infected with force of infection in the model.

Also, as vaccine induced protection was assumed to wane over time, vaccinated individuals are modelled to flow back to susceptible compartment at a waning rate over time. Van Herck, K et al study reported that vaccine induced anti−HAV antibodies would be expected to maintain for at least 25 years after primary vaccination in 95% to 97% of vaccinated individuals [23]. Therefore, according to these results, annual waning rate after the first dose and second dose were assumed as 1.62% and 0.12%, respectively.

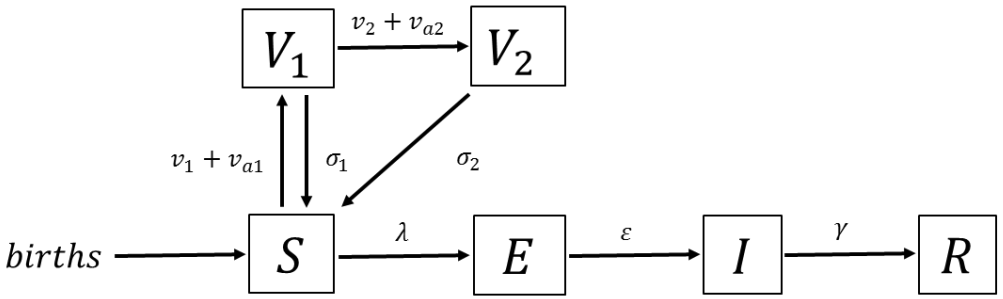
Probability of primary vaccine failure was assumed to be zero. Vaccine coverage per dose was estimated using empirical vaccine coverage data from KCDC. Because there was absence of data, vaccine coverage was assumed to be constant at 2001 levels from 1997 to 2000 and after 2009, it was linearly extrapolated. The maximum of vaccine coverage was estimated as 98%, as the coverage of other vaccines in NIP like MMR, DTP, which were performed for a long time in Korea are known to be 98% [24, 25]. Second dose was assumed as 95% of those individuals receiving the first dose. For the first dose, same percentage of individuals in the susceptible compartment was assumed to receive vaccination every month from 12 to 23 months of age. Second dose also used the same assumption for individuals in 18 to 41 months of age.

In this study, two scenarios were brought up to evaluate the impact of adult HAV vaccination program with the two doses. The first scenario assumed two dose course of adult vaccination program aimed at those in their 20s, according to the recommended adult immunization schedule of the Korea Society for Infectious Disease (KSID), while maintaining the status quo [17]. As vaccine coverage of influenza in Korean 20s were estimated to be 20% in a survey conducted by KCDC [25],

vaccine coverages of adult vaccination was set as 10%, 20%, 30%, 40%, and 50%.

The second scenario assumed two dose course of adult vaccination program for those in their 30s. According to the guideline by KSID, since costs for adult vaccination are fairly expensive and almost half of the people in their 30s get naturally acquired immunity, performing an anti-HAV test before vaccination is strongly recommended. Thus, in the second scenario, we assumed that only people whose serum test result is negative get vaccinated and vaccine coverages were also set as 20%, 30%, 40%, 50%, and 60% which are higher than the first scenario. The second scenario also assumed to maintain the status quo, which is the universal child vaccination program.

Differential equations, schematic diagram of hepatitis A model with adult vaccination strategy (Figure 5), and parameters used in the model (Table 1 and Table 2) are as follows.



$$\frac{dV_1}{dt} = (v_1 + v_{a1})S - (\mu + \sigma_1 + v_2 + v_{2a})V_1$$

$$\frac{dV_2}{dt} = (v_2 + v_{a2})V_1 - (\mu + \sigma_2)V_2$$

$$\frac{dS}{dt} = bN + \sigma_1 V_1 + \sigma_2 V_2 - (\lambda + \mu + v_1 + v_{a1})S$$

$$\frac{dE}{dt} = \lambda(S + (1 - \eta_1)V_1 + (1 - \eta_2)V_2) - (\varepsilon + \mu)E$$

$$\frac{dI}{dt} = \varepsilon E - (\gamma + \mu)I$$

$$\frac{dR}{dt} = \gamma I - \mu R$$

Figure 5. Differential equations and schematic diagram of hepatitis A model with HAV adult vaccination in Korea

Table 1. Natural history parameters used in the model

Symbol	Parameters	Source	Value
$\boldsymbol{\lambda}$	force of infection	estimated within the model *	–
$\mathbf{c}_{ij}$	contact rate between age groups	POLYMOD (Mossong et al, 2008[26])	–
$\mathbf{q}_j$	transmission probability per contact	calibrated	0.0009
$\boldsymbol{\epsilon}$	1/latent period	assumed **	1/30 days
$\boldsymbol{\gamma}$	1/infectious period	assumed **	1/30 days
$\boldsymbol{\rho}_1$	reporting rate for the age of 11 or older	assumed #	0.25
$\boldsymbol{\rho}_2$	reporting rate for under the age of 10	assumed	0.10

* $\boldsymbol{\lambda_{i,t} = \sum_{j=1}^{1081} C_{ij} \times q_j \times \frac{I_{j,t-1}}{N_{j,t-1}}}$

** Roughly approximation due to limitation of monthly time step

Calculated the ratio of notification from KCDC and number of patients from Healthcare Big data provided by HIRA (Health Insurance Review and Assessment Service)

Table 2. Vaccine parameters used in the model

Symbol	Parameters	Source	Value
$\mathbf{v}$	protection probability by vaccines	estimated within the model *	−
$\boldsymbol{\nu_1}$	vaccine coverage (1st dose)	empirical data (KCDC)	−
$\boldsymbol{\nu_2}$	vaccine coverage (2nd dose)	empirical data (KCDC)	−
$\boldsymbol{\theta}$	proportion of primary vaccine failure	Satori et al, 2012 [27]	0 (0−0.1)
$\boldsymbol{\eta_1}$	vaccine effectiveness (1st dose)	Thierry et al, 2012 [19]	0.97
$\boldsymbol{\eta_2}$	vaccine effectiveness (2nd dose)	Thierry et al, 2012 [19]	0.99
$\boldsymbol{\sigma_1}$	rate of immunity loss (1st dose)	Thierry et al, 2012 [19]	0.0162
$\boldsymbol{\sigma_2}$	rate of immunity loss (2nd dose)	Thierry et al, 2012 [19]	0.0012

* $v = \sum_{i=1}^{2} \boldsymbol{\nu_i} \times (\mathbf{1} - \boldsymbol{\theta}) \times \boldsymbol{\eta_i}$

As indicated above, there are some underlying assumptions in the model. The following assumptions were made for the base case analysis.

