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## Article

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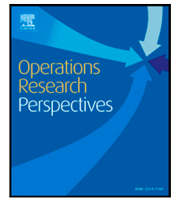
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# Interventions in demand and supply sides for vaccine supply chain: An analysis on monkeypox vaccine

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## ABSTRACT

After a pandemic, all countries experience a shortage in vaccine supply due to limited vaccine stocks and production capacity globally. One particular problem is that it is hard to predict demands for vaccines during the global crisis. On the other hand, vaccines are usually made and packaged in different places, raising logistical issues and concerns that can further delay distribution. In this paper, we propose an optimization formulation model to link infectious disease dynamics and supply chain networks considering a one-to-one relationship between demand and supply for vaccines. We focus on designing a vaccine coordination system using government subsidy that considers the equilibrium behaviors of manufacturers under an actual demand for the vaccine. This study evaluates vaccine manufacturers and government behaviors that help the vaccine market to reach the socially optimal. Different decisions, such as vaccine demands and vaccine production and distribution are investigated. A study of the monkeypox pandemic in the U.S. is performed to validate our model and its results. The obtained results from testing the proposed system problem revealed that the vaccine coverage increased by up to 35%, while the unmet demand reduced by up to 60%, in comparison to when vaccine manufacturers act individually.

## 1. Introduction

Monkeypox (MPX) is an infectious disease caused by the monkeypox virus. It is a viral zoonotic infection that can be spread between people and certain animals or between people. According to World Health Organization (WHO, 2022) the first human infection was reported on September 22, 2017, in the Democratic Republic of the Congo (DRC). Monkeypox is part of a community of viruses similar to smallpox. The symptoms are similar but milder, and monkeypox is rarely fatal. People with monkeypox get a rash that may be located on the face, chest, feet, hands, or mouth. Other symptoms of monkeypox can include muscle aches and backache, exhaustion, fever, chills, swollen lymph nodes, headache, and respiratory symptoms (e.g., cough, nasal congestion, or sore throat) (WHO, 2022). A summary of the literature on monkeypox is provided by Hatmal et al. [1].

By the beginning of February 1, 2023, more than 85,301 cases of monkeypox had now been reported to WHO from 110 countries and territories, with 17 deaths (WHO). The 2022 monkeypox pandemic in the U.S. is part of the more significant human monkeypox outbreak caused by the monkeypox virus's West African clade (CDC, 2022). The United States was the fourth country to experience an outbreak in 2022 (CDC, 2022). The U.S. has the most significant jump in monkeypox cases. Currently, many national governments are practicing

community-based measures to mitigate the spread of the monkeypox virus. Vaccination is a significant tool in preventing the spread of the virus. The smallpox vaccine is also used to protect against monkeypox which is the first vaccine to have been developed against a contagious disease. Vaccination preparedness is illustrated in various countries by Chakraborty et al. [2] that describes the important points and issues for vaccines and vaccinations related to the monkeypox vaccination. Governments and policymakers have tried to control the epidemic based on limited vaccine resources. However, national governments face a shortage of the monkeypox vaccine as the outbreak overgrows. A list of strategies is formulated by Mahmud et al. [3] to develop a sustainable and resilient vaccine supply chain.

Vaccine shortages can result from higher than expected demand and interruptions in supply/production. One particular problem for vaccine manufacturers is that pandemics are not predictable and it is impossible to predict where and when the virus will spread. For instance, during the monkeypox pandemic in 2022, the U.S. Department of Health and Human Services (HHS) ordered an additional 2.5 million doses of Bavarian Nordic's JYNNEOS [4], a vaccine approved to prevent monkeypox and smallpox, while there are the largest smallpox vaccine stockpiles in the United State to vaccinate every person [4]. Another problem is that the production of the smallpox vaccine was low because

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it was not necessary since smallpox was eradicated in 1980. Therefore, the only smallpox vaccine manufacturer in the world that exists in Denmark has been temporarily closed [4]. This study investigates a supply chain resilience model to ramp that system up and bring that vaccine supply system to life for epidemic response.

The epidemiological consequences of not having a robust vaccine supply can be observed after the spread of any disease. There are chronic and fundamental weaknesses in the vaccine production and distribution system, which makes it difficult to supply the vaccine needed to protect against new outbreaks and infections. Pharmaceutical manufacturers are not able to produce vast doses and few countries buy the vaccine that is not used. On the other hand, the locations where this disease grows more have faced the limitation of storage and production capacity. As a result, all countries experience a shortage in the supply of vaccines after a pandemic. A comprehensive study that considers the logistical issues and concerns of firms for the pharmaceutical supply chain is investigated by Settanni et al. [5]. In this study, an epidemiology model is applied into the vaccine supply chain model to estimate demands for vaccines by monitoring the outbreak.

In a purely free vaccine market, vaccine manufacturers and consumers arrive at prices based only on demand and supply. Szavvar et al. [6] proposed a sustainable- resilient supply chain network between vaccine manufacturers and consumers. The free vaccine market cannot reach optimal coverage of vaccines without government intervention. For example, a supply chain model using government subsidy is proposed by Sayarshad [7] to respond to the reported shortage of PPE items during the Covid-19 pandemic. Li et al. [8] studied a supply chain model for critical medical devices after a pandemic. A supply chain model for face masks with government intervention is investigated by Fan and Xie [9]. Yang et al. [10] evaluated the healthcare sector with government subsidy using a hybrid decision-making method. Sayarshad [11] investigated an international trade model to maximize the social benefit that manages domestic manufacturers and the global trade network to improve the supply of PPE items during the global crisis. However, the vaccine production and distribution system is different from other medical products.

National governments provide funding to reduce the shortage of vaccine supply during the monkeypox pandemic. Governments are seriously considering stretching the very limited supply of monkeypox vaccines. For example, the HHS provided approximately \$11 million to support activities to reduce or eliminate barriers to monkeypox vaccine supply. This agreement supports domestic vaccine manufacturers that can bring more vaccines sooner to end this pandemic [4]. In this study, we consider a network for the supply chain of vaccines that includes suppliers, manufacturers, distribution centers, and the demand market. The proposed system model monitors the outbreak and vaccine equity in the market that eliminates barriers between governments and vaccine manufacturers to reach an optimum coverage of vaccines. We also incorporate an epidemiology model into the vaccine coordination system to determine actual vaccine demands.

There have been several studies in production and distribution models to determine the optimal coverage of vaccines after a pandemic. For example, Chick et al. [12] and Arifoglu et al. [13] investigated a supply chain game model for influenza vaccines with government intervention. Mamani et al. [14] developed a vaccine supply chain model under social welfare maximization. Sinha et al. [15] proposed a strategic inventory model for COVID-19 vaccine distribution. [16] considered a Nash equilibrium strategy to assess smallpox vaccine strategies that evaluate individuals' behavior toward getting a vaccine. [17] introduced intuitionistic fuzzy sets (IFS) to identify the logistical issues of vaccine supply after the Covid-19 pandemic. However, epidemic models that monitor the outbreak must be applied to forecast vaccine demand.

The SEIR model is a classical epidemic model, named for its four compartments (susceptible, exposed, infected, and recovered). [18] proposed an SEIR model to consider monkeypox vaccine strategies.

Bankuru et al. [19] adopted the epidemiological model investigated in [18] to assess vaccination strategies for monkeypox vaccination. Augsburger et al. [20] studied a vaccination game model to determine the monkeypox vaccination should be mandated. Savachkin and Uribe [21] studied a non-myopic distribution strategy to allocate limited resources such as antivirals and vaccines during an influenza pandemic. They estimated the total cost of the outbreak in the regions that consider the loss of wages of individuals who get an infection and the medical cost of infected people. Liu et al. [22] developed this model by modifying the limited capacity of resources in order to use it in China for controlling the 2009 H1N1 pandemic.

