Modeling the Impact of Vaccine Supply Chain on Seasonal Infectious Disease

Abstract: An ability to optimize policy to mitigate infectious disease helps ensure significant health and economic benefits. This research approach integrates the well-known SEIR disease model with a vaccine supply chain model to explore the impact of vaccination supplies on the progression of seasonal influenza infectious disease. Policy makers are facing challenges in determining an optimal immunization strategy. Vaccine supply chain planning plays a crucial role to help to control the spread of seasonal influenza. All public health organizations encourage vaccination throughout the influenza season. Health professionals aim to achieve seasonal influenza vaccine coverage equal to the Herd Immunity Threshold (HIT) to protect the maximum susceptible population. In this research, the system dynamics model presents vaccine supply effects on seasonal infectious diseases. we include a homogeneous population and derived model parameter values from the published literature. Comparisons are made between cases with and without vaccination policy, with different vaccine order quantities and conditions. Sensitivity analysis includes parameters R_0, vaccine order, vaccine deployment, disease attack rate, vaccine yield and vaccine cost. The analysis reveals that vaccine policy effect the spread of seasonal influenza infectious disease. The results identify seasonal influenza vaccination programs within immunization time frames is an effective strategy in the context of public health.

Keywords: Seasonal Influenza; Vaccination; HIT; SEIR Model; Vaccine Supply Chain

1. Introduction

1.1 Seasonal Influenza

Infectious diseases are disorders caused by organisms' fungi, parasites, bacteria, and viruses. Seasonal influenza viruses periodically spread through a susceptible population. The virus infects people and has the ability to spread efficiently. The flu illnesses can range from mild to severe. It can cause even death among high-risk groups. The World Health Organization (WHO) estimated, "500 million to 1 billion people are affected by influenza every year; hundreds of thousands of those cases result in fatalities" (WHO, 2016). The flu vaccine protects against viruses. "The most effective way to prevent the disease is vaccination" (WHO, 2018). The vaccine helps the human immune system to produce antibodies to fight against the influenza virus. If a vaccinated person encounters the virus, these antibodies will attack the virus and stop a vaccinated person from getting sick. The flu vaccine starts to work within two weeks. The seasonal influenza viruses constantly change their genetic structure from one season to another and even change within one season. This means immunity from previous flu vaccination may not protect against the new subtype and no vaccine inventory surplus can be used during the following flu season. Every year WHO monitors the virus epidemiology throughout the world and recommend for the strains to be included in the influenza vaccine. The number of people falling ill with flu is increasing in Europe every year and have a high impact on the health system. Bekkat-Berkani and Romano-Mazzotti, (2018) stated, "Seasonal influenza results in substantial morbidity, mortality and socioeconomic burden". They further identified that the vaccination is recommended for everyone over 6 months of age, but coverage remains substantially below the 2020 target in most age groups. Robert et al., (2020) reported that "Immunization coverage against influenza in France remains well below the target of 75% set by the World Health Organization". Euro.who.int., (2020) documented that

> "Low and declining use of seasonal influenza vaccines not only reduces the number of vulnerable people who are protected during annual epidemics but can also negatively impact the capacity to produce vaccines in the event of a pandemic".

1.2 Vaccination

Infectious diseases can transmit rapidly through a population and accelerate in a short time. "The complexity of containing seasonal flu from person to person has increased with the ease of global travel and closer connection of countries" (Morens and Fauci, 2013). Immunization can protect a large population from seasonal flu and its effects, human suffering, and mortality. Seasonal Influenza vaccine effectiveness varies from season to season. The vaccine effectiveness depends upon the person being vaccinated, for example, their age and health conditions. Annual vaccination is recommended before the onset of each influenza season. Most countries in the Northern Hemisphere start immunisation in the early autumn. It takes 10 to 14 days following vaccination before an immune response and protection develop. There are some important parameters of infectious diseases.

- **R_0** is an average number of secondary infectious cases that one infected case would generate in a susceptible population. Yong, (2020) described, "Ro is a measure of a disease's potential". Ro for seasonal influenza is 2 to 4.
- **Herd Immunity** is the proportion of immune individuals in a population that should make a decline in the rate of infection. In other words, if one person is not vaccinated then he/she can gain indirect benefit from other vaccinated persons (Fine et al., 2011). Seasonal influenza herd immunity is 50% to 75%, which dramatically decreases the chance of the disease outbreak.

In 2003 the World Health Assembly urged EU/EEA Member States to increase influenza vaccination coverage of all people at high risk and to attain coverage of ≥75% among older people and persons with chronic illnesses by 2010. This motion was reaffirmed by a European Parliament declaration in 2005, calling on the Member States to increase influenza vaccination in accordance with the WHO's 2010 goal. European Council extended the recommendation to reach 75% vaccination coverage by 2019. There are budgetary constraints to fulfil the seasonal vaccination coverage in low-income countries. The Centers for Disease Control and Prevention (CDC) stated majority receives their vaccine in October or November. Optimal protection against influenza occurs within the first 3 to 4 months following vaccination. It is expected vaccine protection lasts for at least one influenza season.

1.3 The Vaccine Supply Chain

Seasonal influenza vaccine supply consists of vaccine production, testing and shipment. Seasonal influenza vaccine production takes about 7 or 8 months. The vaccines are packaged for distribution and kept at appropriate temperatures. Influenza vaccines preservation system is called "cold-chain" i.e. vaccines must be stored between 2-8 degrees Celsius and remain refrigerated from their initial production to their eventual usage. World Health Organization (WHO, 2014) provided details of the influenza vaccine timeline. The manufacturer produces the vaccine, whose type and production rate are established according to the requirements of the World Health Organization (WHO). The Centers for Disease Control and Prevention (CDC) recommends that vaccination should become available every year before autumn. Hovav et al., (2017) presented a seasonal influenza vaccination timeline.

Stage 1: WHO strain selection, instructions to manufacturers

Every year in January, WHO recommends viruses for inclusion in influenza vaccines for the forthcoming influenza season. The virus's inclusion recommendation is based on all seasonal influenza viruses detected worldwide between previous years from September to December.

Stage 2: Influenza viruses' manipulation and cultivation

From February to May, viruses are manipulated for high-yield in eggs and distributed to manufacturers who cultivate each virus separately and then blend them. The manufacturing is lengthy and there are no shortcuts.

Stage 3: Influenza vaccine testing and verification

From June to July, Vaccine testing and verification are conducted.

Stage 4: Vaccine packing and shipping

In August, Packing and shipping are done. Sometimes, the distribution process takes a number of months, especially if the volume of the vaccines is high.

Stage 5: Deployment of vaccines

In September deployment of vaccines to clinics starts and finally the vaccination of the designated population is conducted.

Therefore, influenza vaccine orders are taken by manufacturers and distributors as early as January of the prior season. The vaccine distribution normally begins in September and continues for as long as vaccine supplies are available. Vaccines have maximum benefit when supply chains work timely and efficiently. Seasonal influenza vaccine delivery is essential within immunization time frames. Many developing country immunizations programs struggle to manage larger stocks and minimize wastage while improving immunization coverage. "The national immunization programmes are struggling to meet the demands of routine immunization" (Who.int, 2014). There is a need to explore better planning that can reduce hospitalization and economic burden. Influenza vaccine is produced by private manufacturers. The manufacturers have the freedom to decide the production rate according to their requirements.

> "In order to avoid producing an excess of vaccines and suffering major financial losses some manufacturers produce well below their capacities, aiming to meet "just below" demand. Especially when a flu epidemic worsens in the latter months of the winter season, the delayed demand is not met with adequate supply, this may have dangerous consequences…luckily, bulk purchase assurances from organizations like UNICEF help to stabilize the annual demand and prevent major shortages of vaccine supply" (Smith et al., 2011).

This paper is organized into the following sections. Section 2 presents a literature review of related system dynamics work and models; Section 3 a case study: epidemiology of 2018/2019 influenza Season in Ireland; Section 4 describes the research framework, objective, the model's structure; Section 5 describes the Disease/Vaccine Supply Chain model's simulations and experiments results; and Section-6 presents insights from the experiments, discussion, and future work.

2. Literature Review

2.1 Related System Dynamics Work

System dynamics (SD) is a methodology for applying mathematical equations in stock and flow structure. It is a computer-based approach for policy analysis and design. Systems dynamics was developed by Forester in 1961. Systems dynamics helps in analysing the behaviour of complex socio-economic systems due to underlying interactions which governs the dynamics (Forrester, 1994). The system dynamics approach has been increasingly recognized as a powerful method for understanding and addressing complex health issues. (Darabi N, 2020). The SIR mathematical model for acute infectious diseases is widely used in epidemiology (Kermack, 1927). Feng, et al., (2011) employed a simple mathematical model to study influenza disease dynamics and various control programs via vaccination and antiviral treatment. Their experiment results showed that the benefits of vaccination use might be significantly compromised if the control programs are not designed appropriately. Chen et al.,

(2020) developed a compartmental model to replicate the circumstances of limited vaccines for emergency situations. They analysed that limited vaccine quantity could reduce the infectious disease if individuals' effective contact rate is low. The vaccine also reduces an individual's ability to transmit infectious diseases. It is important to explicitly consider the interaction of vaccine strategies with influenza infectious disease dynamics.