Assumption 1.

Only person-to-person transmission was assumed.

Assumption 2.

Latent period and infectious period of HAV were approximately assumed to be 30 days.

Assumption 3.

Under-reporting probability of HAV infection for ages 11 and above were assumed to be 25% and for under the age of 10, only 10% of cases were assumed to be reported.

Assumption 4.

First dose at 12 months of age, maximum size of first dose coverage was assumed to be 98%. Second dose at 6-18 months later, 95% of those receiving the first dose.

Assumption 5.

Vaccine induced protection was assumed to wane over time. After the first dose, a rate of 0.12% decrease per year and after the second dose , a rate of 1.62% decrease per year.

2.6 Analysis

The main analysis in this present study is constructing a mathematical model of hepatitis A in Korea and projecting the impact of universal adult vaccination program for two doses at 20s and 30s. With the developed model, we examined dynamics of individuals in each compartment and compared the results with reported notification cases using a graph. Furthermore, by projecting a model from 2017 to 2030, we evaluated not only the incidence rate over time, but also the percentage of reduction in the incidence rate derived from the adult vaccination program.

In a sensitivity test, we evaluated outcomes mentioned above, under different assumptions, in primary vaccine failure, and presence of waning rate.

All simulations were conducted by using program R package "POMP" (ver. 3.2.3, Stanford University, CA, USA)

Chapter 3. RESULTS

3.1 Model calibration with empirical data

Figure 6 shows the quality of fit between the number of empirical monthly notified cases from disease web statistics system of KCDC and simulated results by using developed model during 2012 to 2016 across all age groups.

Figure 7 presents the mean incidence rate (per 100,000 population) of symptomatic HAV cases by age groups from 2012 to 2016, considering assumed age-specific under-reporting probability, compared with observed incidence during the same period. Yearly empirical notified cases were assumed to be distributed uniformly in each month, as HAV infection does not show seasonality. Therefore, compared to empirical data, slight differences were observed in mean incidence rate of age groups under 30 years old. However, the best-fit model outcomes were quite close to both total notification data and age-specific HAV incidence data obtained from KCDC.

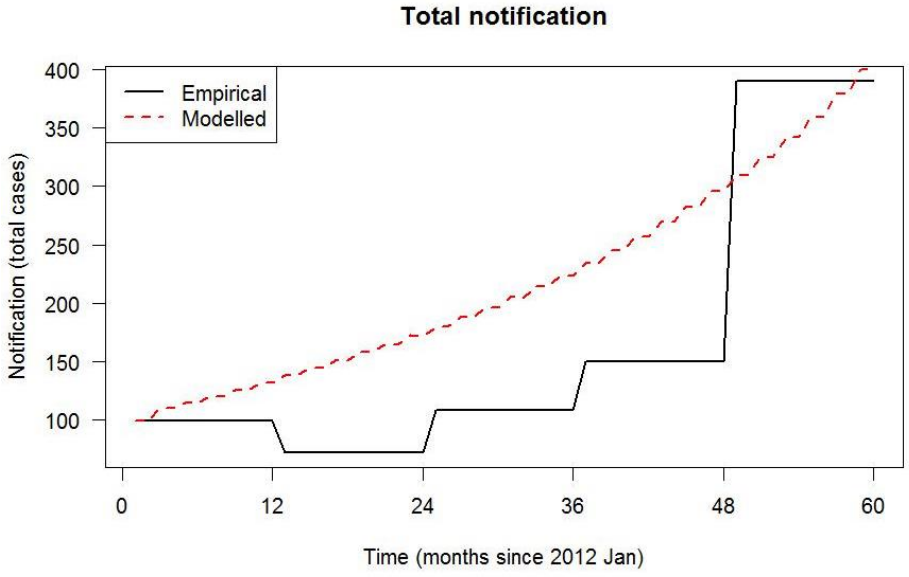


Figure 6. Monthly notification cases of HAV across all age groups model in Korea from 2012 to 2016

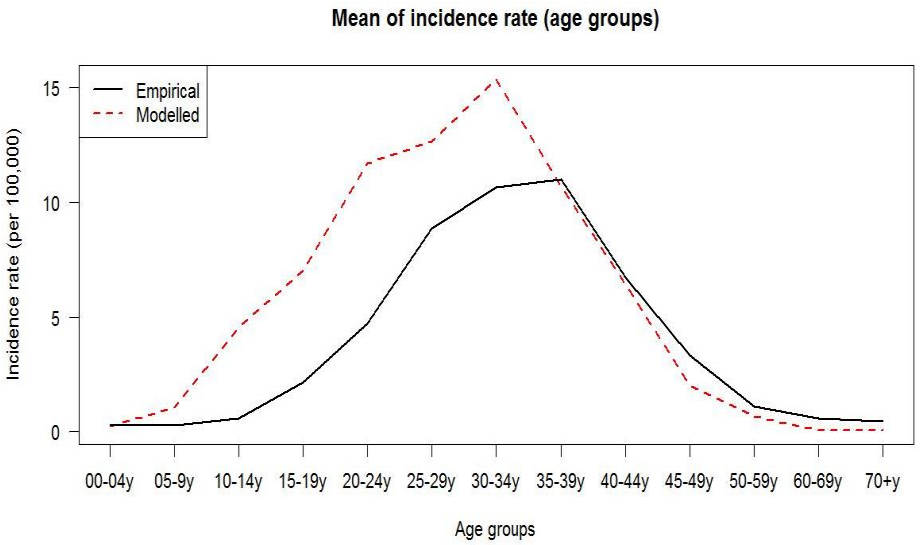


Figure 7. Mean incidence rate (per 100,000 population) by age groups during 2012–2016

