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Redesigning human vaccines supply chain network post-COVID-19 pandemic: a case study of Iran

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Abstract: The emergency need for vaccination during the COVID-19 pandemic has reminded the significance of having an efficient vaccine supply chain network. The fact that the COVID-19 vaccine (C19V) is a newly added member of the vaccine basket highlights the importance of redesigning the current vaccine supply chains, particularly in countries with some existing vaccine manufacturers. In addition, the economic and social drawbacks of the COVID-19 pandemic have led to the vagueness of some factors, such as birth rate and childhood vaccine demand. Hence, this paper proposes a fuzzy multi-period mixed-integer mathematical model to modify the current vaccine supply chain to deal with new challenges after the COVID-19 pandemic. The proposed model is solved using the CPLEX solver in a case study from Iran. Results show that Iran needs four new vaccine manufacturers and eight distribution centres to handle the vaccine transmission between factories and all customers in the new vaccine supply chain network.

Keywords: COVID-19 pandemic effects; COVID-19 vaccine; optimality grade; location-allocation-inventory problem; redesigning supply chain network; uncertain demand; vaccine supply chain; vague vaccine waste rate.

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1 Introduction

It is undeniable that vaccination is the most effective way to prevent or control the outbreak of infectious diseases such as influenza, diphtheria, Ebola, hepatitis and COVID-19, eliminating the drawbacks of the corresponding epidemic or pandemic. Vaccine supply chain planning involves some conventional problems such as location, allocation, transportation, inventory, or equity (Duijzer et al., 2018; De Boeck et al., 2020; Enayati and Özaltın, 2020; Gamchi et al., 2021; Yang et al., 2021; Tavana et al., 2021; Rastegar et al., 2021). Nowadays, all countries are experiencing the various negative social, economic, and political consequences of the COVID-19 pandemic (Rath et al., 2020; Ali and Alharbi, 2020; Nicola et al., 2020; Xiong et al., 2020). After a new vaccine development, the modification of the vaccine supply chain network on a worldwide and national scale is a topic of concern for healthcare systems (Brown et al., 2014; Chen et al., 2014). The C19V is a new family member in the vaccines basket, and its supply network has been investigated by some researchers recently (Georgiadis and Georgiadis, 2021; Balcik et al., 2022; Gilani and Sahebi, 2022; Jahani et al., 2022; Lusiantoro et al., 2022). Nobody knows that humankind will need the C19V in the future, even for newborns. On the other hand, some adverse effects of the COVID-19 disease on the various aspects of life can affect the demand for vaccines in the future. For example, the stressful situation under the COVID-19 pandemic could cause to decline in the goal of a couple to bring a new child. Hence, it is predictable that an increase occurs in the childhood vaccine demand after the COVID-19 immunisation. This situation could cause difficulty in vaccine demand forecasting. Consequently, handling this uncertainty in vaccine supply chain network redesign could be a significant issue for healthcare system authorities. Fuzzy decision-making methods, such as fuzzy mathematical modelling, are one of the several remedies to deal with the uncertainty in supply chain network design (Gargari et al., 2021).

This paper considers the problem of redesigning the vaccine supply chain network after the COVID-19 pandemic occurrence. The demand for vaccines and the vaccines' waste rates are considered fuzzy parameters. It is supposed that the new supply chain must satisfy the domestic demand completely and could fulfil the orders from some foreign customers. A fuzzy mixed-integer mathematical model is developed to redesign the vaccine supply chain network to minimise the total cost and allocate manufacturers, distribution centres, customers' orders, and vaccines' flow across the new supply chain network. Considering the logistical problems of vaccine manufacturers and vaccine distribution planning in a unique decision-making procedure is the main contribution of this paper. Besides, combating several sources of uncertainty involved in vaccine

demands and vaccine waste rate could be mentioned as another aspect of novelty. Additionally, the new proposed model is applied in a real case study.

The remained sections of the paper are as follows. Section 2 provides a literature review on vaccine supply chain planning, and some related materials and methods are reviewed in Section 3. Then, Section 4 provides a problem description and details of the proposed fuzzy mathematical model. Section 5 represents the results of model solving in the case study, and finally, conclusions and some remarks for future works are provided in Section 6.

2 Literature review

In this section, we review the literature on vaccine supply chain planning ranging from cost analysis of distribution networks to decision making about logistical problems, to highlight that there is no literature on redesigning the vaccine supply chain network, particularly under uncertainty resulting from the negative consequences of the COVID-19 pandemic.

Assi et al. (2013) applied a discrete-event simulation to examine the economic effect of removing the regional distributor centre (DC) from a four-tier (central-regional-district-healthcare centres) vaccine distribution network in Niger (Assi et al., 2013). Brown et al. (2014) investigated the effect of adding a new type of vaccine in the vaccine distribution network without suiting the network. They applied a computational method to analyse the influence of joining a new member in the vaccine basket of the Republic of Benin, which showed that there would be a decrease in vaccine availability and an increase in the logistical cost per vaccine dose from 0.23 USD to 0.26 USD. Chen et al. (2014) proposed the first mathematical model to study a four-tier (national DC, regional DCs, district DCs, clinics) vaccine distribution network in developing countries. This model maximises the number of fully immunised children. The model was solved using the CPLEX solver in a case study from Niger under four scenarios, including removing a wire from the distribution network, changing the vial size, adding a new vaccine member, and capacity expansion. Yarmand et al. (2014) proposed a two-stage stochastic mathematical modelling procedure to allocate the vaccines to geographic regions. They aimed the simulation to capture epidemic dynamics and applied their method in the case of seasonal influenza in North Carolina (Yarmand et al., 2014). Hovav and Tsadikovich (2015) proposed a linear mathematical model to minimise the total cost of the influenza vaccine distribution network. They applied this model in the case of CLALIT health services. They considered one manufacturer, one distributor, and five clusters for customers (Hovav and Tsadikovich, 2015).

Duijzer et al. (2018) reviewed the relevant literature to conclude that the current research on the vaccine supply chain mainly focuses on the following four aspects: vaccine quality, demand, allocation, and transport. They identified the same attributes for different vaccine supply chains: high uncertainty in both supply and demand, misalignment of objectives and decentralised decision making between supplier, public health organisation, and end customer; complex political decisions concerning allocation and the crucial importance of deciding and acting in time. Kis et al. (2019) proposed two models to study the potential impact of four vaccine platform production technology on the profitability of Kenya's vaccine supply chain network. They mentioned five layers for

the vaccine supply chain network in Kenya, including vaccine manufacturers in Kenya, Ethiopia, and the USA, national stores in Nairobi, regional stores, district stores, and hospitals (Kis et al., 2019). Lim et al. (2022) proposed a mixed-integer programming model to redesign the traditional four-tier vaccine distribution network in low and medium-income countries. They considered intermediate DCs between the national stores and health clinics. In other words, they replaced the regional and district DCs with intermediate DCs. The model was applied to determine the location of intermediate DCs, the routes, and the allocation of cold vehicles to paths in some countries in Sub-Saharan Africa (Lim et al., 2022). Enayati and Özaltın (2020) proposed a mathematical formulation for equity constraints to have a fair influenza vaccine distribution network. De Boeck et al. (2020) reviewed the literature on vaccine distribution chains in low- and middle-income countries. They highlighted many sources of uncertainties in real-life problems of vaccine distribution. In addition, their review of uncertainty issues involved in the vaccine supply chain showed that some major approaches to deal with uncertainty, including fuzzy theory or possibility theory, have not been used in vaccine supply chain analysis. Lin et al. (2020) considered a two-tier vaccine distribution network, including a distributor and a retailer. They proposed a mathematical model to investigate the effect of two inspection scenarios of retailers using a cold-chain or non-cold-chain for vaccine shipping toward retailers (Lin et al., 2020).

