

DOKUZ EYLÜL UNIVERSITY
GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

**OPTIMIZING THE COVID-19 COLD CHAIN
VACCINE DISTRIBUTION NETWORK WITH
MEDICAL WASTE MANAGEMENT: A ROBUST
OPTIMIZATION APPROACH**

by
Eyüp Ensar IŞIK

September, 2021
İZMİR

OPTIMIZING THE COVID-19 COLD CHAIN VACCINE DISTRIBUTION NETWORK WITH MEDICAL WASTE MANAGEMENT: A ROBUST OPTIMIZATION APPROACH

**A Thesis Submitted to the
Graduate School of Natural and Applied Sciences of Dokuz Eylül University
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Science in Industrial Engineering**

**by
Eyüp Ensar IŞIK**

September, 2021

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M.Sc THESIS EXAMINATION RESULT FORM

We have read the thesis entitled “**OPTIMIZING THE COVID-19 COLD CHAIN VACCINE DISTRIBUTION NETWORK WITH MEDICAL WASTE MANAGEMENT: A ROBUST OPTIMIZATION APPROACH**” completed by **EYÜP ENSAR IŞIK** under supervision of **PROF. DR. ŞEYDA A. YILDIZ** and we certify that in our opinion it is fully adequate, in scope and quality, as a thesis for the degree of Master of Science.

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ABSTRACT

The COVID-19 virus, which emerged at the end of 2019, spread worldwide and causing a pandemic. This situation affected the whole world adversely, both socially and economically. COVID-19 vaccine studies started from the very beginning of the process for the vaccine, which is our strongest weapon against such epidemics. Although the production and development process for the COVID-19 vaccine is the most challenging, it also requires a challenging distribution process to vaccinate the population to ensure social immunity fully. Vaccines have special transport and storage conditions due to their compositions. For example, they must be kept within certain temperature ranges. Therefore, cold chain systems are needed. Breaking the cold chain can cause vaccines to deteriorate or become ineffective.

This thesis focuses on the distribution of the COVID-19 vaccine at the provincial level in Turkey together with medical waste management, considering the cold chain requirements and the perishable nature of vaccines. In this context, first, a literature review is conducted, and previous studies on the vaccine distribution network are examined. In addition, considering the differences in the COVID-19 vaccine, gaps in the literature are revealed. Afterward, a Mixed-integer Linear Programming Model is presented to solve the problem. Then, the presented model is tested for the province of Izmir with deterministic data, and the results are analyzed. Additionally, a Robust Model is created using Robust Optimization techniques to handle uncertainties and analyze different situations that may arise. Finally, some suggestions are made for future work.

Keywords: Healthcare supply chain, cold chain, vaccine distribution, COVID-19 vaccine, mixed-integer linear programming, robust optimization.

COVID-19 SOĞUK ZİNCİR AŞI DAĞITIM AĞININ TIBBİ ATIK YÖNETİMİ İLE OPTİMİZE EDİLMESİ: BİR SAĞLAM OPTİMİZASYON YAKLAŞIMI

ÖZ

2019 yılının sonunda ortaya çıkan COVID-19 virüsü tüm dünyaya yayılarak bir pandemiye neden olmuştur. Bu durum tüm dünyayı hem sosyal hem de ekonomik olarak kötü yönde etkilemiştir. Bu tür salgınlara karşı en güçlü silahımız olan aşı için sürecin en başından itibaren çalışmalar başlamıştır. COVID-19 aşısı için üretim ve geliştirme süreci her ne kadar en zorlu süreç olsa da toplum bağışıklığının sağlanması için nüfusun tamamen aşılması zorlayıcı bir dağıtım sürecini de gerektirmektedir. Aşılar kompozisyonları neden ile özel taşıma ve saklama koşullarına sahiptirler. Örneğin belirli sıcaklık aralıklarında tutulmaları gerekir. Bu nedenle soğuk zincir sistemlerine ihtiyaç duyulmaktadır. Soğuk zincirin kırılması aşılarda bozulmasına ya da etkisiz hale gelmesine neden olabilmektedir.

Bu tez çalışmasında aşılarda soğuk zincir gereklilikleri ve çabuk bozulabilen yapıları dikkate alınarak Türkiye’de il düzeyinde COVID-19 aşısının dağıtımına tıbbi atık yönetimi ile birlikte odaklanılmaktadır. Bu bağlamda öncelikle literatür araştırması yapılmakta ve daha önce aşı dağıtım ağı ile ilgili yapılmış çalışmalar taranmaktadır. Ayrıca COVID-19 aşısının farklılıkları da dikkate alınarak literatürdeki boşluklar ortaya konmaktadır. Ardından problemin çözümü için bir Karışık Tamsayılı Doğrusal Programlama Modeli sunulmaktadır. Daha sonra, sunulan model deterministik gerçek hayat verileri ile İzmir ili için test edilmekte ve sonuçlar analiz edilmektedir. Ayrıca belirsizlik durumlarını da ele alabilmek için sağlam optimizasyon teknikleri kullanılarak bir sağlam model oluşturulmakta ve ortaya çıkabilecek farklı durumlar analiz edilmektedir. Son olarak gelecek çalışmalar için birtakım öneriler yapılmaktadır.

Anahtar kelimeler: Sağlık tedarik zinciri, soğuk zincir, aşı dağıtım, COVID-19 aşısı, karışık tamsayılı doğrusal programlama, sağlam optimizasyon.

CONTENTS

	Page
M.Sc THESIS EXAMINATION RESULT FORM.....	ii
ACKNOWLEDGMENT.....	iii
ABSTRACT.....	iv
ÖZ	v
LIST OF FIGURES	viii
LIST OF TABLES	ix
CHAPTER 1 – INTRODUCTION	1
1.1 The Motivation of the Thesis.....	5
CHAPTER 2 – LITERATURE REVIEW.....	8
2.1 Cold Chain Logistics.....	8
2.2 Perishable Supply Chain.....	11
2.3 Vaccine Supply Chain.....	12
2.4 Vaccine Distribution	15
2.5 Robust Optimization	22
CHAPTER 3 – PROBLEM DEFINITION AND MATHEMATICAL MODEL.....	29
3.1 Problem Definition.....	29
3.2 Mathematical Model	33
3.2.1 Sets	34
3.2.2 Parameters	34
3.2.3 Decision Variables	35
3.2.4 Objective Functions	36
3.2.5 Constraints	38
CHAPTER 4 – APPLICATION OF PROPOSED MODEL IN IZMIR TURKEY	44
4.1 Data Preparation.....	44
4.1.1 Demand	45
4.1.2 Capacities	46

4.1.3	Deteriorations.....	48
4.1.4	Costs.....	49
4.1.5	Distances	50
4.1.6	Medical Waste Rates.....	50
4.2	Results for Deterministic Data.....	51
CHAPTER 5 – ROBUST OPTIMIZATION APPROACH.....		59
5.1	Robust Convex Optimization.....	60
5.2	Robust Counterpart Model.....	64
5.3	Robust Model Implementation	72
5.4	Experimental Results	73
CHAPTER 6 – CONCLUSION AND FUTURE RESEARCH		86
REFERENCES.....		90
APPENDICES		102

LIST OF FIGURES

	Page
Figure 2.1 Classification of uncertainty types and modeling approaches according to availability of data	24
Figure 3.1 Immunization Supply Chain (HSGM, 2018).....	30
Figure 3.2 Distribution network of COVID-19 vaccines and medical waste at provincial level.....	31
Figure 4.1 Pareto optimal solutions corresponding to ε values.....	53
Figure 5.1 The effect of the budget of uncertainty on total cost and the total number of FIPs for demand uncertainty	75
Figure 5.2 The effect of the budget of uncertainty on different types of costs for demand uncertainty	76
Figure 5.3 The effect of the budget of uncertainty on total cost and the total number of FIP for capacity uncertainty	78
Figure 5.4 The effect of the budget of uncertainty on different types of costs for capacity uncertainty.....	79
Figure 5.5 The effect of the budget of uncertainty on total cost and the total number of FIPs for deterioration in storage uncertainty	81
Figure 5.6 The effect of the budget of uncertainty on total cost and the total number of FIP for deterioration in storage uncertainty	81
Figure 5.7 The effect of the budget of uncertainty on total cost and the total number of FIP for deterioration during transportation uncertainty	83
Figure 5.8 The effect of the budget of uncertainty on different types of costs for deterioration during transportation uncertainty	84

LIST OF TABLES

	Page
Table 2.1 Vaccine distribution in OR/MS literature	21
Table 4.1 Vaccine storage capacity amounts by population	47
Table 4.2 Personnel hour capacity by population	48
Table 4.3 Cost types and corresponding costs	50
Table 4.4 Deterministic model results	51
Table 4.5 Pareto optimal solution chosen according to the results of the ε -constraint method.....	54
Table 4.6 The solution obtained by cost minimization with the cost of unsatisfied demand	55
Table 4.7 Results obtained according to the planning horizon contraction	57
Table 5.1 The results of the robust model for demand uncertainty	74
Table 5.2 The results of the robust model for capacity uncertainty	77
Table 5.3 The results of the robust model for deterioration during transportation uncertainty.....	80
Table 5.4 The results of the robust model for deterioration during transportation uncertainty.....	82

CHAPTER 1

INTRODUCTION

Infectious diseases are disorders usually caused by microbes like viruses or bacteria and affect living life negatively. Since such diseases can be transmitted between the same or different species, they can turn into epidemics and affect millions worldwide (Infection, 2003). Since epidemics affect a significant majority of the population, besides their physical effects on living life, they also negatively affect economic, environmental, and social life (Kreiss, 2016).

So far, human beings have witnessed multiple epidemics worldwide (Smallpox, Plague, Yellow Fever, etc.). However, most of these diseases remained regional in their occurrence and did not show a worldwide spread (Green et al., 2002). The coronavirus (COVID-19) outbreak, which emerged in China in early 2020, quickly spread worldwide due to its easily transmissible structure. By the end of 2020, over 76 million cases have been reported, and 1.68 million cases of COVID-19 have been lost (WHO, 2020, December 20). Countries have had to take mandatory action to address the pandemic, which has negatively impacted social life around the world. Working life has also been affected by the restrictions, and in turn, economic issues have emerged.

Vaccination is the most effective weapon in the fight against infectious diseases so far. Vaccines are biological products, and they function by destroying the disease-causing properties of viruses, bacteria, etc., in humans and animals (Var, 2020). Vaccination aims to rapidly remove the effects of the disease by speeding up the process of social immunity (Yang et al., 2021). As a result of vaccination, epidemics that have killed many people in the past on a regional and global scale are no longer visible (HSGM, 2018). Vaccination studies for coronavirus have started from the first moment of the epidemic. However, since the production and approval process took a long time, the vaccination process could only start at the end of 2020 (Levine, 2020).

While the manufacturing process is the most challenging part, the distribution of vaccines produced for such an effective global epidemic is also challenging (Wilding, 2020). Since vaccines are perishable products, they must be kept at certain

temperatures, and when these temperatures are exceeded, they decay and lose their effectiveness. For this reason, vaccines need cold chain systems (Saif and Elhedhli, 2016). Cold chain logistics applications cover operations such as transporting and storing products that need to be kept at certain temperatures, such as fresh or frozen food. Logistics of these products are expensive as both transport and storage stages require additional cooling equipment.

For this reason, cold supply chain management has recently become a frequently studied subject (Al Theeb et al., 2020). The adequacy of the cooling equipment is crucial for distribution. Disrupting vaccines purchased by countries for distribution to citizens results in the necessary number of people not being vaccinated and huge economic losses (Ebong and Levy, 2011). It is critical for the cold chain to be adequate and to work properly for such reasons.

For vaccine distribution, the cold chain consists of people and materials that maintain the effectiveness of a vaccine from its production until it is administered to the person and ensures that a sufficient amount of effective vaccine reaches those who need it (HSGM, 2018). Apart from cold chain applications, other difficulties arise in vaccine distribution. Identifying the priority classes to which the vaccine will be administered is at the top of these problems. When priority groups are identified, the environment and administration of vaccination should be determined (Hu et al., 2014). Several components must be present in the same place at the same time for a proper vaccination: the patient, the vaccine, the healthcare workers, and any necessary additional materials (e.g., syringes, needles, diluents) (De Boeck et al., 2020). Therefore, human and equipment resources to be used in the implementation of vaccination are also essential. The fact that one of the parties mentioned is inadequate makes the presence of the others unimportant.