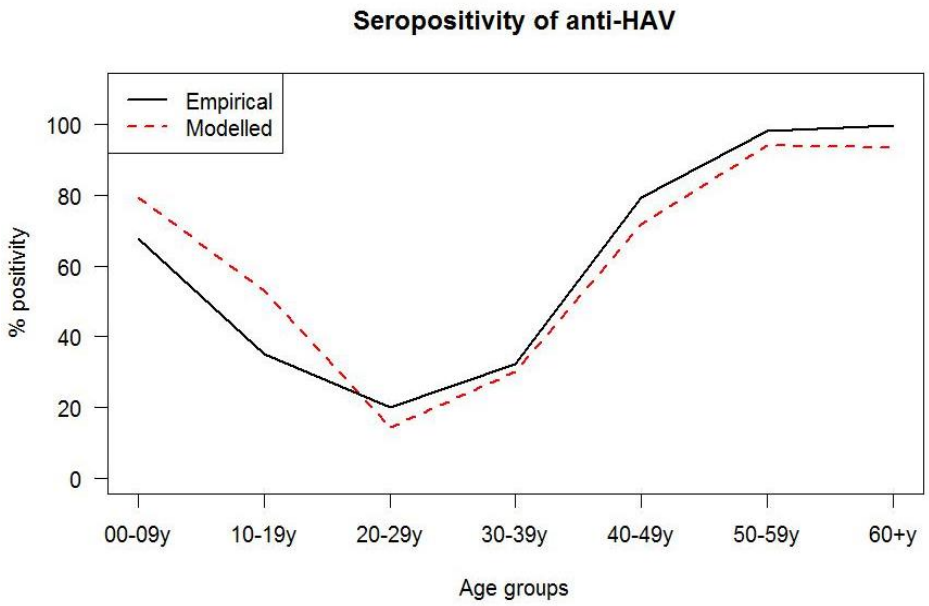


Figure 8. Percentage of seropositivity of anti-HAV by age groups in 2014 in Korea

Figure 8 shows the projected seropositivity of anti-HAV in 2014 by age groups, in comparison with the most recent empirical data conducted in 2014 by Kim et al [28]. The number of individuals with anti-HAV seropositivity was estimated by sum of infected individuals and vaccinated individuals in 2014. Modelled seroprevalence result was fitted well with empirical data.

Proportion of each compartment (Susceptible, Exposed, Recovered, Vaccinated after first dose and second dose) and changes in total population are described in Figure 9.

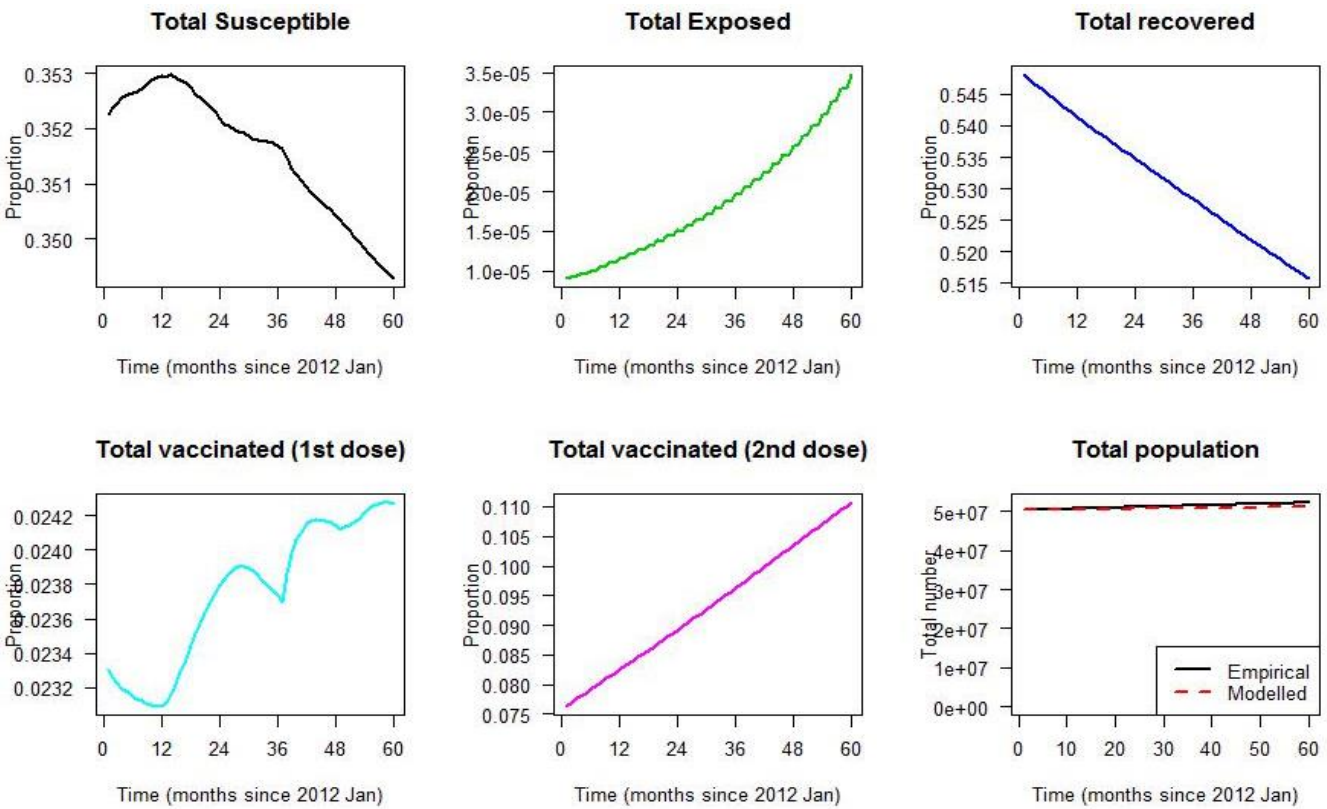


Figure 9. Proportion of individuals in each compartment in hepatitis A model in Korea