Many studies address medical resource distribution using the SIR model. A basic SIR model using satellite equations is proposed by Jahedi and Yorke [23] to determine the ratio of susceptible and infected individuals. Sayarshad [24] estimated the personal protective equipment (PPE) burn rate after the Covid-19 crisis by considering a dynamic disease model. Rachaniotis et al. [25] introduced a static resource scheduling problem for controlling pandemics using a SIR model where the susceptible individuals become infected in several regions, and a single resource needs to be available for the population. Büyüktaktakın et al. [26] studied an integrated epidemics-logistics model to allocate the limited resources using a SIR model during the Ebola pandemic in West Africa. Liu and Zhang [27] investigated an optimal strategy to allocate medical resources under stochastic demand to control the pandemics using a SIR model. Mehrotra et al. [28] proposed a stochastic optimization model to allocate ventilators to different regions during the Covid-19 pandemic to respond to the reported shortage. A summary of recent contributions to vaccine supply chain is provided in Table 1.

Our study differs from the ones mentioned in this section, as we are addressing a game model that incorporates vaccine supply chains with the unique characteristics of epidemiology. We incorporate an actual demand for vaccines in the game model, which is estimated by an epidemiology model. This study shows how the demand and supply chain can shift due to pandemics to improve the supply of vaccines in the market. Moreover, a vaccine supply chain network that can increase firms' capability by investing in vaccine production is also studied. We consider a supply chain resilience model between governments and manufacturers to reach optimal coverage of vaccines. Under the epidemiological conditions and actual demand function, we estimate the optimal production volume that minimizes system cost between governments and manufacturers to achieve the most significant market coverage of vaccines.

This paper is organized as follows: Section 2 introduces the proposed supply chain resiliency model for vaccine coordination. An algorithm for solving the proposed model is illustrated in Section 3. Section 4 presents a numerical example to illustrate the effectiveness of the proposed method. Conclusions and discussions regarding the strengths and weaknesses of the proposed approach are given in Section 5.

## 2. The proposed model

This study incorporates a dynamic disease model into the proposed vaccine supply system to determine vaccine demands. First, an epidemiology model for a zoonotic disease is used to provide a framework for finding the optimal rate of vaccination for the entire population. The dominant way of disease transmission, such as monkeypox disease, is through animal-human interaction. We determine the total demand for monkeypox vaccines in each region (or state) based on the dynamic disease model. Lastly, we propose a supply chain game model to reach an equilibrium coverage of the monkeypox vaccine in the market where firms' performance and healthcare costs can be investigated. The proposed vaccine supply model can monitor the outbreak and allocate vaccines based on the equity in the market.

**Table 1**  
Summary of vaccine supply chain studies.

#	Studies	Model feature(s)
1	Usman and Isa Adamu [18]	An epidemiology model with control strategies of combined vaccine and treatment interventions is investigated.
2	Bankuru et al. [19]	A Monkeypox vaccine policy using a dynamic disease model is studied.
3	Sinha et al. [15]	An inventory policy is studied to identify critical nodes for COVID-19 vaccine distribution.
4	Chick et al. [12]	A supply chain/health economics model is proposed for epidemics that have a short seasonal cycle such as influenza outbreaks.
5	Arifoglu et al. [13]	Interventions in demand and supply sides for influenza vaccine supply chain are considered.
6	Bauch et al. [16]	A smallpox vaccination policy is developed using an epidemiology model.
7	Current study	An integration of supply chain and epidemiology model between manufacturers and government for vaccine supply chain during pandemics is proposed.

## 2.1. The methodology: problem description

This section defines a supply chain game network model for suppliers, manufacturers, and distribution centers to coordinate the vaccine supply in the market. In the supply chain network, we have a set of vaccine manufacturers  $M$ , distribution centers  $D$ , and demand markets  $K$ , where distribution centers may have distribution storage centers. The manufacturers' plants are connected to distribution centers and market demand by the links  $A$ . These links correspond to the possible shipment of vaccines between manufacturers and demand markets. The vaccine supply chain network is presented in Fig. 1.

Our vaccine coordination system is denoted by  $\Omega = [Q, A]$  where  $Q$  denote nodes and  $A$  is the set of links. We consider the set of links  $A = A_1 \cup A_2$  where  $A_1$  is the set of links in which the manufacturers can improve vaccine production capacity by investing in technologies and machines. Let  $A_2$  denote the set of links with a fixed vaccine production in the supply chain network. We define the demand nodes  $K$ ,  $k = 1, 2, \dots, K$  where  $k$  represents the vaccine demand at each region (or country). This model can be formulated for each region (or country)  $k \in \{1, \dots, K\}$ ; however, the index  $k$  is dropped for convenience. Due to the availability of the vaccine distribution data and monkeypox disease data in the US, this study investigates an experimental study for the supply chain of vaccines in the US, thus  $k = 1$ . The notations for the proposed framework are given in Table A.4 in the Appendix section.

## 2.2. Vaccine supply chain model

This section combines several modules, including vaccine supply, vaccine demand, and an epidemiology model of the disease, to create a reliable vaccine supply chain model. The proposed framework of our vaccine supply chain model is depicted in Fig. 2. The proposed model integrates four components, including (1) an SEIR model between humans and animals is applied to estimate the special characteristics of the epidemic, (2) an optimization model is investigated to estimate the optimal vaccination rate in the society, (3) a vaccine supply system is proposed to find the optimal vaccine converges in the market. Combining all these together, (4) a system problem is studied between governments and vaccine manufacturers that minimizes the sum of expected healthcare costs and operational costs for both players that are higher than if each player acts individually.

This study estimates the equilibrium coverage of vaccines in the market by considering production capacity and actual vaccine demands. The link flow of vaccine production is also investigated that analyze the equilibrium behaviors of vaccine manufacturers. Moreover, the capacity of links can be increased by investing in machines and other technologies. Thus, we divide the set of links and flows on arcs based on the supplier's capabilities which can add capacity to arcs or have fixed capacity on arcs.

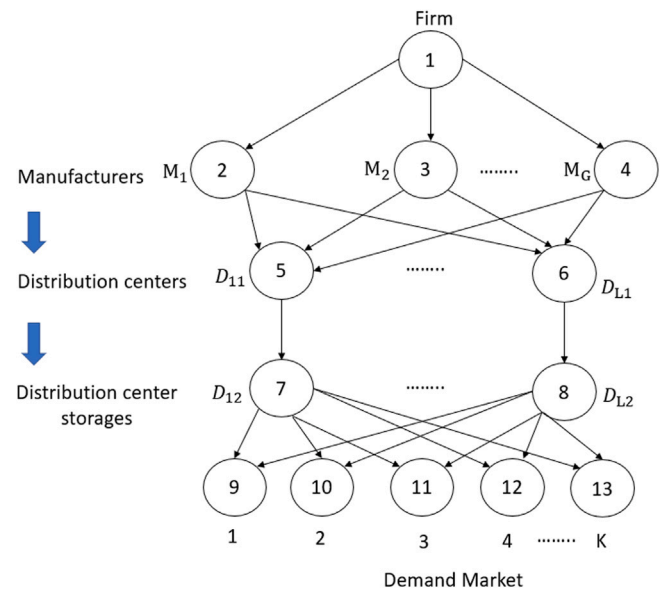


Fig. 1. The framework of vaccine production and distribution network in the market.