Gamchi et al. (2021) presented a bi-objective mathematical model for cold vehicle routing problems in vaccine distribution chains. The proposed model minimises the social and transport costs simultaneously. They applied the new model in a cholera vaccine distribution. Petroianu et al. (2021) developed an optimisation tool based on the Excel spreadsheet to solve a vehicle routing and scheduling problem to allocate vaccines and other medical resources in Mozambique (Petroianu et al., 2021). Rastegar et al. (2021) proposed a single-objective mixed-integer linear programming model to encounter inventory-location problems in the equitable distribution of influenza vaccine doses during the COVID-19 outbreak. They solved the model in the case of Iran provinces. Tavana et al. (2021) proposed a mixed-integer linear mathematical model to distribute the C19V in developing countries under equity considerations. They solved the model using the CPLEX solver in GAMS software in a case study from India. Yang et al. (2021) proposed a single-objective mixed-integer mathematical model to minimise the total cost in childhood vaccine distribution networks in low and middle-income countries. They developed a new algorithm to solve the model in four countries in sub-Saharan Africa using commercial MIP software. Georgiadis and Georgiadis (2021) proposed a deterministic single-objective model to minimise the total cost of C19V supply, distribution, and injection in a case study from Greece. A three-wire supply chain network including vaccine manufacturers, Hubs, and vaccination centres is considered.

Balcik et al. (2022) proposed a deterministic single-objective mathematical model to reach the maximum equity in C19V allocation to regional centres. They solved it using a hierarchical optimisation approach (HOA) and CPLEX solver in a case study in Turkey. The corresponding C19V distribution network involves a national storage centre in C19V and one main vaccine entry. Gilani and Sahebi (2022) proposed a deterministic multi-objective mathematical model for the C19V supply chain network design problem countrywide, considering three objective functions, including supply chain total cost, environmental emissions, and social effects. They provide a robust solution to the proposed model using polyhedral sets of vaccine accessibility parameters in the case

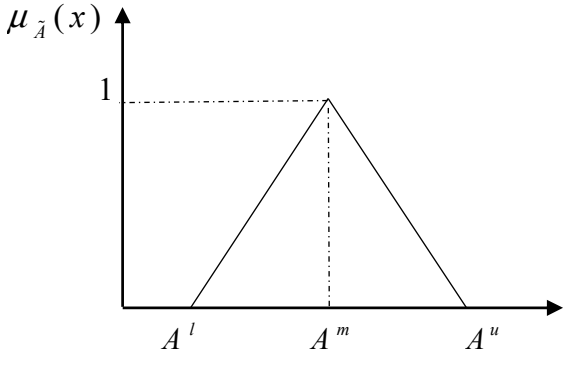
study of Iran. Also, they recommended considering the uncertainty in the vaccine supply and demand for future works. Jahani et al. (2022) proposed a deterministic bi-objective mathematical model to provide more coordination between C19V providers, hospitals, and vaccine applicants, and then optimise the total cost and expected waiting time for vaccination. They used goal attainment programming and NSGA-II to apply the model in a case study of Australia. Lusiantoro et al. (2022) proposed a mathematical model for the location-allocation problem in C19V distribution network design. This model maximises the vaccination coverage and the distance traveled by the population who should be vaccinated. The proposed model is solved using the GUROBI solver in a case study in Indonesia.

According to Brown et al. (2014) and Chen et al. (2014), introducing a new vaccine could affect the vaccine's availability and the logistical cost of the vaccine supply chain. Additionally, Duijzer et al. (2018) and De Boeck et al. (2020) highlighted that uncertainty in the vaccine supply chain is an important topic that could be considered in vaccine supply chain planning. Hence, after the COVID-19 pandemic, it is reasonable that the vaccine supply chain network would receive some adaptation under uncertainty considerations. The literature mentioned above is only about the vaccine distribution network and does not cover problems corresponding to the vaccine manufacturers, such as production line establishment. In this paper, a fuzzy multi-period mixed-integer mathematical model is developed to redesign the vaccine supply chain, involving the current manufacturers and some candidates as new vaccine manufacturers.

3 Background

This section describes the required concepts and methods, including triangular fuzzy number (TFN) and an approach to convert a fuzzy mathematical model into a crisp one, naming optimality grade.

Figure 1 The membership function of $\tilde{A} = (A^l, A^m, A^u)$



3.1 Triangular fuzzy numbers

The membership function of a triangular fuzzy number $\tilde{A} = (A^l, A^m, A^u)$ is defined as equation (1) and shown in Figure 1 (Zimmermann, 1983).

$$\mu_{\tilde{A}}(x) = \begin{cases} 0 & x < A^l \\ (x - A^l)/(A^m - A^l) & A^l < x < A^m \\ (A^u - x)/(A^u - A^m) & A^m < x < A^u \\ 0 & A^u < x \end{cases} \tag{1}$$

When A^l is equal to A^m, the $\tilde{A}$ is called right triangular fuzzy numbers. Equation (2) represents some arithmetic operations on positive triangular fuzzy numbers $\tilde{A} = (A^l, A^m, A^u)$ and $\tilde{B} = (B^l, B^m, B^u)$.

$$\begin{aligned} &\tilde{A}\,(+)\,\tilde{B} = \left(A^l, A^m, A^u\right)(+)\left(B^l, B^m, B^u\right) = \left(A^l + B^l, A^m + B^m, A^u + B^u\right) \\ &\tilde{A}\,(-)\,\tilde{B} = \left(A^l, A^m, A^u\right)(-)\left(B^l, B^m, B^u\right) = \left(A^l - B^u, A^m - B^m, A^u - B^l\right) \\ &\tilde{A}\,(\times)\,\tilde{B} = \left(A^l, A^m, A^u\right)(\times)\left(B^l, B^m, B^u\right) = \left(A^l B^l, A^m B^m, A^u B^u\right) \\ &\tilde{A}\,(\div)\,\tilde{B} = \left(A^l, A^m, A^u\right)(\div)\left(B^l, B^m, B^u\right) = \left(A^l / B^u, A^m / B^m, A^u / B^l\right) \\ &K\tilde{A} = \left(KA^l, KA^m, KA^u\right) \end{aligned} \tag{2}$$

Remarkably, the fuzzy vaccine demands and fuzzy waste rates are non-negative quantities and the aforementioned relations could be helpful to make the corresponding fuzzy mathematical model.