3.2 Model projections with adult HAV vaccination

Figure 10 shows the projected cases of symptomatic HAV over time for the base case (status quo) and five detailed scenarios of adult immunization program targeted individuals in their 20s from 2012 to 2030. Each detailed scenario was defined as follows; 10%, 20%, 30%, 40%, and 50% coverage for the first dose and 95% coverage for the second dose and all adult vaccination programs for 20s were assumed to begin from 2018.

Figure 11 presents the percentage of reduction in the notification cases of HAV by variation in vaccine coverage of the first dose. For the first year after the start of vaccination, all curves were close to zero indicating very few differences between the status quo and introducing adult vaccination program for individuals in their 20s. However, after a few years, the curves begin to diverge dramatically, shown in Figure 11 and as the vaccine coverage of adult HAV vaccination increases, percentage of reduction is also increased. Furthermore, if vaccine coverage of adult vaccination for 20s was assumed to be above 20%, almost 50% of reduction was observed before 2027.

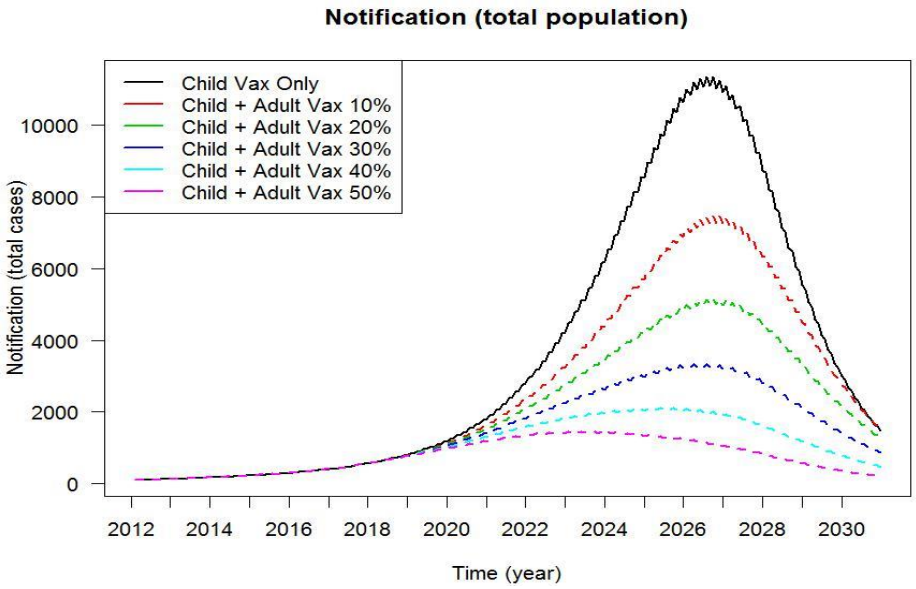


Figure 10. Model projections over time of notification cases with adult vaccination for 20s during 2012–2030

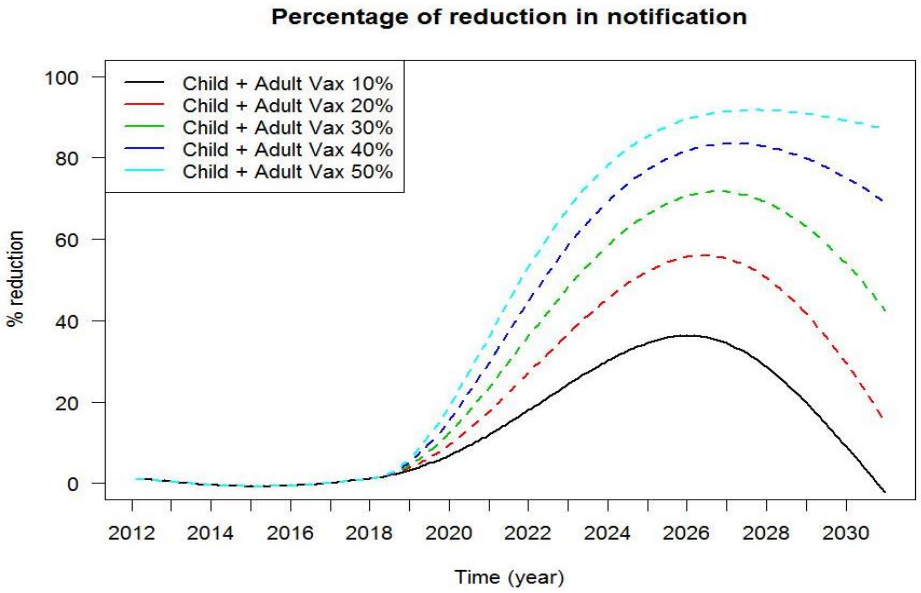


Figure 11. Percentage of reduction in notification cases of HAV with adult vaccination for 20s during 2012–2030

In Figure 12, for each first dose coverage rate which was set at 20%, 30%, 40%, 50%, 60%, respectively, the five curves represent the projected notification cases with vaccination for 30s across all ages. We assumed that adult vaccination program for those in their 30s were also introduced in 2018 and second dose coverages were set as 95%, equivalent as the first scenario.