### 2.2.1. Epidemiology model

One of the most basic epidemiological models is the SEIR model, named for its four compartments (susceptible, exposed, infected, and recovered). A summary of the literature on mathematical modeling of monkeypox is given by Molla et al. [29]. The epidemiology model must be applied to forecast demand for vaccines. Hence, we apply an SEIR model introduced by [18,19] to estimate actual vaccine demands. The population is divided into humans and animals, denoted by  $h$  and  $m$  subscripts, respectively. The non-human the population was further divided into animal sub-populations in terms of Susceptible  $S_m$ , Exposed  $E_m$ , Infected  $I_m$ , and Removed  $R_m$ . Animal birth and death rate is  $\Lambda_m$  and  $\mu_m$ , respectively. Similarly, the total human population was also divided into human sub-populations in terms of Susceptible  $S_h$ , Vaccinated  $V_h$ , Exposed  $E_h$ , Infected  $I_h$ , and Removed  $R_h$ . Human birth and death rate is  $\Lambda_h$  and  $\mu_h$ , respectively. The notation is summarized in Table A.4. Hence, we derived the following differential equations.

$$\frac{dS_m}{dt} = \Lambda_m - \left( \mu_m + \beta_{mm} \frac{I_m}{N_m} \right) S_m \quad (1)$$

$$\frac{dE_m}{dt} = \beta_{mm} \frac{I_m}{N_m} S_m - (\mu_m + \nu_m) E_m \quad (2)$$

$$\frac{dI_m}{dt} = \nu_m E_m - (\mu_m + d_m + \rho_m) I_m \quad (3)$$

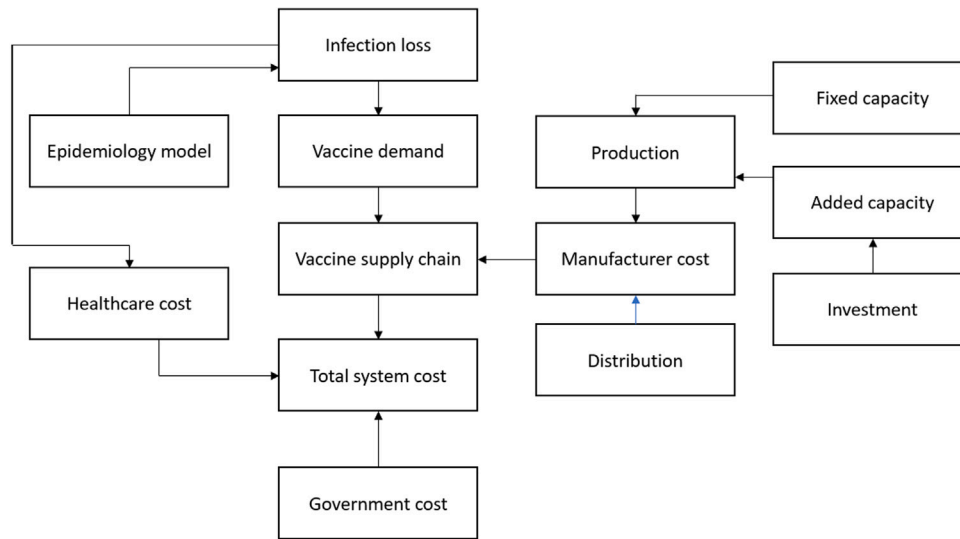


Fig. 2. The proposed framework of vaccine supply chain model.

$$\frac{dR_m}{dt} = \rho_m I_m - \mu_m R_m \quad (4)$$

$$\frac{dS_h}{dt} = \Lambda_h - \left( \mu_h + \left( \beta_{mh} \frac{I_m}{N_m} + \beta_{hh} \frac{I_h}{N_h} \right) + \alpha_h \right) S_h \quad (5)$$

$$\frac{dV_h}{dt} = \alpha_h S_h - \mu_h V_h \quad (6)$$

$$\frac{dE_h}{dt} = \left( \beta_{mh} \frac{I_m}{N_m} + \beta_{hh} \frac{I_h}{N_h} \right) S_h - (\mu_h + \nu_h) E_h \quad (7)$$

$$\frac{dI_h}{dt} = \nu_h E_h - (\mu_h + d_h + \rho_h) I_h \quad (8)$$

$$\frac{dR_h}{dt} = \rho_h I_h - \mu_h R_h \quad (9)$$

Subject to the following non-negative initial conditions.

$$S_m^0 \geq 0; E_m^0 \geq 0, I_m^0 \geq 0, R_m^0 \geq 0 \quad (10)$$

$$S_h^0 \geq 0; V_h^0 \geq 0, E_h^0 \geq 0, I_h^0 \geq 0, R_h^0 \geq 0 \quad (11)$$

$$S_m^0 + E_m^0 + I_m^0 + R_m^0 \leq N_m^0 \quad (12)$$

$$S_h^0 + V_h^0 + E_h^0 + I_h^0 + R_h^0 \leq N_h^0 \quad (13)$$

### 2.3. Demand-side intervention

The average cost of not vaccinating  $\Theta(\alpha_h)$  when the ratio of vaccination for the entire population is  $\alpha_h$  determines by a product of the probability that susceptible individuals  $S_h$  who are getting infection  $I_h$  and the burden of new monkeypox infection on healthcare sector  $\Theta_{MPX}$  [19].

$$\Theta(\alpha_h) = \left( \frac{\left( \beta_{mh} \frac{I_m}{N_m} + \beta_{hh} \frac{I_h}{N_h} \right)}{\left( \beta_{mh} \frac{I_m}{N_m} + \beta_{hh} \frac{I_h}{N_h} \right) + \mu_h} \right) \left( \frac{\nu_h}{\mu_h + \nu_h} \right) \Theta_{MPX} \quad (14)$$

Now we determine the optimal rate of vaccination is by solving P1. We need only evaluate the right-hand side of Eq. (14) for different values of variables that determines by Eqs. (1) to (13), and choose the one which yields the minimum value.

#### P1: Vaccine demand

$$\text{Min NVC} = \sum_t \Theta(\alpha_h^t)$$

Subject to: Eqs. (1) to (13)

Then, the population vaccination rate  $\alpha$  is obtained based on the cost of monkeypox infection as shown in P1. Finally, the total demand for vaccines at each region in period  $t$  is determined by Eq. (15).

$$V_h^t = V_h^{t-1} + \alpha_h^{t-1} S_h^{t-1} - \mu_h V_h^{t-1} \quad \forall t \in T \quad (15)$$

### 2.4. Supply-side intervention

Few studies have focused on the supply of critical medical devices after a pandemic. For instance, Sayarshad [7] proposed a supply chain game model to respond to the reported shortage of PPE items during the Covid-19 pandemic. The vaccine market also needs a balance between demand and supply. However, it can provide the issue of excess inventory buildup if the suppliers cannot capture the actual demand for vaccines during the pandemic. In order to address the issue, we determine the optimal coverage of vaccines by considering demands and the percentage of vaccine coverage by suppliers. Therefore, the quantity coverage of vaccines is defined by the minimum value of vaccine production capacity and a ratio of vaccine coverage in the market during each time period  $t$  [7].

$$W_t = \min \left[ \sum_{p \in P} x_{t,p} \delta_{a,p}, \sigma_t V_h^t \right] \quad \forall t \in T \quad (16)$$

Let  $y$  denote a new binary variable which is either 1 or 0, and  $M$  be a big constant value. Thus, Eq. (16) can be linearized by the following constraints.

$$W_t \leq \sum_{p \in P} x_{t,p} \delta_{a,p}, \quad \forall t \in T, \forall a \in A \quad (17)$$

$$W_t \leq \sigma_t V_h^t, \quad \forall t \in T \quad (18)$$

$$W_t \geq \sum_{p \in P} x_{t,p} \delta_{a,p} - M(1 - y), \quad \forall t \in T, \forall a \in A \quad (19)$$

$$W_t \geq \sigma_t V_h^t - M y, \quad \forall t \in T \quad (20)$$

Now we formulate the flow of vaccine production in the network which is calculated by Eq. (21) [7].

$$f_{a,t} = \sum_{p \in P} x_{t,p} \delta_{a,p} \quad \forall t \in T; \forall a \in A, \quad (21)$$



where  $\delta_{a,p}$  is equal to 1 if an element of the incidence matrix of link  $a$  on path  $p$ , and 0 otherwise.