3.2 Optimality grade approach

To solve a fuzzy mathematical model, the first step is considered as its transformation into a crisp model (Tzeng and Huang, 2013; Lai and Hwang, 1992). Suppose there is a fuzzy model as equation (3).

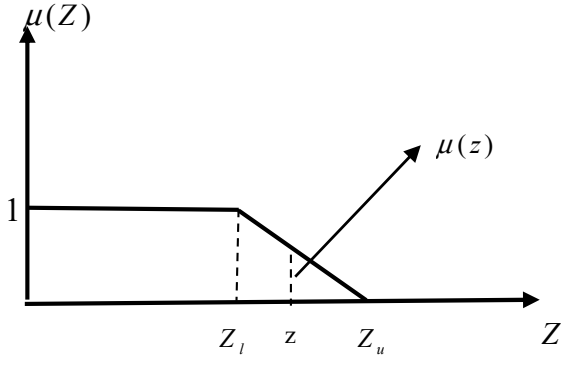
$$\begin{aligned} &\min Z = f(X) \\ &s.t. \\ &AX = \tilde{B} \\ &CX = D \end{aligned} \tag{3}$$

where $CX = D$ is a set of crisp constraints, $AX = \tilde{B}$ is a set of fuzzy constraints, and $\tilde{B}$ is a TFN denoted by (B^l, B^m, B^u). The fuzziness of constraints leads to uncertainty in the value of the objective function. Hence, there is an obligation to handle the uncertainty of both objective function and fuzzy constraints using approaches such as optimality grade.

Suppose Z_u and Z_l are the maximum and minimum values of Z when $\tilde{B}$ is replaced with B_u and B_l, respectively. The membership grade of Z is defined as equation 4 and represented in Figure 2.

$$\mu(z)=\begin{cases}1 & z \le z_l \\ \dfrac{z_u - z}{z_u - z_l} & z_l \le z \le z_u \\ 0 & z \ge z_u\end{cases} \tag{4}$$

Figure 2 The membership function of Z



Equation (5) represents the crisp model corresponding to the primal fuzzy model using the optimality grade approach.

$$\begin{aligned} &Max\ \lambda \\ &s.t. \\ &\quad Z - \lambda(z_u - z_l) \le z_u \\ &\quad AX - \lambda(B^m - B^l) \ge B^l \\ &\quad AX + \lambda(B^u - B^m) \le B^u \\ &\quad CX \le D \\ &\quad 0 \le \lambda \le 1 \end{aligned} \tag{5}$$

where λ is assumed to be the maximum of the minimum value of $\mu(z)$. In the case of multi-objective models, λ is considered as the maximum of the minimum value between all membership grades allocated to several objective functions.

4 Problem formulation

This section contains a description of the mentioned problem, some basic assumptions, and details of the proposed model.

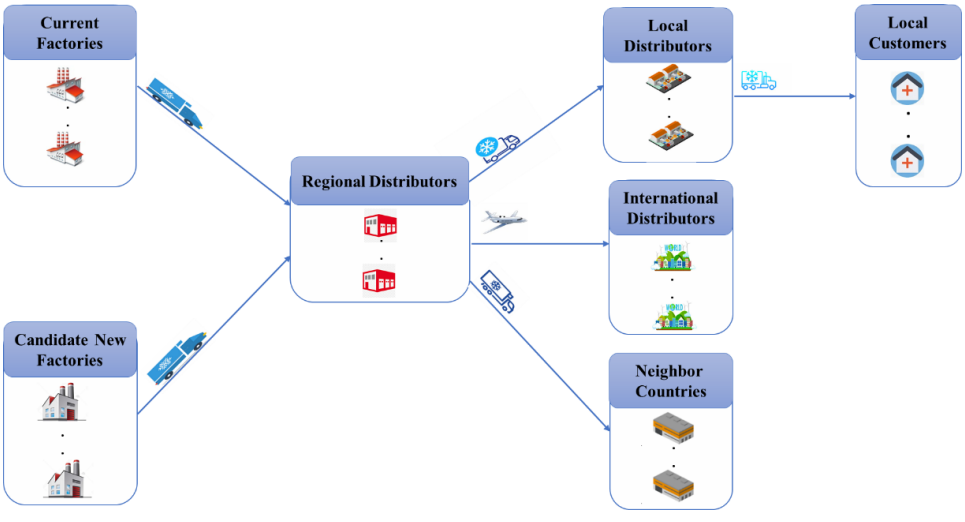
4.1 Problem description

There is no doubt that the COVID-19 pandemic has had a wide range of harmful effects on social relationships, individuals' feelings, and the economy. One of these downsides is

to delay in the child bringing by some couples. They may prefer to do it after the COVID-19 pandemic. Nowadays, vaccination against the COVID-19 virus has been going worldwide at a different rate in any corner of the world. It seems that some undeveloped and also developing countries will be in a struggle with COVID-19 vaccination. In other words, one or more years after 2021, a high need for C19V would occur. Also, there is no reliable information that confirms the lack of necessity for repeating the COVID-19 vaccination after a specific period. In addition, there might be an obligation to enter the C19V into the childhood vaccines basket. Hence, redesigning the current vaccines supply chain network could be a noticeable problem for healthcare systems. After the COVID-19 pandemic, it is difficult to forecast the rate of newborns because of factors such as stress, economic issues, and limitations on required services for pregnant that negatively affected the motivation of parents to bring a new child during the pandemic. As a result, it is impossible to forecast a crisp value for the demand for childhood vaccines post-COVID-19 pandemic. In addition, historical data shows a wide range of vaccine waste rates. It might be rooted in the multi-dose packing for vaccine vials. When a vial is opened, it must be consumed during a short period because of its high potential perishability nature.

In this paper, it is supposed there are some active vaccine manufacturers in the supply chain network present. To expand the market and involve new members in the vaccine basket, a set of candidates of new manufacturers, several candidates of distribution centres, and some new customers are considered in the new vaccine supply chain. The main issues are the location of new manufacturers, the allocation of vaccines' production lines to manufacturers, the location of major distributors, the flow of vaccines across the network, and the inventory level. Figure 3 represents the structure of the considered network for the vaccines supply chain.

Figure 3 Schematic representation of suggested vaccine supply chain network (see online version for colours)



Some other considered assumptions in this problem are as follows:

- demand must be fully satisfied
- foreign orders are in crisp quantities
- the newborn population size is an uncertain parameter
- the vaccine waste rate is an uncertain parameter
- shortage is not allowed
- when a new factory is established, it must be active up to the end of the planning period
- when a new vaccine production line is created, it must be active up to the end of the planning period.

In the following subsection, a new fuzzy mixed-integer mathematical model is proposed to encounter the problem mentioned above.