Figure 13 shows the percentage reduction in the symptomatic cases of HAV during 2012–2030 by variation in first dose vaccine coverage. In the second scenario, we could observe similar results to that of the first scenario. As for Figure 11, compared to base case, after a few years since the adult vaccination program began, there was little difference in the number of symptomatic HAV incidence cases and a sharp decrease was observed after 2020. However, the drop of reduction in notification cases derived from the adult vaccination was much larger and faster than the first scenario which assumed an adult vaccination for 20s. Thus, the percentage of reduction in HAV notification cases was almost 100% in detailed scenarios with over 40% of vaccine coverage.

Table 3 presents maximum size of incidence rate with peak year and the year achieving aimed incidence rate of less than 30 per 100,000 across all ages projected by the developed model. Rapid

decrease in maximum size of incidence rate was shown after adjusting for adult vaccination strategies, compared to the status quo. In scenarios with the adult vaccination program, as vaccine coverage increased, the period of time to achieve aimed incidence of less than 30 per 100,000 population became shorter, whereas there was no year with an incidence rate of lower than 30 per 100,000 population in the status quo. The year with incidence rate of below 30 per 100,000 in adult vaccination for 30s was shorter than that of adult vaccination for 20s when compared for with the same coverage. In addition, in intervention with over 40% vaccination for individuals in their 30s, incidence rates of notification HAV cases were lower than 30 per 100,000 in every year during 2012–2030.

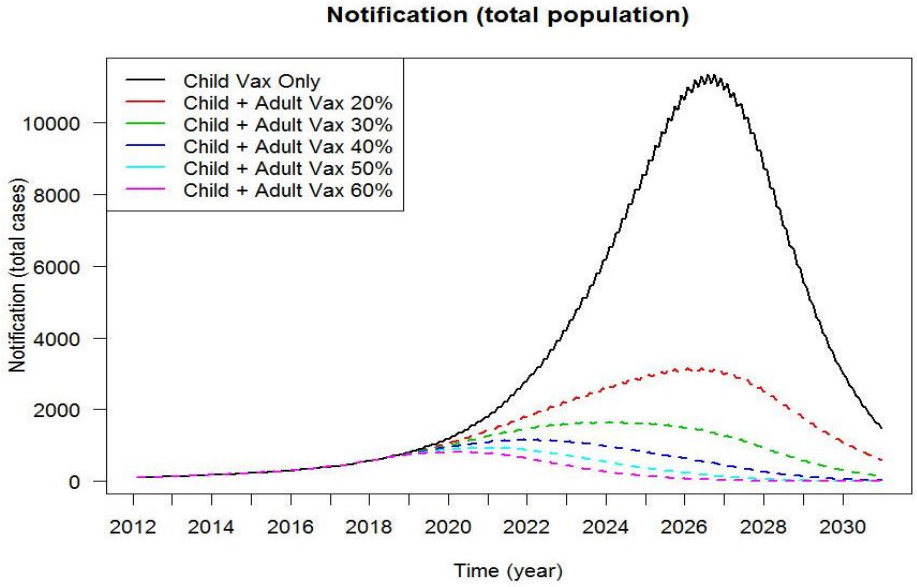


Figure 12. Model projections over time of notification cases with adult vaccination for 30s during 2012–2030

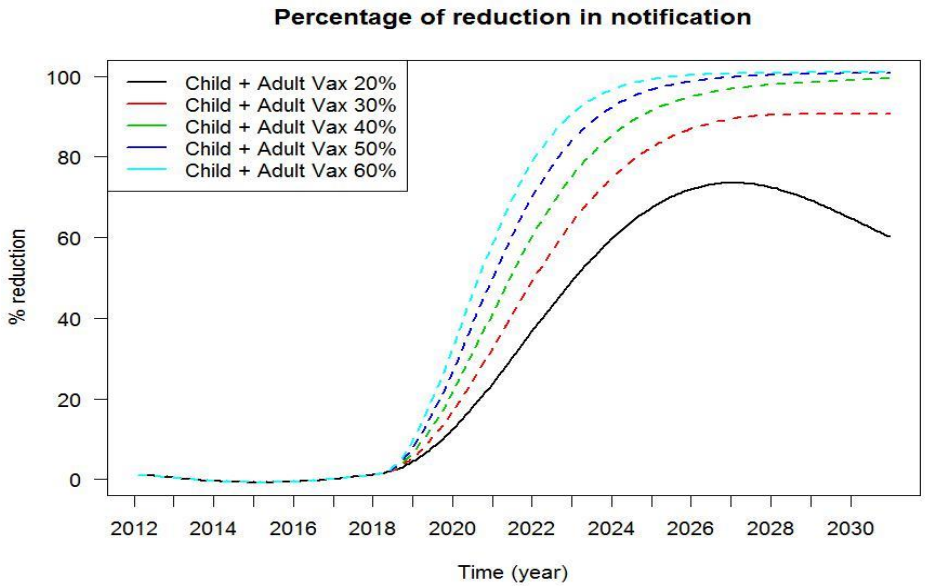


Figure 13. Percentage of reduction in notification cases of H with adult vaccination for 30s during 2012–2030

Table 3. The year achieving aimed mean incidence rate of less than 30 per 100,000 population

Scenario	Adult vaccine coverage (1^{st} / 2^{nd} dose*)	Maximum size of incidence rate (peak year)	Year of incidence rate ≤ 30/100,000
Status quo	N/A	233.19 (2026)	N/A
Scenario 1. Adult vaccination for 20s	10% / 95%	167.11 (2026)	N/A
	20% / 95%	115.57 (2026)	N/A
	30% / 95%	75.44 (2026)	2030
	40% / 95%	47.86 (2025)	2029
	50% / 95%	33.09 (2023)	2024
Scenario 2. Adult vaccination for 30s	20% / 95%	71.24 (2026)	2030
	30% / 95%	37.53 (2023)	2027
	40% / 95%	26.27 (2021)	In every year
	50% / 95%	21.38 (2020)	In every year
	60% / 95%	18.70 (2020)	In every year

* 2^{nd} dose vaccine coverage among individuals who were vaccinated with 1^{st} dose

3.3 Sensitivity analysis

In this study, sensitivity analyses were conducted to assess the change of incidence rate of notification cases of HAV for different combinations of assumptions of proportion of primary vaccine failure and waning of vaccine protection. Sensitivity analysis of primary vaccine failure was set at 0% (base case), 5%, and 10% and waning rate of vaccine was taken into account by dividing with waning (base case) and without waning. For sensitivity analysis, only detailed scenarios which assumed vaccine coverage of first dose to be 20% were used.

