

Project 1 Report

Background

In 2009, an H1N1 pandemic hit 306.8 million people in the U.S. and caused approximately 60.8 million people to get sick, hospitalized 274,304, and killed 12,496. H1N1 hit in two waves: an outbreak in July followed by another larger outbreak in December. Because this flu was new, no previous protection worked. Vaccines were produced a few months after the first outbreak. After the H1N1 vaccines were used, the H1N1 morbidity and mortality rate successfully declined. However, not everyone who got vaccinated could become immune. Only a part of the population can get immune, because vaccines work differently: for some people, they are naturally unresponsive to the vaccine while for others, antibodies take a while to develop in the body system after vaccination. During this developing time, the vaccinated population still has the possibility to get infected by others. Producing vaccines is time consuming, and the vaccine released date affects the population. The expedition of vaccine production can increase or lower the morbidity and mortality, also generating economic cost or benefit.

In this project, for studying H1N1 influenza, we aim to study how the change of vaccine release date and change of vaccine efficacy rate bring variation of cost and benefit, based on the equations and mathematical models we come up with.

Assumptions

Because our model is a simplification of the real life situation, few assumptions need to be made before calculations and analyzations.

1. Overall timeline (see Appendix A)

1.1. t starts on January 1st, 2009. ($t = 0$)

- 1.2. The H1N1 influenza starts on February 24th, 2009. ($t = 55$) and ends on February 24th, 2010, this pandemic lasting for a year. ($t = 55 + 365 = 420$)
- 1.3. The initial vaccine release date is October 16th, 2009. ($t = 289$)
2. During this pandemic year, we focus on the H1N1 influenza only and do not consider other diseases that may be present at the same time.
3. In 2009, the total population in the U.S. is 306.8 million.
4. Also, the overall population change is negligible and therefore we assume it stays to be constant, which means the birth rate equals to the death rate.
5. Vaccination assumptions
 - 5.1. The actual data is 108 million people got vaccinated because of H1N1.
 - 5.2. The vaccination rate is constant.
 - 5.3. 89% of the population is responsive to the H1N1 vaccine.
 - 5.4. Nobody is naturally immune to H1N1 virus and they need to get vaccinated to be immune. After the vaccination, people can get immune 14 days later because it takes time for vaccines to work. The rate of being immune is constant.
6. The expected recovery time is three days and the recovery rate is constant.

Model 1

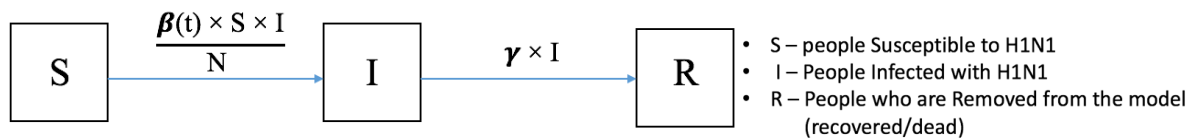


Figure 1 – Model without Vaccine

In late February, a boy in California got H1N1 and he was capable of infecting others. Therefore, the rest of the population, 306.8million population – 1 infected person, all fell into the susceptible (S) group, as Figure 1 listed above. When there was no vaccine available, the

susceptible population might fall into infected (I) group by interacting with sick people and eventually they are removed (R), no matter if they are dead or recovered.

The differential equation of each variable:

$$\begin{aligned}\frac{dS}{dt} &= -\frac{\beta(t) \times S \times I}{N} \\ \frac{dI}{dt} &= \frac{\beta(t) \times S \times I}{N} - \gamma \times I \\ \frac{dR}{dt} &= \gamma \times I\end{aligned}\quad \begin{aligned} &\bullet \beta(t) - \text{contact rate} = 0.52 \left(1 + 0.35 \cos \left(\frac{2\pi t}{365} \right) \right) \text{ eq4} \\ &\bullet N - \text{U.S. total population in 2009} = 306,800,000 \\ &\bullet \gamma - \text{recovery rate} = \frac{1}{3}\end{aligned}$$

Eq1 is the differential equation of the susceptible group. Infected population (I) contact ($\beta(t)$) with the susceptible group (S) divided by the whole population (N) to see the individual contact rate. This is how we got $\frac{\beta(t) \times S \times I}{N}$. The sign is negative because people is removed from the susceptible group (S) to infected group (I) when they get sick. As Figure 1 shows, only one arrow comes out from S.

Eq2 is the differential equation of the infected group. $\frac{\beta(t) \times S \times I}{N}$ people come from the susceptible group but also a part of people get removed because they are removed, either dead or recovered. The removed group is the denoted as recovery rate multiply with the infected group, $\gamma \times I$, and the sign is negative because recovery people leave the group. In figure 1, the arrow fluxes in is the new infected group and the arrow points out is the removed population.

Eq3 is the differential equation of the recovery group. Removed people come from the infected group (same as $\gamma \times I$), illustrated in Figure 1. The sign is positive because the flux in population. Starting from eq4 is the parameters. In eq4, we used cosine function to denote our contact rate. One period of a cosine function, $\cos(t)$, is 2π . If we multiplied the domain with 2π , then the cosine function became $\cos(2\pi t)$, and the period of it shrank to 1 because $\frac{2\pi(\text{initial period of } t)}{2\pi(\text{multiple})} =$

1. Then, we divided the domain by 365 because we want to study a one solid year. Therefore, we divided 365 to enlarge the domain. The new period of the cosine function was:

$$\frac{2\pi t}{365} = \frac{2\pi(\text{initial period of } t)}{365} / \frac{1}{365} = \frac{1(\text{updated period})}{\frac{1}{365}} = 365$$

which is one year (365 days). Then, generally the range of cosine function is from -1 to 1.

However, all the $\beta(t)$ numbers we used were positive numbers because the contact rate could never be negative. Hence, for lifting the range one up, from (-1, 1) to (0, 2), we added one in the $\beta(t)$ function. Furthermore, we adjusted the amplitude of the graph to get the two waves graph of the infected group (as mentioned in the Background). What we did was to multiply two scalars in the cosine function and MATLAB helped us to figure out the precise numbers, 0.52 and 0.35. That is how we got eq4.

In eq5, as assumption 6 states, the expected recovery time is three days and the recovery rate is constant, then the recovery rate should be 1/ 3 because the expected recovery time equals to the inverse of recovery rate (see Appendix B).

