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A mathematical model for vaccine cold chain network design considering social sustainability

Sosyal sürdürülebilirlik kapsamında aşı soğuk zincir ağ tasarımı için matematiksel model önerisi

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Abstract

Breakages that may occur in the cold chain cause serious economic, environmental, and social costs, as well as a substantial risk for human and public health. Therefore, it is necessary to design an effective, robust, and strong vaccine cold chain network. Sustainable Development Goal 3 titled "Good Health and Well Being" emphasizes children's health and specifies reducing the mortality rate for under five ages. In this study, we consider the Expanded Programme on Immunization (EPI) vaccine cold chain in Türkiye and develop a linear programming model for a multi-product, multi-period, multi-stage vaccine cold chain network in light of Sustainable Development Goal 3. The study aims to maximize fully immunized children for up to five years and propose a framework for a vaccine cold chain network design. The proposed model is applied to a real case. Finally, various scenario analyzes are applied to show the results of the model under different conditions.

Keywords: Expanded program on immunization, Linear programming, Network design, Social sustainability, Vaccine cold chain

Öz

Aşıların tabii olduğu soğuk zincirde meydana gelebilecek kırılmalar; ciddi ekonomik, çevresel ve sosyal maliyetlerin yanında insan ve halk sağlığı açısından da önemli risklere neden olmaktadır. Bu nedenle etkili, sağlam ve güçlü bir aşı soğuk zincir ağının tasarlanması gerekmektedir. Diğer yandan, "Sağlıklı Bireyler" başlıklı Sürdürülebilir Kalkınma Hedefi 3, çocukların sağlığına vurgu yapmakta ve beş yaş altı ölüm oranlarının düşürülmesini hedeflemektedir. Bu çalışmada, Türkiye'deki Genişletilmiş Bağışıklama Programı EPI aşı tedarik zinciri ele alınarak Sürdürülebilir Kalkınma Hedefi 3 ışığında çok ürünlü, çok dönemli, çok aşamalı bir aşı soğuk zincir ağı için doğrusal programlama modeli geliştirilmiştir. Çalışma, beş yaşa kadar tam bağışıklanmış çocuk sayısını en üst düzeye çıkarmayı ve aşı soğuk zincir ağ tasarımı için bir çerçeve önermeyi amaçlamaktadır. Önerilen model vaka çalışmasına uygulanmıştır. Son olarak, çeşitli senaryo analizleri ile model sonuçları değerlendirilmiştir.

Anahtar kelimeler: Genişletilmiş bağışıklama programı, Doğrusal programlama, Ağ tasarımı, Sosyal sürdürülebilirlik, Aşı soğuk zinciri

1 Introduction

Immunization is considered one of the indisputable human rights. However, annually an excessive amount of people, including infants that are around 20 million, do not have access to vaccines, specifically in developing countries. Children under 5 years are particularly at risk. Approximately 5.2 million children under the age of 5 died in 2019. These deaths correspond to the age ranges that are under 28 days (2.4 million deaths), 1 to 11 months (1.5 million deaths), and 1 to 4 years (1.3 million deaths) [1]. Many factors play a role in child mortality. Despite the fact that leading causes of death remain almost the same, there is progress in reducing the under-5 mortality rate [1]. In addition to these improvements, advances in the scope of vaccination are also vital. Thanks to vaccination, child mortality rates have declined significantly since 1990. Today, more than 20 diseases mostly life-threatening are able to be prevented by vaccines [2].

UNICEF indicates that vaccines are among the ultimate improvements in global health and development and the safest method to protect children from critical diseases [3]. Unfortunately, the ratio of children who receive the vaccines has remained the same last few years [2]. On the other hand, the third title of the Sustainable Development Goals (SDG) aims to "ensure healthy lives and promote well-being for all at all ages". Specifically, goal 3.2 aims to reduce newborn and under 5 mortalities at least as low as 12 and 25 respectively per 1000 live births in every country, and goal 3.8 aims to increase to access vaccines for all [4]. It is essential for countries to increase their immunization rates to the best possible level in order to reach SDG 2030.

Studies in the literature regarding the vaccine cold chain cover countries with varying levels of development. Yet, developing countries are of particular importance. Türkiye, which is one of the developing countries, takes into account the vaccines within the scope of the EPI, which WHO recommends for the protection of children from childhood diseases and also provides significant improvements in vaccination services in countries. Since EPI has successfully been implemented, the immunization rate in Türkiye has increased, the infant mortality rate has decreased as low as 9, and the under-5 mortality rate has decreased as low as 9.5

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per 1000 live births in 2020 [5-7]. However, considering the current conditions, in consequence of the various problems in several countries, there are more refugees than ever in Türkiye, such as millions of Syrian, Afghani, Pakistani, and other nationalities up to 320.000 people [8]. Unfortunately, Syria, Afghanistan, and Pakistan have higher mortality rates than other countries [9]. It is a fact that worsening humanitarian conditions accelerate the spread of infectious diseases [10] and also cause children to miss their doses of vaccination [11] Sudden refugee movements with large groups and poor access to vaccination programs may affect the immunization rates adversely in Türkiye [10, 11].

Vaccines are medical products that require exceptional care. Some of them are sensitive to temperature, some to light, and some both. Each vaccine needs different storage conditions, therefore knowing which vaccine can be stored for how long and at what temperature is of foremost importance so that the vaccines do not lose any quality until they are used. Vaccines lose their effectiveness if they are exposed to temperatures from the recommended temperature range. The effectiveness of vaccines is protected by the cold chain. The cold chain refers to the process in which vaccines are transported, stored, and handled under optimum temperature conditions, starting from the point of production until they are administered [12]. The interruption of the cold chain causes product losses and disruption of vaccination programs. A vaccine cold chain is a complex structure that includes various processes, the right temperature, the right equipment, and locations from the vaccine supply to the destinations. Maintaining the efficacy of vaccines depends on understanding and properly addressing this structure [13]. An accomplished vaccination process and higher immunization rate are only possible with the successful design of the vaccine cold chain, which is stronger, robust, and efficient. Hereby, it can be possible to reduce disease transmission.