Figure 14 and Table 4 shows annual mean incidence rate by waning rate. Projected annual incidence rates with waning of vaccine induced immunity were much larger than the incidence rate without immunity waning in every scenario.

Figure 15 and Table 5 presents mean incidence rate by proportion of primary vaccine failure. As the assumption of proportion of primary vaccine failure increases, incidence rate was also critically increased. Also, as proportion of primary vaccine failure was increased, width of epidemic curve became narrower and the time period spent reaching to peak year became shorter.

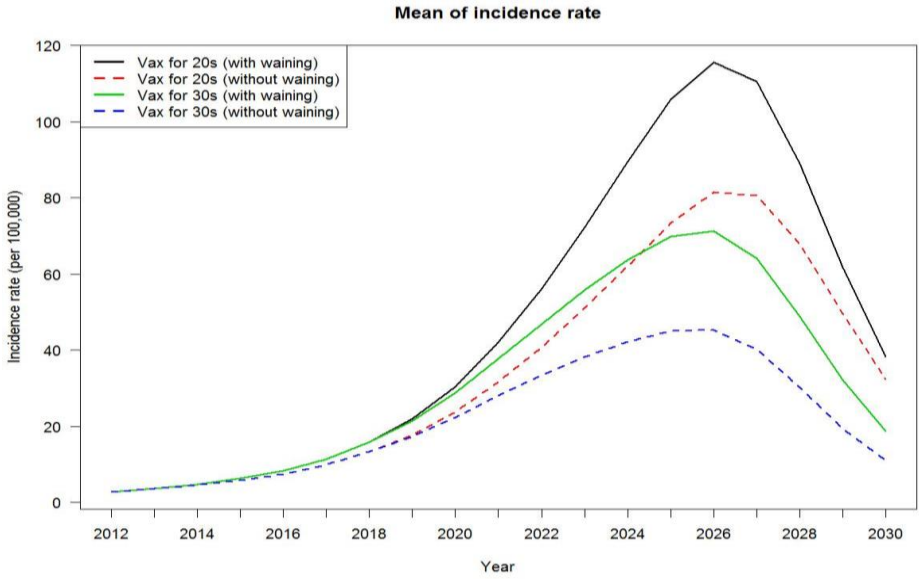


Figure 14. Mean of incidence cases with waning and without waning of vaccine protection during 2012–2030

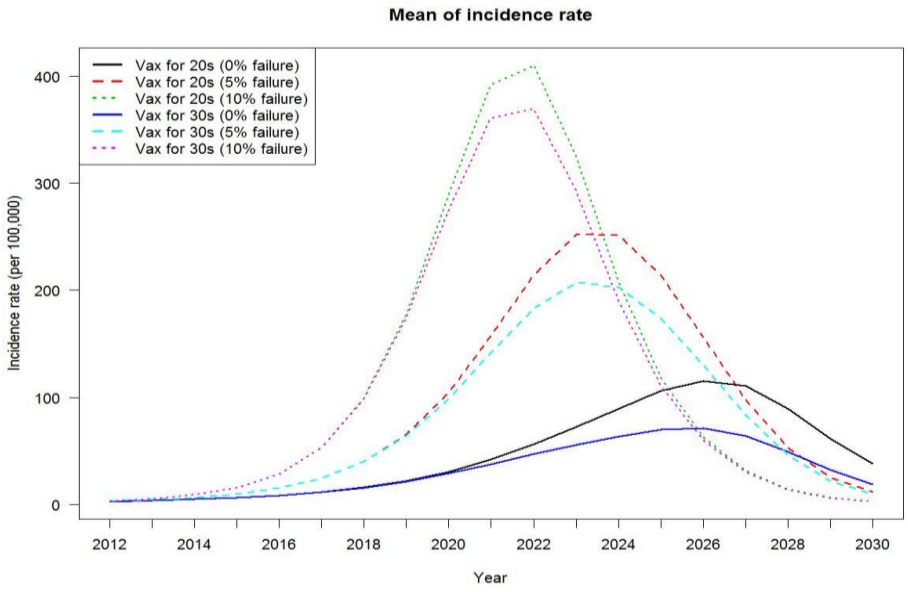


Figure 15. Mean of incidence cases by proportion of primary vaccine failure during 2012–2030

Table 4. Sensitivity analysis, annual incidence rate by waning rate (with waning and without waning)

Scenario	Waning of vaccine protection *	Mean annual incidence rate (per 100,000)												
		2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
Status quo	With waning	15.89	22.65	33.50	50.50	75.47	110.25	154.78	202.98	233.19	218.52	161.65	98.90	53.19
	Without waning	13.36	18.34	26.16	38.08	55.21	19.06	110.99	150.00	18342	1874.30	152.28	101.70	58.84
Vaccination for 20s (20%)	With waning	15.82	21.90	30.48	42.02	56.15	72.30	89.51	105.91	115.57	110.56	89.03	61.75	38.21
	Without waning	13.31	17.74	23.80	31.64	40.84	51.11	62.16	73.45	81.54	50.64	67.96	49.66	32.43
Vaccination for 30s (20%)	With waning	15.79	21.48	28.83	37.66	46.93	55.82	63.70	69.86	71.24	64.08	48.84	32.14	18.78
	Without waning	13.28	17.38	22.40	28.07	33.52	38.30	42.22	45.17	45.32	40.18	30.13	19.40	11.02