Vaccine supply management during a seasonal infectious disease outbreak is a challenging task. It is widely recognized that insufficient vaccine supplies can lead to delay in desired results and goals achievements. Thompson et al., (2006) showed that faster outbreak response, even with initially lower coverage, caused lower incidence. A trade-off between response time and vaccination coverage shows, reduce response time is better (Thompson et al., 2015). This research work builds on previous research work by Thompson and Tebbens; *"Optimal vaccine stockpile design for an eradicated disease: Application to polio"* (2010) and "*Optimal Global Vaccine Stockpile Design for Vaccine-Preventable Diseases*" (2014). Thompson and Tebbens developed models of polio and measles vaccine supply chain to identify key stocks, inflows and outflows of vaccine production and shipment. They highlighted the importance of vaccine planning with time delays in the supply chain. Vaccine supply chain challenges are associated with a complex dynamic system of uncertain vaccine demand. Literature review suggests that vaccine supply chains have not gotten much attention. "The policymakers may not consider the impact on the vaccine supply chains, which affects vaccine availability" (Assi et al., 2012). Many vaccines supply chains around the world have substantial constraints and bottlenecks and are not delivering vaccines to many people who need them (Lee et al., 2015).

3. Case Study

3.1 Epidemiology of 2018/19 Influenza Season in Ireland

Influenza infectious diseases flourish when the weather is cold. Seasonal influenza causes sustained epidemics in the non-tropical areas of the Northern Hemisphere and Southern Hemisphere during their respective late fall to early spring Months (Cox, N. and Subbarao, K., 2000). Winter in Ireland starts on December 1st and ends on February 28th. The 'law' of mass action states that the number of new infectious cases depends on the product of influenza transmission parameter, the number of infected individuals and the number susceptible. Seasonal susceptibility in a population can be calculated by using the accumulation of influenza infections and influenza vaccinations over previous years. The influenza virus is responsible for a substantial health burden with annual infection attack rates of 5–10% in adults and 20–30% in children (World Health Organization, 2014). Annual vaccination before the winter season is recommended for the elderly and other individuals at high risk of developing the serious disease (Centers for Disease Control and Prevention. 2018).

HSE Health Protection Surveillance Centre reported the key facts of the 2018/19 Influenza Season in Ireland (Hpsc.ie. 2020). Some essential facts are as follows.

- The 2018/19 influenza season was moderate but still had a high impact on the Irish health system.
- High levels of influenza hospitalisations and ICU admissions were reported.
- Influenza-associated deaths and influenza outbreaks were reported throughout the season but at relatively low levels.

- High levels of hospitalisations for confirmed influenza cases resulted in a significant impact on the health system.

Figures 3.1 and 3.2 show 2018/19 influenza season, the annual epidemiological report from HSE Health Protection Surveillance Centre. The plots present the number of confirmed influenza cases notified, and the number of confirmed influenza cases hospitalized in Ireland.

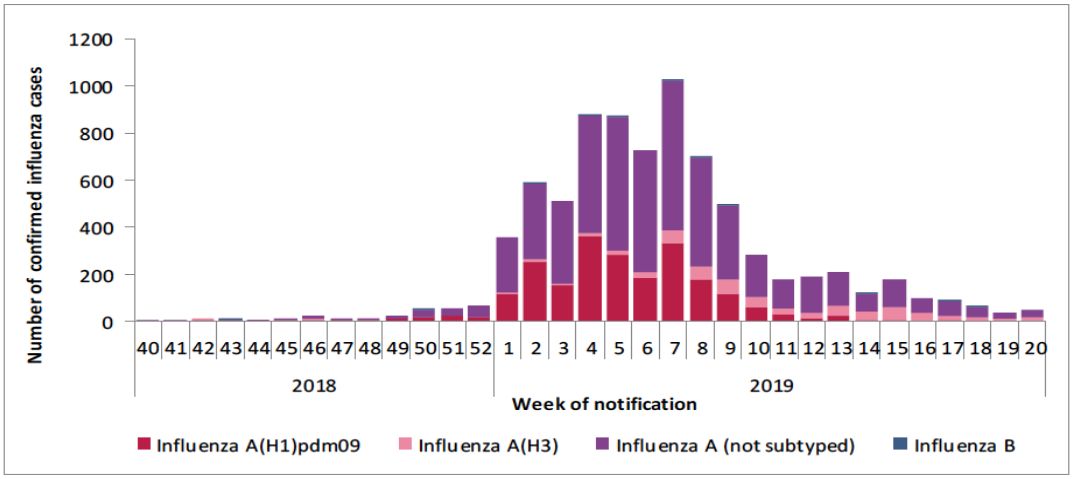

Figure 3.1: Number of confirmed influenza cases notified in Ireland (Hpsc.ie. 2020)

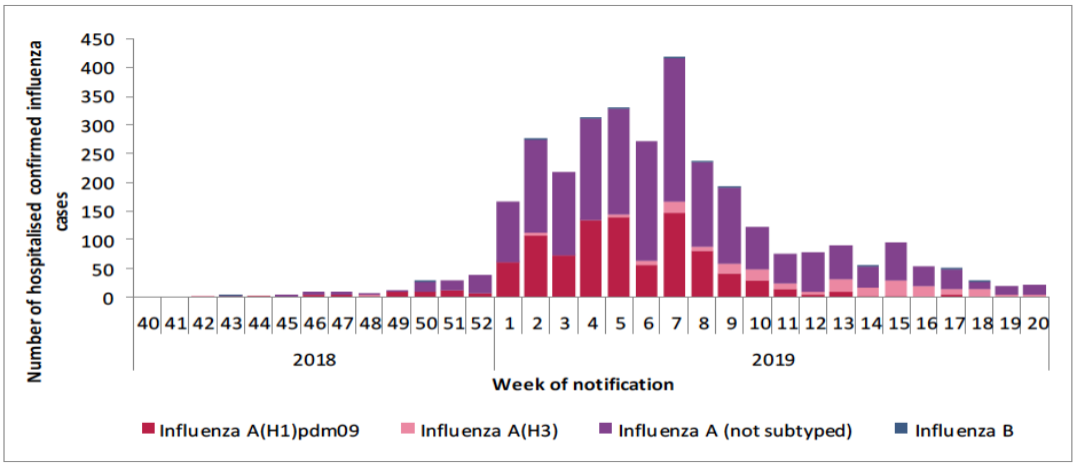

Figure 3.2: Number of hospitalized confirmed influenza cases in Ireland (Hpsc.ie. 2020)

The report data shows that the influenza season 2018/19 started almost from week 50/2018 and within a few weeks the infected cases almost 1K per week. The disease starts to slow down or fade from week 18/2019. The total number of notified influenza cases were 7,943 and the total number of confirmed influenza cases hospitalised were 3,244. The total number of confirmed influenza cases admitted to ICU were 159 and the total number of influenza cases that died were 97. The World Health Assembly and European Council urged EU/EEA Member States advised to increase influenza vaccination coverage of all people at high risk and to attain coverage of ≥75% among older people, pre-school children and persons with chronic illnesses by 2019. Ireland had a population ≈ of 4.867 million in 2018 whereas the required coverage of ≥75% among older people, pre-school children and persons with chronic illnesses was nearly

1.4 million in 2018. Ireland had purchased vaccine doses of almost 1.1 million in 2018/2019 (European Centre for Disease Prevention and Control. 2018) (European Centre for Disease Prevention and Control. 2018). The case study present that with reasonable vaccine coverage still 2018/19 influenza season was not a mild season and had a high impact on the Irish health system. Many other sensitive factors need to explore the spread of infectious diseases, such as time to start an infection, R_0, time to start vaccination, HIT and vaccine deployment duration and budgetary constraints.

The literature review summarised useful existing models that explore the spread of infectious diseases and vaccine supply. The case study presented a real complex scenario during the seasonal influenza infectious disease. "Policymakers rely on complex models that are required to be robust, realistically approximating epidemics and consistent with all relevant data" (De Angelis et al., 2015). Most researchers developed separate infectious disease models or vaccine supply, models. None of the researchers (1) combined an infectious disease model with a vaccine supply chain model and (2) analysed interaction between the structures. This approach integrates the well-known disease model with a vaccine supply chain model to explore threshold conditions that can be used to assess the effectiveness of seasonal influenza vaccine supply, within the scope of the vaccine supply chain, and budgetary constraints. The model simulation will be helpful to understand the behaviour of seasonal influenza and vaccine supply chains. An efficient vaccine supply chain is one of the most effective preventions for seasonal influenza.