Moreover, manufacturers can increase vaccine productivity by investing in machines and other technologies; thus, the flow of products in the links can be increased as Eq. (22) [7].

$$\Gamma_{t,\omega} \leq \bar{\Gamma}_{t,\omega} \quad \forall t \in T; \forall \omega \in A_1, \quad (22)$$

where  $\bar{\Gamma}_{n,\alpha}$  denote the upper bound on the added capacity of vaccine production on link  $\alpha$ . Hence, we assume that the production capacity at each link is a linear production function as Eq. (23) [7].

$$f_{\omega,t} \leq \Gamma_{t,\omega} \quad \forall t \in T; \forall \omega \in A_1 \quad (23)$$

We also formulate the scenario that firms have a fixed vaccine production. A bound on production capacity on each link is defined by Eq. (24) [7].

$$f_{\gamma,t} \leq \bar{\Gamma}_{t,\gamma} \quad \forall t \in T; \forall \gamma \in A_2 \quad (24)$$

### 2.5. System setting

This section considers the total system cost between governments and manufacturers for vaccine supply in the market which minimizes operating costs and healthcare costs. The first expression of Eq. (25) is firms' revenue. The second term of Eq. (25) is the operation costs of vaccine production at each link in the chain. The third expression of Eq. (25) is the total investment cost at each link in the chain that increases vaccine production. The burden of new infection on the healthcare system as a result of the shortages of vaccines is also considered in the last term of Eq. (25).

$$\begin{aligned} \text{Min MC} = & \sum_t \hat{w}(W_t) + (1 - \theta) \sum_t \sum_{a \in A} \hat{c}_a(f_{a,t}) + (1 - \theta) \sum_t \sum_{\alpha \in A_1} \hat{\pi}_{t,\alpha}(\Gamma_{t,\alpha}) \\ & + \sum_t \theta (\alpha_h^t) [V_h^t - W_t], \end{aligned} \quad (25)$$

where  $\theta$  represents the proportion of government funding that covers the expenses of producing vaccines. Governments of various nations provide financial support to companies that produce vaccines in order to ensure the availability of vaccines for the population. The subsidy is typically used to cover the operational costs associated with the production of vaccines, such as research and development, manufacturing, and distribution.

Combining all these together, the system problem is defined as P2. The system problem finds an optimal production that minimizes the total system cost between governments and vaccine manufacturers subject to the constraints of demand, supply, and epidemiology modules.

### P2: System setting for vaccine supply

$$\begin{aligned} \text{Min MC} = & \sum_t \hat{w}(W_t) + (1 - \theta) \sum_t \sum_{a \in A} \hat{c}_a(f_{a,t}) + (1 - \theta) \sum_t \sum_{\alpha \in A_1} \hat{\pi}_{t,\alpha}(\Gamma_{t,\alpha}) \\ & + \sum_t \theta (\alpha_h^t) [V_h^t - W_t] \end{aligned}$$

Subject to:

$$W_t = \min \left[ \sum_{p \in P^k} x_{t,p} \delta_{a,p} \sigma_t V_h^t \right] \quad \forall t \in T, \forall a \in A, k = 1$$

$$f_{a,t} = \sum_{p \in P} x_{t,p} \delta_{a,p} \quad \forall t \in T; \forall a \in A$$

$$\Gamma_{t,\omega} \leq \bar{\Gamma}_{t,\omega} \quad \forall t \in T; \forall \omega \in A_1$$

$$f_{\omega,t} \leq \Gamma_{t,\omega} \quad \forall t \in T; \forall \omega \in A_1$$

$$f_{\gamma,t} \leq \bar{\Gamma}_{t,\gamma} \quad \forall t \in T; \forall \gamma \in A_2$$

$$V_h^t = V_h^{t-1} + \alpha_h^{t-1} S_h^{t-1} - \mu_h V_h^{t-1} \quad \forall t \in T$$

## 3. The proposed algorithm

### Algorithm 1 Vaccine market coordination (VMC) system

**Require:** Dynamic disease and supply chain parameters

**Ensure:** Vaccine coverage, link flow, equilibrium path flow

```

1: function VMC( $S_m^0, E_m^0, I_m^0, R_m^0, S_h^0, V_h^0, E_h^0, I_h^0, R_h^0, \alpha_h^0, \Gamma_{0,\omega}$ )
2:   for  $t \leftarrow 1$  to  $T$  do
3:     Compute the SEIR solutions
4:      $S_h^{t+1} \leftarrow S_h^{t-1} + S_h^t$ 
5:      $V_h^{t+1} \leftarrow V_h^{t-1} + V_h^t$ 
6:      $E_h^{t+1} \leftarrow E_h^{t-1} + E_h^t$ 
7:      $I_h^{t+1} \leftarrow I_h^{t-1} + I_h^t$ 
8:      $R_h^{t+1} \leftarrow R_h^{t-1} + R_h^t$ 
9:     Solve P1
10:     $\alpha_h^{*t} \leftarrow \alpha_h^t$ 
11:     $V_h^{*t} \leftarrow V_h^t$ 
12:    for  $a \in A$  do
13:      for  $\omega \in A_1$  do
14:        for  $\gamma \in A_2$  do
15:          Solve P2
16:           $x_{t,p}^* \leftarrow x_{t,p}$ 
17:           $f_{a,t}^* \leftarrow f_{a,t}$ 
18:           $\sigma_t^* \leftarrow \sigma_t$ 
19:           $W_t^* \leftarrow W_t$ 
20:           $\theta^* \leftarrow \theta$ 
21:        end for
22:      end for
23:    end for
24:    if  $t = T$  then go to step 28;
25:    otherwise, set  $t = t + 1$  and go to 3.
26:  end
27: end for
28: return  $\theta^*, x_{t,p}^*, f_{a,t}^*, \sigma_t^*, W_t^*, V_h^{*t}, \alpha_h^{*t}$ 
29: end function

```

We propose an algorithm for a vaccine market coordination (VMC) system through the global crisis by aggregating the aforementioned mathematical models. The flowchart of the proposed model is shown in Fig. 3. Based on the proposed algorithm (Algorithm 1), we define the vaccine supply chain network, including firms, manufacturers, distribution centers, and demand markets. The operation costs for producing a vaccine are defined. Moreover, the initial parameters of infectious disease dynamics are also determined.

Then, we formulated an optimization model (called P1) to predict the optimal coverage of vaccine supply for the entire population. By solving P1, the set of the optimal number of vaccinations can be determined. Next, we solve a supply chain game model (called P2) to estimate the equilibrium solutions of production and vaccine coverage. If  $t$  has reached the end of time periods (per week), go to step 28. Otherwise, increment  $t$  ( $t = t + 1$ ) and go back to step 3. Lastly, we compute the optimal proportion of cost coverage by government subsidy, the optimal link flows, the optimal path flow, the quantity of vaccine coverage, and the percentage of vaccine coverage in the market.

## 4. Numerical example

This section presents the numerical results of the vaccine supply chain model described above to demonstrate its effectiveness. We consider a network with one vaccine firm, three vaccine manufacturers, two distribution centers, and two distribution storages. The supply chain network responds to vaccine demands in the United State. Fig. 4 illustrates the supply chain network of the monkeypox vaccine. The mathematical models were coded in Julia 1.7.1, and a component