4.2 Proposed model

Details of the proposed fuzzy mathematical model are as follows.

4.2.1 Indices

f Index of candidate locations of new factories ($f = 1, 2, \ldots, F$).

m Index of the current factories ($m = 1, 2, \ldots, M$).

i Index of the foreign customers, including neighbour countries and international distributors ($i = 1, 2, \ldots, I$).

e Index of the candidate locations of regional DCs ($e = 1, 2, \ldots, E$).

p Index of the candidate locations of local DCs ($p = 1, 2, \ldots, P$).

r Index of the local customers ($r = 1, 2, \ldots, R$).

q Index of vaccine type ($q = 1, 2, \ldots, Q$).

t Index of periods ($t = 1, 2, \ldots, T$).

t' Index of periods ($t' = 1, 2, \ldots, T$).

4.2.2 Parameters

$\tilde{D}_{rqt}$ Fuzzy demand of local customer r for vaccine type q during period t.

Di_{iqt} Demand of foreign customer i for vaccine type q during period t (doses).

$fixf_{ft}$ Fixed cost of new factory f establishing.

$fixe_{et}$ Fixed cost of regional distributors e establishing.

$fixfq_{fqt}$ Fixed cost per capacity for vaccine type q production in the new factory f during period t.

dfe_{fe} Distance from candidate new factory *f* to regional distributor *e*.

dme_{me} Distance from existing factory *m* to regional distributors *e*.

dep_{ep} Distance from regional distributors *e* to local distributor *p*.

dpr_{pr} Distance from local distributor *p* to local customer *r*.

dei_{ei} Distance from regional distributor *e* to foreign customer *i*.

$tcfe_{fet}$ The transportation cost of each dose of vaccines per distance from candidate new factory *f* to regional distributors *e* during period *t*.

$tcme_{met}$ The transportation cost of each dose of vaccines per distance from existing factory *m* to regional distributor *e* during period *t*.

$tcep_{ept}$ The transportation cost of each dose of vaccines per distance from regional distributor *e* to local distributor *p* during period *t*.

$tcpr_{prt}$ The transportation cost of each dose of vaccines per distance from local distributor *p* to local customer *r* in the period *t*.

$tcei_{eit}$ The transportation cost of each dose of vaccines per distance from the regional distributor *e* to foreign customer *i* during period *t*.

hce_{eqt} The holding cost of each dose of vaccine *q* in regional distributor *e* during period *t*.

hcp_{pqt} The holding cost of each dose of vaccine *q* in local distributor *p* during period *t*.

hcr_{rqt} The holding cost of each dose of vaccine *q* in local customer *r* during period *t*.

$pcfe_{feqt}$ The price of each dose of vaccine *q* shipped from candidate new factory *f* to regional distributor *e* during period *t*.

$pcme_{meqt}$ The price of each dose of vaccine q shipped from existing factory m to regional distributor during period t.

$pcep_{epqt}$ The price of each dose of vaccine *q* shipped from regional distributors *e* to local distributor *p* during period *t*.

$pcpr_{prqt}$ The price of each dose of vaccine q shipped from local distributor *p* to local customer *r* during period *t*.

$pcei_{eiqt}$ The price of each dose of vaccine *q* shipped from regional distributor *e* to foreign customer *i* during period *t*.

vpf_{fqt} The capacity of candidate new factory *f* to produce vaccine *q* during period *t*.

vpm_{mqt} The capacity of existing factory *m* to produce vaccine *q* during period *t*.

vhe_{eqt} The capacity of regional distributor *e* to hold vaccine *q* during period *t*.

vhp_{pqt} The capacity of local distributor *p* to hold vaccine *q* during period *t*.

vhr_{rqt} The capacity of local customer *r* to hold vaccine *q* during period *t*.

$\tilde{\alpha}_{rqt}$ Fuzzy waste rate of vaccine q in local customer r during period t.

λ_q The consumption rate of vaccine q per individual.

s The annual interest rate.

4.2.3 Decision variables

QFE_{feqt} The number of doses of vaccine q shipped from candidate new factory f to regional distributor e during period t.

QME_{meqt} The number of doses of vaccine q shipped from existing factory m to regional distributor e during period t.

QEP_{epqt} The number of doses of vaccine q shipped from distributor e to local distributor p during period t.

QPR_{prqt} The number of doses of vaccine q shipped from local distributor p to local customer r during period t.

QEI_{eiqt} The number of doses of vaccine q shipped from distributor e to the foreign customer i during period t.

IQE_{eqt} Inventory level of vaccine q (in doses) in regional distributor e at the end of period t to use during period $t + 1$.

IQP_{pqt} Inventory level of vaccine q (in doses) in local distributor p at the end of period t to use during period $t + 1$.

IQR_{rqt} Inventory level of vaccine q (in doses) in local customer r at the end of period t to use during period $t + 1$.

YF_{ft} 1 if candidate new factory f is active during period t, otherwise 0.

YE_{et} 1 if the regional distributor e is active during period t, otherwise 0.

YFQ_{fqt} 1 if the production line of vaccine q is active in candidate new factory f during period t, otherwise 0.

YMQ_{mqt} 1 if the production line of vaccine q is active in the existing factory m during period t, otherwise 0.

YCF_{ft} 1 if candidate new factory f is constructed during period t, otherwise 0.

YCE_{et} 1 if the regional distributor e is contracted for the first time during period t, otherwise 0.

4.2.4 Mathematical model

By using the aforementioned definitions, the proposed fuzzy mixed-integer linear programming model for the vaccines supply chain network redesigning problem is as follows:

$$
\begin{aligned}
Min\ Z = & \sum_{f}\sum_{t} fixf_{ft} YCF_{ft} + \sum_{f}\sum_{t'\geq t} fixf_{ft} YCF_{ft} s + \sum_{e}\sum_{t} fixe_{et} YCE_{et} \\
& + \sum_{e}\sum_{t'\geq t} fixe_{et} s YCE_{et} + \sum_{f}\sum_{q}\sum_{t} vf_{fqt}\, fixfq_{fqt} YFQ_{fqt} \\
& + \sum_{f}\sum_{q}\sum_{t'\geq t} vf_{fqt}\, fixfq_{fqt} s YFQ_{fqt} + \sum_{m}\sum_{q}\sum_{t} vm_{mqt} YMQ_{mqt}\, fixmq_{mqt} \\
& + \sum_{m}\sum_{q}\sum_{t'\geq t} vm_{mqt}\, fixmq_{mqt} s YMQ_{mqt} \\
& + \sum_{m}\sum_{q}\sum_{t} fixmq_{mqt}\left(vm_{mqt} YMQ_{mqt} - \sum_{e} QME_{meqt} \right) \\
& + \sum_{f}\sum_{e}\sum_{q}\sum_{t} pcfe_{feqt} QFE_{feqt} \\
& + \sum_{f}\sum_{q}\sum_{t} fixfq_{fqt}\left(vf_{fqt} YFQ_{fqt} - \sum_{e} QFE_{feqt} \right) \\
& + \sum_{m}\sum_{e}\sum_{q}\sum_{t} pcme_{meqt} QME_{meqt} + \sum_{e}\sum_{p}\sum_{q}\sum_{t} pcep_{epqt} QEP_{epqt} \\
& + \sum_{e}\sum_{i}\sum_{q}\sum_{t} pcei_{eiqt} QEI_{eiqt} + \sum_{f}\sum_{e}\sum_{q}\sum_{t} dfe_{fe} ctfe_{fet} QFE_{feqt} \\
& + \sum_{p}\sum_{r}\sum_{q}\sum_{t} pcpr_{prqt} QPR_{prqt} + \sum_{m}\sum_{e}\sum_{q}\sum_{t} dme_{me} ctme_{met} QME_{meqt} \\
& + \sum_{e}\sum_{p}\sum_{q}\sum_{t} dep_{ep} ctep_{ept} QEP_{epqt} + \sum_{p}\sum_{r}\sum_{q}\sum_{t} dpr_{pr} ctpr_{prt} QPR_{prqt} \\
& + \sum_{e}\sum_{q}\sum_{t} hce_{eqt} IQE_{eqt} + \sum_{e}\sum_{i}\sum_{q}\sum_{t} dei_{ei} ctei_{eit} QEI_{eiqt} \\
& + \sum_{p}\sum_{q}\sum_{t} hcp_{pqt} IQP_{pqt} + \sum_{r}\sum_{q}\sum_{t} hcr_{rqt} IQR_{rqt}
\end{aligned}
\tag{6}
$$

$$
\sum_{e} QEI_{eiqt} = Di_{iqt} \qquad \forall i, q, t \tag{7}
$$

$$
IQR_{rq,t-1} + \sum_{p} QPR_{prqt} = \left(1 + \tilde{\alpha}_{rqt}\right) \lambda_q \tilde{D}_{rqt} + IQR_{rqt} \qquad \forall r, q, t = 2, \ldots, T-1 \tag{8}
$$

$$
\sum_{p} Qpr_{prqt} = \left(1 + \tilde{\alpha}_{rqt}\right) \lambda_q \tilde{D}_{rqt} + IQR_{rqt} \qquad \forall r, q, t = 1 \tag{9}
$$

$$
IQR_{rq,t-1} + \sum_{p} QPR_{prqt} = \left(1 + \tilde{\alpha}_{rqt}\right) \lambda_q \tilde{D}_{rqt} \qquad \forall r, q, t = T \tag{10}
$$

$$
IQP_{pq,t-1} + \sum_{e} QEP_{epqt} = \sum_{r} QPR_{prqt} + IQP_{pqt} \qquad \forall p, q, t = 2, \ldots, T-1 \tag{11}
$$

$$
\sum_{e} QEP_{epqt} = \sum_{r} QPR_{prqt} + IQP_{pqt} \qquad \forall p, q, t = 1 \tag{12}
$$

$$IQP_{pq,t-1} + \sum_{e} QEP_{epqt} = \sum_{r} QPR_{prqt} \qquad \forall p, q, t = T \qquad (13)$$

$$IQE_{eq,t-1} + \sum_{f} QFE_{feqt} + \sum_{m} QME_{meqt} = \sum_{p} QEP_{epqt} + \sum_{i} QEI_{eiqt} + IQE_{eqt} \qquad \forall e, q, t = 2, \ldots, T-1 \qquad (14)$$

$$\sum_{f} QFE_{feqt} + \sum_{m} QME_{meqt} = \sum_{p} QEP_{epqt} + \sum_{i} QEI_{eiqt} + IQE_{eqt} \qquad \forall e, q, t = 1 \qquad (15)$$

$$IQE_{eq,t-1} + \sum_{f} QFE_{feqt} + \sum_{m} QME_{meqt} = \sum_{p} QEP_{epqt} + \sum_{i} QEI_{eiqt} \qquad \forall e, q, t = T \qquad (16)$$

$$\sum_{i} QEI_{eiqt} + \sum_{p} QEP_{epqt} \le YE_{et} M \qquad \forall e, q, t \qquad (17)$$

$$YE_{et} \le \sum_{i} QEI_{eiqt} + \sum_{p} QEP_{epqt} \qquad \forall e, q, t \qquad (18)$$

$$\sum_{f} QFE_{feqt} + \sum_{m} QME_{meqt} \le YE_{et} M \qquad \forall e, q, t \qquad (19)$$

$$YE_{et} \le \sum_{f} QFE_{feqt} + \sum_{m} QME_{meqt} \qquad \forall e, q, t \qquad (20)$$

$$YE_{et} \ge YE_{e,t-1} \qquad \forall e, t \ge 2 \qquad (21)$$

$$YCE_{et} = YE_{et} - YE_{e,t-1} \qquad \forall e, t \ge 2 \qquad (22)$$

$$YCE_{et} = YE_{et} \qquad \forall e, t = 1 \qquad (23)$$

$$YF_{ft} \ge YF_{f,t-1} \qquad \forall f, t \ge 2 \qquad (24)$$

$$YCF_{ft} = YF_{ft} - YF_{f,t-1} \qquad \forall f, t \ge 2 \qquad (25)$$

$$YCF_{ft} = YF_{ft} \qquad \forall f, t = 1 \qquad (26)$$

$$YFQ_{fqt} \ge YFQ_{fq,t-1} \qquad \forall f, q, t \ge 2 \qquad (27)$$

$$YF_{ft} \ge YFQ_{fqt} \qquad \forall f, q, t \qquad (28)$$

$$YF_{ft} \le \sum_{q} YFQ_{fqt} \qquad \forall f, t \qquad (29)$$

$$\sum_{e}\sum_{q} QFE_{feqt} \le YF_{ft} M \qquad \forall f, t \qquad (30)$$

$$\sum_{e} QFE_{feqt} \le vpf_{fqt} YFQ_{fqt} \qquad \forall f, q, t \qquad (31)$$

$$\sum_{e} QME_{meqt} \le vpm_{mqt} YMQ_{mqt} \qquad \forall m, q, t \qquad (32)$$

$$YMQ_{mqt} \ge YMQ_{mq,t-1} \qquad \forall m, q, t \qquad (33)$$

$$IQE_{eqt} \le vhe_{eqt} \qquad \forall e, q, t \qquad (34)$$

$$IQP_{pqt} \le vhp_{pqt} \qquad \forall p, q, t \qquad (35)$$

$$IQR_{rqt} \le vhr_{rqt} \qquad \forall r, q, t \qquad (36)$$

$$QFE_{feqt}, QME_{meqt}, QEP_{epqt}, QEI_{eiqt}, QPR_{prqt}, IQE_{eqt}, IQP_{pqt}, IQR_{rqt} \in Z^{+}, YF_{ft}, YE_{et}, YCF_{ft}, YCE_{et}, YFQ_{fqt}, YMQ_{mqt} = 0 \text{ or } 1 \qquad \forall m, f, e, p, r, q, t \qquad (37)$$