* waning rate was assumed as 1.62 for fist dose and 0.12% for second dose

Table 5. Sensitivity analysis, annual incidence rate by proportion of primary vaccine failure

Scenario	Proportion of vaccine failure	Mean annual incidence rate (per 100,000)												
		2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
Status quo	0%	15.89	22.65	33.50	50.50	75.47	110.25	154.78	202.98	233.19	218.52	161.65	98.90	53.19
	5%	40.40	67.31	113.28	184.28	271.25	339.94	347.66	289.64	200.07	117.02	59.18	27.20	11.77
	10%	99.15	181.58	309.43	443.98	483.54	388.56	246.72	138.28	73.13	36.82	17.39	7.83	3.42
Vaccination for 20s (20%)	0%	15.82	21.90	30.48	42.02	56.15	72.30	89.51	105.91	115.57	110.56	89.03	61.75	38.21
	5%	40.24	65.31	104.24	157.60	214.39	252.22	251.46	213.66	155.86	97.80	52.79	25.49	11.39
	10%	98.80	176.70	287.96	391.80	410.03	325.37	208.53	118.45	62.95	31.44	14.47	6.23	2.55
Vaccination for 30s (20%)	0%	15.79	21.48	28.83	37.66	46393	55.82	6370	69.86	71.24	64.08	48.84	32.14	18.78
	5%	40.15	64.03	98.65	142.11	183.43	206.94	202.51	173.54	129.87	83.60	45.85	22.16	9.73
	10%	98.59	173.49	274.26	360.87	369.16	292.51	190.64	110.95	60.13	30.21	13.78	5.79	2.28

Chapter 4. DISCUSSION

The main purpose of this present study was to develop a mathematical model with parameters reflecting recent transmission dynamics of HAV in Korea. As a result, evaluate the impact of adult vaccination strategies arising from the application of the developed model.

To the best of our knowledge, this is the first study which developed an age-structured dynamic model of hepatitis A in Korea, using empirical data which included national mandatory surveillance and vaccine coverage data. Even though we used modified demography data due to increasing population within the same cohort for our study, in comparison to the mid-year population and estimated future population data from KOSTAT, the difference was estimated to be lower than three percent. In addition, this model accounted for age stratified under-reporting probabilities, contact pattern between age groups, and vaccine characteristics by dose, which differentiates this very study from previous hepatitis A mathematical modeling studies conducted in Korea.

Only annual notification data by age was available in Korea and the seasonality was not observed in monthly notification data

provided by KCDC from 2012 to 2016. Therefore, annual symptomatic cases of HAV infection were assumed to be distributed uniformly in each month. Consequently, due to this assumption, inevitable difference occurred in the projection. However, despite the assumption mentioned above, the model achieved a reasonably satisfying fit with the empirical data, with respect to both annual incidence tendency and age-specific incidence rates of HAV. This in turn provided insight on the HAV dynamics in Korea.

In comparison with not only the incidence rate, but also the empirical anti-HAV seroprevalence data in 2014, similar trends were projected by the model. Seropositivity of anti-HAV was estimated to be 79.16% in the age group of 0 to 10, and over 95% in those aged 50 and greater. However, the seropositivity of anti-HAV began to drop critically in individuals in their 20s and 30s, as 14-30%. These trends projected by the model has shown the good match to the general pattern of the cohort effect in countries with low HAV endemicity and universal child immunization programs. A subdivision of individuals aged between 20 and 49, and with HAV immunity from natural infection were progressively replaced by birth cohorts who were born between 1970-1996. These replaced birth cohorts had less

early natural HAV exposure, but were not vaccinated due to the time of introduction of the HAV vaccine [28].

The projected results indicated that the number of symptomatic hepatitis A cases were dramatically decreased after applying the adult vaccination program. The difference in the projected HAV notification cases by the introduction of the adult vaccination program was minor for the first few years; however, it began to increase 1–2 years after the introduction, and dramatically increased further upon introduction of the adult vaccination program. Approximately, more than 50% of the reduction was observed roughly eight years after the vaccination program was introduced, with 20% of vaccine coverage. These results imply that adult vaccination strategy can be a highly effective method of controlling continually increasing HAV infections in Korea.

The reduction in symptomatic HAV cases due to the introduction of the adult immunization program was greater at a higher coverage of adult vaccination in both scenarios; vaccination program for the 20s and 30s. This implies that the impact of adult HAV vaccination program in Korea would be strongly influenced by the success of the immunization program in accomplishing high vaccine coverage rates.

Of the two scenarios which presumed the adult vaccination program for those in their 20s and 30s, respectively, immunization programs for individuals in their 30s produced a greater reduction in symptomatic case of HAV infection than the vaccination program for the 20s. The time of introduction of the HAV vaccine could be considered to have possibly influenced the results. HAV vaccines were first introduced in 1997 in Korea and according to survey results on the immunization rate of each vaccine conducted by the KCDC, the average immunization rate of HAV vaccine over time was estimated to be 40–87%, prior to the introduction of the HAV vaccine in the NIP in May 2015. Hence, some proportion of 20s were already vaccinated, whereas individuals in their 30s were not all vaccinated. This then simply infers that implementing an immunization program for the 30s could be highly effective in reducing HAV cases in Korean adults.