Result 1

We put the equations and parameters into MATLAB and graphed the Susceptible group (Appendix C.1), Infected group (Appendix C.2), and Removed group (Appendix C.3). Appendix C.1 shows that as time goes by, the number of people stay in the susceptible group decreases. Two red cycles point out the time when two waves of outbreak happened and susceptible group decreased rapidly. When t exceeds around 300, the slope of the graph becomes flatter. In the end, the graph does not intersect with 0 on y-axis because there are uninfected people stay in the susceptible group. Appendix C.2 is the graph of infected group and it demonstrates the two waves graph of H1N1 pandemic. Two peaks in this graph correspond to the two red cycles in

Appendix C.1 (when a large number of people get infected and susceptible group decreases rapidly, infected group then increases dramatically). Appendix C.3 starts from zero when no one gets removed from the infected group (I). As time increases, more people are removed to group R and the curve bids up. Also, we found the number of morbidity via Appendix C.3 by obtaining the maximum value. The reason behind finding the morbidity by choosing maximum value of the removed group instead of the infected group is because we plot the population stay in each group as time goes by. People are infected and fall into I group but later get removed into R group, which explains why we cannot use the maximum number from I group. However, all then infected people then fall into the removed group, which is a dead end. Detailed data analysis of no vaccination is in the ‘Cost and Benefit’ section.

Model 2

Few months later, on October 16th, 2009, vaccines were released and distributed to the public. We built up a new model to study the effect of vaccination basing on Model 1. The difference between Model 1 and Model 2 is, we started with two susceptible groups, S_1 and S_2 , depending on whether people are instinctively responsive to vaccines, which has a sharp contrast to Model 1. 89% of the population who are responsive to vaccines fall into S_2 and the rest of 11% unresponsive population are in S_1 . The detailed graph is listed below.

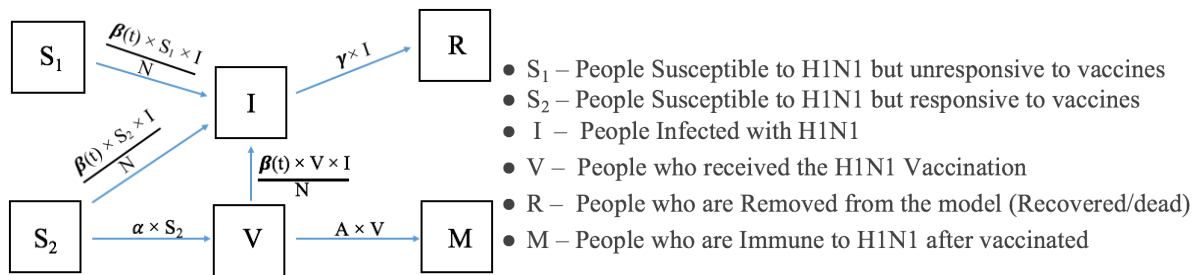


Figure 2 - Model with Vaccines Available

From the graph, people in S_1 are either uninfected and stay in S_1 group or infected and removed to the infected group (I). As for S_2 group, people are uninfected, infected, or choose to get vaccinated: the uninfected population stays in S_2 , infected population is removed to I, and vaccinated population is removed to the vaccinated group (V). However, for these vaccinated people (group V), it takes two weeks for antibodies develop in the body system after vaccination. During this developing time, vaccinated population still have the possibility to get infected by other H1N1 virus carriers. Therefore, part of V gets immune to M and another part goes to I. For I, people are moved in I group from S_1 , S_2 , and V but all I group are in R, either recovered or dead, after 3 days.

The differential equation of each variable is:

$$\frac{dS_1}{dt} = -\frac{\beta(t) \times S_1 \times I}{N}$$

eq6

$$\frac{dS_2}{dt} = -\frac{\beta(t) \times S_2 \times I}{N} - \alpha \times S_2$$

eq7

$$\frac{dV}{dt} = \alpha \times S_2 - \frac{\beta(t) \times V \times I}{N} - A \times V$$

eq8

$$\frac{dI}{dt} = \frac{\beta(t) \times S_1 \times I}{N} + \frac{\beta(t) \times S_2 \times I}{N} + \frac{\beta(t) \times V \times I}{N} - \gamma \times I$$

eq9

$$\frac{dM}{dt} = A \times V$$

eq10

$$\frac{dR}{dt} = \gamma \times I$$

eq11

Parameters:

$$\bullet \beta(t) - \text{contact rate} = 0.52 \left(1 + 0.35 \cos \left(\frac{2\pi t}{365} \right) \right)$$

$$\bullet \alpha - \text{vaccination rate} = 0.0033 \quad \text{eq11}$$

$$\bullet A - \text{immune rate} = 1/14 \quad \text{eq12}$$

$$\bullet \gamma - \text{recovery rate} = 1/3$$

The differential equations we used are listing on the top left while the parameters we used in this model are on the top right. Eq6 is similar to eq1 in Model 1, because all the people who fall into this group end up with either stay in this group or get infected, the only difference is we replaced S with S_1 . As for Eq7, part of the population chooses to get vaccinated and fall into group V but another part of it choose not to and may get infected. Therefore, there are two ways of fluxing out, one to group I, $\frac{\beta(t) \times S_2 \times I}{N}$, and another one to group V, $\alpha \times S_2$. Eq8 is derived from vaccination rate multiplying with the S_2 group (only S_2 group is capable of successful

vaccination and comes from S_2) minus the vaccinated but still infected population minus the immune group. People from S_1 , S_2 , and V are all have the possibility to get infected. Therefore, in eq9, these infected people from these three group flow into I and all the infected population end up with in the removed group. Eq10 is the immune number by using the immune rate multiply with vaccinated population and eq11 is the same as eq3 in Model 1.

As for the parameters, contact rate and recovery rate are the same in Model 1, and they were discussed as eq4 and eq5 before. However, due to vaccines are available in Model 2, we have another two parameters relating to vaccinations: vaccination rate (α) and immune rate (A).