Vaccine deterioration is not just about temperature. In addition to the deterioration caused by temperature incompatibility, the short shelf life and the limited application time from the moment a vial has opened also lead to deterioration (De Boeck et al., 2020). A strong vaccine supply chain is crucial for protecting public health and not harming countries' economies for all these reasons.

According to Duijzer et al. (2018), Vaccine Supply Chain consists of four stages: Product, Production, Allocation, and Distribution. The Product section includes problems such as the composition of the vaccine content and from which manufacturer the vaccine should be purchased. As different companies currently produce vaccines for the coronavirus, governments need to determine which vaccine to buy. Vaccine producers are taken into consideration in the Production section. Since the demand for vaccines is uncertain, the most urgent problem for manufacturers is how many doses of vaccine should be produced. The storage cost of the vaccine produced in large quantities is much higher than a usual product as it requires cooling equipment. In addition, vaccines with a short shelf life can turn directly into waste and negatively affect the manufacturer. However, production below demand is also risky, which means that patients do not have access to the vaccine. In the coronavirus context, the amount of vaccine doses to be purchased between countries and manufacturers is determined by prior agreements. In the Allocation section, priority should be determined for the population groups to which the vaccine will be delivered. Here, the age group, region of residence, or risk group specific to the illness is usually decisive. Finally, the Distribution section, which is also the scope of this thesis, focuses on distributing the vaccine. This section covers many OR/MS (Operations Research/Management Science) problems such as inventory management, routing, and scheduling.

How to distribute the vaccine has been the subject of the literature before (Jacobson et al., 1999; Chen et al., 2014; Hu et al., 2014; Hovav and Tsadikovich, 2015; Saif and Elhedhli, 2016; Lemmens et al., 2016; Erdogan et al., 2017; Azadi, 2018; Lim et al., 2019; Sadjadi et al., 2019; Günay et al., 2019; Yang and Rajgopal, 2019; De Boeck et al., 2020; Enayati and Özaltın, 2020; Rastegar et al., 2020; Yang, 2020; Musamih et al., 2021; Tavana et al., 2021; Yang and Rajgopal, 2021; Yang et al., 2021). The World Health Organization (WHO) plays an important role in vaccination studies in low-and-middle-income countries, with UNICEF and the Global Alliance for Vaccines and Immunization (GAVI). As such, the Expanded Program on Immunization (EPI) aims to vaccinate all children worldwide. Due to problems such as lack of energy and cooling equipment, distribution in these countries results in much more difficult problems. Therefore, researchers focus on this area (Chen et al., 2014; Erdogan et al.,

2017; Azadi, 2018; Yang and Rajgopal, 2019; De Boeck et al., 2020; Yang, 2020; Tavana et al., 2021; Yang and Rajgopal, 2021; Yang et al., 2021). Another issue that attracts the attention of researchers after WHO-EPI vaccines is influenza (seasonal flu) vaccines (Longini et al., 1978; Jacobson et al., 1999; Hovav and Tsadikovich, 2015; Sadjadi et al., 2019; Enayati and Özaltın, 2020). Since the influenza virus gets mutated annually, vaccines are reproduced every year according to the characteristics of the previous year. This situation requires a process that starts from the beginning every year from the production stage to the distribution stage. Researchers are working to deliver the right number of vaccines to the right people at the right time (Hovav and Tsadikovich, 2015). Since the general characteristics of all vaccines mentioned here are similar, storage temperatures are between 2 - 8° C, and they can be stored and transported in standard coolers (Yang et al., 2021). Since some of the new vaccines developed for coronavirus are based on mRNA, these vaccines have to be stored and distributed in ultra-cold environments. This situation brings along other problems (Wilding, 2020).

Yang and Rajgopal (2019) describe the overall four-level conventional vaccine delivery system for vaccines covered by the WHO-EPI. Accordingly, vaccines come by airline once or twice a year and are stored in the national warehouse. Refrigerated vehicles are used to transport vaccines from here to regional distribution centers. This transport occurs every three months. District centers have monthly shipments from regional distribution centers. 4 x 4 trucks are used for transportation, and vaccines are loaded onto the truck in refrigerated boxes or vaccine containers. Finally, vaccines are delivered to clinics or health centers. Refrigerated boxes are used for this transportation, but it is done by smaller size vehicles. This replenishment usually occurs once a month.

Different solution methods are proposed for vaccine distribution optimization in the literature. The size, difficulty, and uncertainty of the problem in question play an important role in determining the optimization method used. Mathematical programming methods come to the fore since the problem is often solved by analogy with a Supply Chain Network Design (SCND) model. Due to the nature of the decisions made, Integer Programming (IP), Mixed-integer Programming (MIP), and

Mixed-integer Linear Programming (MILP) methods are generally used. Since challenging operational decisions such as routing decisions are not considered, these methods are often sufficient to solve the problem in a reasonable amount of time. In cases where it is insufficient, researchers tend to decompose the problem or use heuristic algorithms (Lim et al., 2019; Saif and Elhedhli, 2016; Yang et al., 2021; Yang and Rajgopal, 2019, 2021). As with most supply chain problems, real-life applications in vaccine distribution contain many uncertainties. Researchers use Stochastic Programming and Robust Optimization methods (Azadi, 2018; Sadjadi et al., 2019; Saif and Elhedhli, 2016; Yang and Rajgopal, 2021) to handle these uncertainties.

In Turkey, in the vaccine selection process, vaccines are assessed not only in terms of effectiveness but also in terms of transport, storage, and application flexibility (Anonymous, 2020). Concerning production, some vaccines are still being investigated. If these vaccines are approved, the production part is also open to studying. The government also announces the priority group to which the vaccine will be administered. There is no definite structure announced for distribution; however, it is estimated that the system applied in childhood and flu vaccines within the scope of general immunization will work.

COVID-19 vaccine, CoronaVac, approved for emergency use by WHO and used in Turkey, can be stored at $2 - 8^{\circ} \text{C}$, similar to general immunization and influenza vaccines (WHO, 2021). According to Brazilian officials, who have completed the Phase-III studies, the vaccine can be stored in normal refrigerators for three years. This makes it much easier to distribute than other vaccines, particularly concerning cooling equipment. (Staff, 2020).

1.1 The Motivation of the Thesis

The aim of this thesis is the distribution of the COVID-19 vaccine at the provincial level in Turkey. It is of great economic and social importance that the vaccines, which are our most powerful weapon in getting out of the epidemic, are distributed in the shortest time and in the most accurate way. Almost all vaccines, including COVID-19 vaccines, have special storage and transportation conditions. This situation further complicates the distribution process. In addition to vaccine distribution, the

management of emerging medical waste is an issue of environmental sensitivity. While these issues are addressed separately in the relevant literature, this is the first time they have been addressed together in this study. Mathematical programming methods are used to solve such a comprehensive optimization problem that deals with many constraints. A MILP model is proposed to solve the problem, and it is tested with deterministic data for Izmir province.

The vaccine distribution optimization problem has mostly been solved for optimizing a single objective, the total cost minimization. Our problem has to consider two objectives due to the uniqueness of the epidemic: maximizing the number of individuals immunized and minimizing the total cost. In this thesis, we have considered these conflicting objectives using multi-objective optimization methods. Here, the ϵ -constraint method, one of the multi-objective optimization methods, is first used because of its easy use and wide selection area. Adding the penalty cost of the unsatisfied demand to the cost minimization objective is another method that allows addressing the two objectives simultaneously. The appropriate method is selected from the results obtained after applying the two methods.

However, in real-life applications, data may contain uncertainty. Therefore, there is a need to treat demand, capacity, and deterioration parameters as uncertain. Although many methods have been proposed to handle uncertainties, selecting which of these methods is also critical. Since the COVID-19 vaccine is a new product, there is no historical data about it. Therefore, it is not possible to fit the uncertain data into a statistical distribution. The robust optimization method is the most suitable method for uncertain situations where we do not have enough data, and we know that it only varies within a certain interval set. The applications of this method in the literature are generally on SCND. So, the Robust Optimization method stands out as the most appropriate method to apply.

For this reason, in this thesis, the Robust Convex Optimization approach, which is a Robust Optimization method, is used with the modeling technique of Bertsimas and Sim (2004). After determining the interval sets in which the uncertain parameters vary, the robust model created is solved at different conservatism levels. The solutions obtained at different levels allow us to see how the established model behaves at

different uncertainty levels. In this way, reliable results can be obtained even in the worst-case situations. In addition, the results obtained at different levels provide a wide range of choices for the decision-maker. In this way, the decision-maker can easily determine the most appropriate level of conservatism.

The remainder of this thesis is as follows. In Chapter 2, the literature is reviewed, and information is given about the previous studies for Vaccine Distribution. Chapter 3 defines the problem based on this information and the features of the new COVID-19 vaccine, and a MILP model is presented. Then, in Chapter 4, the proposed model is tested with real-life data gathered for Izmir province, and the effectiveness of the objective functions used is questioned. The Robust Optimization method used to handle uncertainties is described in Chapter 5. In this chapter, a robust model is presented using the Robust Convex Optimization approach, and the results are analyzed according to the different values of the new parameter introduced in the model. Finally, Chapter 6 summarizes the overall structure of the study and gives directions for future studies.

CHAPTER 2

LITERATURE REVIEW

As mentioned earlier, vaccines are perishable products that require cold chain systems. Due to their perishable structure, they must be stored and transported at certain temperature ranges. Cold chain logistics applications are important applications extensively studied in the literature. It has attracted the attention of the OR/MS community with its unique problems such as different equipment requirements, the limited shelf life of transported or stored goods, types of refrigerated vehicles that consume more fuel and produce more carbon emissions than regular vehicles.

The literature review is conducted in four steps, taking into consideration the structural characteristics of vaccines. First, cold chain logistics applications are examined, and in this section, issues such as green supply chain, sustainable supply chain, and location routing problems are discussed. Afterward, the perishable supply chain studies are examined, and then the vaccine supply chain is reviewed with the sub-sections. Finally, studies on vaccine distribution, which is the focus of this thesis, are examined. The review of the solution methodology is also presented at the end of this section.

2.1 Cold Chain Logistics

Cold chain logistics applications cause more CO₂ emissions due to fuel consumption, resulting in economic and environmental problems. For this reason, researchers have frequently discussed this issue in a sustainable and Green framework. Saif and Elhedhli (2016) addressed the Cold Supply Chain Design problem with environmental conditions. The authors indicated that more CO₂ emissions occur due to greater energy consumption in the cold supply chain. They also discussed the effects of this on global warming and the role of enterprises. Then, they stated that there is a concave relationship between cost and global warming effect and developed a concave MIP model for the problem. Strategic and tactical decisions are taken in the model, assuming that the capacity cost function is concave. The objective of the model is to minimize the cost and CO₂ emissions simultaneously. A Lagrangian decomposition

was used as a solution method, and a simulation-optimization algorithm was applied to find the optimum control parameters. The method was applied for two different cases. One of them is about cold supply chain design for a prepared meats producer, and the other deals with the cold supply chain system for vaccines in Ontario. As a result, they stated that the global warming effects could be reduced with small increases in costs.

In the following years, Fang et al. (2018) discussed the design of cold chain networks within the scope of the Green Supply Chain and evaluated it for fresh agriproducts. The authors developed a multi-objective MILP model to simultaneously address economic and environmental impacts and determined the objectives as cost minimization and CO₂ emissions minimization. They conducted numerical experiments by considering the developed model with different scenarios as single and multi-objective and questioned the cost that a company can accept to reduce CO₂ emissions.

As the scope of the sustainable supply chain addresses environmental impacts similarly, it has also been the subject of many studies. Jouzdani and Govindan (2021) discussed a food supply chain in which the product lifetime is uncertain and used the Chance-Constrained Programming method to address this uncertainty. In another study conducted within the same scope, uncertainty was addressed in demand, and an Iterated Local Search and MIP-based metaheuristic were used in addition to the two-stage stochastic programming method (Babagolzadeh et al., 2020).

The location-routing problem has also been frequently studied in this scope, as the cold chain applications include selecting the location for storage and transportation. Yan et al. (2020) focused on a location-routing problem that aims to minimize the total cost in which the vehicle capacity varies at different stages. They introduced an IP model to solve the problem and developed a hybrid genetic algorithm to reach the solution quickly. Later, the two-stage distribution location-routing problem was compared with the single-stage vehicle routing over randomly generated instances. It was found that the two-stage distribution location-routing system is efficient for the cold chain and can reduce distribution costs. In another study investigating the same problem, Wang et al. (2020) focused on fuel consumption. They presented a bi-

objective mathematical model to address economic, environmental, and social impacts simultaneously and developed a multi-objective hyper-heuristic optimization method for the solution. The methods were tested with actual data derived from a seafood supermarket in Hangzhou. The solution results are presented comparatively according to different parameters and performance measures.