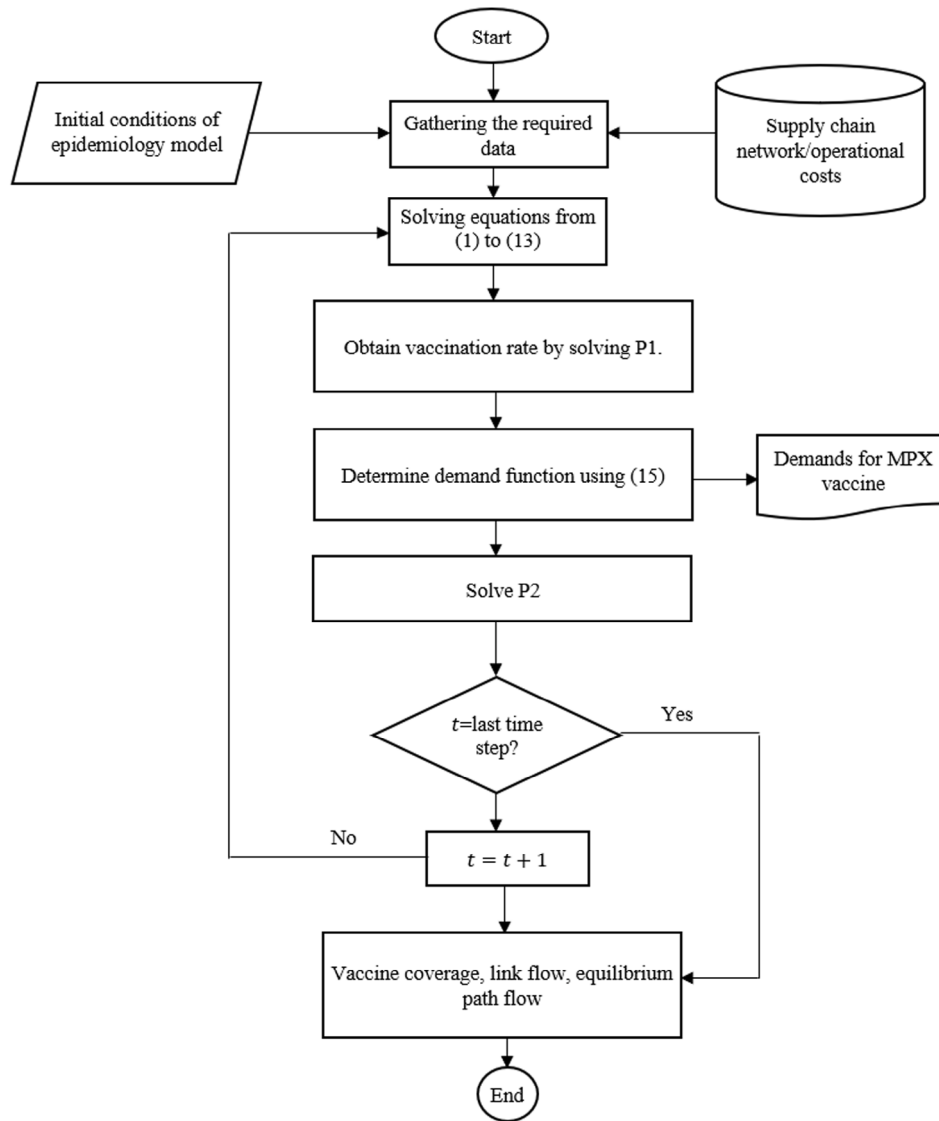


Fig. 3. Flowchart of the proposed model for MPX vaccine supply.

package in the DifferentialEquations ecosystem [30] is used to solve the SEIR model. We also solved the optimization models using the Ipopt package in Julia, Jump package [31], and Juniper package [32].

#### 4.1. Data

Numerical calculations were performed to verify the efficiency of the proposed vaccine production and distribution system in real-world applications. Monkeypox transmission in the US is in progress or development. We study a Monkeypox dataset for the US to validate our supply chain model and its results. Data on the 2022 monkeypox outbreak is collated by the World Health Organization. We are continuously gathering the dataset from June 3, 2022, until October 27, 2022. We apply the infection data in the United State for solving the SEIR model [33].

We define least-squares error terms with an initial guess for the parameter values. The preassigned parameter values of the infectious disease model are shown in Table 2. The mean rates that were adopted from the literature are used in this study. We estimate the parameters of an epidemiology model. We collect several observations of positive MPX cases from June 3, 2022, until October 27, 2022, then

Table 2

Input parameters of epidemiology model.

Parameter	Values
$\Lambda_h$	0.0328 [34]
$\Lambda_m$	2 [35]
$\mu_h$	1/60 [36]
$\mu_m$	0.5 [37]
$d_h$	3.12 [38]
$d_m$	17.5 [39]
$\rho_h$	28.08 [40]
$\rho_m$	12 [39]
$v_h$	30.42 [40]
$v_m$	120 [39]
$\beta_{hh}$	32.85 [41]
$\beta_{mh}$	0.05 [37]
$\beta_{mm}$	40 [37]
$\sigma$	\$4 [42]
$\theta_{MPX}$	\$100 [43]

the nonlinear least squares method (NLS) is used numerically to calibrate parameters. In detail, our objective is to estimate the parameters of the infectious disease model by fitting the model to monkeypox disease data in the US. Hence, we found the set of parameters  $\hat{Y} = (\hat{S}_m, \hat{E}_m, \hat{I}_m, \hat{R}_m, \hat{S}_h, \hat{V}_h, \hat{E}_h, \hat{I}_h, \hat{R}_h)$  that minimizes the sum of

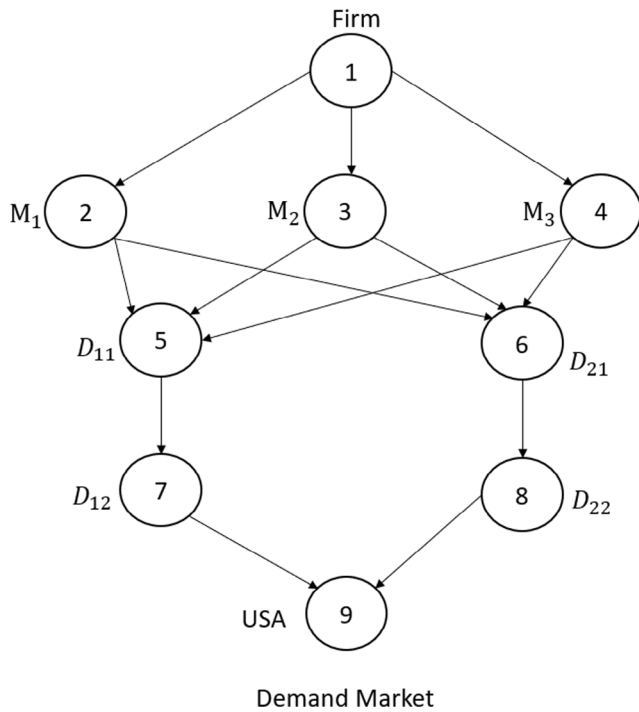


Fig. 4. The supply chain network of monkeypox vaccine.

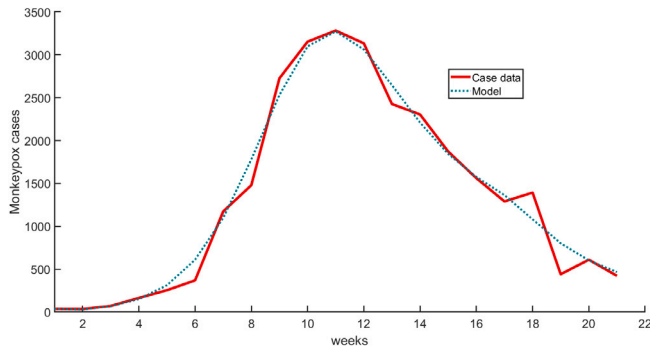


Fig. 5. Fitting results of solutions: USA.

squared differences between the corresponding model solution denoted by  $f(t_i, \hat{Y})$  and the observed data  $y = (y_{t_1}, y_{t_2}, \dots, y_{t_n})$  [44]. Hence, we modify the least-squares error term to reflect this change and obtain the set of best-fit parameters.

$$\hat{Y} = \operatorname{argmin} \sum_{i=1}^n \left( f(t_i, \hat{Y}) - y_{t_i} \right)^2, \quad (26)$$

where  $n$  is the number of data points available for parameter inference and  $t_i$  are the time points at which the time series data are observed.

The model solution  $f(t_i, \hat{Y})$  provides the best-fit to the time series data  $y_{t_i}$ . Solutions to the model with the best-fit parameter values are shown in Fig. 5. Several Matlab functions are developed for to estimate parameter values. By evaluating the fitness of the epidemiology model from the actual observation of the monkeypox dataset in the U.S., the root mean square error (RMSE) is found about 16%.

Now we estimate the optimal number of vaccinations by solving the P1. Fig. 6 shows the estimated vaccine demands in the United States during 20 weeks. The total of vaccination during 20 weeks is 790, 533, this agrees with the results of HHS [4]. According to the U.S. Department of Health and Human Services (HHS), 830,000 vaccines in the US during 20 weeks are distributed [4].