The purpose of the sensitivity analysis in this study was to figure out which parameters have a major impact on the dynamics of HAV infection. Although the assumed annual waning rate was very small, since the vaccinated individuals increased rapidly due to the introduction of adult vaccination, change in waning rate had a great influence on symptomatic HAV incidence. However, there were few studies on the waning in HAV vaccine and no such data

is currently available on the waning rate of HAV vaccination over periods. In the second sensitivity analysis, which was on the proportion of primary vaccine failures, as vaccine failure rate increased, the epidemic curve became narrower and declined more rapidly. Moreover, it showed a general pattern of an epidemic curve without intervention.

The present model has multiple strengths. The model is fully dynamic, in terms of both epidemiology and demography, as it utilized the empirical data and was stratified by monthly age groups to account for the different contact patterns and under-reporting probabilities between age groups. Also, the model presented fits well with the observed data on HAV notification case, age-specific incidence and seroprevalence. This then denotes that the model thoroughly represented the transmission dynamics of HAV infection in Korea.

However, several limitations exist within this study which require further interpretations arising from the projected results. As empirical data of notification cases collected for a long duration are lacking, the model was fitted with only a small quantity of data obtained from 2012 to 2016. Furthermore, although mathematical modeling studies may be the only means to predict the future dynamics and evaluate the potential impact

of preventive interventions, which can produce effects over time, there were many uncertainties present within the parameters used in our model. In the absence of the data on contact patterns between age groups in Korea, the model assumed that the contact patterns in Korea were the same with the POLYMOD, which shows age-specific contact patterns in eight European countries. Likewise, as the result of when considering for the monthly time step, latent periods and infectious periods were assumed to have a slightly bigger value, compared to other previous studies. As a result, further studies focusing on fundamental factors such as, contact patterns and long-term effectiveness of HAV vaccines are needed to construct a more precise mathematical model of HAV infection.

Chapter 5. CONCLUSION

Our study offered not only the age-structured dynamic model of hepatitis A, which was well fit with the HAV infection epidemiology and seroprevalence status in Korea, but also valuable projection of HAV infection dynamics from 2017 to 2030. Results of these projections indicate that, as vaccine coverage increases and along with the introduction of adult vaccination for those in their 30s, the reduction of notified cases of HAV dramatically decreased. Therefore, adult vaccination programs for individuals in their 30s can be an effective intervention to control increasing HAV incidence in Korea.

Nevertheless, while adult HAV immunization programs for the 30s were shown to have a better effect in reducing HAV infection cases than that of the 20s, the most effective adult vaccination strategy could be changed over time, depending on the vaccination coverage and proportion of seropositivity by birth cohorts. Therefore, many new novel studies are strongly needed, in order to assess the best adult HAV immunization strategy.

Finally, this model could be used to evaluate the potential impact of diverse interventions and also could be used as the basis for

research in an economic evaluation of adult HAV vaccination programs in Korea.

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국문초록

수학적 모델링을 이용한 국내 A 형간염 전파 특성 및 성인대상 예방접종 효과 연구

A 형간염은 A 형간염 바이러스에 의해 발생하며, 분변-경구로 감염자와 직접 접촉하거나 감염자의 대변으로 오염된 식수나 음식물을 섭취함으로써 간접적으로 전파된다. 이러한 A 형간염은 2015 년 5 월부터 A 형간염 예방접종을 국가예방접종으로 도입함에도 불구하고 2012 년부터 2015 년까지 연간 1,000 건을 넘어서며 2016 년에는 무려 4,679 건이 보고되는 등 기하급수적으로 급증하고 있는 추세이다. 하지만, 이렇게 급증하는 발생건수에도 불구하고 국내에서는 국가예방접종 시행 후의 자료를 활용한 A 형간염 수학적 모델링 연구가 이루어지지 않고 있다. 이러한 맥락에서 본 연구는 최근 데이터를 활용한 수학적 모델을 구축함으로써 최근 급증하고 있는 국내 전파 양상을 파악하고 성인대상 A 형간염 예방접종의 효과를 확인하고자 하였다.

본 연구에서 개발한 국내 A 형간염 모델은 질병관리본부 웹통계시스템에서 제공하는 전수감시조사 자료를 기반으로 하였으며, 월령별로 1081 개의 세부그룹으로 세분화 함으로써 연령별 접촉 패턴 및 과소신고(under-reporting) 정도 역시 고려하였다. 연구결과, 본 모델은 2012 년부터 2016 년까지의 국내

A 형간염 보고 건수 및 항체양성률과 비교적 잘 맞음을 확인할 수 있었다. 또한, 동일한 예방접종률을 상정하여 비교하였을 때, 20 대를 대상으로 한 성인예방접종 전략보다 30 대를 대상으로 한 성인예방접종 전략에서 A 형간염 발생건수가 더 크게 감소하는 것을 확인할 수 있었기에 30 대 대상 성인예방접종이 현재 급증하는 A 형간염 발생건수 감소에 효과적인 중재방법임을 확인하였다. 또한, 두 전략 모두 성인대상 예방접종 시행 후 처음 1 년동안은 성인대상 예방접종을 시행하지 않았을 때 차이가 없었으나, 약 8 년 후에는 A 형간염 발생건수가 무려 50% 이상 급격히 감소하는 것을 확인하였다. 민감도 분석 결과, 백신 효과 감소(waning rate)가 감소할수록, 또한 백신 실패(proportion of primary vaccine failure)가 증가할수록 A 형간염 발생건수가 증가하는 것으로 보아, 두 요인이 성인대상 예방접종 효과에 상당한 영향을 끼침을 확인할 수 있었다.

본 연구를 통해 구축된 모델은 국내 A 형간염 전수감시자료를 기반으로 구축된 최초의 수학적 모델이라는 점에서 의의가 있으며, 본 모델은 국내 A 형간염 전파 양상 파악 및 다양한 A 형간염 관련 중재의 효과를 확인하는데 사용할 수 있으며, 추후 비용-효과 분석의 기초자료로도 충분히 사용될 수 있으리라 생각된다.

주요어: A 형간염, 수학적 모델, 전파 예측, 성인예방접종

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