4. Methods

4.1 Research Framework and Objective

This paper presents a Disease/Vaccine Supply Chain model to look at the effects of vaccine supply on the spread of influenza infectious disease. Public health leaders agree that vaccines are the best way to control the spread of influenza but maybe not consider the impact of vaccine supply chains on vaccine availability. Vaccine availability should be completed within immunization time frames. There is a possibility of bottlenecks that reduce the availability. Uncertainty of vaccine ordering, and capacity leads to a significant risk of insufficient vaccine supplies. If the vaccine needs for immunization are not estimated correctly this may result in a shortage of vaccines or excess stock. Jorgensen et al., (2018) presented, behind the low vaccine coverage is vaccine shortages and declining demand. They further described the two major reasons:

1. There are a number of low resource countries in the region, where influenza may not be considered a high-priority disease. The low vaccine coverage in the countries is a consequence of limited vaccine acquirement.

2. There are a number of high resource countries where vaccines are widely available but lack of confidence in vaccines and health authorities has been dropping vaccine coverage.

A good strategy of vaccine stock management includes, (1) avoiding shortages of vaccines and (2) efficient use of vaccines without wastage. "Mathematical models can be very useful for understanding the effects of various factors on the spread and control of infectious diseases" (Feng et al., 2011). This research uses the case study data as sample parameters in Disease/Vaccine Supply Chain model to replicate the 2018/19 influenza season. The research experiments will be analysing sensitive parameters to improve decision-making process.

Sensitivity analysis will be showing how responsive the model outputs to changes in specific parameters or policies.

4.2 The Disease/Vaccine Supply Chain Model Structure

In 1927, SIR model was developed by Kermack and McKendrick (1927) for acute infectious diseases, which is widely used in epidemiology (Kermack, W.O.; McKendrick, A., 1927). The Disease model is based on the well-known SIR structure, although the total population is divided into six stocks or compartments:
(1) *Susceptible* individuals are at risk from the influenza infectious disease.
(2) *Exposed* individuals are incubating the infection but not yet transmitting it.
(3) *Infected* individuals are infected with the influenza infectious disease and spreading it.
(4) *Recovered Disease* individuals are healed from the disease and no longer spread it.
(5) *Total Vaccinated* individuals are healed from the disease due to vaccination.
(6) *Zero Patient* individual is the first infectious case to start the influenza infectious disease.

In the Disease model, the *Total Population* size is 10000 people with 9999 initial *Susceptible Disease*, 1 initial *Zero Patient*, 0 initial *Exposed, Infected, Recovered Disease* and *Recovered Vaccine.* The Vaccine Supply Chain model is divided into different stocks or compartments to present the whole process of vaccine order, production, arrival, etc. In the Vaccine Supply Chain model, all stocks have 0 initial conditions.

(1) *Vaccine Orders* are vaccines for the public health system.
(2) *Vaccine Production/Shipping* are vaccines during the process of production.
(3) *Vaccine Arrived* are vaccines arrived after shipment.
(4) *Vaccine Used* are vaccines dispensed after arrival.
(5) *Total Vaccine Produced* are total vaccines produced at the end.

4.2 The Disease/Vaccine Supply Chain Model Interaction

The Disease and Vaccine Supply Chain models interact through (1) the Disease model's *Suceptible*, and (2) the Vaccine Supply Chain model's *Total Vaccine Dispensed*. Figure 4.1 presents the Disease/Vaccine Supply Chain model's structure.

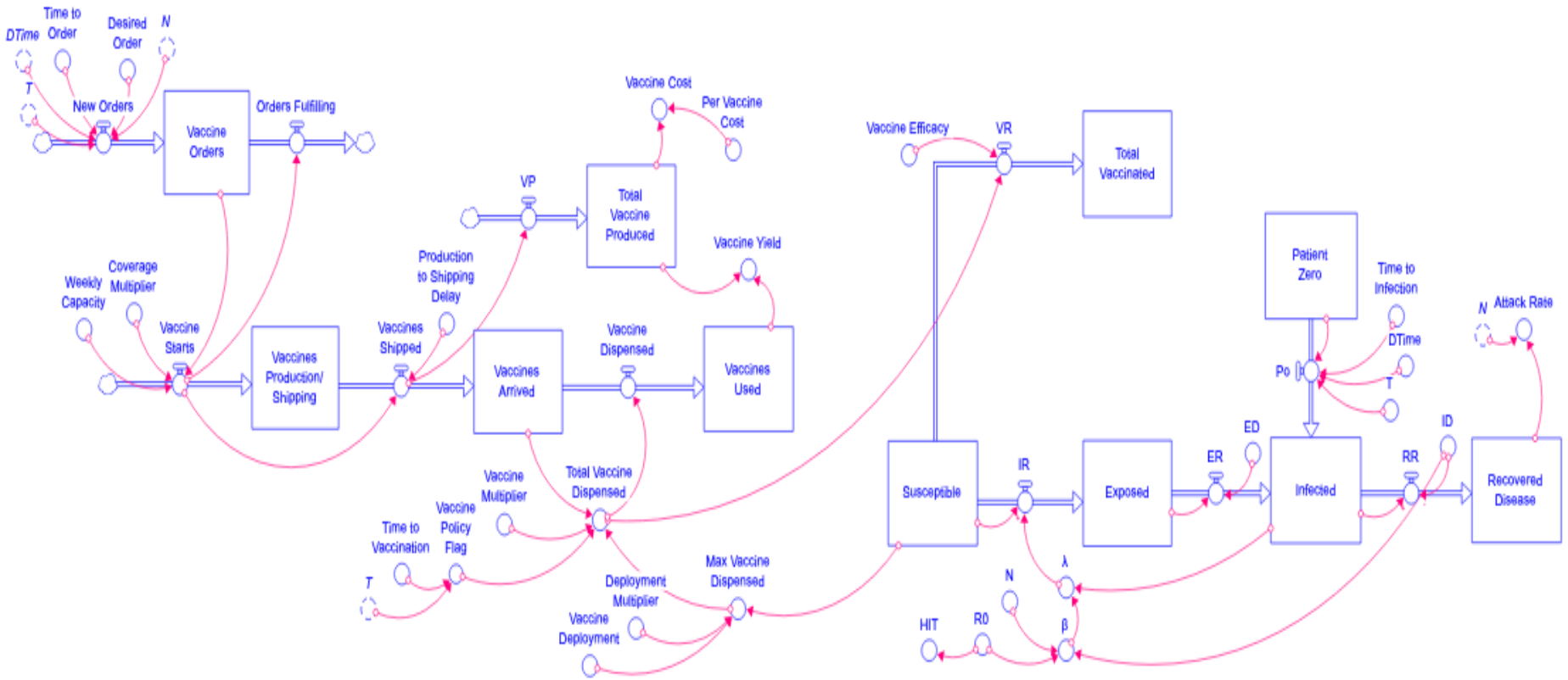

Figure 4.1: The Disease/Vaccine Supply Chain Model Structure
Note: The model parameter's definitions and units are included in appendix A.

5. Experiments

5.1 The Disease/Vaccine Supply Chain Model Simulation

In this section, we study the Disease/Vaccine Supply Chain model simulation results under two cases: case (1) for population size 10,000 as a base case and case (2) for population size 4.867 million to show similar circumstances of the 2018/19 influenza season.

Case 1: Figure 5.1 shows the model simulation result with fixed variable values. It shows the impact of vaccination on the control of seasonal influenza infectious diseases. Every year for new vaccine virus's inclusion recommendation is based on previous years' viruses from September to December. We assumed time to order vaccine quantities to manufacturers is the second week of January. From February to June is time for vaccine production, testing and verification. Every year vaccine packing, and shipping starts around August if there are no extra manufacturing or budgetary constraints. From September to October is time for vaccine deployment to its designated population. Vaccine deployment takes some time due to several factors such as multiple orders from different manufacturers. The severity of seasonal influenza infectious disease depends on the magnitude of the reproduction number R_0. The Figure 5.1 left plot shows the vaccine supply chain model stocks; *Vaccine Orders, Vaccines Production/Shipping, Vaccines Arrived* and *Vaccines.* In the model, Vaccine "Desired Orders" is based on population size and *Time to Order* starts from January. Figure 5.1 right plot shows the Disease model stocks; *Susceptible, Infected, Recovered Disease and Recovered Vaccination.* Infected population stock peak is not very high due to moderate vaccine treatment. The vaccination process reduces the rate of infection.