The unique characteristic of the vaccine cold chain makes the processes more challenging for developing Countries, such as the need for quick response, sufficient resources, strategic decisions regarding equipment, personnel, and transportation vehicles. On the other hand, population density, access and transportation conditions that differ due to the geographical structure also cause difficulties. Chen et al. [14] specify other situations that negatively affect the cold chain process for developing countries in their paper and some of them correspond to the current problem in Türkiye. For instance, migrant populations, changes in birth rates, poor forecasts, and unexpected epidemics or pandemics (such as COVID-19) may cause variations in demand and affect the vaccination process and resources [14].

In developing countries, vaccination coverage may be increased by the efficient delivery of EPI vaccines. The literature contains vaccine cold chain studies with different perspectives. Unfortunately, studies addressing the optimization of the EPI vaccine cold chain from an operations research perspective are limited. In this study, the EPI vaccine distribution chain in Türkiye is considered and four of the EPI vaccines have been involved in the analysis (BCG, DtaP-Hib-IPV, PCV, OPV). Since under five ages are at most risk, 0-4 age children has been taken into account. All doses of vaccines included in the analysis are completed before the age of 4. This study aims to propose a framework for a vaccine cold chain network design to maximize the number of immunized children up to 4 years old. A linear programming model has been developed for a vaccine cold chain network. The proposed model has been applied to a real case. This study has academic, practical, and policy-related contributions. We hope that using the proposed framework will assist policy and decision makers, and practitioners in making integrated decisions for their complex cold chain networks that consider various issues, such as multi-periods, multi-products, storage, and multi-stage. The main contributions of the study can be summarized as below: (a) the proposed model may be used as a framework for the countries which have similar vaccine cold chain processes, (b) the model helps maximizing the immunized population, (c) scenario analyses assist to improve the process and to make the policies regarding vaccination, and (d) lastly, the study has several positive effects for achieving SDG.

The paper is organized as follows. Section 2 consists of relevant literature. The problem statement, mathematical model, and case study are stated in Section 3. Results and scenario analyzes are discussed in Section 4. Section 5 finalizes the study with the conclusion, limitations, and future work suggestions.

2 Related work

In this section, we review the existing literature regarding the vaccine cold chain including mathematical models. Table 1 summarizes the related literature. Vaccine cold chain studies mostly focus on the case study, and they aim to optimize the distribution chain by minimizing the cost, maximizing the immunized children, and considering equity in distribution. Jacobson et al. [15] developed a MIP model for the procurement and delivery of childhood vaccines. They aimed to minimize the total cost of fully immunizing a child by considering the cost of the purchased vaccine, the costs of clinic visits, and the costs of preparing the vaccine by healthcare staff.

Some of the researchers proposed optimization models with the aim of minimizing the overall costs of vaccine supply chains [16, 19]. Hovav and Tsadikovich [16] presented a mathematical model for influenza vaccine distribution and inventory management. Hovav and Herbon [19] applied the model that they developed to the supply chain of the vaccination program conducted by Israel health services. Yang et al. [25] developed a mathematical model to minimize the total costs of EPI vaccine distribution networks in low- and middle-income countries. Saif and Elhedli [18] aimed to minimize total cost and environmental impacts. They proposed mixed-integer concave minimization problem and solved the problem with simulation-optimization approach.

Current doses of vaccines are insufficient when there are outbreaks that require vaccination of the entire population. Thus, an allocation problem arises as to who should be vaccinated.

Table 1. Literature review

Author(s)	Year	Case study	Objective function: Minimize	Objective function: Maximize	Objective function: Multi-objective	Model
Jacobson et al. [15]	1999		✓			MIP
Chen et al. [14]	2014	✓		✓		LP
Hovav and Tsadikovic [16]	2015	✓	✓			MIP
Smalley et al. [17]	2015	✓	✓			MIP
Saif and Elhedli [18]	2016	✓			✓	MIP
Hovav and Herbon [19]	2017	✓	✓			MIP
Carvalho et al. [20]	2019	✓			✓	MILP
Günay et al. [10]	2019	✓		✓		MILP
Lim et al. [21]	2019	✓	✓			MIP
Sadjadi et al. [22]	2019	✓	✓			MILP
Abbasi et al. [23]	2020	✓	✓			MILP
Enayati and Ozaltın [24]	2020		✓			MILP
Yang et al. [25]	2020	✓	✓			MIP
Qasem et al. [26]	2020	✓		✓		MIP
Alizadeh et al. [27]	2021	✓			✓	MIP
Georgiadis and Georgiadis [28]	2021	✓	✓			MILP
Rastegar vd. [29]	2021	✓		✓		MILP
Tavana et al. [30]	2021	✓		✓		MILP
Gilani and Sahebi [31]	2022	✓			✓	MILP
Balcik et al. [32]	2022	✓	✓			IP
Khodaee et al. [33]	2022	✓	✓			MIP

MILP: Mixed integer linear programming, MIP: Mixed integer programming, LP: Linear programming IP: Integer programming