In eq6, we evaluated the vaccination rate (α) by using the number of actual vaccinated people divided by the number of total U.S. population, to get the vaccinated ratio, and then we divided 100 because the first vaccine release date in our model was April 10th, when t equals to 100.

$$\alpha = \frac{\# \text{ of actual vaccinated people}}{\# \text{ of total population} \times \text{first vaccine release date}} = \frac{1.08 \times 10^8}{3.06 \times 10^8 \times 100} \approx 0.0033$$

In eq7, A is our immune rate and it is constant, as assumption 5-4 states. The time took to get immune is 14 days and the immune rate is the inverse of 14 days, which is $1/14$.

Result 2

All our graphs for Model 2 are in Appendix D. In this model, we used vaccine release date at $t = 289$, which is the yellow line in all the graphs and we only focus on the yellow lines for now.

The general trends for S_1 and S_2 graph, Appendix D.1 and D.2, are basically the same except the starting point of S_2 is higher because 89% of the population is naturally responsive to the vaccines. When t exceeds 300, S_2 decreases gradually versus S_1 is almost flat showing that less people get infected in S_2 . Appendix D.3, the infected graph is consistent with Appendix C.2, which is the graph of infected group in Model 1, both of them have the similar shape with two peaks. Appendix D.4 is the vaccinated group, no one gets vaccinated until $t = 289$ and the

number of vaccinated population increases really quick by vaccinations. Even though people may still get infected and leave the group, the overall slope is positive because the new vaccinated number exceeds infected number. Around 14 days later, there is an obvious turning turns in the graph. The slope is negative because not many people get vaccinated and people leave the graph by getting immune. The graph of immune group in Appendix D.5 is accumulating total immune number and the graph of removed group in Appendix D.6 is accumulating total immune number. These two graphs have positive slope because there is no further population flow.

Costs and Benefits Analysis

After we got our models, we utilized the data from them and did the cost-benefit analysis to figure out the effect of vaccines to the overall population. We wanted to dig into both the population impacts and the economic impacts for these three cases:

- 1) no vaccination comparing to vaccine released on Oct.16th
- 2) changing in vaccine release date
- 3) changing in vaccine efficacy rate

Part I: Calculating Population Impacts

In this section, we evaluate the morbidity, hospitalized population, and mortality of H1N1 virus. For getting the number of hospitalized population and mortality, firstly we found the morbidity number in our model. Both in Model 1 and Model 2, all the infected population eventually went into the removed group, and then we got the morbidity value by obtaining the maximum value of the removed group. Then, because our model did not give us the exact hospitalized population or mortality number, we used the actual hospitalization and actual mortality number divided by the actual morbidity separately to get the ratio:

$$\text{Hospitalization/morbidity ratio} = \frac{\text{actual hospitalization}}{\text{actual cases}} = \frac{274,304}{60,800,000}$$

$$\text{Mortality/ morbidity ratio} = \frac{\text{actual deaths}}{\text{actual cases}} = \frac{12,469}{60,800,000}$$

One key point to be notified is, in reality, not all the infected people reported themselves. When we did the calculation, we multiplied the report rate for data accuracy.

Report Rate Calculation

Our Model 2 shows that 192.56 million got infected but CDC reported only 60.8 cases.

We calculated the report rate by using the actual data divided by our data,

$$\text{report rate} = \frac{60.8 \text{ million reported cases}}{192.56 \text{ million total infected population}} = 0.316.$$

Actually there were 192.56 million sick people but only 60.8 million people were sick enough to report themselves as infected.

Equations

- Hospitalized population = morbidity × report rate × hospitalization/morbidity ratio
- Mortality = morbidity × report rate × mortality/morbidity ratio

Data

Case 1-1: no vaccination comparing to vaccine released on Oct 16th (t = 289)

As our Model 1 illustrated, when there was no vaccine used, 198 million people were infected by H1N1 virus. By applying two equations above, we calculated hospitalized population and mortality:

$$\text{Hospitalized population} = 198,000,000 \times 0.316 \times \frac{274,304}{60,800,000} \approx 282,280$$

$$\text{Mortality} = 198,000,000 \times 0.316 \times \frac{12,469}{60,800,000} \approx 12,832$$

Replacing the number 198 million (infected population when no vaccine available) with 192.56 million (infected population under vaccination), we got the new hospitalized population and mortality number and then gathered all the data in the Table 1.1 below:

Table 1.1- Population Impacts on Vaccine Availability

<div>Vaccination Availability</div> <div>Number of People</div>	no vaccines	vaccines released (on Oct.16th)
morbidity	198,000,000	192,560,000
hospitalized population	282,280	274,530
mortality	12,832	12,479

Compared to no vaccines, releasing vaccines on Oct 16th was definitely a good action because less people got sick, were hospitalized, or died. However, when vaccines were available, the vaccine release date needs to be considered.

Case 1-2: Changing in Vaccine Release Date (detailed graphs are in appendix E)

Table 1.2 - Population Impacts on Different Vaccine Release Dates

<div>Vaccine Release Date</div> <div>Number of People</div>	April 10th (t=100)	Sep. 16th (t=259)	Oct. 16th (t=289)	Nov.16th (t=319)
morbidity	15,482,000	170,530,000	192,560,000	197,560,000
hospitalized population	22,072	243,120	274,530	281,650
mortality	1,003	11,051	12,479	12,803

As vaccines were released earlier from right to left, Table 1.2 reflects a decreasing trend in morbidity (second row), hospitalized population (third row), and mortality (fourth row).

Therefore, we conclude that the earlier the vaccines released, the better for the overall group. If we release vaccine one month earlier, 22.03 million less people who get infected, 31410 less people who get hospitalized, and 1428 less people who would die. If we release vaccine one month later, 5 million more people get infected, 7120 more people get hospitalized, and 324

more people would die. As the number shown, if we release the vaccine late, the difference is smaller.

Case 1-3: Changing in Vaccine Efficacy Rate

We accomplished our third case by changing the vaccine efficacy rate 89% (assumption 5-3) to 79% and 99%. It was the only variable in this case. Thus, we fixed the vaccine release time on Oct 16th. Table 1.3 shows the data we got (E stands for vaccine Efficacy rate):

Table 1.3 - Population Impacts on Different Vaccine Efficacy Rate

Vaccine Efficacy Rate Number of People	E = 99%	E = 89%	E = 79%
morbidity	191,970,000	192,560,000	193,170,000
hospitalized population	273,680	274,530	275,390
mortality	12,441	12,479	12,519

If we use our initial vaccine efficacy rate 89% to compare with the higher one (E = 99%) and the lower one (E = 79%), the higher one has less casualties and the lower one has higher casualties.