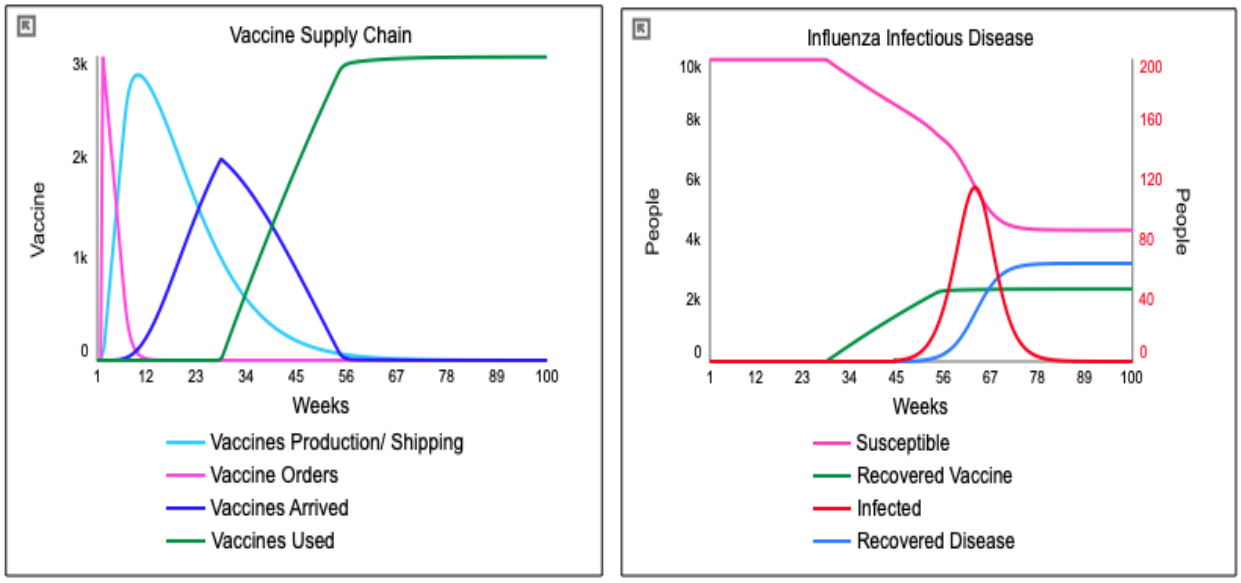

Figure 5.1: The Disease/Vaccine Supply Chain Model Simulation

Case 2: The model simulation generates a similar result of the 2018/19 influenza season in Ireland with a population size of 4.867 million. Figure 5.2 shows the impact of vaccination on the control of seasonal influenza infectious diseases. We assumed vaccination starts as early as possible after

vaccine deployment. Every year the severity of seasonal influenza infectious disease depends on the magnitude of the reproduction number R_0. We assumed that R_0 is 1.32 and the vaccine desired order is 30% of the population size. The model simulation result are a better fit for the data trends taken from HSE Health Protection Surveillance Centre. The model simulations are just a hypothetical representation of the real-world scenario and generate similar infected cases for the 2018/19 influenza season. The simulations are never completely a one-to-one comparison, it is important to ensure the simulations follow the overall trend of historical data. The Figure 5.2 left plot shows the vaccine supply chain model stocks; *Vaccine Orders, Vaccines Production/Shipping, Vaccines Arrived* and *Vaccines*. In the model, the vaccine order starts from January. Figure 5.2 right plot shows the Disease model stocks; *Susceptible, Infected, Recovered Disease and Recovered Vaccination.* Infected population stock peak is moderate with vaccine treatment.

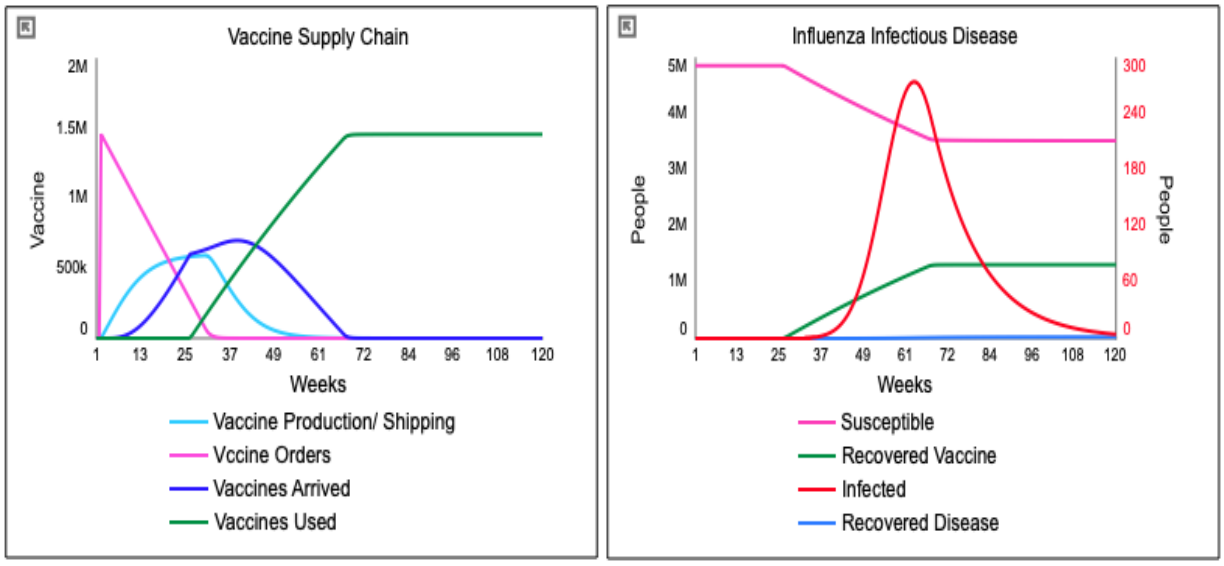

Figure 5.2: The Disease/Vaccine Supply Chain Model Simulation (2018/19 influenza)

5.2 The Cases of Time Dependent Parameters

In this section, we study the Disease/Vaccine Supply Chain model simulation results under three scenarios and each scenario has three cases. The model population size is 10,000 with variable parameters: *Desired Order, Time to Vaccination* and *Time to Infection.* The model remaining all variables have the base values. Seasonal influenza vaccine desired order quantity, time to vaccination and time to infection varies in every season. The order of vaccine quantity has a significant effect on disease attack rate, vaccine cost and vaccine yield. The same vaccine quantity effect very differently if the time of pathogen introduction or time to start vaccination change into the system. We will focus on three important parameters: *Desired Order, Time to Vaccination* and *Time to Infection* to find a good strategy of efficient use of vaccines and reduce wastage. Tables: 5.1, 5.2 and 5.3 present the cases details and effect of the changing parameter values. Figures 5.3, 5.4 and 5.5 show the model simulation results.

5.2.1 Scenario-1 Cases 1-3

Table 5.1: Cases 1-3 for the Disease *Attack Rate*, *Vaccine Cost* and *Vaccine Yield*

Case Description	Input Parameter Values	Output Result
1- There is no vaccination policy, but seasonal influenza infection starts spreading very early from week 28.	*Desired Order* = Non *Time to Vaccination* = Non *Time to Infection* = 28	The disease attack rate is maximum without a vaccination policy. The disease attack rate ≈ 70%. The vaccine cost and yield are zero.
2- The vaccine order is placed equal to HIT, which is 40% of the total population. Seasonal influenza infection and vaccination starts at the same time.	*Desired Order* = HIT *Time to Vaccination* = 28 *Time to Infection* = 28	The disease attack rate is reduced to ≈ 50%. The vaccine cost is an average ≈ of 40K. The vaccine yield is gradually increased and covered almost 36% of the HIT population. The remaining 4% of vaccines are wastage.
3- The vaccine order is placed to vaccinate the whole population. The infection and vaccination start at the same time.	*Desired Order* = N *Time to Vaccination* = 28 *Time to Infection* = 28	The disease attack rate is the same ≈ 50% as in case 2. The vaccine cost is the highest ≈ 100K. The vaccine yield is reached only 40% of the whole population as in case 2. The remaining 60% of vaccines are wastage.