The objective function, equation (6), is total cost of supply chain network and contains twenty-three items, including fixed cost of new factories construction, opportunity cost of new factories construction, fixed cost of regional distributors establishment, opportunity cost of regional distributors establishing, fixed cost of vaccine production line providing in the new factories, opportunity cost of vaccine production line establishment in the new factories, fixed costs of vaccine production line providing in the existing factories, opportunity cost of vaccine production line providing in the existing factories, penalty cost for unused provided capacity in the existing factories, penalty cost for unused provided capacity in the new factories, purchasing cost of vaccines shipped from new factories to regional distributors, purchasing cost of vaccines shipped from existing factories to regional distributors, purchasing costs of vaccines shipped from regional distributors to the local distributors, purchasing cost of vaccines shipped from local distributors to local customers, purchasing cost of vaccines shipped from regional distributors to foreign customers, transportation cost of vaccines shipped from new factories to regional distributors, transportation cost of vaccines shipped from existing factories to regional distributors, transportation cost of vaccines shipped from regional distributors to local distributors, transportation cost of vaccines shipped from local distributors to local customers, transportation cost of vaccines shipped from regional distributors to foreign customers, holding cost of vaccines in regional distributors, holding cost of vaccines in local distributors, and holding cost of vaccines in local distributors, respectively. Equation (7) ensures that the whole demand from foreign customers is satisfied. Equations (8)–(10) ensure that the demand from local customers is completely satisfied. Equations (11)–(13) guarantee the balance between the outputs and inputs in each local distributor in any period, and equations (14)–(16) ensure the balance of flows in each regional distributor. Constraint (17) guarantees that when a regional distributor is established, shipping vaccines from this distributor to foreign customers and

local distributors is possible. Inversely, constraint (18) guarantees when there is no need to ship any vaccine from a regional centre, it must not be established. Constraint (19) ensures that when a candidate regional distributor is created, shipping vaccines from factories to this distributor is possible. Adversely, constraint (20) guarantees when there is no need for shipping any vaccine from factories to a regional centre, it is not possible to establish that regional distributor. Constraint (21) guarantees that when a regional distributor is provided in a period, it must be active afterward. Equations (22) and (23) determine the creation period of regional distributors. Constraints (24)–(26) have a role similar to constraints (21)–(23), but about new factories. Constraint (27) guarantees that when the production line of any vaccine is established in a factory in a specific period, it must be active in the following periods too. Constraint (28) ensures that even if there is a need for at least one type of vaccine production line in a factory, that factory must be established. Constraint (30) guarantees that when a new factory is created, shipping vaccine from it to regional distributions is possible. Constraints (31) and (32) make sure that the capacity limits of factories are satisfied. Constraints (34)–(36) satisfy the holding capacity of the regional distributors, local distributors, and local customers. Finally, Constraint (37) defines the type of decision variables.

5 Case study

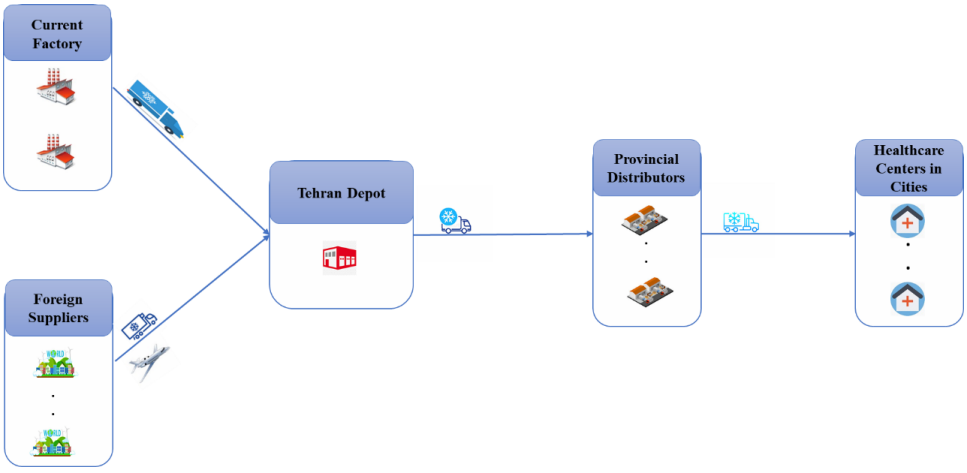
Iran has a vaccine supply chain with more than one-century history and two major vaccine manufacturers, named Pasteur and Razi. In this section, the proposed model is solved to modify the Iran vaccine supply chain after the COVID-19 pandemic.

5.1 Current Iran vaccine supply chain network

Pasteur Institute of Iran was established in 1920 and is an organisation that belongs to the Iran health and medical training ministry. The mission of this centre is to perform research about human vaccines and facilitate vaccine production in Iran. Although the list of Iran Pasteur institute's products consists of a wide range of human vaccines already, nowadays, it is producing only two types of human vaccines, including the Bacillus Calmette-Guérin (BCG) vaccine and the hepatitis B (HB) vaccine. It also makes some by-products, especially a wide range of solvents. Razi is a research institute about vaccines and serums under Iran's agricultural ministry administration. Its history backs to 1923 with a primal objective to produce cattle plague, and nowadays, it provides several products, such as animal vaccines, human vaccines, serums, and solvents. Its human vaccines family includes the diphtheria vaccine, tetanus vaccine, diphtheria-tetanus (DT) vaccine, polio vaccine, measles vaccine, rubella vaccine, mumps vaccine, and some other products based on a combination of several vaccines. The factory of these major vaccine manufacturers is located in Karaj City, the capital of Alborz Province, approximately 50 kilometres far distance from Tehran. Currently, Iran imports a proportion of its needs from foreign sources, such as some institutes from France, Germany, and India, especially those vaccines that are not produced nationally due to economic considerations or lack of production technology. For example, all annual national demand for the Influenza vaccine has been supplied from outer countries. In Iran, there is at least one provincial university of medicine, particularly in the capital city of each province, managing the distribution network of vaccines there. The produced vaccines in

manufacturers and the imported vaccines by cargo should be transported to a depot in Tehran. Monthly, the cold truck of each provincial medicine university travels to this depot and then ships the required vaccines to the corresponding local DC. Then, the orders from local healthcare centres in various cities will be shipped by smaller cold trucks. In addition, there is a cold warehouse in each element of the Iran vaccine supply chain to keep inventories. If any vaccine vials would not be used for a specific duration after its opening, the remained doses must be disposed of. Figure 4 shows a schematic representation of the present Iran vaccine supply chain network.