Considering the risk and transmission levels within a population, it can be determined which groups should be given priority [26]. The vaccine allocation problem has been addressed by many researchers [17, 10, 23, 24, 26, 29]. Smalley et al. [17] proposed a mathematical model to find the optimal vaccine allocation strategy to minimize cholera cases in Bangladesh. They analyzed different distribution strategies for different age groups. Günay et al. [10] developed a MILP model to determine the optimal quantities of polio vaccines to be administered in regions with high Syrian refugee populations in Türkiye. The model aimed to maximize the refugee population vaccinated against polio and applied in five cities that have the highest refugee population. In addition, different vaccination strategies were compared for cost-effectiveness in the study. Abbasi et al. [23] developed a mathematical model for vaccine allocation that included operational constraints such as vaccine stocks, storage, and transportation capacities, as well as non-operational constraints such as exposure risks. Enayati and Özaltın [24] considered the equity distribution of influenza vaccines in the model they had developed. The model aimed to minimize necessary vaccine doses to prevent a disease outbreak at the initial stages of the epidemic. Qasem et al. [26] determined the optimal number of cholera vaccines that needed to be distributed based on the risk level of age groups and the population of regions. The authors compared different vaccine policies considering age, population, and both. Rastegar et al. [29] presented an inventory-location model for equitable distribution of influenza vaccine during the COVID-19 pandemic. Then, the authors analyzed the model's performance using real-world data from the influenza vaccine distribution chain in Iran. Balcik et al. [32] discussed the equitable and effective allocation of COVID-19 vaccines to different priority demand groups within the country such as elderly and healthcare workers. They also considers multiple vaccine types and regional characteristics such as storage capacities and infection risk levels. The model aimed to minimize the total deviation from the adequate coverage level. Khodaee et al. [33] developed a MIP model to minimize logistic costs, considering the equitable distribution of COVID-19 vaccines. The authors applied the model to actual vaccine distribution data during the COVID-19 pandemic in Europe. Similarly, Tavana et al. [30] focused on equitable distribution of COVID-19 vaccine in developing countries and developed an inventory-location model. The authors classified vaccines as cold, very cold, and ultracold based on the temperature level requiring for storage and transportation.

Additionally, Lim et al. [21] developed a mathematical model for the optimal design of an EPI vaccine distribution network. Sadjadi et al. [22] aimed to design a vaccine supply chain in Iran. They considered several factors like demand and cost uncertainties, perishability, limited capacity, and different priorities for demands. Alizadeh et al. [27] discussed a vaccine supply chain network design for influenza vaccines during the COVID-19 pandemic. The developed model focused on three main issues; demand allocation based on customer prioritization, loss of customer demand, and cost. The authors applied the model to a case study in Mazandaran, Iran. Few studies in the literature addressed the planning of the vaccine supply chain [14, 28]. Chen et al. [14] developed a planning model for the EPI vaccine distribution chain in developing countries. The model aimed to maximize the number of fully immunized children under current network capacity and adapted to the supply chains of three countries: Niger, Thailand, and Vietnam. Georgiadis and Georgiadis [28] developed a mathematical model for the optimal planning the COVID-19 vaccine supply chain. The developed model considered vaccine perishability, multiple cold storage technologies, transportation lead-times, and demanding vaccination targets. Sustainability of the vaccine supply chain has been also one of the remarkable issues in the literature. Gilani and Sahebi [31] focused on modeling a sustainable COVID-19 vaccine supply chain. The authors developed a multi-stage and multi-period MILP model for a case study in Iran. They offered a multi-objective model including economic, environmental, and social aspects. Costs, emissions, and jobs created within the process are considered for the economic, environmental, and social aspects, respectively. Carvalho et al. [20] focused on the optimal design of a sustainable vaccine supply chain in Europe. They proposed a multi-objective and multi-period MILP model considering triple bottom line. Cash flow, environmental impact, and jobs created within the process are considered for the economic, environmental, and social aspects, respectively. The study aimed to ensure the fulfillment of vaccination through efficient utilization of resources. The developed model was applied to a case study.

Immunization in preventive health care practices rather than cost is vital for public health and social sustainability (SDG 3.2 and 3.8). Child health and long-term public health are possible through effective design and management of the vaccine cold chain. Studies considering child vaccinations [10, 14, 15, 21, 25] are limited, and the number of papers maximizing the vaccinated population [10, 14, 26] is insufficient in the literature. In addition, studies consider social sustainability as job creation within the vaccine cold chain [20, 31]. In this light, we aim to develop a mathematical model to maximize the number of fully immunized children under budgetary constraints aiming directly at goal number three of the SDG. To the best of the authors' knowledge, except for Günay et al. [10], no study takes child immunization into account for Turkey. Our study differs from Günay et al. [10] in that it takes into account the whole child population, more than one vaccine, vaccination under four years old, and SDG-3.

3 Material and method

Although vaccine distribution network varies for each country, they consist of four tiers in general: a central store, regional stores, provincial stores, and clinics [34]. In this study, we discuss the supply chain of vaccines administered within the scope of the EPI in Türkiye. Figure 1 shows the EPI vaccine cold chain network structure in Türkiye. In Türkiye, the EPI supply chain also consists of four tiers. The Ministry of Health is responsible for supplying vaccines, storage, transferring vaccines to the end user, and monitoring the entire process in Türkiye. Vaccines from various manufacturers are first shipped to the central store and according to the amount of vaccine demanded by the regional store they are shipped from central store to the regional store at certain periods by refrigerated trucks. There are 14 refrigerated trucks in Türkiye that deliver vaccines from the central store to the regional stores. The demand of the provincial stores is met from the regional stores to which it is affiliated. The same structure continues between clinics and provincial stores, which are the last stage of the chain. Vaccines are delivered to provincial stores and clinics by refrigerated vehicles smaller than trucks.

In this study, we focus on the part of the vaccine cold chain between the central store and the provincial stores and develop an LP model for a multi-period, multi-product, multi-stage cold chain network for EPI vaccines. The aim of the developed model is to maximize the number of fully immunized children aged 0-4 years by administering all doses of each vaccine. Determined structures and assumptions of the developed model are given below:

- By the phrase "fully immunized child", we mean children who have received all the doses on the EPI immunization schedule.
- Although there are ten vaccines in Türkiye's EPI vaccine schedule, four of these vaccines are considered due to the collectability of the data.
- Wastage rate has been incorporated into the model to take into account the loss of vaccines as a result of breaking the cold chain.
- A capacity utilization rate for both facilities and vehicles has been determined for effective storage and handling in each store and shipping vehicle.
- Safety stock for regional stores have been considered.
- The capacity limitations for the vehicles that deliver vaccines from the regional stores to the provincial stores are ignored.