We conclude that the vaccines with high efficacy rate minimize the number of morbidity, hospitalized population and mortality.

Part II: Calculating Economic Costs

In this section, we will focus on the economic costs in the lost wages costs, vaccination costs, hospitalization costs, and total costs. Lost wages costs are the wages that sick workers could gain but instead they did not, for all the infected population. Vaccination costs are the cost for all the getting vaccinations. Hospitalization costs are for the a portion of H1N1 patients who are in bad situation and they need to get treatment in the hospital. Total costs are the overall costs of H1N1, including the lost wages costs, vaccination costs, and hospitalization costs.

- Before calculating the costs, assumptions are needed:

- A. The U.S. annual average salary is 59,039.
- B. Half of the infected population is children and they don't have salary.
- C. For each patient, the average cost per inpatient day is \$1,986.
- D. Ignoring the vaccine production cost and cost for paying researchers' salary. We only focused on the cost for susceptible group to get vaccinated.

- Calculating The Vaccination Costs

The U.S. government spent 6.15 billion dollars on H1N1 prevention. We decided that the vaccination cost is roughly half of it, which is 3.075 billion dollars.

$$\frac{\$3.075 \text{ billion vaccination cost}}{\$118 \text{ million vaccinated population}} \approx \$26 \text{ per vaccination}$$

- How to derive the vaccinated population?

A new variable V_2 is defined. Unlike V , which is the total number of people staying the vaccinated group, V_2 is the total number of accumulating vaccinated population. The

differential equation of V_2 is $\frac{dV_2}{dt} = \alpha \times S_2$. As the same parameters used in Model 2, α is the vaccination rate and S_2 is people susceptible to H1N1 but responsive to vaccines.

Multiplying α and S_2 gives us the total number of vaccinated population at certain date.

We found the number of vaccinated group by getting the maximum value from V_2 group.

Equations

- lost wages cost = US average daily salary \times number of recovery days \times morbidity group /2
- vaccination cost = average cost of producing one dose \times vaccinated group
- hospitalization cost = average cost per inpatient day \times recovery day \times hospitalized population
- total cost = lost wages cost + vaccination cost + hospitalization cost

Case 2-1: No vaccination comparing to vaccine released on Oct 16th ($t = 289$)

Table 2. 1 - Economic Impacts on Vaccine Availability

<div>Vaccination Availability</div> <div>Million Dollars</div>	no vaccines	vaccines released (on Oct.16th)
lost wages cost	48040.2	46720.0
vaccination cost	0.0	1169.3
hospital cost	1681.8	1635.6
total cost	49722.0	49524.9

When there was no vaccine available, the vaccination cost was 0 compared to 1169.3 million dollars under vaccination. However, lost wages cost and hospital cost were costlier when there was no vaccine than when vaccine was available. In total, when we summed all the costs up, the cost under no vaccines was more expensive than the one under vaccinations.

Case 2-2: Changing in Vaccine Release Date (detailed graphs are in appendix F)

Table 2. 1 - Economic Impacts on Different Vaccine Release Dates

<div>Vaccine Release Date</div> <div>Million Dollars</div>	April 10th (t=100)	Sep. 16th (t=259)	Oct. 16th (t=289)	Nov.16th (t=319)
lost wages cost	3756.3	41375.0	46720.0	47933.0
vaccination cost	4648.3	1710.5	1169.3	894.6
hospital cost	131.5	1448.5	1635.6	1678.1
total cost	8536.1	44534.0	49524.9	50505.6

When we distributed the vaccines earlier, from the right ($t = 319$) to the left ($t = 100$), lost wages cost, hospital cost, and total cost decreased whereas the vaccination cost increased. The increasing vaccination cost was because, when we released the vaccines earlier, more people would get vaccinated and the total spent on vaccination bided up. On the other hand, more vaccinated population meant a decreasing morbidity number and less missing work or hospitalization, which lowering the cost of lost wages and cost of hospitalization, as vaccines released earlier. Even though there was an increasing trend as we released vaccine earlier, in general, lost wages cost dominated vaccination cost (except when $t = 100$, vaccination cost outweighed lost wages cost because we released vaccine too early that more people get

vaccinated versus less infected). If we release vaccine one month earlier, we could save 4.99 billion dollars and If we release vaccine one month later, we could cost 981 more million dollars.

As the number shown, if we release the vaccine late, the difference is smaller.

Case 2-3: Changing in Vaccine Efficacy Rate

Table 2. 2 - Economic Impacts on Different Vaccine Efficacy Rate

<div>Vaccine Efficay Rate</div> <div>Million Dollars</div>	E = 99%	E = 89%	E = 79%
lost wages cost	46576.0	46720.0	46868.0
vaccination cost	1304.1	1169.3	1035.2
hospital cost	1630.6	1635.6	1640.8
total cost	49510.7	49524.9	49544.0

As we increased the vaccine efficacy rate, vaccination cost increased because high efficacy rate led to more people taking the vaccines and less people getting infected, which also decreased the lost wages cost and the hospital cost. The overall total cost decreased as efficacy rate increased because lost wages cost outweighed other costs. Even though the cost differences exist by varying vaccine efficacy rate, the differences were not as enormous as the numbers we got by changing vaccine release dates.