Figure 4 The old human vaccine supply chain network of Iran (see online version for colours)



5.2 Input data

In this case study, it is assumed that there are two existing factories, including Razi (m = 1) and Pasteur (m = 2) institutes. Also, four provinces of West Azerbaijan (f = 1), Razavi Khorasan (f = 2), Yazd (f = 3), and Kermanshah (f = 4) are considered four candidates to establish new vaccine factories. In addition, eight provinces including West Azerbaijan (e = 1), Yazd (e = 2), Kermanshah (e = 3), Bushehr (e = 4), Alborz (e = 5), Chaharmahal and Bakhtiari (e = 6), Razavi Khorasan (e = 7), and Sistan and Baluchestan (e = 8) are supposed to be candidates of regional DCs. Additionally, 31 provincial DCs, and 426 local customers, eight types of commonly used vaccines, including BCG, HB, oral poliovirus vaccine (OPV), pentavalent vaccine (diphtheria, pertussis, tetanus, HB, and haemophilus influenza type B), DTP vaccine (diphtheria, tetanus, and pertussis), MMR vaccine (measles, mumps, and rubella), influenza vaccine, and C19V are mentioned in this case study. Moreover, six neighbour countries, including Pakistan (i = 1), Afghanistan (i = 2), Azerbaijan (i = 3), Armenia (i = 4), Iraq (i = 5) and Tajikistan (i = 6), in addition to one far-distance international distributor (i = 7) are considered seven foreign customers. The time window is supposed to be ten years, from 2022 to 2031. The orders of the international distributors must be shipped by cargo, and all other quantities should be transported by cold trucks.

The demand for each type of vaccine in each of the 424 local customers is forecasted using the annual rate of human generation. It is supposed that after 2022, the C19V will be a member of the childhood vaccination basket. During the two early periods, the demand of each city for the C19V is approximately considered equal to 25% of Iran's population size as the unvaccinated population of Iran up to then. After the second period, the forecasted number of newborn children is considered the base value of the C19V demand. Overall, we applied a 30% decrease and a 10% increase on the forecasted demand parameters to get the lower and upper values of the corresponding fuzzy demand. These extreme values help to consider the effect of the COVID-19 pandemic on regeneration rate reduction. For the influenza vaccine, it is supposed that 35% of the forecasted population of Iran in forthcoming years has demand for it. Other types of vaccines belong to the conventional childhood vaccination program in Iran. To change the forecasted crisp values for vaccine demand in Iran, we follow the same approach as the C19V. In addition, we considered 25% of each foreign country's annual demand as their order. Also, the order (million doses) of one international distributor in each vaccine during the first period is supposed to be 10, 10, 60, 10, 45, and 90, respectively. These values are considered to rise by a rate of 10% annually. In this case study, only the demand of international distributors is involved in decision making, and its transportation cost is neglected because there may be various destinations during each period. It is supposed that this demand is on behalf of the World Health Organization (WHO) to use in immunisation programs in several developing countries, such as some African countries. The fixed costs (million USD) for new factories establishing are 60, 58, 53 and 50, respectively. Also, the establishing costs of regional DCs (million USD) are considered equal to 10, 11, 13, 10, 10, 12, 11.5, and 12, respectively. The distances between any couple of items are derived from official national or international geographical publications.

In Iran, any public vaccination program performs under governmental administration, and so is gratis. For this, we considered the price of vaccines as constant numbers across the network during all periods. The purchasing cost (USD) per dose of these eight vaccines is supposed to be 0.006025, 0.245, 0.0945, 1.152, 0.0165, 2.235, 11.8, and 10, respectively. In fact, in the case of Iran, vaccines' selling economic benefits are not significant objectives in vaccine logistical decisions. The holding cost of each dose of vaccines is supposed to be 5% of the vaccine price and will be increased by 10% annually. The transportation costs (USD) of each dose of vaccines per distance are considered as $tcfe_{fet} = 0.00005$, $tcme_{met} = 0.00005$, $tcep_{ept} = 0.00003$, $tcpr_{prt} = 0.00002$ and $tcei_{eit} = 0.00007$. The capacity of each new factory to produce eight mentioned vaccines in millions is 5, 5, 40, 5, 5, 5, 30, and 30 doses. The production capacity (million) for these eight vaccines in existing factories is 5, 5, 40, 5, 5, 5, 30, and 50 doses. The holding capacity of regional DCs, provincial DCs, and local healthcare centres are supposed to be 100,000, 10,000 and 1,000. The fuzzy waste rate $\tilde{\alpha}_{rqt}$ is assumed to be (0.14, 0.2, 0.26) for all vaccines in all local customers during all periods. Some proportions are supposed as $\beta e_{eqt} = 0.2$, $\beta p_{pqt} = 0.2$, $\beta r_{rqt} = 0.2$, and $\delta_{fqt} = 0.5$. The consumption rate of each vaccine per person is 1, 2, 7, 1, 5, 2, 1, and 2 doses, respectively. The annual interest rate is supposed to be 0.03.

5.3 Model solving

Due to the fuzziness of some parameters, including national demand and vaccine waste rate, constraints (3), (4) and (5) contain uncertainty, causing vagueness in the optimum value of the objective function. To encounter this issue, the fuzzy value of these parameters should be replaced by their corresponding minimum and maximum values, and two new deterministic models must be solved separately. After that, there are two optimum values of the objective function, naming Z^l and Z^u, in order. In the case study, these two crisp mathematical models are solved using the CPLEX solver of GAMS software in 84,659 seconds. Results present the values Z^l = 32,590,110,566 and Z^u = 78,146,692,862 as lower and upper bounds of the objective function, respectively. By using the optimality grade approach, the primal fuzzy model can be transformed into the following crisp model:

$$Max\ \lambda$$

$$Z - \lambda(78{,}146{,}692{,}862 - 32{,}590{,}110{,}566) \le 78{,}146{,}692{,}862$$

$$QIr_{rq,t-1} + \sum_p Qpr_{prqt} - QIr_{rqt} - \lambda\left(\left(1+\alpha^m_{rqt}\right)\lambda_q D^m_{rqt} - \left(1+\alpha^l_{rqt}\right)\lambda_q D^l_{rqt}\right) \ge \left(1+\alpha^l_{rqt}\right)\lambda_q D^l_{rqt}$$

$$QIr_{rq,t-1} + \sum_p Qpr_{prqt} - QIr_{rqt} + \lambda\left(\left(1+\alpha^u_{rqt}\right)\lambda_q D^u_{rqt} - \left(1+\alpha^m_{rqt}\right)\lambda_q D^m_{rqt}\right) \le \left(1+\alpha^u_{rqt}\right)\lambda_q D^u_{rqt}$$

$$\sum_p Qpr_{prqt} - QIr_{rqt} - \lambda\left(\left(1+\alpha^m_{rqt}\right)\lambda_q D^m_{rqt} - \left(1+\alpha^l_{rqt}\right)\lambda_q D^l_{rqt}\right) \ge \left(1+\alpha^l_{rqt}\right)\lambda_q D^l_{rqt}$$