In another study where environmental factors and location-routing decisions are discussed simultaneously, Leng et al. (2020) discussed the cold chain with its environmental impacts and presented a bi-objective MIP model. Like other studies, they indicated that refrigeration of vehicles leads to higher fuel consumption and that this situation has environmental, economic, and social consequences. The authors aimed to minimize these effects in the model they created. They handled the environmental and economic impacts with cost minimization and social impact while minimizing quality degradation. They stated that the deterioration of perishable products is due to temperature changes during loading and unloading operations. Location-routing decisions are made in the assumed model where demand, capacity, cost, and travel times between points are known in advance. For the solution method, a novel multi-objective hyper-heuristic was proposed in which three selection strategies and three acceptance criteria were combined with three decomposition methods.

For cold chain logistics applications, deciding on the inventory level is as important as selecting the storage area. If inventory level decisions are taken into account with routing decisions, these problems are called Inventory Routing Problems. Al Theeb et al. (2020) tried to optimize vehicle routing and inventory allocation problems simultaneously in cold supply chain logistics. Pointing out that the cost is higher in the cold supply chain and that the shelf life of perishable products is low, the authors aimed to maximize the benefit by minimizing the material loss while minimizing the total cost. They developed a MILP model for the solution, assuming that information like demand and time between points is known. The developed model makes many decisions such as pick-up, delivery, consumption, and inventory quantities. Later, they proposed a heuristic method that splits the model into three phases: vehicle clustering, route construction, and the modified model solution. In the first phase, the vehicles are

divided into two groups: those which have refrigerators and freezers, and assignment decision variables values are determined. In the second phase, a route is determined for each vehicle based on a greedy random search algorithm. In the third phase, the new values of the assignment decision variables are added to the model as a constraint, and the model is solved. They tested the model and solution method with small, medium, and large-sized test instances and a case study in the food industry.

Since vaccines are cold chain products, the studies reviewed in this section are also important for the vaccine supply chain. The perishable nature of vaccines makes the vaccine supply chain more complex since the perishable supply chain is a subject of study in itself.

2.2 Perishable Supply Chain

Products that require cold chain systems are generally perishable. Due to the difficulties caused by these structures, the perishable supply chain has been extensively researched in the literature. Firoozi et al. (2013) focused on the distribution network design and proposed a model and solution method for perishable products with a fixed lifetime. The authors reported that most products manufactured worldwide have a short lifespan and that drugs are included in this group. They also emphasized that the design of distribution networks is one of the most comprehensive decision problems in logistics and supply chain management and that although strategic decisions are usually made to address this problem, these decisions are not sufficient. Therefore, strategic and operational decisions such as location selection and inventory management are considered in their study. A nonlinear mixed-integer mathematical model, which is an extension of the location model with risk pooling, was proposed, and Economic Order Quantity was used as the inventory policy, assuming that the demand conforms to the normal distribution. They further proposed a heuristic Lagrangian Relaxation Algorithm as a solution method. The authors conducted a sensitivity analysis to test the model's accuracy and implemented the algorithm for a blood platelets case. In another study, de Keizer et al. (2017) discussed the logistics network design for perishable products together with a heterogeneous quality decay. The problem was handled as a hub location problem, and they proposed a MILP model to maximize the total benefit. The proposed model was tested using data from a fresh

produce supply chain in the floricultural sector in which quality decay may occur at different stages at different rates. Numerical experiments verified the model, and the results showed that using multiple hubs leads to significantly higher profits.

2.3 Vaccine Supply Chain

In the vaccine supply chain, issues such as the effects of varying vaccine vial sizes, bundling of vaccines, vaccine packaging, (re-)design of the vaccine distribution network, use of passive cold storage devices, and the impact of making vaccines thermostable are discussed at the strategic decision level. At the tactical decision level, important decisions are made on storage and transportation capacities, transportation frequency, transportation modes, and inventory relocation. Finally, topics such as vaccine administration policies, vial-opening decisions, ordering policies, and demand forecasting are considered at the operational decision level.

Several studies have been published on vaccine distribution and the vaccine supply chain, as mentioned in the previous section. Duijzer et al. (2018) wrote a literature review article, especially by examining the articles covered by OR/MS. This article divides the vaccine supply chain into four sections, and each section is branched within itself. A discussion section is added to the end of each section, summarizing the subject and suggestions for future studies. The first of these sections is the Product section divided into three parts: Vaccine Composition, Vaccine Selection, and Packaging. Decisions on the vaccine composition are discussed in the Vaccine Composition section, while the Vaccine Selection section deals with the purchase of vaccines at a minimum cost appropriate to governments that are typically on the receptor side. In such cases, studies are conducted to ensure the balance between public health facilities or governments and vaccine manufacturers regarding cost-benefit (Robbins et al., 2014; Robbins and Lunday, 2016). Since the ease of application of the chosen vaccine is also important to public health institutions or governments, planning children's vaccination programs is also considered in this scope (Hall et al., 2008; Robbins and Jacobson, 2011). Finally, considering that vaccine prices are important to vaccine manufacturers, studies on this issue are also examined in the Vaccine Selection section. For the Packaging section, the studies deal with how many vaccine doses should be in a vial. This problem is considered as Optimum Vial Size Problem in the literature, and

Decision Support Systems or Simulation-based methods are developed to solve the problem (Assi et al., 2011; Lee et al., 2010, 2011, 2012). The Products section asserts that scheduling multiple vaccination moments during a certain period should be considered for future studies for low- and middle-income countries. Since there are various vaccines, each immunizing against a certain combination of diseases, it is not easy to establish an effective and affordable schedule for immunizing children. Moreover, these studies should be conducted not only for seasonal but also for pandemic situations.

The Production section is divided into three parts: Production Uncertainties, Market Coordination, and Funding. Vaccine production contains many uncertainties. The most important parameters involving uncertainty are demand and supply parameters. While minimizing the cost in such uncertainties, how often, how much to order, and from which supplier are the most important problems. In the Market Coordination part, researchers are focused on ensuring coordination between governments and manufacturers (Arifoğlu et al., 2012; Chick et al., 2008, 2017). As the vaccine is a community health product, donors may be willing to fund expenses. Studies conducted to transfer these donations to the right products and methods are also included in the literature (Demirci and Erkip, 2017; Taylor and Xiao, 2014). Planning where and how much production will be made for sudden epidemics is emphasized in the Production section.

In the third section, Allocation is discussed and divided into four parts: Multiple decision-makers, Central coordination, Cost-effectiveness, and Bioterror. The Vaccine Allocation Problem is crucial in terms of ethics as vaccines are nonprofit products for public health. In such allocation problems, fairness and efficiency may be inversely proportional, so a decision that minimizes the number of contaminants may be unfairly considered by society. For these reasons, Simulation and Differential Equation models, which establish the balance between them, are used in the literature (Ajelli et al., 2010). Methods such as Game Theory are also useful in environments with more than one decision-maker (P. Sun et al., 2009). For Central Coordination, there are two commonly used distinctions; age groups and regional distinctions. Since there is considerable uncertainty in these distinctions, stochastic methods (Tanner and Ntaimo,

2010; Yarmand et al., 2014) and simulation (Teytelman and Larson, 2013; Uribe-Sánchez et al., 2011) are frequently used in the literature. Cost-effectiveness analysis is a different way of addressing vaccine allocation, which is frequently used in OR/MS studies. Bioterror attack situations are situations that require quick decision-making. In such cases, the aim is to deliver vaccines and other health supplies to the required place as soon as possible to reduce the number of people affected. Since uncertainty and time pressure are high, methods such as discrete event simulation and Greedy Algorithms are used in studies addressing this topic (Berman et al., 2012). According to the authors of the article; Allocation cannot be considered separately from other parts, but it contains high-level decisions. Although there are many studies in the epidemiological literature on the subject, these studies can be further strengthened with OR/MS techniques.

The Distribution section, which will also be discussed in this study, examines how vaccines will be delivered from the manufacturer to the end-user (patient). In this literature review, the Distribution section is divided into four: Supply Chain Design (SCD), Inventory Control, Points of Dispensing, and Mobile Facilities. There are two segments in SCD. The first involves transporting the vaccine from the manufacturer in the country of purchase, and the second involves delivering the vaccine to the country's end-user. Highly Extensible Resource for Modeling Event-Driven Supply Chains (HERMES), a discrete event simulation program, is frequently used for this subject (Assi et al., 2012, 2013; Haidari et al., 2013). In the second part, inventory control is handled. Inventory control is critical for vaccines because they are perishable products, so their shelf life can be short and deteriorate when kept in inventory for a long time. Another important issue is that the vaccine requires cold chain systems; the inventory in vaccine stores should be kept at certain temperatures. Such situations cause additional costs. In the Points of Dispensing part, the locations of vaccine stores and administration centers and their layouts and capacities are studied. Transportation and storage of vaccines are significant because of their perishable nature, even for in-building processes (Aaby et al., 2006; Luangkesorn et al., 2012). This section also deals with staff requirements (Whitworth, 2006). Lastly, the Mobile Facilities section focuses on planning additional mobile vaccine application points required in epidemics. In this section, for future studies, it is suggested that vaccine distribution

and storage should be addressed in a sudden outbreak, the uncertainties should be included in the models to be applied, and the vaccine supply chain should be integrated with other health supply chains.

In another literature review study, Lemmens et al. (2016) discussed the design problem of supply chain network models and focused on key issues in the vaccine supply chain. This study examined the characteristics of the vaccine supply chain network, uncertainty, performance measures, and methodology. Each topic was evaluated separately, and it is stated that strategic decisions are made in terms of network features but that tactical and operational decisions should also be made simultaneously. It is further asserted that there are few studies in the literature for uncertainty, and they are generally limited by demand. In the Performance Measures section, the literature mostly focuses on economic measures, and it is stated that environmental and social measures should be taken into account besides economic measures. Finally, methodologies used in the literature are included.

2.4 Vaccine Distribution

As mentioned in the literature reviews, studies on vaccine distribution are limited in the OR/MS literature. Vaccine distribution is mostly examined in the epidemiological and medical literature. Discrete event simulation methods such as HERMES are generally used for solving distribution problems (De Boeck et al., 2020).

Studies in the OR/MS literature generally address the distribution of pediatric vaccines in low- and middle-income countries and annual influenza vaccines. In addition, studies on cooling equipment and energy shortages in low- and middle-income countries are not rare. WHO-EPI vaccines are generally considered in these studies. Although no study was conducted directly in an OR/MS journal, Longini et al. (1978) 's study is one of the first papers that attempted to optimize vaccine distribution. A deterministic model for the influenza epidemic was presented to distribute the vaccine to different age groups in the best way for a limited number of vaccines. In another pioneering study, Jacobson et al. (1999) emphasized that vaccination is important, but systems are unprepared for a new vaccine. They conducted a pilot study showing how OR/MS applications can be used for vaccine

selection and procurement to overcome this deficiency. It is the first study in which IP was used for the selection and procurement problem in which three types of vaccines and four manufacturers are handled to optimize vaccine supply and distribution. The model chooses the most economically sound package of vaccine types. The authors concluded that OR applications could be used for the vaccine schedule and provide beneficial results for the manufacturer, the distributor, and the government.

Studies on influenza vaccines have continued in the following years. Hovav and Tsadikovich (2015) designed a network flow problem for the distribution and storage of influenza vaccines within the healthcare supply chain. The distribution phase was examined within a timeline for the influenza vaccine after the production, control, and packaging phases. They developed a model that decides on vaccine consumption and quantity of vaccine transported between facilities in addition to inventory and flow decisions to minimize the total cost. The model was tested for the real-world influenza vaccination program using different scenarios with what-if analysis. In addition to solving the model with the classical optimization program, it was solved with the Mosek optimizer using the network flow solution algorithm. The results showed that as the problem size grows, the solution time increases exponentially with classical optimization programs, while the solution can be reached within seconds with the Mosek optimizer. In the optimum results obtained, it was found that the cost was less than that spent. Hovav and Herbon (2017) studied optimizing the influenza vaccine distribution program. The prioritization of high-risk groups was taken into account in the study, in which multiple manufacturers were handled. A MIP model was developed to minimize the total cost, and it was emphasized that the developed model is especially useful when there are limited resources. In another study, Sadjadi et al. (2019) discussed the design of the vaccine supply network with uncertainties in demand and cost for strategical and tactical decisions simultaneously. The authors developed a MILP model for the problem and used the robust counterpart approach to address uncertainty. In their study, the demand parameter was divided into two parts, according to their priorities. The cost of not satisfying the demand was addressed in both constraints and objective function. The objective of the presented model is to minimize the total cost. They assessed the validity and usefulness of the model and its robust counterpart method by real-life vaccine supply chain data in Iran. The authors

attempted to solve the model using CPLEX Solver software and compared different levels of uncertainty. Monte Carlo simulation was used for this evaluation, and sensitivity analysis was performed. As a result, it was stated that the robust model has better performance.