Different number of doses that is required for immunization for different vaccines is considered in the model. Since vaccines should be placed in the refrigerator in a way that allows sufficient air flow between them [35], a certain part of the total capacity is considered for efficient storage and transportation.

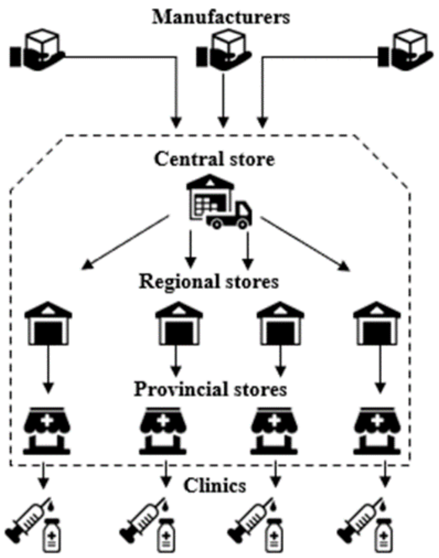

Figure 1. Vaccine cold chain network in Türkiye

3.1 Mathematical model

Indices

I	Index of vaccines, $i \in I$
J	Index of regional stores, $j \in J$
K	Index of provincial stores, $k \in K$
K^j	Index subset of provincial stores that can be served by j, $k^j \in K^j \in K$
T	Index of periods, $t \in T$

Parameters

n_i	Number of doses administered of vaccine i within the vaccine regimen
F_i	Minimum fraction of demand for vaccine i at location j that must be met each period
T_{ikt}	Target population for vaccine i at location k each period
r_i	Target immunization coverage expressed as a decimal number for vaccine i
α_i	Fraction of lost vaccine i
α_{ij}	Fraction of lost vaccine i arisen while transferring vaccine to regional store and/or at regional store
α_{ik}	Fraction of lost vaccine i arisen while transferring vaccine to provincial store and/or at provincial store
c_i	Cost of vaccine i
c_i^w	Waste cost of vaccine i
B	Annual budget of the vaccination campaign
β	Capacity utilization factor considering effective storage
Σ	Fraction of safety stock
w_i	Waste factor for vaccine i
p_i	Effective package volume of one dose of vaccine i
D_{ij}	Annual demand for vaccine i at j (dose)
cap_j	Cold chain capacity of regional store j
cap_k	Cold chain capacity of provincial store k
t_{cap}	Transportation capacity of refrigerated trucks between the central store and regional stores

Decision Variables

X_{ijt}	Number of transported doses of vaccine i from central store to location j in period t
Y_{ijkt}	Number of transported doses of vaccine i from location j to location k in period t
I_{ijt}	Inventory of location j for vaccine i at the end of period t
D_{ikt}	Demand of location k for vaccine i in period t
Z_{ikt}	Number of administered doses at location k in period t
V_j	Annual number of fully immunized children at location j
Q_i	Amount of loss of vaccine i

The model for maximizing the number of fully immunized children formulated as follows:

$$Max \sum_{j} V_j \quad (1)$$

$$D_{ij} = \sum_{\substack{t \in T \\ k \in K^j}} D_{ikt} \qquad i \in I, j \in J \quad (2)$$

$$D_{ikt} = T_{ikt} \,.\, r_i \,.\, n_i \,.\, w_i \qquad i \in I,\ k \in K,\ t \in T \quad (3)$$

$$I_{ijt} = \left(I_{ijt-1} + X_{ijt}\right)\left(1 - \alpha_{ij}\right) - \sum_{k \in K^j} Y_{ijkt} \qquad i \in I,\ j \in J,\ t \in T \quad (4)$$

$$I_{ijt} \geq D_{ij} \,.\, \sigma \qquad j \in J, t \in T \quad (5)$$

$$\sum_{i \in I} X_{ijt} \,.\, p_i \leq cap_j . \beta \qquad j \in J, t \in T \quad (6)$$

$$\sum_{i \in I} Y_{ijkt} \,.\, p_i \leq cap_k . \beta \qquad t \in T,\ k \in K^j,\ j \in J \quad (7)$$

$$\sum_{\substack{i \in I \\ j \in J}} X_{ijt} \,.\, p_i \leq cap_t . \beta \qquad t \in T \quad (8)$$

$$F_i . D_{ikt} \leq Y_{ijkt} \leq D_{ikt} \qquad i \in I,\ k \in K,\ t \in T, j \in J \quad (9)$$

$$V_j \leq \sum_{\substack{t \in T \\ k \in [K^j]}} Z_{ikt} \ / \ n_i \qquad i \in I, j \in J \quad (10)$$

$$Z_{ikt} \leq Y_{ijkt} \,.\, (1 - \alpha_{ik}) \qquad i \in I,\ k \in K^j,\ t \in T, j \in J \quad (11)$$

$$\sum_{\substack{i \in I \\ k \in K \\ t \in T}} c_i . Z_{ikt} + \sum_{i \in I} c_i^w . Q_i \leq B \quad (12)$$

$$Q_i = \sum_{\substack{j \in I \\ t \in T}} X_{ijt} . \alpha_{ij} + \sum_{\substack{j \in J \\ t \in T}} (I_{ijt-1}) . \alpha_{ij} + \sum_{\substack{j \in J \\ k \in K \\ t \in T}} Y_{ijkt} . \alpha_{ik} \quad i \in I \quad (13)$$

$$X_{ijt}, Y_{ijkt}, D_{ikt}, I_{ijt}, Z_{ikt}, Q_i \geq 0 \quad \forall i, j, k, t \quad (14)$$