Conclusion

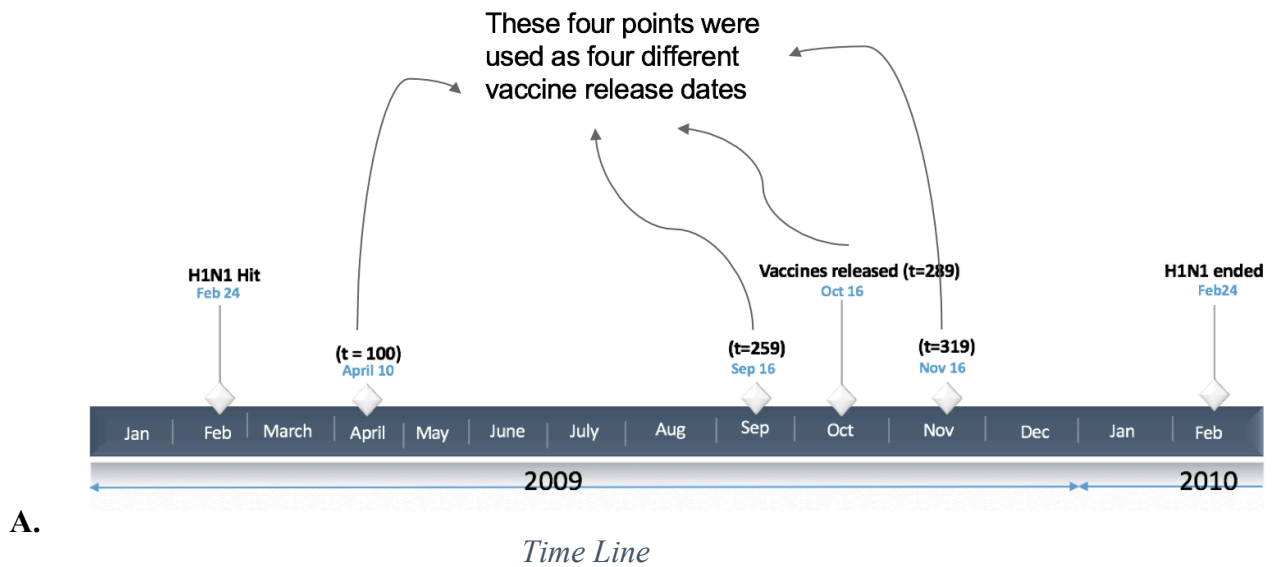
It is better to have a vaccine for the virus than not having a vaccine. Even though producing vaccines is time consuming, the earlier the vaccine is released and used, the better for the population due to less morbidity, hospitalization, and mortality, and for the economy due to less economic cost. If vaccines are distributed later, there is a smaller difference among the population and economic impacts. Changing vaccine release dates generates a bigger impact than varying vaccines efficacy rate. Therefore, it is better to release vaccines early. Even though the

vaccines efficacy rate may be low when the vaccines are early released, because scientists do not have enough time for experimentations, effects of date outweighs effects of vaccine efficacy rate.

Reference

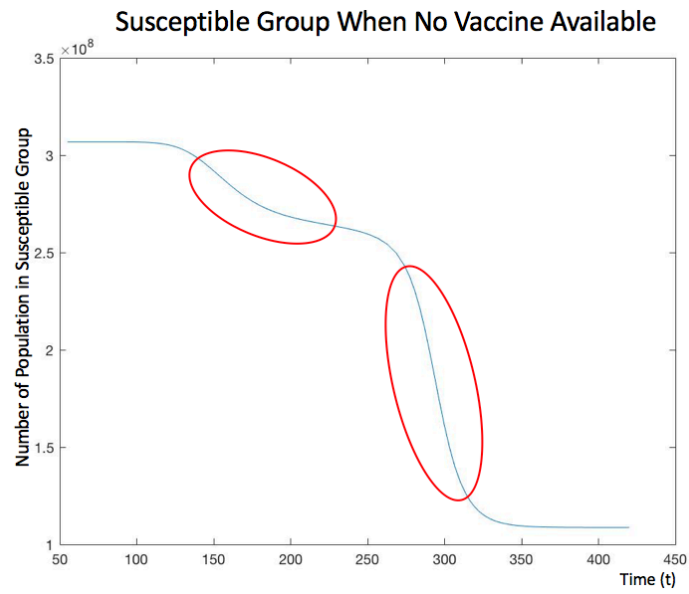
- Dawood, F.S. et al. (2012). Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study. In C.V.(Eds.), *The Lancet Infectious Diseases* (pp. 647-736). Retrieved from [http://thelancet.com/journals/laninf/article/PIIS1473-3099\(12\)70121-4/abstract](http://thelancet.com/journals/laninf/article/PIIS1473-3099(12)70121-4/abstract)
- Shrestha, S. S. et al. (2011). *CDC Estimates of 2009 H1N1 Influenza Cases, Hospitalizations and Deaths in the United States*. Retrieved from CDC website: https://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm
- Mummert, Anna, et al. “A Perspective on Multiple Waves of Influenza Pandemics.” *PLOS ONE*, Public Library of Science, Retrieved from: journals.plos.org/plosone/article?id=10.1371/journal.pone.0060343.
- Rappleye, Emily. “Average Cost per Inpatient Day across 50 States.” *Becker's Hospital Review*, www.beckershospitalreview.com/finance/average-cost-per-inpatient-day-across-50-states.
- Robert Roos, May 07, 2010. “Study: Adjuvanted H1N1 Vaccine Was Very Effective.” *CIDRAP*,

Appendix

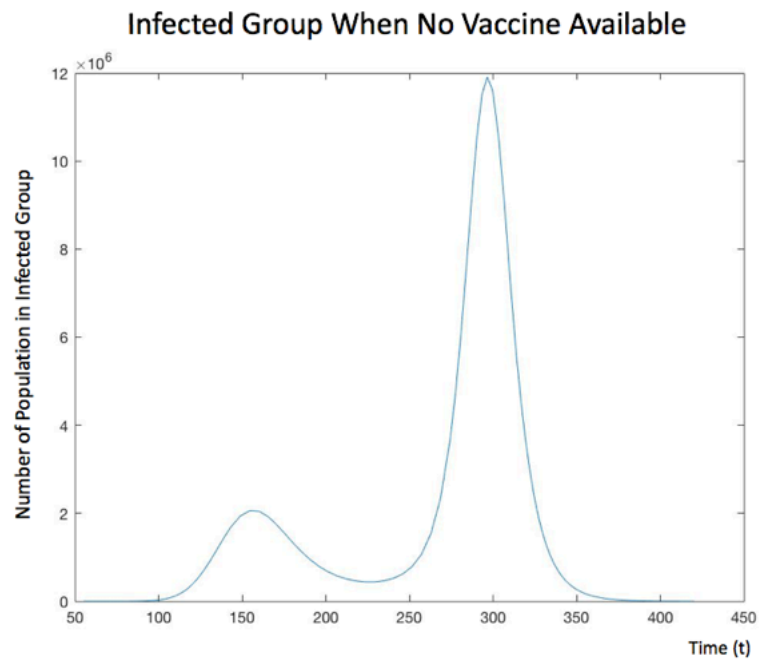


$$\begin{aligned}
 E(X) &= \int_0^{\infty} x f(x) dx && \text{where } f(x) = \lambda e^{-\lambda x} \\
 &= \int_0^{\infty} x \lambda e^{-\lambda x} dx \\
 &= [-x e^{-\lambda x}]_0^{\infty} + \int_0^{\infty} e^{-\lambda x} dx && \text{(integrating by parts)} \\
 &= (0 - 0) + \left[-\frac{1}{\lambda} e^{-\lambda x} \right]_0^{\infty} = 0 + \left(0 + \frac{1}{\lambda} \right) = \frac{1}{\lambda},
 \end{aligned}$$