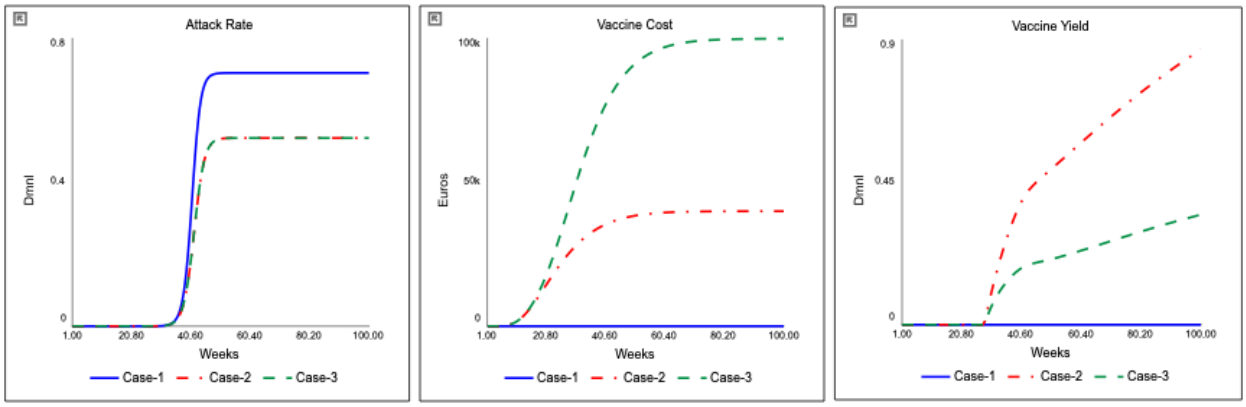

Figure 5.3: Cases 1-3 for the Disease *Attack Rate*, *Vaccine Cost* and *Vaccine Yield*

5.2.2 Scenario-2 Cases 4-6

Table 5.2: Cases 4-6 for the Disease *Attack Rate*, *Vaccine Cost* and *Vaccine Yield*

Case Description	Input Parameter Values	Output Result
4- There is no vaccination policy, but seasonal influenza	*Desired Order* = Non *Time to Vaccination* = Non	The disease attack rate is maximum without a vaccination

infection starts spreading as normally from week 44.	*Time to Infection* = 44	policy. The disease attack rate ≈ 70%. The vaccine cost and yield are zero.
5- The vaccine order is placed equal to HIT, which is 40% of the total population. Seasonal vaccination starts from week 28 and influenza infection starts from week 44.	*Desired Order* = HIT *Time to Vaccination* = 28 *Time to Infection* = 44	The disease attack rate is reduced to ≈ 20%. The vaccine cost is an average ≈ of 40K. The vaccine yield is quickly covered all 40% of the HIT population. The vaccine wastage is null.
6- The vaccine order is placed to vaccinate the whole population. The infection and vaccination start at the same time.	*Desired Order* = N *Time to Vaccination* = 28 *Time to Infection* = 44	The disease attack rate is the same ≈ 20% as in case 5. The vaccine cost is the highest ≈ 100K. The vaccine yield is reached only 50% of the whole population. The remaining 50% of vaccines are wastage.

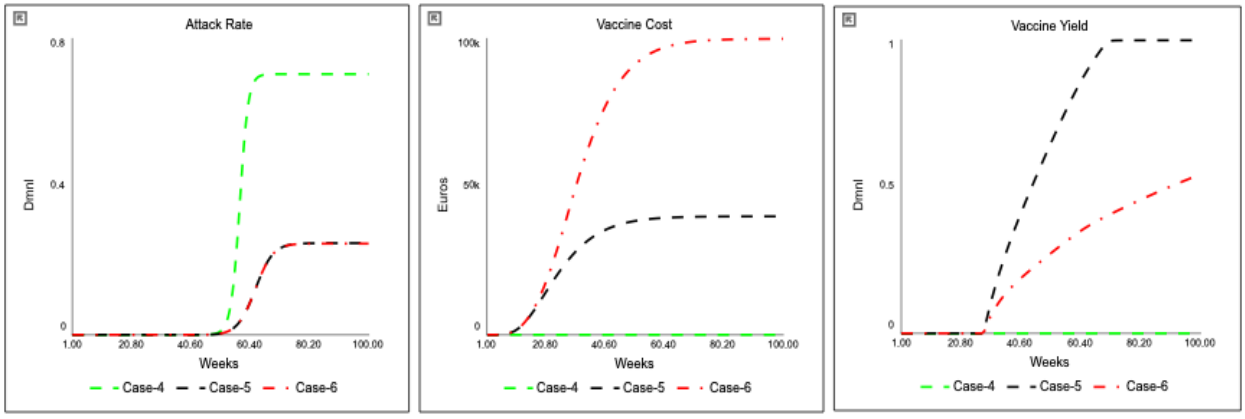

Figure 5.4: Cases 4-6 for the Disease *Attack Rate*, *Vaccine Cost* and *Vaccine Yield*

5.2.3 Scenario-3 Cases 7-9

Table 5.3: Cases 7-9 for the Disease *Attack Rate*, *Vaccine Cost* and *Vaccine Yield*

Case Description	Input Parameter Values	Output Result
7- There is no vaccination policy, but seasonal influenza starts spreading early from week 30.	*Desired Order* = Non *Time to Vaccination* = Non *Time to Infection* = 30	The disease attack rate is maximum without a vaccination policy. The disease attack rate ≈ 70%. The vaccine cost and yield are zero.
8- The vaccine order is placed equal to HIT, which is 40% of the total population. Seasonal vaccination starts from week	*Desired Order* = HIT *Time to Vaccination* = 38 *Time to Infection* = 30	The disease attack rate is slightly reduced ≈ by 60%. The vaccine cost is an average ≈ of 40K. The vaccine yield is gradually

38 and influenza infection starts from week 30.		covered 55% of the HIT population. The remaining 45% of vaccines are wastage.
9- The vaccine order is placed to vaccinate the whole population. Seasonal vaccination starts from week 38 and influenza infection starts early from week 30.	*Desired Order* = N *Time to Vaccination* = 38 *Time to Infection* = 30	The disease attack rate is the same ≈ 60% as in case 8. The vaccine cost is the highest ≈ 100K. The vaccine yield is reached only 18% of the whole population. The remaining 82% of vaccines are wastage.

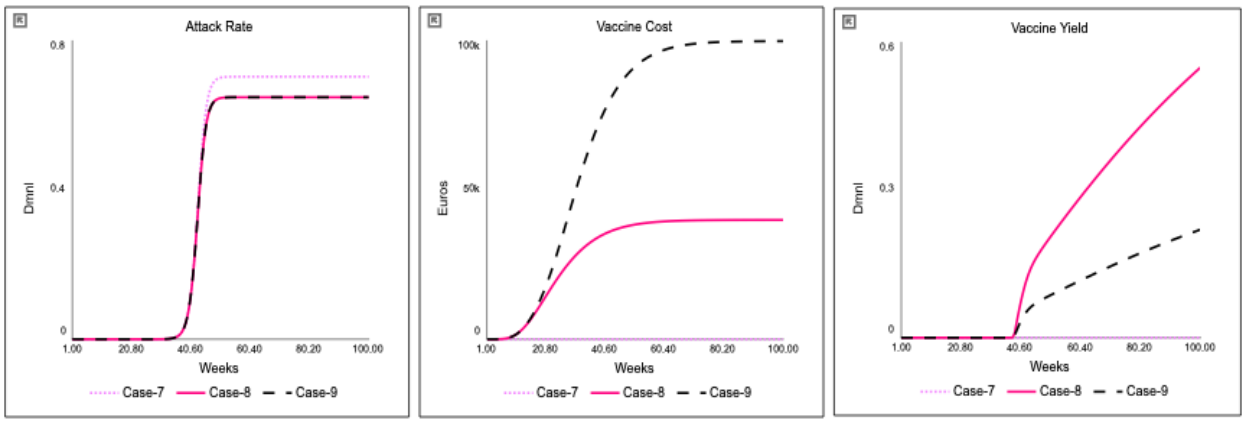

Figure 5.5: Cases 7-9 for the Disease *Attack Rate*, *Vaccine Cost* and *Vaccine Yield*

The cases analysis presented, the most desirable policy was case 5, where vaccine order was equal to HIT (Herd Immunity Threshold) and time of vaccination started earlier than influenza season, which dramatically decreased the chance of the disease outbreak. The disease attack rate was ≈ 20%. The vaccine cost was an average ≈ of 40K. The vaccine yield covered a fully HIT proportion of the population. The vaccine wastage was null. Therefore, the best policy is to start immunization before the onset of the influenza season to cover at least the HIT proportion of the population. Vaccine order equals to Herd Immunity Threshold percentage produces good results without costing a lot of money. It is cost-effective prevention from seasonal influenza.