Equation (1) represents the objective function that maximizes the annual number of fully immunized children. Constraint (2) indicates that the annual vaccine i demands of regional store j is equal to the annual demand of the provincial stores to which the vaccine is shipped. Constraint (3) determines the requested dose amount of vaccine i in the provincial stores for each period, taking into account the target immunization coverage and the waste factor. Constraint (4) determines the stock amount of regional store j. Constraint (5) ensures the minimum stock quantity of regional stores. Constraint (6) stipulates that the total volume of vaccines shipped from the central store to the regional stores at the t time period must not exceed the capacity of the regional stores, considering effective storage. Constraint (7) is a storage capacity constraint for provincial stores. Constraint (8) indicates the transportation capacity between the central store and the regional stores. Constraint (9) indicates the range of required vaccine i supply at each provincial store k in each time period. Constraint (10) determines the number of fully immunized children in the location where the regional store j is located. Constraint (11) stipulates that the number of doses administered in the provincial stores in the period t must not exceed the amount shipped to the provincial store, taking into account the amount of loss. Constraint (12) states that the total cost of administered and lost vaccines must not exceed the budget. Constraint (13) indicates the amount of vaccine lost during shipment to the regional store and the provincial store or while stored there. Lastly, Constraint (14) shows the non-negative decision variables.

3.2 *Case study*

The proposed model has been applied for the vaccine cold chain in Kars province located in the Eastern Anatolia Region of Türkiye with a population of 284.923. The data has been obtained from the Kars Provincial Health Directorate, the EPI circular of the Republic of Türkiye Ministry of Health, literature research, and the Ministry of Health's official website. There is 1 regional store with a vaccine storage capacity of 27 m^3, 8 provincial stores, and 28 clinics in the province. Table 2 contains data for the four EPI vaccines considered in the model.

In Table 2, vaccines are numbered from 1 to 4 and referred so in the following sections of the study. The number of doses required for immunization against each disease varies. For example, for complete immunization, a single dose is required for the vaccine 1, while four doses are required for the vaccine 4. Some vaccines are reconstituted with a diluent before administration, these are called lyophilized vaccines. Vaccine 1 is a lyophilized vaccine, and the required volume of diluent is 0.7 c.c. [14]. The effective package volumes of vaccines, which are taken into account in transportation and storage, are also given in the table. The package volumes of the vaccines in Table 2 are based on data obtained from other studies in the literature [14, 25]. In the model, the volume of diluent is included in the dose-volume of the vaccine 1. Based on the studies in the literature, the costs have been taken as $2 for vaccines 1, 2, and 3 per doses and $3.60 for the vaccine 4 [17, 34] and adapted to the Turkish lira using the current exchange rate (1$≈10₺). The annual vaccination budget for Türkiye was 882.841.000 ₺ in 2016. For the case study, the annual vaccination budget for considered four EPI vaccines has been determined as 40.000.000 ₺. Vaccines may be lost for several reasons while being stored and shipped between stores. The wastage rates in Table 2 have been calculated by summing the rate of vaccine lost while being shipped to or stored in the regional store (αij), and in the provincial store (αik). The wastage rates have been considered as 15% for both stages and 30% in total. The wastage rate directly determines the waste factor that is required for vaccine requirement planning and must be defined for each vaccine [36]. Waste factor information has been calculated with the formula 100/100-% αi for each vaccine. Table 3 contains data regarding provincial stores in Kars.

Table 2. Data about vaccines

No.	Vaccine	Doses administered	Packed volume / dose (c.c)	Diluent volume / dose (c.c)	Waste factor	Fraction of wastage vaccine	Cost (₺)	Waste cost (₺)
1	BCG	1	1.2	0.7	1.42	%30	20	5
2	OPV	2	1.0	-	1.42	%30	40	8
3	PCV	3	12	-	1.42	%30	60	15
4	DTaP-Hib-IPV	4	16.8	-	1.42	%30	144	36

Table 3. Data about provincial stores in Kars province

No	Provincial Stores	Total capacity (m^3)	Target population aged 0-4 (monthly)
1	Selim	0.2	263
2	Arpaçay	0.25	268
3	Susuz	0.25	70
4	Akyaka	0.2	92
5	Digor	0.2	275
6	Sarıkamış	0.4	518
7	Kağızman	0.28	581
8	Merkez	0.5	1315

The total vaccine capacity of each provincial store and the target population for 2020 has been obtained from the Kars Provincial Health Directorate. It has been aimed to immunize 90% of the target population according to the EPI circular of the Ministry of Health. The capacity utilization rate has been determined for effective storage and handling of the regional store, provincial stores, and transportation vehicles as 40% of the total capacity [14].

4 Results and discussion

We have tested the model using a computer with 1.50 GHz processor and 2 GB of RAM and the computation time required to solve the model optimality using the GAMS-CPLEX solver is less than 1 CPU second. The number of fully immunized children expressing the objective function value is 42.188 in Kars in 2020. The dose amounts requested by the regional store for each vaccine during the year are indicated in Table 4.

Table 4. Annual demand of the regional store

D_{ij}	Value
D_{11}	518.076
D_{21}	103.728
D_{31}	155.604
D_{41}	207.456

The total demand in all periods for each vaccine of the provincial stores constitutes the annual demand of the regional store given in Table 4, since the demand of provincial stores is met by the regional store. Transported doses of vaccines from central stores are given in Table 5.