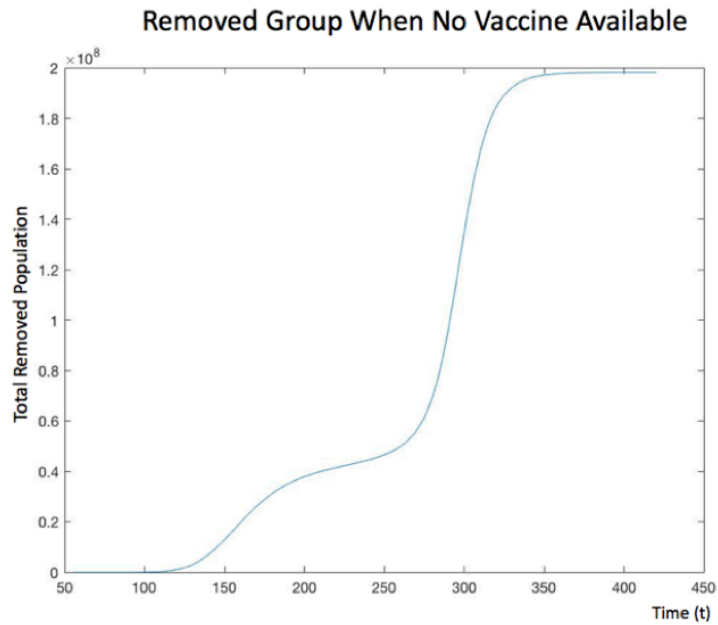
B.



C. 1.



C. 2.

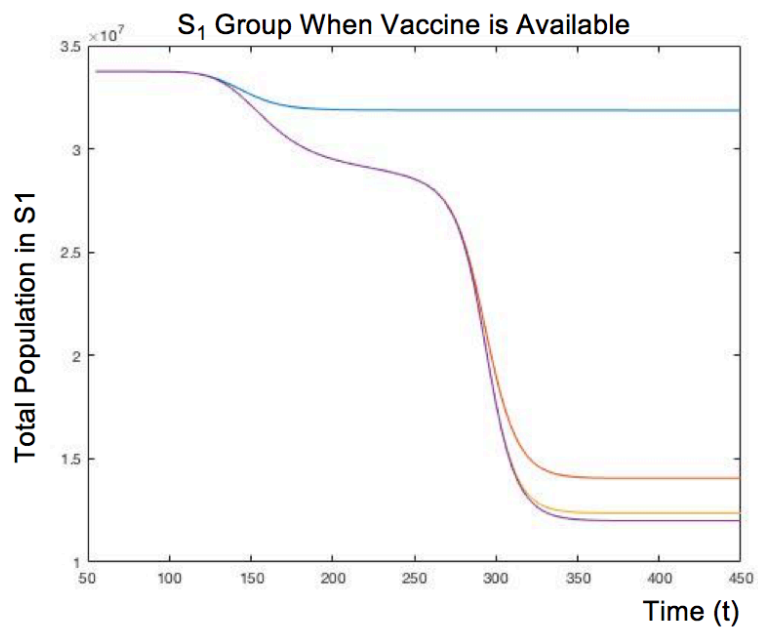


C. 3.

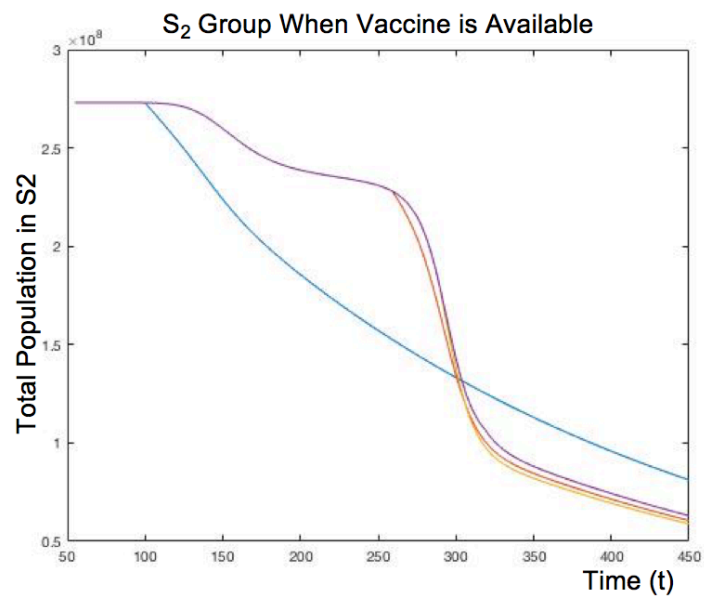
D. The following six graphs all contain four lines:

- $t = 100$ (blue)
- $t = 259$ (red)
- $t = 289$ (yellow)
- $t = 319$ (purple)

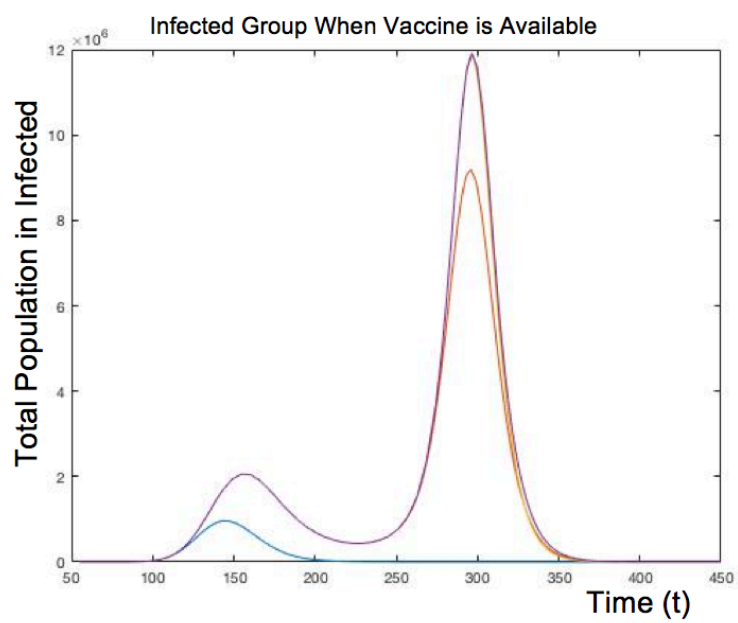
That is the graph we used to study changing vaccine release date at $t=100, 259, 289, 319$, basing on Model 2.