In addition, the input parameters of the supply chain of monkeypox vaccines are presented in Table A.5. The information contains the set of paths and the set of links from the vaccine firm to the vaccine demand market. As shown in Table A.5, the set of links is divided into fixed production capacity and added production capacity. The parameters of cost functions are also illustrated in Table A.5. The operation costs of vaccine production at each link in the chain are assumed as Eq. (27).

$$\hat{c}_a(f_{a,t}) = c_a + 1.1f_{a,t} \quad (27)$$

We assume that the investment cost to increase vaccine production is given as Eq. (28).

$$\hat{\pi}_{t,\alpha}(\Gamma_{t,\alpha}) = \pi_a + 1.2\Gamma_{t,\alpha} \quad (28)$$

In addition, the total purchasing cost of vaccines is assumed as Eq. (29).

$$\hat{\omega}(W_t) = \omega W_t \quad (29)$$

where the price of the monkeypox vaccine is assumed to be  $\omega = \$4$  for our real case study [42].

We incorporate the average cost of not vaccinating into the game model that considers the infection loss of individuals due to the shortage of vaccine supply in the market. By solving the P1, we found that the optimal rate of vaccination is  $\alpha_h = 0.03$ . Therefore, the average healthcare cost is estimated when the rate of vaccination for the entire population is  $\alpha_h = 0.03$ . Fig. 7 shows the average cost of not vaccinating in the United State for 50 weeks from the beginning of the pandemic. We also assumed that the average cost of vaccination is \$4.

The basic reproduction numbers  $R_0$  corresponds to a number of secondary human infections caused by a single infected human in an otherwise healthy population and are given by [18]

$$R_0 = \beta_{hh} \frac{\mu_h}{\mu_h + \alpha_h + \rho_m} \frac{1}{\mu_h + d_h + \rho_h} \frac{v_h}{v_h + \mu_h} \quad (30)$$

The ability of a new pathogen to spread can be estimated by the basic reproductive rate ( $R_0$ ). It is defined as the average number of secondary transmissions from one infected individual. Under different population vaccination rates, the  $R_0$  values can be determined that have important implications for disease control. We evaluate basic reproduction numbers under different vaccination rates from 0% to 10%. Fig. 8 shows the basic reproduction number with respect to different vaccination rates. For example, if  $R_0$  is greater than 1 that shows the disease is growing.

Developing a resilient supply chain that minimizes the total system costs can motivate manufacturers to improve the supply of vaccines. The resilient supply chain model monitors the outbreak and vaccine equity in the market. Governments provide funding to increase production by covering the percentage of operating costs. The equilibrium results when cost coverage by the government is  $\theta = 0.48$  are reported in Table 3. The equilibrium results in terms of links flow and path flows for vaccine production are presented in Table 3.

Moreover, vaccine manufacturers need to invest in their operations to increase vaccine production in the chain. Therefore, we consider the investment cost of vaccine manufacturers on links to expand the production capacity. The production capacity on links are also shown in Table 3. We reported the results of the model for week 11 of the monkeypox pandemic. As shown in Fig. 5, a higher ratio of positive cases in the U.S. during the selected week was experienced.

The national governments need to pay a proportional production cost to manufacturers for vaccine supply under an emergency allocation. We estimate the expected total system costs between the government and manufacturers by including the government subsidy. We solve the proposed vaccine supply chain model under different ranges of government subsidies. Fig. 9 shows the sensitivity analysis of government subsidy. We test six scenarios where the government subsidies cover the operation costs for vaccine manufacturers by up to 0%, 10%, 20%, 30%, 40%, and 48%. The results show that the system



**Table 3**  
Equilibrium results of vaccine supply.

Link flow of vaccine production $f_{n,a}$			
$f_{11,(1 \rightarrow 2)} = 16224.563,$	$f_{11,(1 \rightarrow 3)} = 15689.435,$	$f_{11,(1 \rightarrow 4)} = 18086.000,$	$f_{11,(2 \rightarrow 5)} = 9526.559,$
$f_{11,(2 \rightarrow 6)} = 6698.003,$	$f_{11,(3 \rightarrow 5)} = 9309.528,$	$f_{11,(3 \rightarrow 6)} = 6379.907,$	$f_{11,(4 \rightarrow 5)} = 11163.911,$
$f_{11,(4 \rightarrow 6)} = 6922.089,$	$f_{11,(5 \rightarrow 7)} = 30000.000,$	$f_{11,(6 \rightarrow 8)} = 20000.000,$	$f_{11,(7 \rightarrow 9)} = 30000.000,$
$f_{11,(8 \rightarrow 9)} = 20000.000.$			
Path flow of vaccine production $x_{n,p}$			
$X_{11,p_1} = 9526.560,$	$X_{11,p_2} = 6698.003,$	$X_{11,p_3} = 9309.529,$	$X_{11,p_4} = 6379.907,$
$X_{11,p_5} = 11163.912,$	$X_{11,p_6} = 6922.089.$		
Vaccine production capacity by investment on links $\Gamma_{n,a}$			
$\Gamma_{11,(2 \rightarrow 5)} = 9526.560,$	$\Gamma_{11,(2 \rightarrow 6)} = 6698.003,$	$\Gamma_{11,(3 \rightarrow 5)} = 9309.529,$	$\Gamma_{11,(3 \rightarrow 6)} = 6379.907,$
$\Gamma_{11,(4 \rightarrow 5)} = 11163.912,$	$\Gamma_{11,(4 \rightarrow 6)} = 6922.089,$	$\Gamma_{11,(5 \rightarrow 7)} = 30000.000,$	$\Gamma_{11,(6 \rightarrow 8)} = 20000.000,$
$\Gamma_{11,(7 \rightarrow 9)} = 30000.000,$	$\Gamma_{11,(8 \rightarrow 9)} = 20000.000.$		

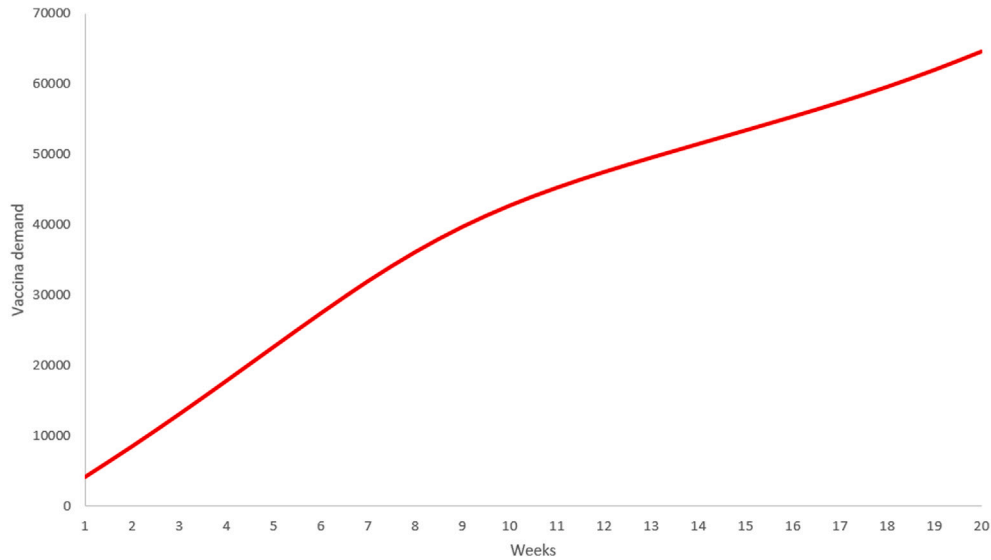


Fig. 6. Estimated vaccine demand in the United State from June 3, 2022, until October 27, 2022.

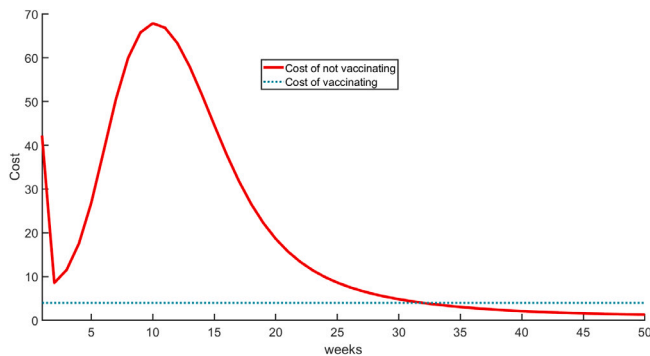


Fig. 7. Costs under optimum vaccination rate ( $\alpha = 0.03$ ).