Table 5. The amount of vaccine i transported from the central store to the regional store in the t period (dose)

X_{ijt}	Value	X_{ijt}	Value	X_{ijt}	Value	X_{ijt}	Value
X_{111}	6.152	X_{211}	12.304	X_{311}	18.833	X_{411}	24.608
X_{112}	5.063	X_{212}	10.126	X_{312}	15.188	X_{412}	20.251
X_{113}	5.063	X_{213}	10.126	X_{313}	15.188	X_{413}	20.251
X_{114}	5.063	X_{214}	10.126	X_{314}	15.128	X_{414}	20.251
X_{115}	5.063	X_{215}	10.126	X_{315}	15.128	X_{415}	20.251
X_{116}	5.063	X_{216}	10.126	X_{316}	15.128	X_{416}	20.251
X_{117}	5.063	X_{217}	10.126	X_{317}	15.128	X_{417}	20.251
X_{118}	5.063	X_{218}	10.126	X_{318}	15.128	X_{418}	20.251
X_{119}	5.063	X_{219}	10.126	X_{319}	15.128	X_{419}	20.251
X_{1110}	5.047	X_{2110}	10.095	X_{3110}	15.128	X_{4110}	20.190
X_{1111}	5.043	X_{2111}	10.085	X_{3111}	15.128	X_{4111}	20.170
X_{1112}	5.043	X_{2112}	10.085	X_{3112}	15.128	X_{4112}	20.170

617.873 doses of vaccine have been transported totally from the central store to the regional store during all periods. From central store to the regional stores vaccine 1 has the lowest amount in terms of transported quantities, while vaccine 4 has the highest (40% of the total amount of the four vaccines). Regional store's stock amounts are determined as 1.089, 2.178, 3.268, and 4.357 for all the periods for vaccines 1, 2, 3, and 4, respectively. According to the results, vaccine 4 constitutes 40% of the annual stock of the regional store.

The total annual demand of each provincial store is directly proportional to the target population of that provincial store. Therefore, the demand of the provincial store 8 has the highest target population, while the demand of the provincial store 3 has the lowest target population.

On the other hand, the amount of dose transported to the provincial store 8, which has a higher demand than other provincial stores, is the highest, in the optimum solution. A total of 191.592 doses of vaccine (63.4% of the total transported vaccine) have been transported during all periods.

In the optimum solution, each vaccine has been administered in all provincial stores in each period. The total number of doses administered during all periods in all provincial stores is 421.871. The highest dose has been administered in the provincial store 8 and 38.6% of the total amount of vaccine have been administered. Figure 2 shows the comparison of results for all provincial stores.

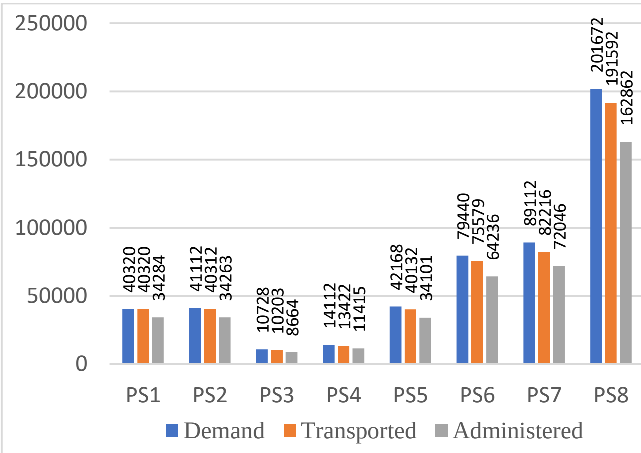

Figure 2. Comparison of results for provincial stores

When we examine the results of the case study that has been solved with the data of 2020, we conclude that the provincial store with the highest total demand depending on the target population is the provincial store 8. Accordingly, the number of doses transported is higher than in other provincial stores, which means more vaccinated children.

4.1 Scenario analysis

The achievement of national immunization programs depends on effective and up-to-date policies and strategies. This part of our study, the effects of budget and wastage rates which are the main problems encountered especially in developing countries in achieving immunization targets on model behavior has been examined. In order to analyze the impact of different budgets and fractions of the lost vaccine on the model, we have developed various scenarios. Then, we have examined the change in the number of immunized children for each scenario.

Table 6. Scenarios

Change	Scenarios 1-6 (Budget)	Scenarios 7-12 (α_{ij})	Scenarios 13-18 (α_{ik})
-30%	28.000.000	10.5%	10.5%
-20%	32.000.000	12%	12%
-10%	36.000.000	13.5%	13.5%
Base	40.000.000	15%	15%
+10%	44.000.000	16.5%	16.5%
+20%	48.000.000	18%	18%
+30%	52.000.000	19.5%	19.5%

In Table 6, scenarios 1-6 have been developed by first decreasing the budget value by 30%, 20%, and 10% respectively, then by increasing it at the same rates. In the following scenarios (7-18), αij (fraction of lost vaccine i raised while transferring vaccine to the regional store and/or at the regional store) and αik (fraction of lost vaccine i raised while transferring vaccine to the provincial store and/or at the provincial store) values have been first decreased by 30%, 20%, and 10%, respectively, and then increased at the same rates. Figure 3 shows the changes in the objective function for scenarios 1-18.

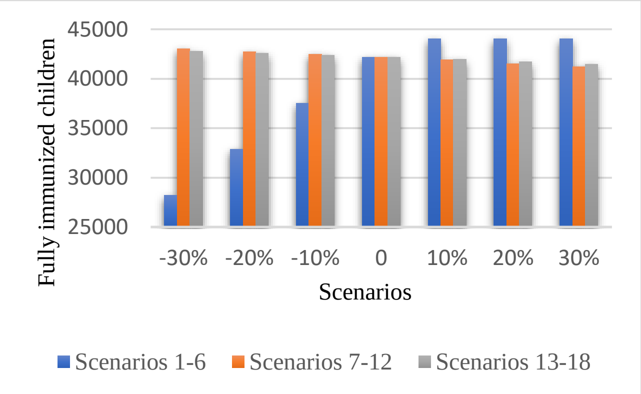

Figure 3. Scenarios

When the annual vaccine budget has been reduced, vaccines could not be administered in each provincial store during each period. For the scenario which the budget has been reduced by 30%, the objective function value is 28.198 and this is the lowest objective function value. For the 20% reduction in the budget, objective function value is 32.871 and for the 10% reduction, it is 37.544. On contrary, when the annual budget has been increased, the objective function value is increased correspondingly. Remarkable that, 10% increase in budget is a sufficient amount to obtain maximum immunization number. That is because, immunization number has no change when 20% and 30% increase take place in budget. Scenario analysis regarding budget change clearly states that decrease in budget threatens the number of immunized children, while increase in budget increases the number up to a level.