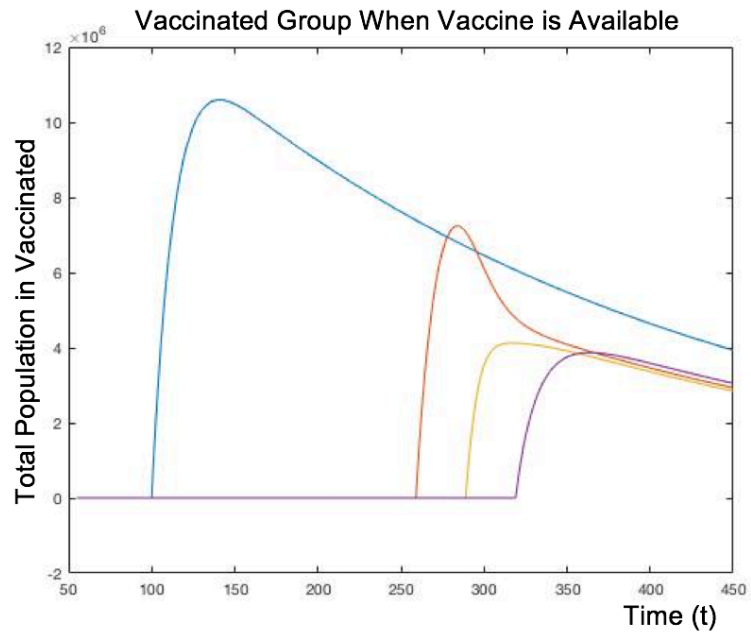
D. 1.



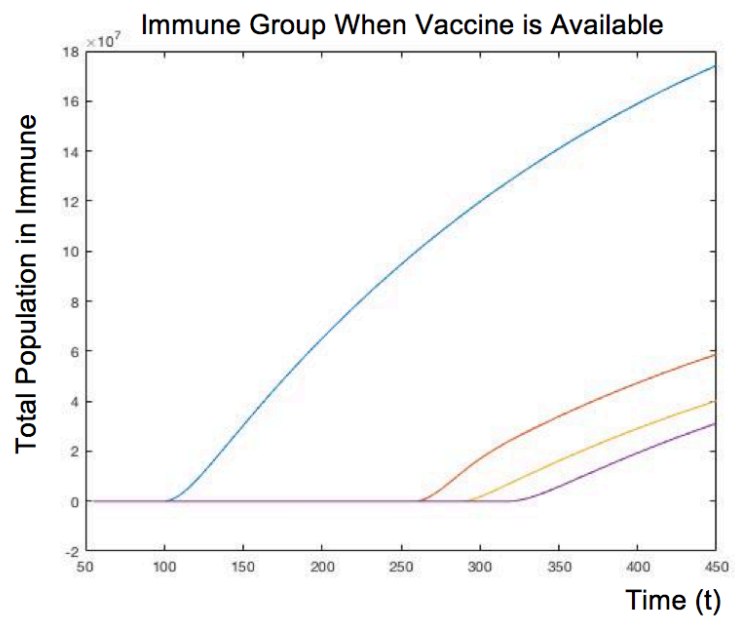
D. 2.



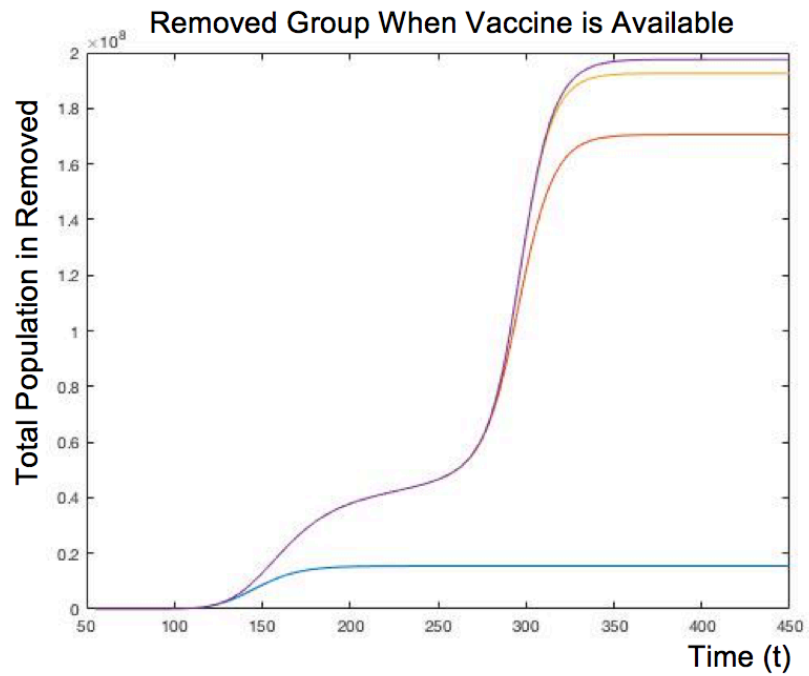
D. 3.