5.3 Sensitivity Analysis

In this section, we study the Disease/Vaccine Supply Chain model simulation results under three scenarios for sensitivity analysis. Sensitivity analysis (SA) is a typical measure to quantify the impact of parameter uncertainty on overall simulation/prediction uncertainty (Helton, 1993). Sensitivity analysis determines how independent variable values will impact a particular dependent variable under a given set of conditions (S, 2006). In system dynamic models, sensitivity analysis is an essential step to test a model's accuracy and understanding of the model's behaviour. The model population size is 10,000 with variable parameters: R_0, *Vaccine Efficacy*, *Vaccine Deployment and Desired Order*. The analysis focus is to reveal how uncertainty in the R_0, *Vaccine*

Efficacy, Vaccine Deployment and Desired Order affect the *Attack Rate*, *Vaccine Yield* and *Vaccine Cost.* Bubble Scatter Plot is used to visualize the sensitivity analysis results.

5.3.1 Scenario-1

In this scenario, R_0 and *Vaccine Efficacy* are two inputs for Sensitivity analysis. Table 5.4 mentions the model's parameters in this experiment with variable range and remaining all variables have the fixed values. The parameters *R_0, and Vaccine Efficacy* can be variable (Biggerstaff, 2014, Okoli et al., 2021). However, R_0 (infection reproduction number) and Vaccine Efficacy (degree of disease prevention) can vary from year to year. Figure 5.6 presents the sensitivity analysis result for influenza disease *Attack Rate*.

Table 5.4 The Model's Variable Parameters

Variables	Value Range
R_0	1.2 - 2.2
Vaccine Efficacy	0.3 - 0.9

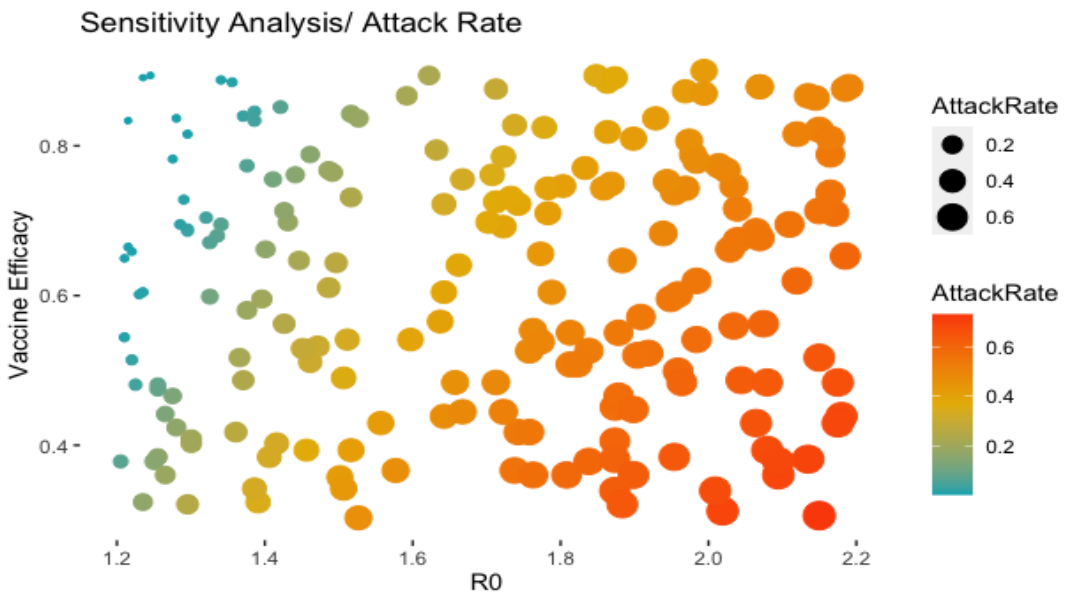

Figure 5.6: Sensitivity Analysis/ *Attack Rate* for Inputs: *R_0* vs *Vaccine Efficacy*

The above figure shows *R_0* on the x-axis and *Vaccine Efficacy* on the y-axis. The *Attack Rate* is the third variable for sizing and colouring bubbles. Each bubble point is sized and scaled according to the range of the *Attack Rate* variable. The changing bubble colours from blue to red present the *Attack Rate* from lower to high numeric value or intensity. In the above plot, the bubble's colour is blue, and the size is very small at the left top corner. It depicts that at the highest *Vaccine Efficacy* and minimum *R_0* value, the seasonal influenza *Attack Rate* is lowest. The bubble's colour is red, and the size is very large at the right bottom corner. It presents that at lowest *Vaccine*

Efficacy and maximum R_0 value, seasonal influenza *Attack Rate* is highest. Therefore, high *Vaccine Efficacy* can decrease the seasonal influenza *Attack Rate.*

5.3.2 Scenario-2

In this scenario, R_0 and *Vaccine Dispense* are two inputs for Sensitivity analysis. Table 5.5 mentions the model's parameters in this experiment with variable range and remaining all variables have the fixed values. There can be disruption or delay in vaccine deployment due to capacity constraints. The literature review has revealed that the *Vaccine Dispense* can be variable (Porter, R., 2020). Figures 5.7 and 5.8 present the sensitivity analysis result for seasonal influenza disease *Attack Rate* and *Vaccine Yield*.

Table 5.5 The Model's Variable Parameters

Variables	Value Range
R_0	1.2 - 2.2
Vaccine Deployment	4 - 16

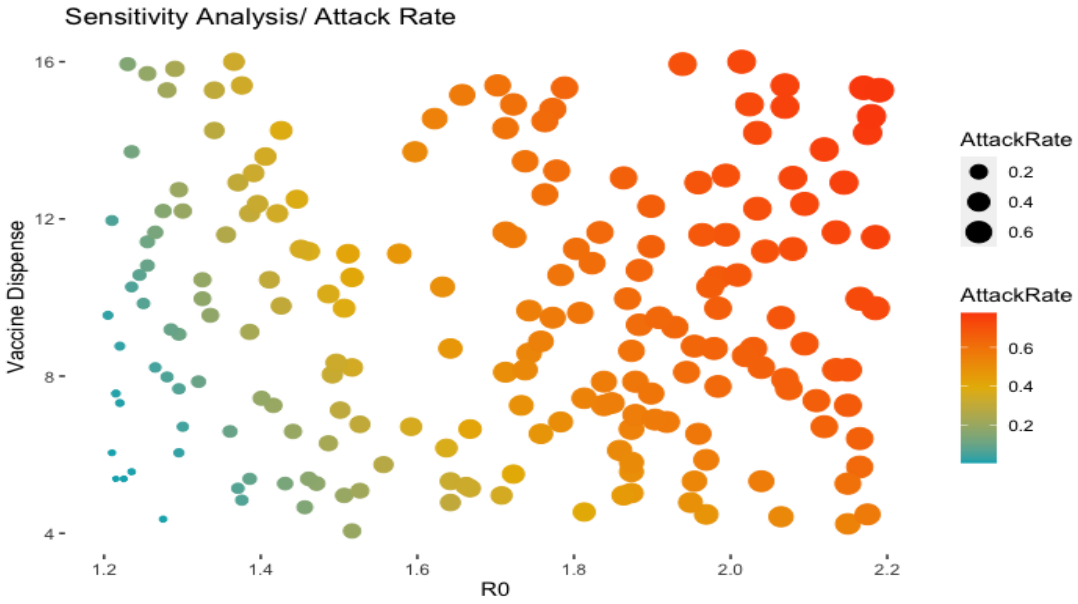

Figure 5.7: Sensitivity Analysis/ *Attack Rate* for Inputs: R_0 vs *Vaccine Dispense*

The above figure shows R_0 on the x-axis and *Vaccine Dispense* on the y-axis. The *Attack Rate* is the third variable. In the above plot, the bubble's colour is blue, and size is very small at the left bottom corner. It illustrates that at minimum *Vaccine Dispense* duration and minimum R_0 value seasonal influenza *Attack Rate* is lowest. The bubble's colour is red, and the size is very large at the right top corner. It indicates that at maximum *Vaccine Dispense* duration and maximum R_0 value seasonal influenza *Attack Rate* is highest. Therefore, the least *Vaccine Depense* duration can decrease the seasonal influenza *Attack Rate.*