The fair and equitable distribution of vaccines is one of the most important issues studied in the literature. In this context, Enayati and Özaltın (2020) developed a mathematical programming model for fair influenza vaccine distribution. They divided the population into several subgroups and evenly distributed necessary vaccines to each subgroup, preventing epidemic outbreaks. Their results showed that considering group-specific transmission dynamics is crucial for the optimal delivery of influenza vaccines. A recent study examined the equal distribution of influenza vaccines in developing countries under COVID-19 pandemic conditions (Rastegar et al., 2020). The study took the problem as an inventory-location problem, and a MILP model was developed. The model was evaluated using a case study conducted in a developing country, and a sensitivity analysis was conducted with seven scenarios dealing with deviations in budget status. Tavana et al. (2021) brought this study into the general form and focused on the equitable distribution of COVID-19 vaccines in developing countries. Although the study was given under the title of vaccine distribution, it included allocation decisions as it focused on the equitable distribution of vaccines. A location-inventory MILP model was developed to distribute vaccines fairly and equitably. In the model, vaccines are categorized as cold, very cold, and ultra-cold. The proposed model was tested using real data, and the results confirmed the efficiency and effectiveness of the model.

Another issue that attracted the attention of the literature is the planning of childhood vaccination in low-and-middle-income countries. De Boeck et al. (2020) conducted a literature review study addressing the vaccine distribution chain. In the first stage of the study, they discussed the nature and difficulties of the problem, while OR/MS literature related to the problem was given in the second stage. In their study, the vaccine distribution chain is examined under four main headings: Sourcing, Storage, Transportation, and Administration. They then evaluated the OR/MS-related literature under Decision Level, Methodology, Uncertainty, Performance Measures,

and Real-life Applicability topics. They indicated gaps in the literature for future studies, such as combining different parts of the vaccine distribution chain. For example, Chen et al. (2014) worked on a planning model for the distribution problem of WHO-EPI vaccines in developing countries by simultaneously giving the transportation and storage decisions. They discussed the problems experienced in developing countries due to resource availability and difficulties adapting existing systems to new developments. Then, they described a typical EPI distribution network, introducing the proposed Linear Programming (LP) model. This model aims to maximize the number of Fully Immunized Children (FIC) and extra vaccine doses by determining the number of vaccines used, transported, and stored. The model was applied to the vaccine distribution chain of three countries, and different scenarios were examined. In another study, Erdogan et al. (2017) focused on optimizing the vaccine distribution operations with regional distribution centers. This study offers a MIP model to minimize costs for developing countries in Africa. The model aims to find the locations of regional distribution centers, allocate countries to these distribution centers and determine transport modes under the capacity and shelf-life information in the cold chain. For testing the model, the South Africa region was examined with five countries. Azadi (2018) developed stochastic optimization models that integrate the vaccine supply chain's transportation, inventory, and replenishment decisions. In the study, demand is assumed uncertain but can be defined with a standard distribution, so stochastic optimization methods were used: Two-Stage Stochastic Mixed-Integer Linear, Two-Stage Stochastic Mixed-Integer Non-Linear, and Chance-Constrained Programming. Actual data from the demographic health surveys of Niger and Bangladesh were used to construct predictive models to meet the requirements for various childhood immunization vaccines.

Since the problem is up-to-date and studies are limited, studies have continued in recent years. Lim et al. (2019) worked on redesigning the vaccine distribution networks. The authors proposed an approach in which the vaccine flow paths from the main repository to the end-user are decided. They developed a MIP model that can solve small and medium-sized problems and presented a hybrid heuristic – MIP method that gives good results for larger problems. The purpose of the presented model is to minimize the annual cost. In the study, WHO-EPI vaccines were taken into

account, and the methods were tested in several countries in sub-Saharan Africa. Yang (2020), who worked on this subject for his doctoral dissertation, conducted different studies (Yang and Rajgopal, 2019, 2021; Yang et al., 2021). These studies focused on optimizing the distribution of WHO-EPI vaccines in low-and-middle-income countries. In the first stage, a MIP model was proposed to design a typical WHO-EPI network to minimize costs, and an Iterative Cyclic Algorithm was proposed due to the model's limitations (Yang and Rajgopal, 2019). In the second stage, information was provided on a conventional WHO-EPI process operation, and a MIP model was developed to minimize the facility opening and transportation costs. Then, a Disaggregation-and-Merging Algorithm was presented to solve larger MIP models. In this method, the problem is solved by dividing it into smaller parts with the divide and conquer approach (Yang et al., 2021). The third phase focused on optimizing outreach efforts, and a MIP model consisting of a combination of set covering and vehicle routing problems was developed. In the model, operation and travel costs of mobile clinics are tried to be minimized. There are two major uncertainties here: demand and travel time. The multi-period stochastic modeling approach addressed these uncertainties, and the worst-case scenario solutions were considered robust solutions (Yang and Rajgopal, 2021). Combining set covering and traveling salesman problems was discussed in the fourth and final stage. Since combining these two difficult problems and solving them with a MIP model would be challenging, a machine learning algorithm was proposed. Here, cost minimization is aimed, and sampling was done for mobile clinics and outreach operations. Training and test data sets were prepared for numerical experiments, and trials were made.

To our knowledge, only one study exists in the literature on the Turkish vaccine distribution system. In this study, Günay et al. (2019) examined the polio vaccine distribution strategies for Turkey scenarios. Drawing attention to the growing number of refugees in Turkey, the authors reported that refugees find it difficult to get vaccinated in recent years. It is noted that the spread of epidemic diseases is easier in worsening humanitarian conditions. It has been stated that avoiding such an outbreak lies in allocating and distributing the optimal number of polio vaccines. The study aims to develop a mathematical model that maximizes the number of vaccinated people while determining the optimal number of vaccines. Considering different age groups

for vaccine allocation, the authors asserted that the vaccine should be administered in two doses in some age groups. Different scenarios were handled concerning the priorities of regional and age groups, and the results obtained for each were compared.

A summary table is presented below to get a clearer idea of the literature on vaccine distribution and see how our study fits into the literature.



Table 2.1 Vaccine distribution in OR/MS literature

Publications	COVID-19 Vaccine	Product	Period	Sourcing	Fleet	MWM	Uncertainty	Objective	EM	H/MH	Decision Level
Jacobson et al., 1999	No	Multi	Multi	Single	Homogeneous	No	No	Min Cost	IP	No	Tactical
Chen et al., 2014	No	Multi	Single	Single	Homogeneous	No	No	Max FIC	LP	No	Strategic
Hovav and Tsadikovich, 2015	No	Single	Multi	Single	Heterogeneous	No	No	Min Cost	MIP	Mosek	Tactical + Operational
Saif and Elhedhli, 2016	No	Single	Single	Single	Heterogeneous	No	Yes (Demand)	Min Cost + CO2 Emissions	Concave MIP	LDA, SOA	Strategic + Tactical
Erdogan et al., 2017	No	Single	Multi	Multi	Homogeneous	No	No	Min Cost	MIP	No	Strategic + Tactical
Hovav and Herbon, 2017	No	Single	Multi	Single	Homogeneous	No	No	Min Cost	MIP	No	Strategic + Tactical
Azadi, 2018	No	Multi	Multi	Single	Homogeneous	No	Yes (Demand)	Max FIC	CCP	SAA	Strategic + Tactical
Günay et al., 2019	No	Single	Single	Single	Homogeneous	No	No	Max FIC	MIP	No	Tactical
Lim et al., 2019	No	Single	Multi	Single	Heterogeneous	No	No	Min Cost	MIP	HES	Strategic + Tactical
Sadjadi et al., 2019	No	Single	Single	Single	Homogeneous	No	Yes (Demand + Cost)	Min cost	MILP	RO	Strategic + Tactical
Yang and Rajgopal, 2019	No	Single	Multi	Single	Heterogeneous	No	No	Min Cost	MIP	ICA	Strategic + Tactical
Rastegar et al., 2020	No	Single	Multi	Single	Homogeneous	No	No	Max (Min {DDR})	MILP	No	Strategic + Tactical
Tavana et al., 2021	Yes	Multi	Multi	Single	Homogeneous	No	No	Max (Min {DDR})	MILP	No	Tactical + Operational
Yang and Rajgopal, 2021	No	Single	Multi	Single	Homogeneous	No	Yes (Demand + Travel Times)	Min Cost	MIP, MP-SMIP	No	Strategic-Operational
Yang et al., 2021	No	Single	Multi	Single	Heterogeneous	No	No	Min Cost	MIP	DMA	Strategic + Tactical
Our Study	Yes	Single	Multi	Single	Heterogeneous	Yes	Yes (Demand + Storage Capacities + Deteriorations)	Max FIP, Min Cost	MILP	RO	Tactical + Operational

MWM: Medical Waste Management, EM: Exact Methods, H/MH: Heuristic/Metaheuristic, FIC: Fully Immunized Children, FIP: Fully Immunized Patient, DDR: Delivery-to-Demand Ratio, IP: Integer Programming, LP: Linear Programming, MIP: Mixed-Integer Linear Programming, MP-SMIP: Multi-Period Mixed-Integer Stochastic Programming, CCP: Chance-Constrained Programming, SAA: Sample Average Approximation, DMA: Disaggregation-and-Merging Algorithm, LDA: Lagrangian Decomposition Algorithm, SOA: Simulation-Optimization algorithm, ICA: Iterative Cyclic Algorithm, HES: Hybrid Evolutionary Strategy, RO: Robust Optimization

As illustrated in Table 2.1, only one study was conducted for the distribution of the COVID-19 vaccine in the OR/MS literature. Given that there is an increase in medical waste during the COVID-19 period, studies specific to this period are emerging in the literature (Kargar, Pourmehdi, et al., 2020; Tirkolaee et al., 2021). As seen in Table 2.1, no literature study combines vaccine distribution and medical waste management. For this reason, this study is the first to combine these two issues and to consider direct vaccine waste. Similar to vaccine waste, one study is based on the medical needle and syringe supply chain (Pishvae et al., 2014). There are also studies where the medical waste management is handled jointly with the reverse supply chain. (Alizadeh et al., 2020; Kargar, Paydar, et al., 2020).

Uncertainty in vaccine distribution is addressed in only four studies. In all of these studies, the demand parameter is considered uncertain. Cost and travel time are also considered uncertain in addition to demand in two of the studies. In this thesis, demand, capacity, and deterioration are considered uncertain. The capacity and deterioration parameters are taken uncertain for the first time in the vaccine distribution literature.

Stochastic Programming, Chance-Constrained Programming, and Lagrangian Decomposition Algorithm are used as solution methods in the studies. Only one study uses the Robust Counterpart Approach. The extensive literature on the Robust Optimization method is given in Section 2.5. The robust optimization approach was used only once in the literature for vaccine distribution (Sadjadi et al., 2019). In this study, only cost and demand parameters were discussed. In our study, the capacity and deterioration parameters along with the demand are handled as uncertain. Because COVID-19 vaccines are new products, we have limited historical data. This situation is the main motivation for using the robust optimization method.

2.5 Robust Optimization

When there is uncertainty, methods such as stochastic programming, fuzzy logic programming, and sensitivity analysis are used for optimization problems. While each method has its advantages and disadvantages, the method employed varies depending on the type of uncertainty. Stochastic programming is more useful when the historical

data on hand can be fitted to a statistical distribution. However, where there is insufficient data to make up a statistical distribution and only personal judgments on uncertainty are available, it is more appropriate to use fuzzy logic programming. In cases where uncertainty is relatively low and the results can be analyzed through repeated experiments, sensitivity analysis is an easier method to use.