Scenarios 7-12 demonstrate that when αij has been reduced by 30% objective function value increases to 43.033. Nevertheless, the increase in the αij value decreases the objective function value to 41.892, 41.558, and 41.211, respectively. As at the regional level, the number of fully immunized children increases as the fraction of lost vaccine decreased at the provincial level. The objective function value is 42.761 for the scenario which the αik value is reduced by 30% and this is the highest value. The lowest objective function value is 41.469 and it is obtained with the scenario which the αik value is increased by 30%. The objective function values of scenarios 7-18 show that reducing vaccine losses means more immunized children. Decision makers and authorities may specify the lost related problems and intervene to improvements regarding the personnel, equipment, storage, transportation process, etc.

In brief, comparing the objective function values for the 18 scenarios, we conclude that the budget-related scenarios are the ones that affect the objective function value the most. However, reducing vaccine losses is very important to reach more children, especially in developing countries with limited budgets for immunization. As a result, avoiding cold chain breaks and increasing the budget are both important for public health and should be evaluated as a whole to make immunization process efficient and reach the targets in developing countries.

5 Conclusion

Although, the COVID-19 pandemic accelerates and enhances the vaccine related studies, studies on childhood vaccines are insufficient. On the other hand, effectively designing and modeling vaccine cold chains is difficult because of having many characteristic constraints. Especially in developing countries, creating an efficient distribution chain is a top priority because of limited budgets for public health and mortality rates depending on preventable diseases with immunization. In this study, we have presented an EPI vaccine cold chain network and proposed a mathematical model with the aim of maximizing the number of fully vaccinated children aged up to 4 years old. We have presented the application of the model in Kars which is one of the important provinces of Türkiye. The number of fully immunized children that expressing the objective function value of the model has been determined as 42.188 for 2020 in Kars. Scenario analyses help to implement some critical policy decisions. Budget scenarios show that if the budget is increased by 10%, the number of children that fully immunized will reach the maximum. In other words, since there will be no difference in the number of children immunized in case of an increase of more than 10% in the budget, the most efficient budget value will be the budget that is %10 more than the current value. Contrary to scenario about budget, other scenarios state that the fewer the number of vaccines lost, the greater the number of children that are fully immunized.

SDG emphasizes that child health needs to be protected as much as possible. As mentioned above, Türkiye has a critical position as the country has more refugees than ever. To be able to provide healthy conditions for every child in the country and equal right to live, this study presents vital insights for decision-makers and practitioners. Additionally, since developing countries have a similar vaccine cold chain networks such as importing vaccines and storing them in a central store and transporting the vaccines to regional and provincial stores and clinics, the model presented in the study may also be used in these countries with the aim of increasing the immunized population. Yet, the study has some limitations such as considering four vaccines of the EPI schedule. In the study, the capacities of the vehicles that deliver vaccines from the regional stores to the provincial stores are ignored and it is assumed that only regional stores have safety stock. Future studies may consider all EPI vaccines, all of the stages of supply chain from production to vaccination, different age ranges, and risk rates.

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Conflict of interest

The authors declare that there is no conflict of interest.

Similarity rate (iThenticate): %14

References

[1] World Health Organization, Children: improving survival and well-being, 08/09/2020. https://www.who.int/news-room/fact-sheets/detail/children-reducing-mortality. Accessed: 19 April 2022.
[2] World Health Organization, Vaccines and immunization, 2021. https://www.who.int/health-topics/vaccines-and-immunization#tab=tab_1. Accessed: 19 April 2022.
[3] UNICEF, Immunization, 2021. https://www.unicef.org/immunization. Accessed: 16 November 2021.
[4] Sustainable Development Goals, Goal 3: Ensure healthy lives and promote well-being for all at all ages, 2022. https://www.un.org/sustainabledevelopment/health/. Accessed: 14 April 2022.
[5] Statista, Infant mortality rate (under one year old) in Turkey from 1950 to 2020, 2022. https://www.statista.com/statistics/1073263/infant-mortality-rate-turkey-historical/. Accessed: 18 April 2022.
[6] UNICEF, Trends in under-five mortality rate in Turkey, 2022. https://data.unicef.org/country/tur/. Accessed: 18 April 2022.
[7] World Bank, Mortality rate under-5 (per 1,000 live births), 2022. https://data.worldbank.org/indicator/SH.DYN.MORT?locations=TR. Accessed: 18 April 2022.
[8] United Nations High Commissioner for Refugees, Refugees and Asylum Seekers in Turkey, 2022. https://www.unhcr.org/tr/en/refugees-and-asylum-seekers-in-turkey. Accessed: 18 April 2022.
[9] World Bank, Mortality rate under-5 (per 1,000 live births), 2022. https://data.worldbank.org/indicator/SH.DYN.MORT?most_recent_value_desc=true. Accessed: 18 April 2022.
[10] E. E. Günay, K. Park, S. Aydoğan and G. E. Okudan Kremer. Vaccine Distribution Strategies against Polio: An Analysis of Turkey Scenario. Industrial and manufacturing systems engineering conference proceeding and posters, Orlando, Florida, USA, 2019.
[11] UNICEF, Immunizaton, 2022. https://www.unicef.org/turkey/en/immunization. Accessed: 16 November 2022.
[12] K. Shafaat, A. Hussain and B. Kumar, An Overview: Storage of pharmaceutical products. World J Pharm Sci, 2499-515, 2013.
[13] B. Y. Lee and L. A. Haidari, The importance of vaccine supply chains to everyone in the vaccine world. Vaccine, 35(35): 4475-4479, 2020. https://doi.org/10.1016/j.vaccine.2017.05.096
[14] S. I. Chen, B. Norman, j. Rajgopal, T. M. Assi, B. Y. Lee and S. T. Brown, A planning model for the WHO-EPI vaccine distribution network in developing countries. IIE Transactions, 46(8): 853-865, 2014. https://doi.org/10.1080/0740817X.2013.813094
[15] S. H. Jacobson, E. C. Sewell, R. Deuson and B. G. Weniger, An integer programming model for vaccine procurement and delivery for childhood immunization: A pilot study. Health Care Management Science, 2(1): 1-9, 1999. https://doi.org/10.1023/A:1019011106198
[16] S. Hovav and D. Tsadikovich, A network flow model for inventory management and distribution of influenza vaccines through a healthcare supply chain. Operations Research for Health Care, 5: 49-62, 2015. https://doi.org/10.1016/j.orhc.2015.05.003
[17] H. K. Smalley, P. Keskinocak, J. Swann and A. Hinman, Optimized oral cholera vaccine distribution strategies to minimize disease incidence: A mixed integer programming model and analysis of a Bangladesh scenario. Vaccine, 33(46): 6218-6223, 2015. https://doi.org/10.1016/j.vaccine.2015.09.088
[18] A. Saif, and S. Elhedhli, Cold supply chain design with environmental considerations: A simulation-optimization approach. European Journal of Operational Research, 251(1): 274-287, 2016. https://doi.org/10.1016/j.ejor.2015.10.056
[19] S. Hovav and A. Herbon, Prioritizing high-risk sub-groups in a multi-manufacturer vaccine distribution program. The International Journal of Logistics Management, 28(2): 311-331, 2017. https://doi.org/10.1108/IJLM-12-2015-0227
[20] M. I. D. Carvalho, D. Ribeiro and A. P. Barbosa-Povoa, Design and planning of sustainable vaccine supply chain. Pharmaceutical Supply Chains- Medicines Shortages, Springer, 2019. http://dx.doi.org/10.1007/978-3-030-15398-4_2
[21] J. Lim, B. A. Norman and J. Rajgopal, Redesign of vaccine distribution networks. International Transactions in Operational Research, 29(1): 200-225, 2019. https://doi.org/10.1111/itor.12758
[22] S. J. Sadjadi, Z. Ziaei and M. S. Pishvaee, The design of the vaccine supply network under uncertain condition: A robust mathematical programming