$$\sum_p Qpr_{prqt} - QIr_{rqt} + \lambda\left(\left(1+\alpha^u_{rqt}\right)\lambda_q D^u_{rqt} - \left(1+\alpha^m_{rqt}\right)\lambda_q D^m_{rqt}\right) \le \left(1+\alpha^u_{rqt}\right)\lambda_q D^u_{rqt}$$

$$QIr_{rq,t-1} + \sum_p Qpr_{prqt} - \lambda\left(\left(1+\alpha^m_{rqt}\right)\lambda_q D^m_{rqt} - \left(1+\alpha^l_{rqt}\right)\lambda_q D^l_{rqt}\right) \ge \left(1+\alpha^l_{rqt}\right)\lambda_q D^l_{rqt}$$

$$QIr_{rq,t-1} + \sum_p Qpr_{prqt} + \lambda\left(\left(1+\alpha^u_{rqt}\right)\lambda_q D^u_{rqt} - \left(1+\alpha^m_{rqt}\right)\lambda_q D^m_{rqt}\right) \le \left(1+\alpha^u_{rqt}\right)\lambda_q D^u_{rqt}$$

Constraints (6)–(35).

The above-mentioned crisp mixed-integer mathematical model is solved by applying the CPLEX solver in GAMS software in 1,804 seconds. Results showed that the optimum value of λ and Z are 0.094 and 37,839,900,000, respectively.

5.4 Results

Table 1 illustrates the year of various vaccine production lines established in each factory.

Table 1 The creation time of each vaccine production line

Vaccine type	*New factories*				*Current factories*	
	f = 1	*f* = 2	*f* = 3	*f* = 4	*m* = 2	*m* = 1
q = 1	3	1	1	2	*	1
q = 2	1	2	1	3	*	1
q = 3	1	1	1	1	1	1
q = 4	1	1	1	3	1	1
q = 5	2	1	1	1	1	*
q = 6	1	1	1	-	1	*
q = 7	10	-	1	1	1	1
q = 8	*1*	*1*	*1*	*7*	*2*	*1*

Table 1 shows that the production lines of vaccines should be created in the new factory established in Yazd in the first year, similar to the Razi institute in Alborz province. In addition, all new factories should be constructed during the first year, and most of the production lines would be run before the third year. Also, OPV is the only type of vaccine that is predicted to be produced in all current and new factories during the first year.

Figure 5 The location of suggested facilities for the vaccine supply chain in Iran (see online version for colours)



Results show that all eight regional DCs should be established during the first period and will be active afterward. Figure 5 illustrates the new structure of vaccine supply chain facilities in Iran.

Table 2 The number of doses of C19V shipped from manufacturers to regional DCs during t = 1

Manufacturer	*e*	*Shipped C19V*
m = 1	8	595,003
f = 1	4	5,000,000
f = 2	1	1,211,975
f = 2	3	541,584
f = 2	6	3,246,440
f = 3	1	3,082,398
f = 3	7	776,263

Table 3 The number of doses of DTP vaccine shipped from regional DCs to provincial DCs during t = 2

p	*e*	*Shipped DTP*	*p*	*e*	*Shipped DTP*	*p*	*e*	*Shipped DTP*
1	7	243,248	12	6	76,638	23	6	65,096
2	1	246,128	13	2	431,322	24	1	198,632
3	6	101,519	14	3	80,741	25	7	131,474
4	2	281,142	15	6	39,053	26	4	124,132
5	1	162,031	16	6	419,311	27	1	143,891
6	8	36,768	17	6	291,137	28	3	75,799
7	3	91,225	18	6	71,990	29	2	175,726
8	-	-	19	6	88,911	30	6	131,226
9	4	78,180	20	2	127,991	31	6	92,129
10	4	92,443	21	2	272,323			
11	7	523,048	22	6	110,228			

Table 4 The number of doses of OPV vaccine shipped from regional DCs to foreign customers during t = 3

i	*e*	*Shipped OPV*
1	7	20,000,000
1	4	1,000,000
3	1	2,500,000
4	8	250,000
5	1	2,500,000
6	6	750,000
7	2	60,000,000

Table 5 The number of doses of vaccines stocked in Yazd regional DC ($QIe_{e=2,qt}$)

t	q	$QIe_{e=2,qt}$
2	6	300,000
2	8	300,000
4	6	300,000
7	2	300,000
9	5	300,000

Table 6 The number of doses of vaccines stocked in the local DCs during the fifth period ($QIp_{pq,t=5}$)

p	q	$QIp_{pq,t=5}$	p	q	$QIp_{pq,t=5}$	p	q	$QIp_{pq,t=5}$
1	5	20,000	11	2	20,000	24	5	20,000
2	6	20,000	12	2	20,000	26	6	20,000
4	6	20,000	16	2	20,000	26	8	20,000
5	2	20,000	16	5	20,000	27	6	20,000
5	7	20,000	17	4	20,000	28	5	20,000
6	4	10,285	19	2	20,000	28	8	20,000
7	7	20,000	20	2	20,000	29	4	20,000
10	2	20,000	23	1	13,259	31	7	20,000
10	4	16,099	24	2	20,000			

It is noticeable that the result contains a considerable number of figures, especially regarding 424 local customers in Iran. Hence, a few results are shown in Tables 2–6 as some instances of shipping quantities and inventories of various vaccines across the newly developed vaccines supply chain network.

6 Conclusions, recommendations and future works

Some effects of the COVID-19 pandemic occurrence were considered in the vaccine supply chain network design. The C19V is a new member of the human vaccines family and must be involved in vaccine supply chain planning. The rate of child generating has been affected by this pandemic, leading to vagueness in demand for childish vaccines. In addition, due to the perishability of vaccine vials, it was considered that the rate of vaccine waste is not a deterministic number. Hence, a fuzzy mixed-integer linear mathematical model was proposed to handle the uncertainty. The model was applied to create a new design for the Iran vaccine supply chain network. The results showed that Iran would need four new vaccine manufacturers and eight regional distribution centres to satisfy the domestic and international demand.

Allocating refrigerated vehicles to ship vaccines between couples of wires in the new vaccine supply chain is a noticeable suggestion for future works. Moreover, adding the vehicle routing problem in the vaccine supply chain network redesigning can enrich the proposed model. Some vaccines, such as the influenza vaccine, follow a seasonal pattern in demand or supply. Fluctuations in demand parameters can affect vaccine accessibility

and its purchasing cost. Hence, considering the demand seasonality in the vaccine supply chain network design can help to optimise the supply chain responsiveness. Supply issues related to raw materials of vaccines could be involved in the vaccine supply chain network design. Proposing a comprehensive supply chain network design involving all types of vaccines, including Animal and human vaccines, in a region can be mentioned in the following research. To be more environmentally friendly, designing a reverse or even closed-loop network for the vaccine supply chain seems a good idea. Finally, the COVID-19 pandemic and Ukraine war teach us that thinking about more reliable and viable suppliers is a significant matter of concern for vital product supply chain planning such as the vaccine supply chain.

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