Robust optimization is used when the data do not correspond to a certain statistical distribution. Robust optimization aims to obtain the optimal solutions for the problem, even under extreme conditions. For this reason, it tries to optimize the results according to the values of the extreme points that the data used can take in the given interval. The robust optimization approach was first introduced to the optimization literature by Soyster (1973). Then, after Mulvey et al.'s (1995) study, it began to be used more widely, and new modeling methods were developed that meet different needs for robust optimization. The new methods developed have made it possible to address different types of uncertainties. Therefore, robust optimization models can be examined under two main headings: Interval set-based and Scenario-based (Govindan et al., 2017).

In scenario-based robust optimization models, different robustness measures with or without probability distributions are defined. The purpose of these models is to minimize expected costs or minimize deviations from the lowest cost. These models are used when the data set is small, and the parameters are discrete (Güçlü and Özdemir, 2017).

Robust interval-based optimization models are generally applied to protect optimization problems against infeasibility due to corruptions in uncertain parameters and maintain computational traceability. In these models, uncertain data vary, provided they remain within a defined set of uncertainties. The aim here is to obtain a feasible solution in all the values that the data can take, even insensitive to the extreme points that the parameter can take within the defined set (Li et al., 2011). Robust interval-based optimization models have been created using different uncertainty clusters (e.g., box, ellipsoidal, polyhedral) in the literature (Soyster, 1973; Ben-Tall and Nomirowski, 1998; Bertsimas and Sim, 2003).

According to Mulvey et al. (1995)’s definition of robust optimization, there are two types of robustness: solution robustness and model robustness. Solution robustness describes the situation in which all solutions of a problem achieved in all situations are “almost” optimal, while model robustness describes the situation in which it is “nearly” feasible. The definition of “nearly” depends on the decision maker’s perspective (Govindan et al., 2017).

Which modeling method to use in robust optimization applications is determined according to the type of uncertainty. Different modeling methods can be used for different types of uncertainty. Different modeling methods can be used for the same uncertainty type. Bairamzadeh et al. (2018) summarize the methods used according to uncertainty types as in Figure 2.1. Accordingly, three types of uncertainty are defined: randomness, epistemic, and deep uncertainty. The type of uncertainty is defined as randomness when sufficient historical data can be fitted to a certain statistical distribution. Stochastic programming or robust scenario-based stochastic programming techniques are used for problems with a randomness uncertainty type.

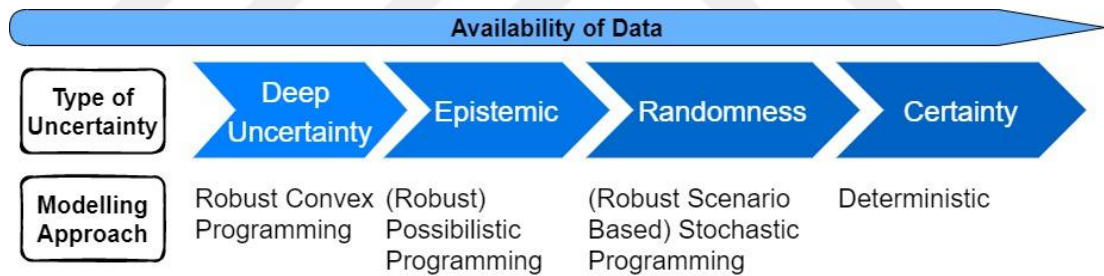


Figure 2.1 Classification of uncertainty types and modeling approaches according to availability of data

The type of uncertainty is epistemic when there is insufficient historical data, and the available information is limited to expert opinion based on personal judgment. The data used in these cases are expressed with fuzzy numbers, and possibilistic programming or Robust Possibilistic Programming (RPP) is used for the solution. RPP was first proposed by Pishvae et al. (2012), and they focused on the socially responsible SCND problem under uncertainty. The method is designed to generate solutions to problems in uncertainty by taking advantage of robust optimization and possibilistic programming methods. Since the method is used in a fuzzy environment, the focus is on making the uncertain parameters considered in the model linear by

expressing them with membership functions. Considering that the logic of robust optimization is to obtain a feasible solution in all conditions of the problem under consideration, different models have been developed in which different situations are handled: hard worst-case, soft worst-case, and realistic robust programming. The method later attracted the attention of different researchers and was frequently applied, especially in SCND problems. Different variations of the proposed method under different conditions are also discussed in the study.

Zahiri et al. (2013) proposed a MILP model to solve the blood collection and distribution network design problem and used RPP to address demand and supply parameters uncertainties. Talaei et al. (2016) proposed a MILP model for solving the multi-product closed-loop green supply chain network problem. They tested the model in a real-life problem in the electronics industry and used RPP to address uncertainties regarding variable costs and demand rates.

Since minimizing cost and CO₂ emissions are two conflicting objectives, the epsilon-constrained method was used to address both objectives simultaneously. Hamidieh et al. (2017) stated that reliability is the most frequently considered issue in recent studies. Thus, they proposed an RPP-based model for the sustainable closed-loop SCND problem under uncertainty. Fazli-Khalaf et al. (2019) developed a three-objective blood SCND model to meet blood needs that may arise in emergencies. Since most parameters are uncertain in real-life applications, possibilistic flexible chance-constraint programming and possibilistic flexible chance-constraint programming models are proposed. In this way, it is aimed to offer risk-averse and robust solutions to decision-makers. Nayeri et al. (2020) used a fuzzy robust optimization approach for a multi-objective sustainable closed-loop SCND problem and benefited from goal programming for its solution.

In cases with insufficient historical data and expert opinion, the type of uncertainty is defined as deep uncertainty. In these cases, the data used are expressed within a certain interval set, and the parameter can only take value within the specified interval set. Robust convex programming is used for solving problems with this type of uncertainty. As mentioned earlier, the robust approach was used for the first time in the optimization literature by Soyster (1973).

Soyster (1973) developed a linear programming model where the decision variable coefficients are assumed to be uncertain. In this approach, the maximum level of conservatism is used in the model by substituting the best or worst-case values of the decision variable coefficients taken as uncertain. The disadvantage of Soyster's (1973) approach is that the robust solution may be according to the worst-case scenario in real-life applications, focusing on the worst values of uncertain parameters. New modeling methods have been proposed to overcome this disadvantage. These new methods also focused on the design of less conservative solution methods that are computationally tractable.

Ben-Tal and Nemirovski (2000) proposed a robust formulation for the linear problem under the box and ellipsoid uncertainty sets in one of the modeling methods developed. In the proposed formulation, uncertain parameters take their worst values, and conservative solutions are obtained. In order to reduce the conservatism level of the proposed formulation in a problem with a Box uncertainty set, they defined the ellipsoid uncertainty set. Thanks to an additional parameter defined in this uncertainty set, while the uncertain parameters get their worst value, the size of the uncertainty can also be determined. The disadvantage of this method is that the complexity of the model increases, and it becomes nonlinear.

In particular, the transformation of the model into a nonlinear form makes it difficult to use the formulation defined by Ben-Tal and Nemirovski (2000). For this reason, Bertsimas and Sim (2004) developed a new modeling method. The advantage of the developed method is that it can adjust the level of conservatism without increasing the complexity of the model in the form of a linear model. In this method, uncertain parameters are defined in the polyhedral uncertainty set. The level of conservatism is provided by a parameter defined in the polyhedral uncertainty set and known as the budget of uncertainty. The method was then introduced for inventory theory (Bertsimas and Thiele, 2006). The modeling method of Bertsimas and Sim (2004) has been frequently used in specially supply chain planning problems (Najafi et al., 2013; Hatefi and Jolai, 2014; Zokaee et al., 2017; Liu et al., 2019; Ahabchane et al., 2021; Sun et al., 2021). In addition, it has applications in different problems such as production planning (José Alem and Morabito, 2012; Modarres and Izadpanahi, 2016).

In robust optimization, hybrid methods are used when different types of uncertainty are handled simultaneously. After determining the uncertainty type of each parameter in the defined problem, the robust programming method suitable for each uncertainty type is applied in order (Bairamzadeh et al., 2018; Hatefi and Jolai, 2014). In addition, hybridization can be done with different methods used under uncertainty (Keyvanshokoo et al., 2016).

There is only one robust optimization application in the vaccine distribution literature (Sadjadi et al., 2019). In their study, cost and demand parameters are defined in interval uncertainty sets. For this reason, robust convex programming modeling methods are used. Different models were presented for box, ellipsoidal and polyhedral uncertainty sets, and it was decided to use the model created for the box uncertainty set. It is shown that the proposed robust model has a better performance and is more reliable than the deterministic model for the vaccine SCND problem.

As mentioned earlier, this study considers optimizing the COVID-19 vaccine distribution process at the provincial level in Turkey and managing medical waste. To that end, a MILP model is developed first. Two objectives are identified in the model developed, with the question of which objective is most effective. Then, a robust optimization method is used to handle the uncertainties. We used the Bertsimas and Sim (2004) modeling methodology for parameters defined in an interval uncertainty set. Different from Sadjadi et al. (2019)'s study, the storage capacity and deterioration parameters are also considered uncertain along with the demand parameter in this study. All discussed uncertainties are handled in deep uncertainty since there is not enough historical information and expert opinion. The proposed model is tested using real-life data prepared for Izmir province. The model's main results are how much of the population can be vaccinated with the current capacity and the cost to the system.

Additionally, the decisions about how much medical waste can be disposed of, how much inventory should be kept, and how many vaccines are administered in each health center are also revealed using this model. The adequacy of the existing capacity according to different uncertainties can be questioned. The results obtained according to the different budget values of uncertainty parameters are given in a trade-off curve. With these curves, decision-makers can decide where they stand on important

decisions such as transportation, storage, and workforce capacities, inventory quantities, and deterioration precautions. The behavior of the distribution network according to different uncertainties and their levels can be analyzed over these curves.



CHAPTER 3

PROBLEM DEFINITION AND MATHEMATICAL MODEL

In this chapter, we present the problem addressed. Then, the assumptions made while determining the scope of the problem are given. Afterward, the mathematical model developed to solve the problem is presented with the required notation given beforehand. Finally, definitions of the relevant equations are set out for the model presented in objective functions and constraints.

3.1 Problem Definition

Turkey has a developed infrastructure for vaccine distribution. Under the EPI, more than ten vaccines are guaranteed to be delivered to citizens. Logistics activities in which cold chain systems are used effectively cover the entire process, from vaccine consumption analysis to supply, storage, shipment, and waste management. The Vaccine Tracking System controls the whole process from vaccine supply to the end-user (patient). This system makes it possible to monitor the stock and temperature of vaccines simultaneously.

As shown in Figure 3.1, Immunization Supply Chain covers the entire process from deliveries to the national warehouse to waste management in Turkey. Once the vaccines are delivered to the national warehouse, they are shipped to provincial warehouses with refrigerated trucks every three months. Vaccines arriving at provincial warehouses are distributed through vaccine transport vehicles based on the needs of Community Health Centers (CHCs). Vaccines stored in refrigerated rooms in CHCs are delivered to Family Health Centers (FHCs) in refrigerated boxes. Vaccines are stored in special refrigerated refrigerators in HFCs and are used from here as needed. Temperature control and vaccine stock status are controlled from a single center at each step in the process. A possible malfunction is directly conveyed to the relevant units, and measures are taken (HSGM, 2018).