approach. Journal of Modelling Management, 841-871, 2019. https://doi.org/10.1108/JM2-07-2018-0093

[23] B. Abbasi, M. Fadaki, O. Kokshagina, N. Saeed and P Chhetri, Modeling vaccine allocations in the COVID-19 pandemic: A case study in Australia, 2020. http://dx.doi.org/10.2139/ssrn.3744520

[24] S. Enayati and O. Y. Özaltın, Optimal influenza vaccine distribution with equity. European Journal Operational Research, 283(2): 714-725, 2020. https://doi.org/10.1016/j.ejor.2019.11.025

[25] Y. Yang, H. Bidkhori and J. Rajgopal, Optimizing vaccine distribution networks in low and middle-income countries. Omega, 99, 2020. https://doi.org/10.1016/j.omega.2020.102197

[26] A. G. Qasem, A. Shamsan and F. Aqlan, Optimal Cholera Vaccine Allocation Policies in Developing Countries: A Case Study. Proceedings of the International Conference on Industrial Engineering and Operations Management, Detroit, Michigan, USA, pp. 2279-2287, 2020.

[27] M. Alizadeh, M. M. Paydar, S. M. Hosseini, and A. Makui, Influenza vaccine supply chain network design during the COVID-19 pandemic considering dynamical demand, Scientia Iranica, 2021. https://doi.org/10.24200/sci.2021.58365.5694

[28] G. P. Georgiadis and M. C. Georgiadis, Optimal planning of the COVID-19 vaccine supply chain. Vaccine, 39(37): 5302-5312, 2021. https://doi.org/10.1016/j.vaccine.2021.07.068

[29] M. Rastegar, M. Tavana, A. Meraj and H. Mina, An inventory-location optimization model for equitable infuenza vaccine distribution in developing countries during the COVID-19 pandemic. Vaccine, 495-504, 2021. https://doi.org/10.1016/j.vaccine.2020.12.022

[30] M. Tavana, K. Govindan, A. K. Nasr, M. S. Heidary and H. Mina, A mathematical programming approach for equitable COVID-19 vaccine distribution in developing countries. Annals of Operations Research, 1-34, 2021. https://doi.org/10.1007/s10479-021-04130-z

[31] H. Gilani and H. Sahebi, A data-driven robust optimization model by cutting hyperplanes on vaccine access uncertainty in COVID-19 vaccine supply chain. Omega, 110: 1-21, 2022. https://doi.org/10.1016/j.omega.2022.102637

[32] B. Balcik, E. Yucesoy, B. Akca, S.Karakaya, A. A.Gevsek, H. Baharmand and F. Sgarbossa, A mathematical model for equitable in-country COVID-19 vaccine allocation. International Journal of Production Research, 1-25, 2022. https://doi.org/10.1080/00207543.2022.2110014

[33] V. Khodaee, V. Kayvanfar and A. Haji, A humanitarian cold supply chain distribution model with equity consideration:The case of COVID-19 vaccine distribution in the European union. Decision Analytics Journal, 4, 100126. https://doi.org/10.1016/j.dajour.2022.100126

[34] Z. Azadi, S. D. Eksioglu and H. N. Geismar, Optimization of Distribution Network Configuration for Pediatric Vaccines using Chance Constraint Programming, 2020. https://doi.org/10.48550/arXiv.2006.05488

[35] World Health Organization, 1998, Safe vaccine handling, cold chain and immunizations: A manual for the Newly Independent States. https://apps.who.int/iris/handle/10665/64776

[36] S. Guichard, K. Hymbaugh, B. Burkholder, S. Diorditsa, C. Navarro, S. Ahmed and M. Rahman, Vaccine wastage in Bangladesh. Vaccine, 28(3): 858-863, 2010. https://doi.org/10.1016/j.vaccine.2009.08.035