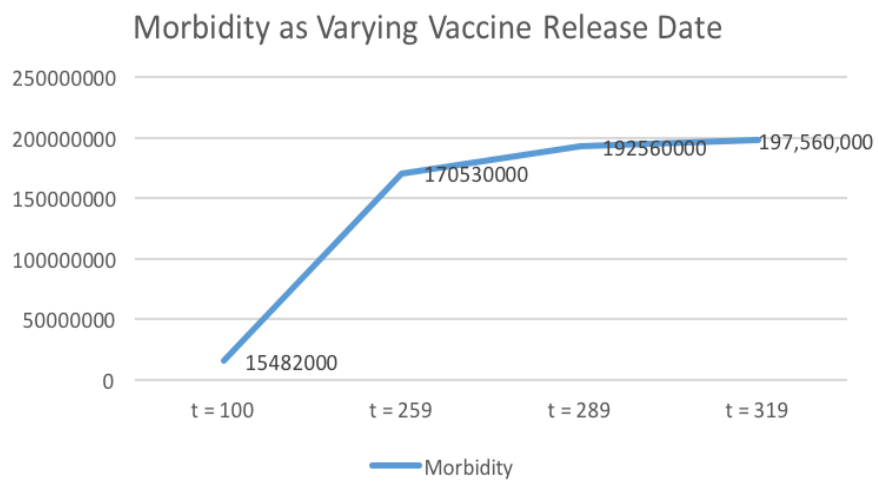
D. 4.



D. 5.

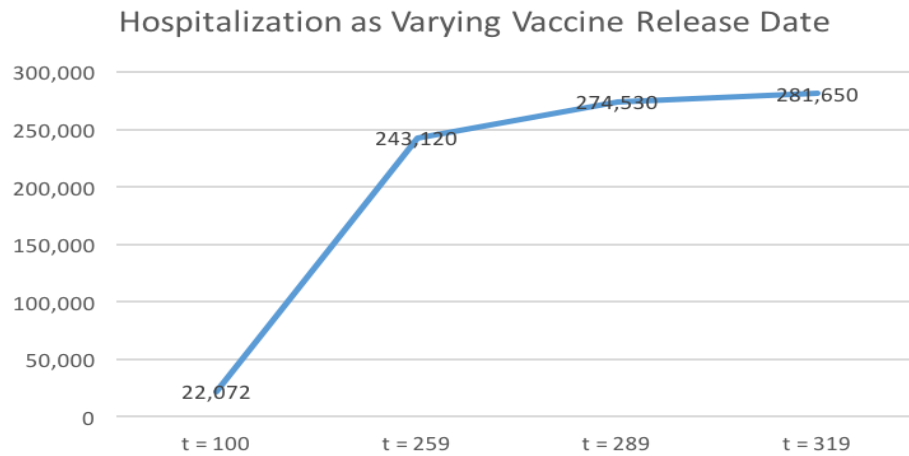


D. 6.

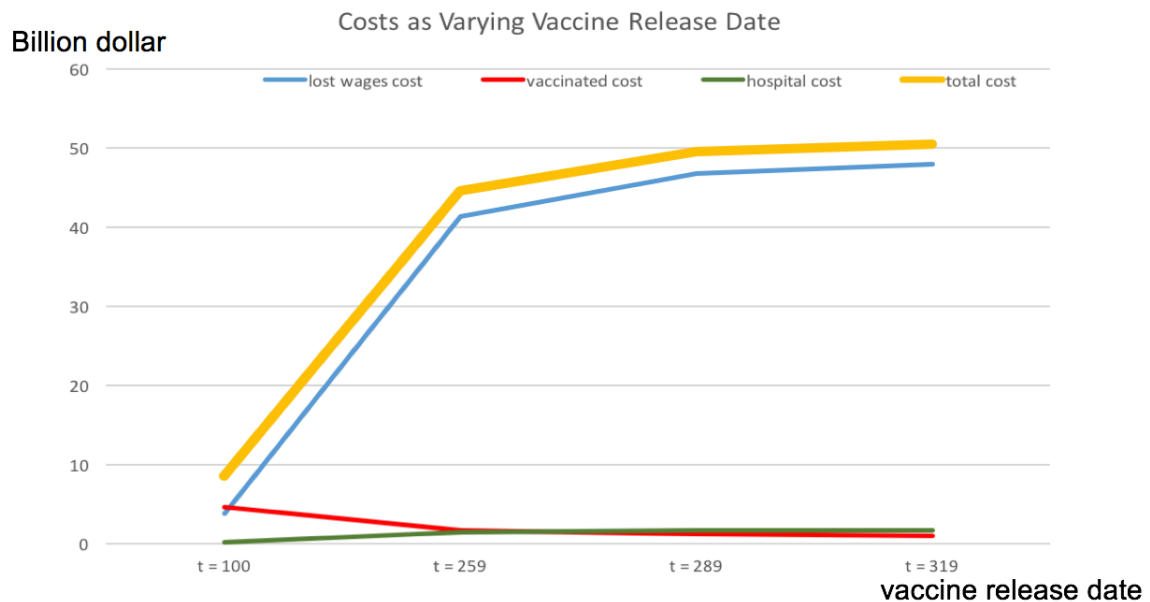
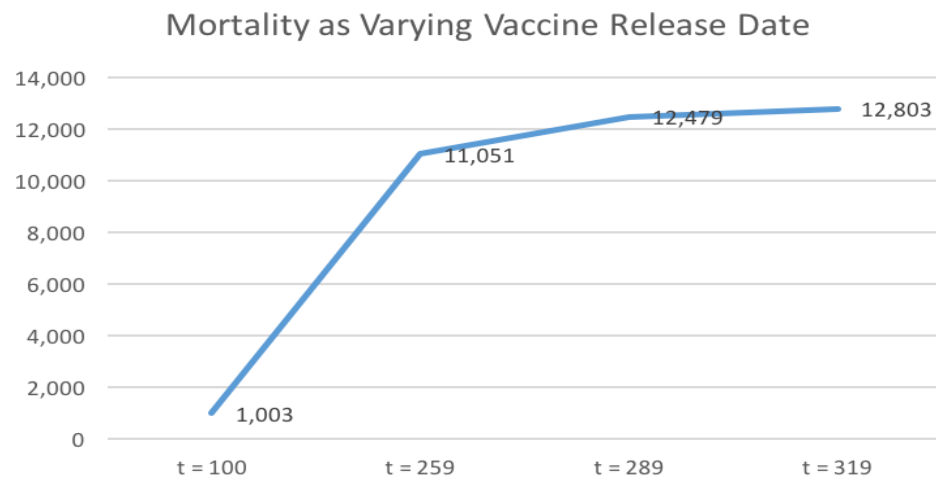


E. 1.

E. 2.



E. 3.



F.