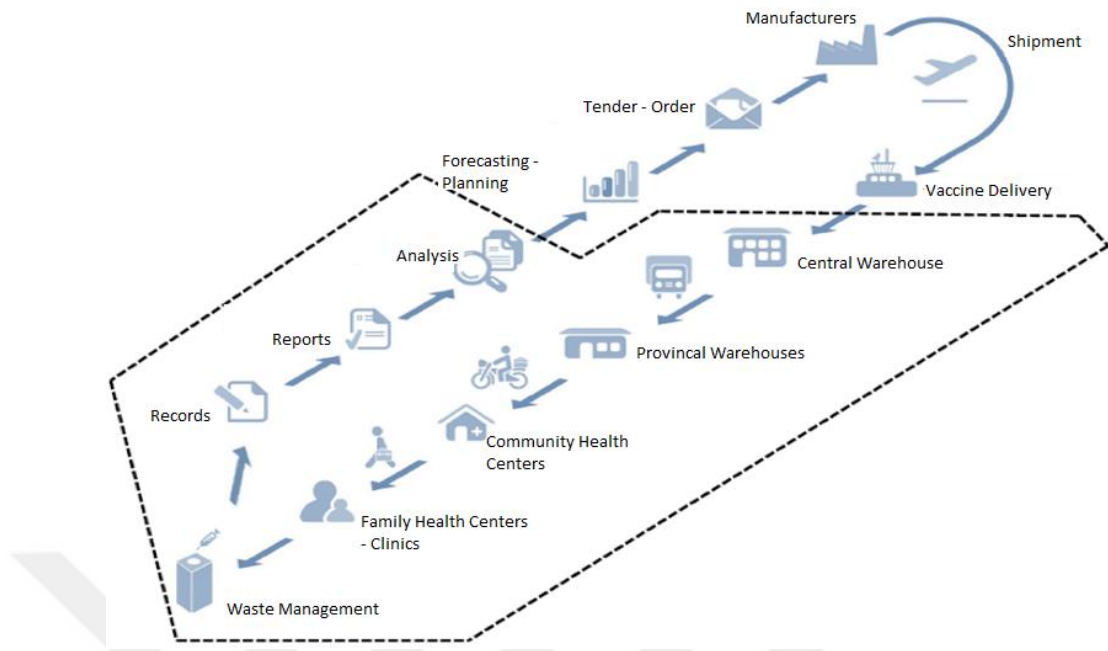


Figure 3.1 Immunization Supply Chain (HSGM, 2018)

According to the Republic of Turkey Ministry of Health, if vaccines are evaluated in terms of the level of logistics management, they can be parsed as “National Level” and “Provincial Level.” This study considers the distribution of COVID-19 vaccines from provincial level warehouses to the end-user (patient). All public, private, and university hospitals are included in vaccine delivery centers for the fastest distribution during the COVID-19 pandemic. As seen in Figure 3.1, the distribution direction of vaccines is from provincial warehouses to CHCs and from CHCs to FHCs and other hospitals (From now on, referred to only as FHC). The locations of all health centers are fixed.

The storage conditions for the COVID-19 vaccine distributed in Turkey are similar to those for vaccines covered by the EPI. Thus, no additional cooling equipment is required. Although vaccines are generally short-lived, the COVID-19 vaccine used in Turkey can be stored for one year under suitable conditions. (WHO, 2021). Therefore, a one-year planning horizon for vaccine distribution is specified, and the shelf-life of the vaccine is not considered within the problem scope. However, deterioration may occur due to temperature changes in the health centers, breakage during transportation, pilferage, etc. Moreover, Open Vial Wastage (OVW) may occur during the administration in health centers. After opening the vaccine vial, there is a certain time

limit for administration. If this time has been exceeded, that vaccine can no longer be used (De Boeck et al., 2020).

Medical waste occurs in two ways: 1) due to the deterioration of vaccines, 2) after vaccine administration (syringes, needles, cotton, etc.). For this reason, medical waste may occur in all health centers, including the provincial warehouse. Medical waste is first transported from health centers to waste collection centers and subsequently to disposal centers. Two centers are established for the disposal of medical waste, namely sterilization and incineration centers. The distribution network of COVID-19 vaccines and their waste, discussed in this study, is schematized in Figure 3.2. In the figure, the solid lines represent the vaccine flow, and the dashed lines represent the medical waste flow.

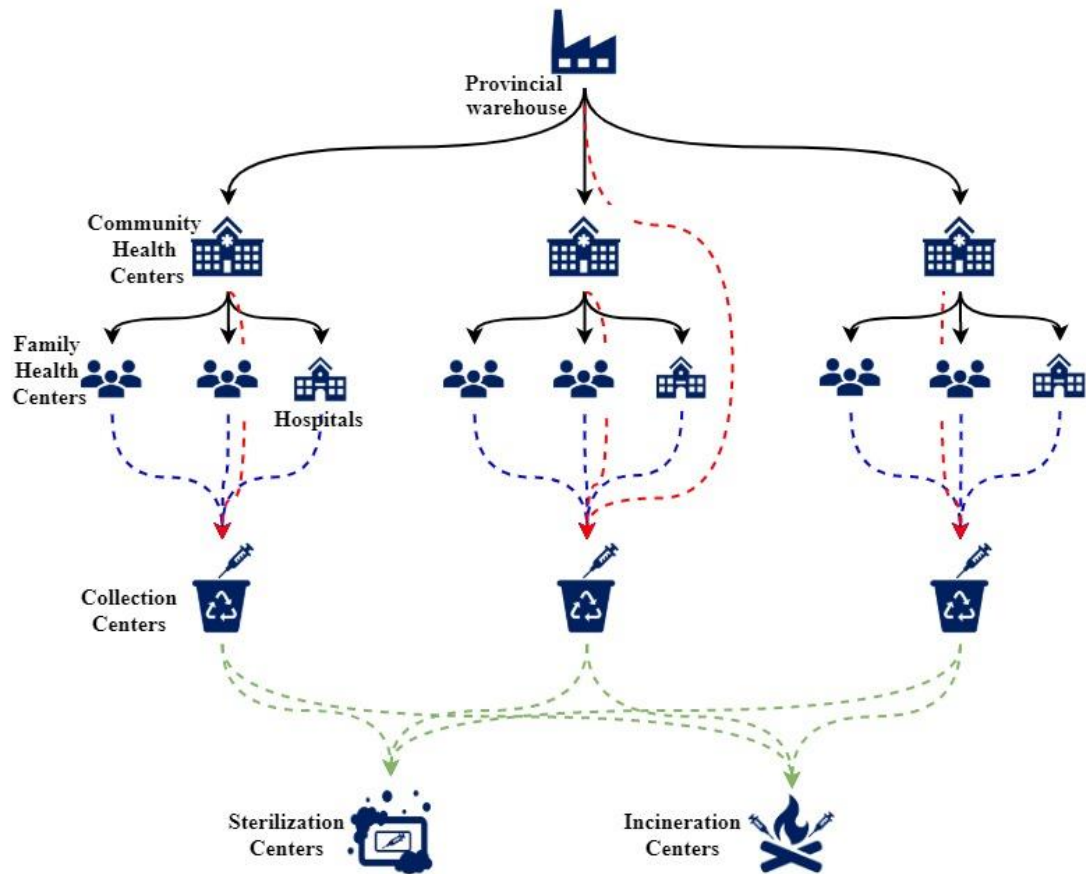


Figure 3.2 Distribution network of COVID-19 vaccines and medical waste at provincial level

A MILP model is suggested to ensure the optimal distribution of the vaccine. In the MILP model, more than one cost is considered: transportation cost, storage cost, cost

of the lost vaccine, and service cost. One of the objectives of the MILP model is to minimize the total cost. COVID-19 vaccines are administered in two doses. Patients who have taken both doses are called Fully Immunized Patients (FIPs), and the other objective is to maximize this number. It is also worthwhile that a minimum of one month must elapse between the two doses administered.

The MILP model decides the inventory level at the end of each period, the number of vaccines transported from the provincial warehouse to CHCs and from CHCs to FHCs, and the number of vaccines used in the centers. Additionally, the amount of waste going from the provincial warehouse and health centers to collection centers and from collection centers to disposal centers is also determined. The amount of unsatisfied demand and the amount of waste not delivered are also calculated. We make the following assumptions to model the COVID-19 vaccine distribution in Turkey:

- Vaccine manufacturers supply sufficient vaccines to meet anticipated demand fully.
- Each province has one vaccine warehouse. Hence, the provincial warehouse is the network's root node and is defined as a zero node.
- CHCs serve certain FHCs, and only one CHC supplies each FHC.
- Only one medical waste collection center serves a health center. Likewise, one disposal center provides services to a collection center.
- Three types of vehicles are available for vaccine transportation. Vehicle types vary between different centers.
- All demand, specified for each location and period and patient type over the planning horizon, is satisfied at CHCs and FHCs. The demand at a health center is determined by the region's population covered by the health center.
- Health centers and vaccine transport vehicles have an appropriately sized storage device with a certain capacity.
- Collection centers have limited storage capacity, and disposal centers have limited processing capacity. In cases where the capacity is not enough, the disposal of medical wastes is outsourced, but this causes additional costs.

- Medical personnel hours available are limited in health centers. Hence, the amount of vaccine administered over a period in the centers is limited.
- Medical waste must be collected and disposed of on time since it poses a risk of infection. When the capacity is insufficient, these operations can be carried out by providing additional capacity at extra cost. Therefore, the cost of undisposed medical waste is also considered.
- Vaccine waste resulting from temperature change during transport is stored at the vehicle's destination and taken there.
- A certain time (x) must elapse between the two doses to be administered. The amount of the second dose vaccine is determined based on the idea that the vaccinated patient during period t will create a repeat demand during period $t + x$.
- When the vaccine is transferred to a health center during period t , it can be used or referred from that center during period $t + 1$.
- All vaccine transfers are at the beginning of the period. The highest inventory level is achieved at the beginning of the period and is equal to the sum of the inventory of the previous period and the amount of vaccine transported at the beginning of this period.
- Finally, no equipment failure is assumed, shipments are made on time, and all patients can go to clinics, i.e., outreach activities are not addressed.

The next section gives the sets, parameters, decision variables, and the model created for the defined problem.

3.2 Mathematical Model

This section describes the proposed MILP model for optimizing COVID-19 vaccine distribution along with medical waste management at the provincial level. Many parameters used in real-life applications contain uncertainty. However, since these uncertainties will be discussed in later chapters, it is assumed that all parameters are known beforehand. That is, the model is presented as deterministic.

3.2.1 Sets

O	Provincial warehouse
I	Set of Community Health Centers (CHCs) $i \in \{1, \dots, I \}$,
J	Set of Family Health Centers (FHCs) and other hospitals, $j \in \{ I + 1, \dots, I + J \}$
N	Set of all health centers, $I \cup J, n \in \{1, \dots, N \}$
C	Set of collection centers, $c \in \{1, \dots, C \}$
S	Set of sterilization centers, $s \in \{1, \dots, S \}$
F	Set of incineration centers, $f \in \{ S + 1, \dots, S + F \}$
P	Set of disposal centers, $S \cup F, p \in \{1, \dots, P \}$
T	Set of time periods, $t \in \{0, \dots, T \}$
K_1	Set of vehicles that can be used for transports between the provincial warehouse and CHC
K_2	Set of vehicles that can be used for transports between the CHCs and FHCs
K	Set of all vehicle types ($K_1 \cup K_2$), $k \in \{1, \dots, K \}$
H	Set of patient types, $h \in \{1, \dots, H \}$
VF_i	Set of FHCs receiving service from CHC i
$WF1_0$	Set of collection centers providing service to provincial warehouse
$WF2_n$	Set of collection centers providing service to health center n
$WF3_c$	Set of health centers receiving service from collection center c
$WF5_c$	Set of sterilization centers receiving service from collection center c
$WF6_c$	Set of incineration centers receiving service from collection center c
$WF7_p$	Set of collection centers providing service to disposal center p

3.2.2 Parameters

Demands:

$D_{n,h,t}$ Total demand at health center n for patient type h in period t

Capacities:

Cap_0 The amount of vaccine that the provincial warehouse can store

Cap_n The amount of vaccine that the health center n can store

Cap_k The amount of vaccine that vehicle type k can carry at the same time

Cap_p The amount of medical waste (kg) that the disposal center p can process

Cap_c The amount of medical waste (kg) that the collection center c can store

$G_{n,t}$ The amount of workforce (duration) that the health center n has in period t

Ap Average time required to administer one dose of vaccine

Deteriorations:

BO Fraction of lost vaccine with OVW

B_0 Fraction of lost vaccine inventory at Provincial warehouse

B_n Fraction of lost vaccine inventory at health center n

$B_{0,i,k}$ Fraction of lost vaccine during transportation from Provincial warehouse to CHC i with vehicle type k

$B_{i,j,k}$ Fraction of lost vaccine during transportation from CHC i to FHC j with vehicle type k

Costs:

C_k	The cost of transporting one dose of vaccine for one km with vehicle type k
C_n	The cost of holding one dose of vaccine for one period in the health center n inventory.
CB	The cost of losing one dose of vaccine
CS	The service cost of administering one dose of vaccine
CW_p	The collection, transportation, sterilization, and disposal cost per kilogram (kg) of medical waste at disposal center p
CWD	The cost of not transporting one kg of medical waste

Distances:

$Dist_{0,i}$	The distance between Provincial warehouse and CHC i
$Dist_{i,j}$	The distance between CHC i and FHC j
$Dist_{0,c}$	The distance between Provincial warehouse and collection center c
$Dist_{i,c}$	The distance between CHC i and collection center c
$Dist_{j,c}$	The distance between FHC j and collection center c
$Dist_{c,s}$	The distance between collection center c and sterilization center s
$Dist_{c,f}$	The distance between collection center c and incineration center f

Rates:

SC	The rate of medical waste to be transported to the sterilization centers
IC	The rate of medical waste to be transported to the incineration centers
M	The weight of medical waste (kg) resulting from the administration of a single dose of vaccine

3.2.3 Decision Variables**Fully Immunized Patient (FIP):**

$FIP_{n,h}$	The number of fully immunized type h patients at health center n
-------------	--

Vaccine Flow

$A_{0,i,k,t}$	The amount of vaccine transported from the provincial warehouse to CHC i with type k vehicle during period t
$A_{i,j,k,t}$	The amount of vaccine transported from the CHC i to the FHC j with type k vehicle during period t

Inventory:

$Inv_{0,t}$	The amount of inventory in the provincial warehouse at the end of period t
$Inv_{n,t}$	The amount of inventory in health center n at the end of period t

Consumption:

$Con1_{n,h,t}$	The amount of first dose vaccine consumed (administered) at health center n for patient type h in period t
$Con2_{n,h,t}$	The amount of second dose vaccine consumed (administered) at health center n for patient type h in period t

Unsatisfied Demand:

$DD_{n,h,t}$	The amount of unsatisfied demand at health center n for type h patient in period t
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Waste Flow:

$WF_{0,c,t}$	The amount of medical waste (kg) transported from the provincial warehouse to collection center c in period t
$WF_{n,c,t}$	The amount of medical waste (kg) transported from health center n to collection center c in period t
$WF_{c,p,t}$	The amount of medical waste (kg) transported from collection center c to disposal center p in period t
Untransported Waste:	
$DDW_{0,c,t}$	The amount of medical waste (kg) that cannot be transported from the provincial warehouse to collection center c , in period t
$DDW_{n,c,t}$	The amount of medical waste (kg) that cannot be transported from health center n to collection center c , in period t
$DDW_{c,p,t}$	The amount of medical waste (kg) that cannot be transported from collection center c to disposal center p , in period t

The proposed MILP model is explained in the following seven sections using the above notations:

1. Objective functions
2. Constraints related to the demand calculations
3. Constraints related to the capacity limitations
4. Constraints related to the inventory balance
5. Constraints related to the medical waste management
6. Constraints related to the objective function
7. Constraints related to the bounds of decision variables

3.2.4 Objective Functions

Two objectives are proposed for the problem, which is commonly used in the literature. The first of these objectives is given in Equation (3.1) and represents maximizing the total number of FIPs. It is important to maximize the total number of FIPs as the main objective of a typical vaccine distribution program. This objective has been discussed in pediatric vaccine literature in studies conducted in low- and middle-income countries to maximize the number of FIC since some pediatric vaccines are also multi-dose. The second main objective is given in Equation (3.2) and represents the total cost minimization.

Maximization total number of FIPs:

$$Max Z_1 = \sum_{n \in N} \sum_{h \in H} FIP_{n,h} \quad (3.1)$$

Minimization of the total cost:

$$\begin{aligned}
Min Z_2 = & \sum_{i \in I} \sum_{k \in K_1} \sum_{t \in T, t \neq 0} C_k * Dist_{0,i} * A_{0,i,k,t} \\
& + \sum_{i \in I} \sum_{j \in VF_i} \sum_{k \in K_2} \sum_{t \in T, t \neq 0} C_k * Dist_{i,j} * A_{i,j,k,t} \quad \{Transportation Cost\} \\
& + \sum_{c \in C} \sum_{s \in WF5_c} \sum_{t \in T, t \neq 0} CW_s * WF_{c,s,t} \\
& + \sum_{c \in C} \sum_{f \in WF6_c} \sum_{t \in T, t \neq 0} CW_f * WF_{c,f,t} \quad \{Waste Processing Cost\} \\
& + CWD * \sum_{c \in C} \sum_{t \in T, t \neq 0} \left(DDW_{o,c,t} + \sum_{n \in WF3_c} DDW_{n,c,t} + \sum_{s \in WF5_c} DDW_{c,s,t} \right. \\
& \left. + \sum_{f \in WF6_c} DDW_{c,f,t} \right) \quad \{The Cost of not Transporting Medical Waste\} \\
& + \sum_{n \in N} \sum_{t \in T, t \neq 0} C_n * Inv_{n,t} \quad \{Inventory Holding Cost\} \\
& + CB * \sum_{t \in T, t \neq 0} \left(B_0 * Inv_{0,t} + \sum_{n \in N} B_n * Inv_{n,t} + \sum_{i \in I} \sum_{k \in K_1} B_{0,i,k} * A_{0,i,k,t} \right. \\
& + \sum_{i \in I} \sum_{j \in J} \sum_{k \in K_2} B_{i,j,k} * A_{i,j,k,t} + \sum_{n \in N} \sum_{h \in H} BO * Con1_{n,h,t} \\
& \left. + \sum_{n \in N} \sum_{h \in H} BO * Con2_{n,h,t} \right) \quad \{Vaccine Loss Cost\} \\
& + \sum_{n \in N} \sum_{h \in H} \sum_{t \in T, t \neq 0} CD_h * DD_{n,h,t} \quad \{The Cost of Unsatisfied Demand\} \\
& + CS * \sum_{n \in N} \sum_{h \in H} \sum_{t \in T, t \neq 0} (Con1_{n,h,t} + Con2_{n,h,t}) \quad \{Service Cost\} \quad (3.2)
\end{aligned}$$

3.2.5 Constraints

Demand Calculation Constraints:

$$DD_{n,h,t} \geq D_{n,h,t} - Con1_{n,h,t}, \quad \forall n \in N, h \in H, t \in \{1..1\} \quad (3.3)$$

$$DD_{n,h,t} \geq D_{n,h,t} + Con1_{n,h,t-1} - Con1_{n,h,t} - Con2_{n,h,t}, \quad \forall n \in N, h \in H, t \in \{2..|T|\} \quad (3.4)$$

$$Con2_{n,h,t} \leq 0, \quad \forall n \in N, h \in H, t \in \{1..1\} \quad (3.5)$$

$$Con1_{n,h,t} \leq D_{n,h,t}, \quad \forall n \in N, h \in H, t \in \{1..|T|\} \quad (3.6)$$

$$Con2_{n,h,t} \leq Con1_{n,h,t-1}, \quad \forall n \in N, h \in H, t \in \{2..|T|\} \quad (3.7)$$

Constraints (3.3) and (3.4) allow the amount of unsatisfied demand to be calculated for each patient type, location, and period. Constraint (3.5) ensures that there is no second dose of vaccine in the first period since a period must pass between two doses. Constraint (3.6) ensures that the first dose vaccine consumed for each patient type, location, and period does not exceed the total demand. The second dose of vaccine to be administered in other periods depends on the amount of the first dose of vaccine administered in the previous period. Constraint (3.7) provides the relationship between these two variables.

Capacity Limitation Constraints:

$$Inv_{i,t} + \sum_{k \in K_1} (1 - B_{0,i,k}) * A_{0,i,k,t} \leq Cap_i, \quad \forall i \in I, t \in \{1..|T|\} \quad (3.8)$$

$$Inv_{j,t} + \sum_{k \in K_2} (1 - B_{i,j,k}) * A_{i,j,k,t} \leq Cap_j, \quad \forall i \in I, j \in VF_i, t \in \{1..|T|\} \quad (3.9)$$

$$A_{0,i,k,t} \leq Cap_k, \quad \forall i \in I, k \in K_1, t \in \{1..|T|\} \quad (3.10)$$

$$A_{i,j,k,t} \leq Cap_k, \quad \forall i \in I, j \in VF_i, k \in K_2, t \in \{1..|T|\} \quad (3.11)$$

$$Inv_{0,0} = Cap_0 \quad (3.12)$$

$$Inv_{n,0} = Cap_n, \quad \forall n \in N \quad (3.13)$$

$$\sum_{h \in H} Ap * (Con1_{n,h,t} + Con2_{n,h,t}) \leq G_{n,t}, \quad \forall n \in N, t \in \{1..|T|\} \quad (3.14)$$

Constraints (3.8) and (3.9) are storage capacity constraints for each location and period. In health centers, the total inventory amount at the end of the period and the amount of vaccine transported to the health center in that period cannot exceed the capacity of the relevant health center. Here, the deterioration that may occur during the transportation is also taken into account. Constraints (3.10) and (3.11) are the capacity constraints of the vehicles to be used in transportation. It is stated that the amount of vaccine carried from one center to another cannot exceed the capacity of the vehicle used. Constraints (3.12) and (3.13) indicate that as many vaccines as the storage capacity are available in the provincial warehouse and health centers at the beginning of the projected horizon. Constraint (3.14) limits the number of vaccines administered during a period in the health centers. The time required to administer the total vaccine consumed over each period cannot exceed the total time available to healthcare workers in that health center.

Inventory Balance Constraints:

$$Inv_{0,t} \leq (1 - B_0) * Inv_{0,t-1} - \sum_{i \in I} \sum_{k \in K_1} A_{0,i,k,t}, \quad \forall t \in \{1 \dots |T|\} \quad (3.15)$$

$$Inv_{i,1} \leq (1 - B_i) * Inv_{i,0} - \sum_{j \in VF_i} \sum_{k \in K_2} A_{i,j,k,1} - \frac{\sum_{h \in H} Con1_{i,h,1}}{(1 - BO)} - \frac{\sum_{h \in H} Con2_{i,h,1}}{(1 - BO)}, \quad \forall i \in I \quad (3.16)$$

$$\begin{aligned}
Inv_{i,t} \leq & (1 - B_i) * Inv_{i,t-1} + \sum_{k \in K_1} (1 - B_{0,i,k}) * A_{0,i,k,t-1} \\
& - \sum_{j \in VF_i} \sum_{k \in K_2} A_{i,j,k,t} - \frac{\sum_{h \in H} Con1_{i,h,t}}{(1 - BO)} \\
& - \frac{\sum_{h \in H} Con2_{i,h,t}}{(1 - BO)}, \quad \forall i \in I, t \in \{2 \dots |T|\}
\end{aligned} \tag{3.17}$$

$$\begin{aligned}
Inv_{j,1} \leq & (1 - B_j) * Inv_{j,0} - \frac{\sum_{h \in H} Con1_{j,h,1}}{(1 - BO)} - \frac{\sum_{h \in H} Con2_{j,h,1}}{(1 - BO)}, \quad \forall j \\
& \in J
\end{aligned} \tag{3.18}$$

$$\begin{aligned}
Inv_{j,t} \leq & (1 - B_j) * Inv_{j,t-1} + \sum_{k \in K_2} (1 - B_{i,j,k}) * A_{i,j,k,t-1} \\
& - \frac{\sum_{h \in H} Con1_{j,h,t}}{(1 - BO)} - \frac{\sum_{h \in H} Con2_{j,h,t}}{(1 - BO)}, \\
& \forall i \in I, j \in VF_i, t \in \{2 \dots |T|\}
\end{aligned} \tag{3.19}$$

Constraints (3.15) – (3.19) define inventory balance constraints for each location and period. Constraint (3.14) computes the inventory amount at the end of the period for the provincial warehouse by subtracting the amount of vaccine transported to CHCs during this period from the amount of vaccine that remained intact in the inventory during the previous period. Since no transportation occurs in period zero, this situation is handled separately in Constraints (3.16) – (3.19). According to Constraints (3.16) and (3.17), for calculating the inventory amount at the end of the period at CHC, the amount of vaccine remaining in the inventory and the amount transported to this health center in the previous period constitutes the inputs. The amount of vaccine used in the same period as the amount of vaccine delivered to FHCs in the same period creates the outputs. The inventory amount at the end of the period is found by subtracting the outputs from the inputs. OVW information is also taken into account here. Since there is no transportation in the first period, the amount received from the provincial warehouse to CHC is not considered in Constraint (3.16).

Similarly, using Constraints (3.18) and (3.19), the inventory amount at the end of the period in FHCs, is found by subtracting the outputs from the inputs. However, there

is no transportation from here to any center. Since there is no transportation in the first period, Constraint (3.18) does not consider the transport from CHC to FHC.

Objective Function Constraints:

$$FIP_{n,h} = \sum_{t \in T} Con2_{n,h,t}, \forall n \in N, h \in H \quad (3.20)$$

Constraint (3.20) calculates the number of FIPs. Given that a patient requires two doses of vaccine to qualify as a FIP, the number of FIPs can be obtained according to the amount of the second dose vaccine administered.