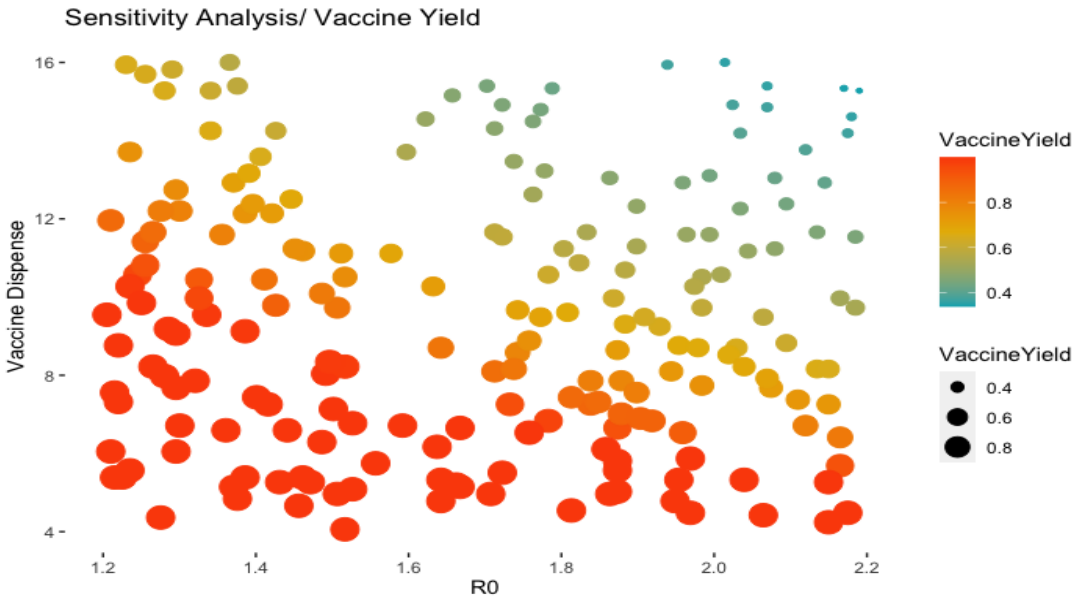

Figure 5.8: Sensitivity Analysis/ *Vaccine Yield* for Inputs: R_0 vs *Vaccine Dispense*

The above figure shows R_0 on the x-axis and *Vaccine Dispense* on the y-axis. The *Vaccine Yield* is the third variable. In the above plot, the colour of the bubbles is blue, and the size is very small at the right top corner, which presents that at maximum *Vaccine Dispense* duration and maximum R_0 value, *Vaccine Yield* is low. The bubble's colour is red, and the size is very large at the right bottom corner. It shows that at minimum *Vaccine Dispense* duration and minimum R_0 value, *Vaccine Yield* is high. Therefore, an increase in *Vaccine Dispense* duration can decrease the *Vaccine Yield* rate.

5.3.3 Scenario-3

In this scenario, R_0 and *Desired Order* are two inputs for Sensitivity analysis. Table 5.6 mentions the model's parameters in this experiment with variable range and remaining all variables have the fixed values. Herd immunity threshold proportion is recommended to protect an entire community against the disease. Seasonal influenza herd immunity is 50% to 75% proportion of immune individuals in a population against the infectious disease. World Health Assembly recommended all people at high risk and to attain coverage of ≥75% among older people and persons with chronic illnesses. In this model, HIT is ≈ 40%. Therefore, *Desired Order* range may vary between 20% to 60%. Figures 5.9, 5.10 and 5.11 present the sensitivity analysis result for seasonal influenza disease *Attack Rate*, *Vaccine Yield* and *Vaccine Cost*.

Table 5.6 The Model's Variable Parameters

Variables	Value Range
R_0	1.2 - 2.2
Desired Order	0.2 – 0.6

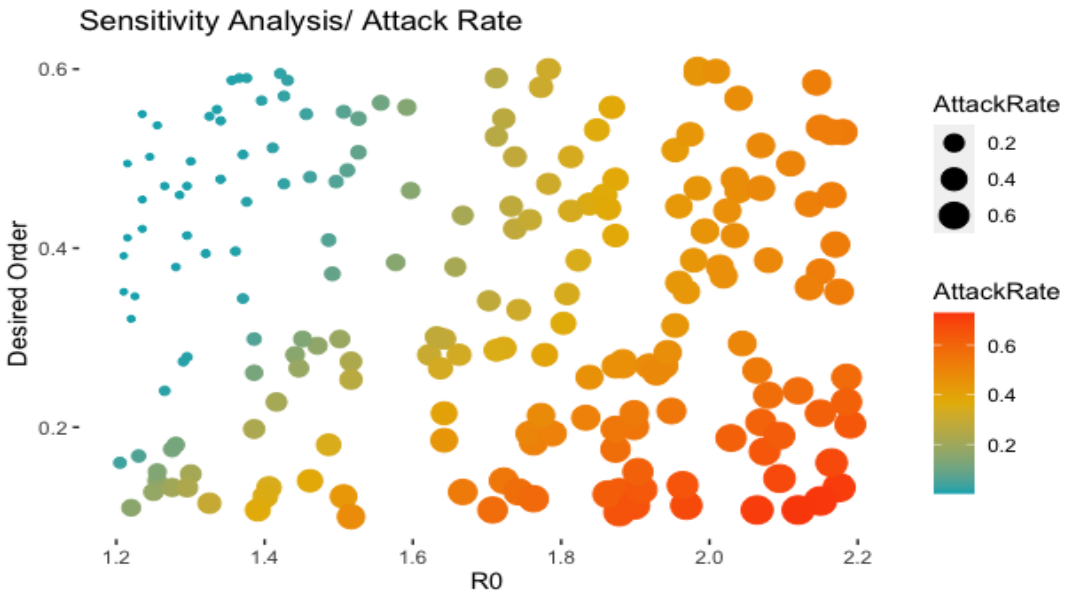

Figure 5.9: Sensitivity Analysis/ *Attack Rate* for Inputs: R_0 vs *Desired Order*

The above figure shows R_0 on the x-axis and *Desired Order* on the y-axis. The *Attack Rate* is the third variable. In the above plot, the bubble's colour is blue, and size is very small at the left top corner. It depicts that at the highest *Desired Order* and minimum R_0 value, the seasonal influenza *Attack Rate* is lowest. The bubble's colour is red, and the size is very large at the right bottom corner. It shows that at the lowest *Desired Order* and maximum R_0 value, the seasonal influenza *Attack Rate* is highest. Therefore, high *Desired Order* can decrease the seasonal influenza *Attack Rate.*

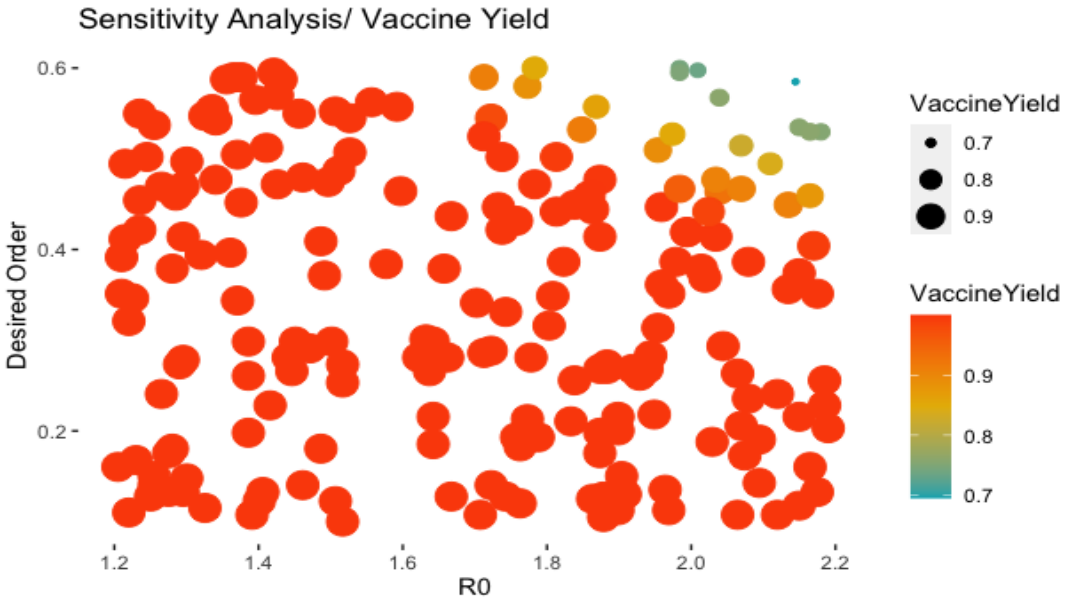

Figure 5.10: Sensitivity Analysis/ *Vaccine Yield* for Inputs: R_0 vs *Desired Order*

The above figure shows R_0 on the x-axis and *Desired Order* on the y-axis. The *Vaccine Yield* is the third variable. In the above plot, the colour of the bubble is blue, and the size is very small at the right top corner, which presents that at maximum *Desired Order* and maximum R_0 value, *Vaccine Yield* is lowest. The bubbles big cluster in red colour, and size is very large at the right bottom corner. It shows that at minimum *Desired Order* and minimum R_0 value, the *Vaccine Yield* is highest. Whereas an increase in R_0 value *and Desired Order* can decrease the *Vaccine Yield* rate.