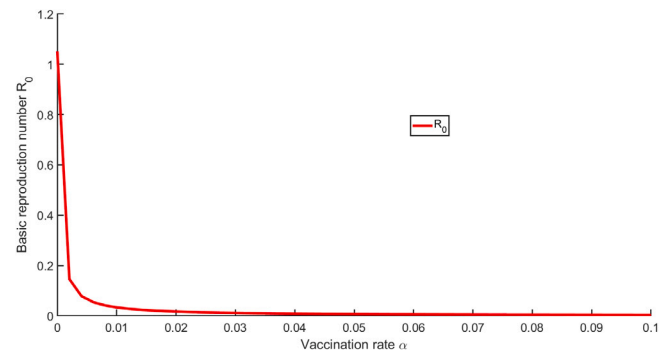


Fig. 8. Basic reproduction number  $R_0$ .

optimum can be fully achieved when cost coverage by subsidy is equal to 48%. Note that other lines are overlapped when cost coverage by the government is less than 48%. Thus, the proposed model can determine an optimal allocation of subsidies for vaccine supply in the market based on the outbreak and vaccine equity.

We test the sensitivity of the proposed system problem under a range of subsidies. We compare the number of vaccine coverage over time with respect to different government subsidies  $\theta$ . Fig. 10 shows the equilibrium results for the number of vaccine coverage per week. The highest percentage of government subsidy is found at about  $\theta = 0.48$  where the system cost can reach an equilibrium point. Note that other

lines are overlapped when cost coverage by the subsidy is less than 48%.

Moreover, the number of infections during the monkeypox pandemic can also be increased by the shortage of vaccine supply in the market. Therefore, we evaluate the number of unmet demands with respect to different subsidies. Fig. 11 denotes equilibrium results for vaccine unmet demands under different government policies. The total unmet demand for vaccines when the government subsidy is 48% is 193,531, while it increases by up to 493,531 when the government subsidy is less than the optimal government subsidy. Note that other lines are overlapped when costs coverage by the government is less than 48%. Under the proposed vaccine supply chain model, the

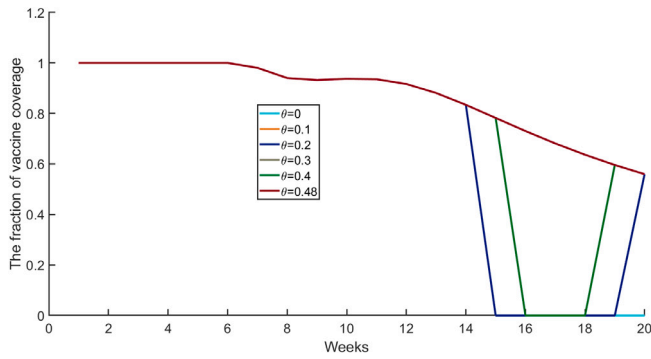


Fig. 9. The fraction of vaccine coverage with respect to government subsidy.

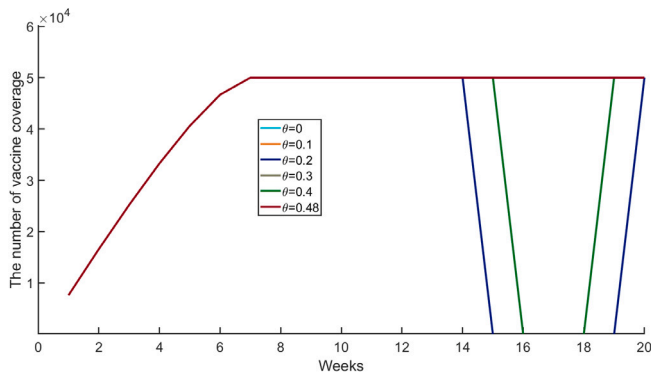


Fig. 10. The number of vaccine supply with respect to government subsidy.

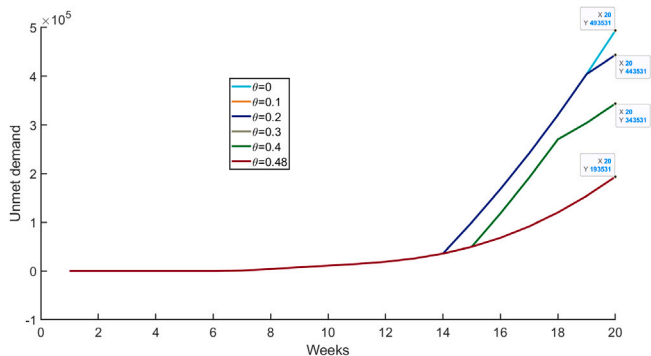


Fig. 11. Unmet demand with respect to government subsidy.

unmet demand for vaccine supply reduces by up to 60% in comparison when vaccine manufacturers act individually without government intervention.

#### 4.2. Discussion and summary

It is always hard for supply chains to cope with surges in vaccine demand, and when it comes to rapid increases in demands under the

circumstance of a pandemic, the shortage in vaccine supply can cause rather serious consequences. The study embeds the SEIR model into the supply chain coordination problem and may provide a framework for combining pandemic prediction and vaccine supply optimization. The effectiveness of the proposed model has been illustrated in the real-world data of the monkeypox pandemic.

Our experimental design focuses on the ability of the proposed game model, where the epidemiology of the disease is studied to capture realistic changes in demand over time. We estimated the vaccine demand based on the infectious disease dynamics model that minimizes the infection loss of individuals. The parameters of the infectious disease model were also calibrated by the nonlinear least squares method. We evaluated the fitness of the epidemiology model from the actual observation which is extracted from the monkeypox disease dataset in the U.S. The root mean square error (RMSE) is found about 16%. By solving the P1, the total of vaccination during 20 weeks was 790, 533, this agrees with the results of HHS [4].

In a purely free vaccine market, manufacturers and consumers arrive at prices based only on demand and supply. The free vaccine market is unable to reach socially optimal coverage without government subsidies. Thus, the percentage of operating costs could be covered by subsidies. A subsidy procurement contract for the government to coordinate the vaccine supply chain was studied in this study. This study also determined the highest percentage of government subsidy which was about  $\theta = 0.48$  where the system cost could reach an equilibrium point. We observed that the vaccine coverage increased by up to 35%, while the unmet demand reduced by up to 60%, in comparison to when manufacturers act individually.

#### 5. Conclusion

This study created a novel mathematical model that aims to optimize the total system costs between firms and governments by monitoring the outbreak using an epidemic model. We focused on a vaccine market coordination system that investigates operation costs, where manufacturers' capabilities were considered to invest in increasing production capacity. We estimated the actual demand for vaccines using a dynamic disease model. The fitness of the model from the actual observation data was evaluated where the RMSE was 16%. Additionally, the  $R_0$  values under different population vaccination rates that have important implications for disease control were estimated.

The proposed system problem coordinated the vaccine supply to reach optimal coverage in the market. The optimal production volume that minimizes the total system cost to achieve the most extensive market coverage was determined. The highest percentage of government subsidy was found at about 48%, where the system cost can reach an equilibrium point. We found that the vaccine coverage increased by up to 35%, while the unmet demand reduced by up to 60%, in comparison to when vaccine manufacturers act individually.

Key directions for future research include introducing climate change impacts on human infectious diseases via pathogen, host, and transmission. Climate change can be linked to the spread of viruses like monkeypox. Precipitation and temperature effects can be considered in the SEIR model. Therefore, modeling the impact of climate change on zoonotic diseases can be also investigated in future research [45]. Moreover, the biggest concern of the supply chain of monkeypox vaccines is equity. For example, In North Carolina, just a quarter of the vaccines have gone to black men and white residents have received 67% of vaccinations, but 70% of the monkeypox cases have been in black men [46,47]. Other factors such as equitable distribution of vaccines can be investigated in the vaccine supply model in a future study to allocate vaccines to high-risk people [48–51]. An effective solution strategy such as blockchain technology can also be integrated into the vaccine supply chain to reduce the risk factors affecting vaccine safety through the entire supply chain [52,53]. Finally, demand for vaccines during pandemics greatly outstrips supply, which causes a shortage of supply. A new decision model for vaccine supply in response to an uncertain vaccine demand can also be considered in future research [54,55].

**Table A.4**  
Nomenclature.

Symbol	Description
$T$	Time per week ( $t \in \{1, \dots, T\}$ )
$Q$	Nodes ( $q \in \{1, \dots, Q\}$ )
$P$	Paths ( $p \in P$ )
$A$	Links ( $a \in \{1, \dots, A\}$ )
$A_1$	Links with added vaccine production ( $\omega \in \{1, \dots, A_1\}$ )
$A_2$	Links with fixed vaccine production ( $\gamma \in \{1, \dots, A_2\}$ )
$\delta_{a,p}$	1 if an element of incidence matrix of link $a$ on path $p$ , and 0 otherwise
$W_t$	The total number of vaccine which is distributed in period $t$
$x_{t,p}$	The number of vaccine production for path $p$ in period $t$
$f_{a,t}$	Vaccine flows on link $a$ in period $t$
$f_{\omega,t}$	Vaccine flows on link $\omega$ in period $t$
$f_{\gamma,t}$	Vaccine flows on link $\gamma$
$\bar{f}_{t,\omega}$	The upper bound of vaccine production per week $t$ on link $\omega$
$\bar{f}_{t,\gamma}$	The upper bound of vaccine production per week $t$ on link $\gamma$
$f_{t,\omega}$	Vaccine capacity per week $t$ on links $\omega$
$I_h^t$	The number of infected humans in period $t$
$I_m^t$	The number of infected animals in period $t$
$S_h^t$	The number of susceptible humans in period $t$
$V_h^t$	The number of vaccinated susceptible humans in period $t$
$S_m^t$	The number of susceptible animals in period $t$
$E_h^t$	The number of exposed humans in period $t$
$E_m^t$	The number of exposed animals in period $t$
$R_h^t$	The number of removed humans in period $t$
$R_m^t$	The number of removed animals in period $t$
$\sigma_t$	The percentage of vaccine coverage in period $t$
$\alpha_h$	Population vaccination rate
$\lambda_m$	Animal birth rate
$\lambda_h$	Human birth rate
$\mu_m$	Animal natural death rate
$\mu_h$	Human natural death rate
$d_m$	Animal MPX related death rate
$d_h$	Human MPX related death rate
$\rho_m$	Animal recovery rate
$\rho_h$	Human recovery rate
$\nu_m$	Animal infection rate
$\nu_h$	Human infection rate
$\beta_{mm}$	Animal to animal transmission rate
$\beta_{hh}$	Human to human transmission rate
$\beta_{mh}$	Animal to human transmission rate
$\sigma$	Price of vaccine
$\theta_{MPX}$	Infection loss of MPX
$N$	Population (human population $N_h$ , animal population $N_m$ )
$\hat{\sigma}(W_t)$	The total purchasing cost of vaccines
$\hat{c}_a(f_{a,t})$	The total operation cost on link $a$
$\hat{\pi}_{t,\alpha}(f_{t,\alpha})$	The investment cost on link $\alpha$
$\theta$	the percentage of government subsidy

## Declaration of competing interest

We wish to confirm that there are no known conflicts of interest associated with this publication. This research did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors. We feel that this work will be of general interest to readers of Operations Research Perspectives.

## Data availability

All dataset sources are cited in the article. Additional data is available upon request to the corresponding author

## Appendix. Tables

See Tables A.4 and A.5.

**Table A.5**

Input parameters of example.

Problem setup
Set of links
$A := \{1 \rightarrow 2, 1 \rightarrow 3, 1 \rightarrow 4, 2 \rightarrow 5, 2 \rightarrow 6, 3 \rightarrow 5, 3 \rightarrow 6, 4 \rightarrow 5, 4 \rightarrow 6, 5 \rightarrow 7, 6 \rightarrow 8, 7 \rightarrow 9, 8 \rightarrow 9\}$ .
$A1 := \{2 \rightarrow 5, 2 \rightarrow 6, 3 \rightarrow 5, 3 \rightarrow 6, 4 \rightarrow 5, 4 \rightarrow 6, 5 \rightarrow 7, 6 \rightarrow 8, 7 \rightarrow 9, 8 \rightarrow 9\}$ .
$A2 := \{1 \rightarrow 2, 1 \rightarrow 3, 1 \rightarrow 4\}$ .
Set of paths ( $p$ )
$p_1 = \{1 \rightarrow 2, 2 \rightarrow 5, 5 \rightarrow 7, 7 \rightarrow 9\}$ , $p_2 = \{1 \rightarrow 2, 2 \rightarrow 6, 6 \rightarrow 8, 8 \rightarrow 9\}$ , $p_3 = \{1 \rightarrow 3, 3 \rightarrow 5, 5 \rightarrow 7, 7 \rightarrow 9\}$ , $p_4 = \{1 \rightarrow 3, 3 \rightarrow 6, 6 \rightarrow 8, 8 \rightarrow 9\}$ , $p_5 = \{1 \rightarrow 4, 4 \rightarrow 5, 5 \rightarrow 7, 7 \rightarrow 9\}$ , $p_6 = \{1 \rightarrow 4, 4 \rightarrow 6, 6 \rightarrow 8, 8 \rightarrow 9\}$ .
The upper bound of vaccine production on link $\omega$ ( $\bar{f}_{t,\omega}$ )
$\bar{f}_{t,2 \rightarrow 5} = 40000$ , $\bar{f}_{t,2 \rightarrow 6} = 30000$ , $\bar{f}_{t,3 \rightarrow 5} = 130000$ , $\bar{f}_{t,3 \rightarrow 6} = 20000$ , $\bar{f}_{t,4 \rightarrow 5} = 40000$ , $\bar{f}_{t,4 \rightarrow 6} = 20000$ , $\bar{f}_{t,5 \rightarrow 7} = 60000$ , $\bar{f}_{t,6 \rightarrow 8} = 90000$ , $\bar{f}_{t,7 \rightarrow 9} = 30000$ , $\bar{f}_{t,8 \rightarrow 9} = 20000$ ,
The upper bound of vaccine production on link $\gamma$ ( $\bar{f}_{t,\gamma}$ )
$\bar{f}_{t,1 \rightarrow 2} = 30400$ , $\bar{f}_{t,1 \rightarrow 3} = 31200$ , $\bar{f}_{t,1 \rightarrow 4} = 80000$ ,
Operation cost ( $c_a$ )
$c_{1 \rightarrow 2} = 0.002$ , $c_{1 \rightarrow 3} = 0.003$ , $c_{1 \rightarrow 4} = 0.004$ , $c_{2 \rightarrow 5} = 0.005$ , $c_{2 \rightarrow 6} = 0.006$ , $c_{3 \rightarrow 5} = 0.004$ , $c_{3 \rightarrow 6} = 0.003$ , $c_{4 \rightarrow 5} = 0.002$ , $c_{4 \rightarrow 6} = 0.003$ , $c_{5 \rightarrow 7} = 0.004$ , $c_{6 \rightarrow 8} = 0.005$ , $c_{7 \rightarrow 9} = 0.006$ , $c_{8 \rightarrow 9} = 0.003$ .
The investment cost on link $\omega$ ( $\pi_{\omega}$ )
$\pi_{2 \rightarrow 5} = 0.003$ , $\pi_{2 \rightarrow 6} = 0.001$ , $\pi_{3 \rightarrow 5} = 0.002$ , $\pi_{3 \rightarrow 6} = 0.004$ , $\pi_{4 \rightarrow 5} = 0.003$ , $\pi_{4 \rightarrow 6} = 0.003$ , $\pi_{5 \rightarrow 7} = 0.003$ , $\pi_{6 \rightarrow 8} = 0.003$ , $\pi_{4 \rightarrow 6} = 0.003$ , $\pi_{7 \rightarrow 9} = 0.007$ , $\pi_{8 \rightarrow 9} = 0.006$ .

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