Figure 5.11 shows R_0 on the x-axis and *Desired Order* on the y-axis. The *Attack Rate* is the third variable and *Vaccine Cost* is the fourth variable for sizing bubbles respectively. Each bubble point is sized and scaled according to the range of the *Vaccine Cost* and *Attack Rate* variables. The changing bubble colours from blue to red present the *Attack Rate is* lower to high numeric intensity. The changing bubble size from small to large presents the *Vaccine Cost* lowest to the highest numeric value. In the following plot, the bubble's colour is blue, and the size is large at the left top corner. It depicts that at maximum *Desired Order* and minimum R_0 value, seasonal influenza *Attack Rate* intensity is lowest, and *Vaccine Cost* is maximum. The bubble's colour is red, and the size is small at the right bottom corner. It shows that at minimum *Desired Order* and maximum R_0 value, seasonal influenza *Attack Rate* intensity is highest, and *Vaccine Cost* is minimal. Seasonal influenza vaccine order equal to *HIT* is considered a strain on low-income countries' budget but the vaccine quantity can decrease seasonal influenza *Attack Rate.*

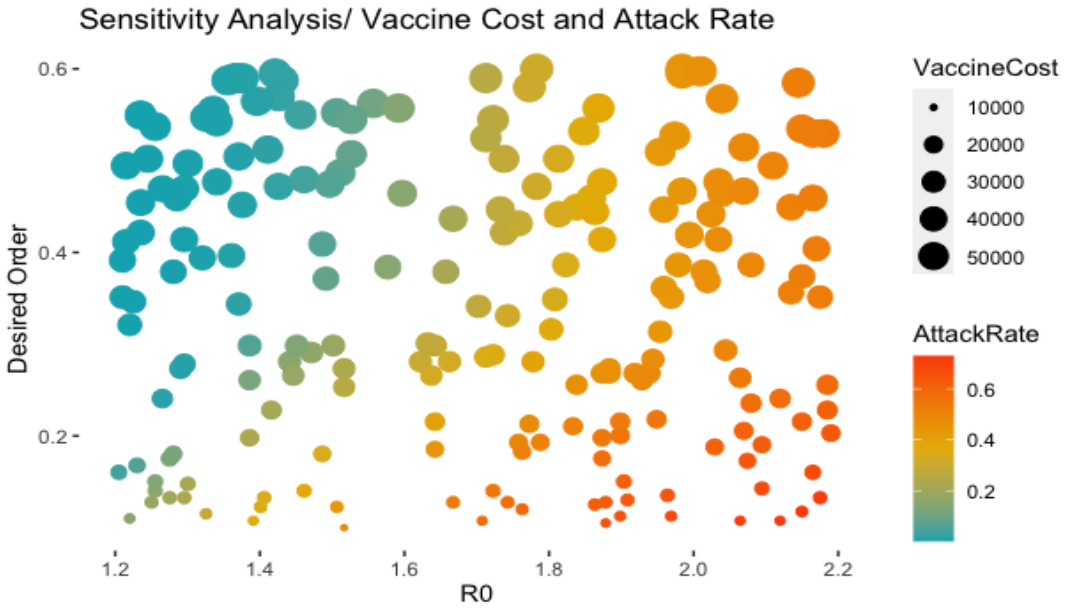

Figure 5.11: Sensitivity Analysis/ *Vaccine Cost* for Inputs: R_0 vs *Desired Order*

6. *Conclusion*

In most countries of the Northern Hemisphere, the influenza season starts in late autumn or early winter. Seasonal influenza response always remains critical and can increase the burden on the healthcare system. “Vaccination reduced hospitalization and mortality and that savings are 3 times

the cost of vaccination" (Lee, 2016). Jorgensen et al., (2018) presented data from EU/EEA states for seven influenza seasons (2008/2009 to 2014/2015). Ireland's trend in influenza vaccination coverage among older people (>= 65 years) between 2008/2009 were 70%, 2009/2010 were 55%, 2010/2011 and 2014/2015 were 60%. Vaccination is a highly cost-effective health intervention. European Centre for Disease Prevention and Control (2018) presented a statement of Dr Zsuzsanna Jakab, WHO Regional Director for Europe,

> "Vaccination is the most effective measure to prevent severe disease caused by influenza. However, according to our research, influenza vaccination uptake has been steadily declining in a number of countries in the European Region".

The model simulations results represented the real-world scenario and generated similar infected cases for the 2018/19 influenza season. The research analysis revealed that influenza vaccine order and time to start vaccination are important decisions. We focused on three important parameters: *Desired Order, Time to Vaccination* and *Time to Infection* to find a good strategy of efficient use of vaccines and reduce wastage. The experiment results showed that order of vaccine quantity has a significant effect on disease attack rate, vaccine cost and vaccine yield. The same vaccine quantity effect very differently if the time of pathogen introduction or time to start vaccination change into the system. Therefore, the best policy is to start immunization before the onset of the influenza season to cover at least the HIT proportion of the population. Vaccine order equals to Herd Immunity Threshold is cost-effective prevention from seasonal influenza.

Vynnycky and G White, (2019) stated that Vaccination programs aim to achieve a coverage which is above the herd Immunity threshold, outbreaks are unlikely to occur". The concern is serious for people at higher risk especially older people and in the future entire population. The production of pandemic vaccines is closely linked to seasonal vaccine use. Influenza vaccine manufacturers take approximately six months to produce, clinical testing and vaccines distribution. The benefit of an influenza vaccination program does not end with the vaccinated person but extends to people who are not vaccinated because they are less likely to be infected and further fewer new cases. Therefore, an influenza vaccination strategy in a timely manner can reduce the disease attack rate.

While the research results are informative and provide valuable insights to highlight the impact of the vaccine supply chain on disease transmission, there is scope for future work with the model. This would focus on: (1) extending the model to different age cohorts to explore heterogeneities between a range of groups in terms of disease spread; and (2) extending the vaccine supply chain structure as new vaccines become available.

Appendix A

Parameters/Symbols	Definitions	Units
Susceptible	Number of susceptible individuals (people)	People
Exposed	Number of exposed individuals (people)	People
Infected	Number of infectious individuals (people)	People
Recovered Disease	Number of recovered individuals (people)	People
Total Vaccinated	Number of people vaccinated	People
Patient Zero	Patient zero stock	People
N	Total Population	People
β	Effective contact rate	1/Weeks*People
λ	Force of infection (rate applied to S stock)	1/Weeks
Ro	Disease Reproduction Number	Dmnl
ED	Average incubation duration	Week
1D	Average infection duration	Week
IR	Infection rate	People/Weeks
ER	Expose rate	People/Weeks
RR	Recovery rate	People/Weeks
Po	Patient zero flow rate	People/Weeks
Time to Infection	Time when seasonal flu starts (October/November)	Weeks
DTime	Time Step	Weeks
T	Time	Weeks
Attack Rate	Proportion of people who get infected	Dmnl
HIT	Herd Immunity Threshold	Dmnl
Vaccine Efficacy	Vaccine efficacy rate	People/Vaccine
VR	Vaccination rate	People/Weeks
Vaccine Orders	Vaccine order for the manufacturer	Vaccine
Vaccines Production/Shipping	Vaccines being produced and shipped	Vaccine
Vaccines Arrived	Vaccines arrived for distribution	Vaccine
Vaccine Used	Vaccines used for immunization	Vaccine
Total Vaccine Produced	Total vaccines produced	Vaccine
Time to Order	Time to make order (January/February)	Week
Desired Order	Estimated vaccine order for a country's population	Vaccine/People
New Orders	New order rate	Vaccine/Week
Orders Fulfilling	Orders Fulfilling rate	Vaccine/Week
Weekly Capacity	Assume capacity to cover population	Vaccine/Week
Coverage Multiplier	To moderate the orders (budgetary constraints)	Per Week
Vaccine Starts	Vaccine production starts rate	Vaccine/Week
Production to Shipping Delay	Production to shipment delay	Weeks
Vaccines Shipped	Shipment starts rate	Vaccine/Week
Time to Vaccination	Time to start immunization (August/September)	Week
Vaccine Policy Flag	Policy flag to start the vaccination	Dmnl

Vaccine Multiplier	Vaccine Multiplier (budgetary constraints)	Per Week
Total Vaccine Dispensed	Actual vaccine distributed	Vaccine/Week
Vaccine Deployment	Average dispensing delay	Weeks
Deployment Multiplier	Vaccines distribution efficiency rate	Vaccine/People
Max Vaccine Dispensed	Max vaccine distributed	Vaccine/Weeks
Vaccine Dispensed	Vaccine dispensing start	Vaccine/Weeks
VP	Vaccine's completion rate.	Vaccine/Weeks
Per Vaccine Cost	Per vaccine cost	Euros/Vaccine
Vaccine Cost	Total vaccine cost	Euros
Vaccine Yield	Percentage of used vaccines.	Dmnl
VP	Vaccine Production fulfilled rate	Per day

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