Medical Waste Management Constraints:

$$\sum_{c \in WF1_0} (WF_{0,c,t} - DDW_{0,c,t}) \geq M * (B_0 * Inv_{0,t}), \quad \forall t \in \{1..|T|\} \quad (3.21)$$

$$\begin{aligned} & \sum_{c \in WF2_i} (WF_{i,c,t} - DDW_{i,c,t}) \\ & \geq M \\ & * \left(\sum_{h \in H} \frac{Con1_{i,h,t}}{(1 - BO)} + \sum_{h \in H} \frac{Con2_{i,h,t}}{(1 - BO)} + B_i * Inv_{i,t} \right. \\ & \left. + \sum_{k \in K_1} B_{0,i,k} * A_{0,i,k,t} \right), \quad \forall i \in I, t \in \{1..|T|\} \end{aligned} \quad (3.22)$$

$$\begin{aligned} & \sum_{c \in WF2_j} (WF_{j,c,t} - DDW_{j,c,t}) \\ & \geq M \\ & * \left(\sum_{h \in H} \frac{Con1_{j,h,t}}{(1 - BO)} + \sum_{h \in H} \frac{Con2_{j,h,t}}{(1 - BO)} + B_j * Inv_{j,t} \right. \\ & \left. + \sum_{k \in K_2} B_{i,j,k} * A_{i,j,k,t} \right), \forall i \in I, j \in VF_i, t \in \{1..|T|\} \end{aligned} \quad (3.23)$$

$$\sum_{s \in WF5_c} (WF_{c,s,t} - DDW_{c,s,t}) \geq SC * \left(WF_{0,c,t} + \sum_{n \in WF3_c} WF_{n,c,t} \right), \quad \forall c \in C, t \in \{1..|T|\} \quad (3.24)$$

$$\sum_{f \in WF6_c} (WF_{c,f,t} - DDW_{c,f,t}) \geq IC * \left(WF_{0,c,t} + \sum_{n \in WF3_c} WF_{n,c,t} \right), \quad \forall c \in C, t \in \{1..|T|\} \quad (3.25)$$

$$WF_{0,c,t} + \sum_{n \in WF3_c} WF_{n,c,t} \leq Cap_c, \quad \forall c \in C, t \in \{1..|T|\} \quad (3.26)$$

$$\sum_{c \in WF7_p} WF_{c,p,t} \leq Cap_p, \quad \forall p \in P, t \in \{1..|T|\} \quad (3.27)$$

Constraints (3.21) - (3.25) are medical waste flow-related constraints. Constraint (3.21) represents the medical waste flow from the provincial warehouse to the collection centers due to deterioration. Constraint (3.22) ensures that the weight of medical waste transported from CHC to collection centers equals the weight of medical waste from the vaccine administered in CHC and the deteriorated vaccine. Constraint (3.23) similarly calculates the weight of medical waste transported from FHC to collection centers. Constraints (3.24) and (3.25) represent the flow of medical waste collected from collection centers to sterilization and incineration centers, respectively. The ratios of the total amount of waste distributed as indicated by SC and IC and the sum of these two ratios is equal to one. Constraints (3.26) and (3.27) are capacity constraints on medical waste management. Constraint (3.26) states that the transported medical wastes to collection centers cannot exceed the collection centers' storage capacity in each period. Constraint (3.27) states that the weight of medical waste transported to disposal centers cannot exceed the waste processing capacity of the disposal centers.

Bounds of Decision Variables:

$$\begin{aligned}
 &FIP_{n,h}, A_{0,i,k,t}, A_{i,j,k,t}, Inv_{n,t}, Con1_{n,h,t}, Con2_{n,h,t}, DD_{n,h,t}, UD_{n,h,t}, WF_{n,c,t}, \\
 &WF_{c,p,t}, DDW_{n,c,t}, DDW_{c,p,t} \geq 0 \tag{3.28} \\
 &\forall i \in I, j \in J, n \in N, k \in K, t \in T, h \in H, c \in C, p \in P
 \end{aligned}$$

Finally, Constraint (3.28) defines the integer variables.

The developed model is handled as deterministic and run with real-life data. The data used and the results obtained are explained in detail in the next chapter.

CHAPTER 4

APPLICATION OF PROPOSED MODEL IN IZMIR TURKEY

In this chapter, the developed MILP model is tested with real data prepared for the province of Izmir for the two defined objectives. The goal of the test is to see how the model will yield results with deterministic data and to question which objective is more effective. Since COVID-19 vaccines are new products, there are not enough data about the parameters used in the model. Therefore, the data preparation part is an important part of the study. Data preparation is explained in detail in the following section.

4.1 Data Preparation

Since COVID-19 is a new virus for the whole world, the distribution and application of the produced vaccines are done for the first time. For this reason, most of the data planned to be used are not available with certainty. However, one can make the most precise prediction by considering similar scenarios that have already occurred.

As part of this study, the vaccine distribution problem in Izmir, one of the largest cities in Turkey, is discussed. Based on the Republic of Turkey Ministry of Health (RTMH) resources, the vaccine distribution is made from the main warehouse to provincial warehouses, to CHCs, and then to FHCs. There are 11 CHCs and 362 FHCs in Izmir. A CHC can serve more than one FHC, while an FHC can receive service from only one CHC. The planning horizon for the vaccine distribution problem is taken as one year. Transport at the provincial level takes place every month. Accordingly, the planning period is considered to be monthly.

Provincial warehouses are used only to store and distribute vaccines, while CHCs are used for storage, distribution, and administration. In FHCs, only storage and application can be made. Three types of vehicles are used in transportation between the provincial warehouse and health centers. These three types of vehicles, known as refrigerated container vehicles, vaccine transport vehicles, and vaccine transport trucks, can be characterized as small, medium, and large. While the medium-size vehicle can be used for transportation between the provincial warehouse and all health

centers, a small vehicle can only be used for transportation between CHC and FHC, and a large vehicle can only be used for transportation between the provincial warehouse and CHC.

The WHO identifies people 60 years of age and older who can be infected with COVID-19 as an at-risk group (WHO, 2021). Therefore, in this study, patients are divided into two groups: patients aged 60 and over and patients under 60 years of age. The patients in this group must be vaccinated first, as the treatment process can be more difficult when the individuals in the risk group get the disease.

4.1.1 Demand

This study aims to vaccinate the entire population over 18 since all individuals can be infected or be carriers of the disease. Hence, the population of 3,320,954 over 18 in Izmir province is our target population (*TP*) (Aytaç, 2021). However, each health center's demand should be determined according to each patient type in each period. For this reason, the target population should be differentiated according to health centers first.

Vaccination is done in CHCs and FHCs. According to the population, these health centers, located in certain regions of the province, are dense in some regions and sparse in some regions. Each center has a population under its responsibility. For health centers, the demand ($D_{n,h,t}$) is obtained by multiplying the ratio (R_n) of that population in the total provincial population of the target population. Since the time period is monthly within a one-year planning horizon, the periodic demand is obtained by dividing the total demand by 11 according to the health centers. Since the COVID-19 vaccine is administered in two doses and a period must pass between the two doses, the total demand is divided into 11 periods, with only the second dose of vaccine administered in the last period. Finally, the demand for patients aged over 60 for a given period is determined by multiplying the rate of patients of these ages over the total population (RP_n) by the periodic demand. If the results are decimal, the calculated value is rounded up. The formula used to calculate the demand is given below.

$$D_{n,1,t} = \frac{TP * R_n}{11} * RP_n, \quad \forall n \in N, t \in 1..|T| \quad (4.1)$$

$$D_{n,2,t} = \frac{TP * R_n}{11} * (1 - RP_n), \quad \forall n \in N, t \in 1..|T| \quad (4.2)$$

4.1.2 Capacities

Five types of capacities are identified to be used in the model. These include vaccine storage capacity, vaccine transportation capacity, medical waste processing capacity, medical waste storage capacity, and workforce capacity. Vaccine storage capacity is determined for the provincial warehouse and health centers. The data obtained from the RTMH are used for these capacities. According to the 2018 data, there is a cold store in each province to store vaccines in Turkey (RTMH, 2021). These cold storage areas can be either 1140 m³ or 2100 m³. The capacity of the provincial warehouse for Izmir is 1140 m³.

Vaccines are stored in vaccine cabinets in FHCs. There are four types of vaccine cabinets with a capacity of 190 liters (L), 365 L, 610 L, and 1000 L from small to large. These cabinets are supposed to be distributed in accordance with the FHC population. FHCs with less than 5000 population have a 190 L vaccine cabinet, those between 5,000 and 10,000 people have a 365 L vaccine cabinet, those between 10,000 and 20,000 have a 610 L vaccine cabinet, and those between 20,000 and 30,000 have a 1000 L vaccine cabinet. The capacity information provided is gross capacity, and three-quarters of gross capacity is considered net capacity (RTMH, 2021). Finally, the required volume for one dose box of vaccine storage is taken 0.1 L, and the required capacities are given in Table 4.1.

Table 4.1 Vaccine storage capacity amounts by population

Population (person)	Gross Capacity (L)	Net Capacity (L)	Net Capacity (unit)
≥ 0 ≤ 5.000	190	142,5	1425
> 5.000 ≤ 10.000	365	273,75	$2737,5 \approx 2735$
> 10.000 ≤ 20.000	610	457,5	4575
> 20.000 ≤ 30.000	1000	750	7500

Since CHCs serve as both distribution and administration centers, they must meet the needs of the FHCs and the population for which they are responsible. For this reason, CHCs also have vaccine storage areas. FHCs have been identified as having a vaccine storage capacity of 7500 compared to a population of 30,000. For CHCs, they have an assumed storage capacity of 25,000 vaccines per 100,000 population.

There are three types of vaccine transport vehicles to carry vaccines at the provincial level, and their capacities are 13 m³, 8 m³, and 1 m³, respectively (RTMH, 2021). This capacity information is accepted as gross capacity information, and net capacity is again considered three-quarters of gross capacity.

The medical waste processing capacity is 110 tons per day for both disposal types (IMM, 2019). Given that no data can be found for collection center capacity, it is considered sufficient based on the region's population area and the medical waste processing capacity of the disposal center.

Staff hours capacity is determined by assuming that the centers have medical staff in proportion to the population for which they are responsible. The number of staff depending on the population range is given in Table 4.2. Medical personnel works nine hours between 8 a.m. and 5 p.m. (540 minutes) per day and 270 hours (16,200 minutes) per month. Based on the number of staff at the health center, staff-hour capacity information is also indicated in Table 4.2. The time taken to administer a vaccine is 10 minutes, along with the patient's waiting time at the center for side effects.

Table 4.2 Personnel hour capacity by population

Population	Number of Staff	Monthly Working Time (min.)	Net Capacity (min.)
≥ 0 ≤ 5.000	1	16200	16200
> 5.000 ≤ 10.000	2	16200	32400
> 10.000 ≤ 15.000	3	16200	48600
> 15.000 ≤ 20.000	4	16200	64800
> 20.000 ≤ 25.000	5	16200	81000
> 25.000 ≤ 30.000	6	16200	97200

4.1.3 Deteriorations

Deterioration is treated in three ways: inventory deterioration due to heat exchange, heat exchange during transportation, and vaccine vials being open for more than a certain time during vaccine administration (OVW). The rate of inventory deterioration due to temperature change is determined considering the rate specified for influenza vaccines based on the similarity of their storage conditions to the COVID-19 vaccine. It is reported that the global rate of deterioration of the influenza vaccine is between 5% and 8% (Jantzi-Bauman, 2017).

Vaccines are kept in inventory at three centers. The deterioration rate is taken as 5% in the provincial warehouse because the equipment used in this warehouse is better than those in the centers, and events causing heat exchange (such as the opening and closing of the door) are experienced less frequently. In CHCs, on the other hand, since these events will likely occur more frequently, the deterioration rate is determined as 6%. Finally, the deterioration rate is 7%, thinking that the equipment may be more inappropriate and that event causing heat exchange may occur much more frequently in FHCs.

The possible deterioration rate during the transport is determined by the distance between the centers and the vehicle type. The deterioration rate is estimated at 7%, 6%, and 5%, respectively, of low to high transportation capacity. In addition, it is increased by 0.5% for every 25 km distance traveled. For distances of less than 10 km,

it is accepted that no deterioration occurs irrespective of the vehicle used for transport. For example, if the distance between centers a and b is 52 km and we use the type-2 vehicle, the deterioration rate is calculated as $(6 + 2 \cdot 0.05) \%$. Finally, the deterioration rate experienced during vaccine administration (OVW) is assumed to be constant and 5%.

4.1.4 Costs

As stated earlier, many types of costs are discussed in the context of this study. One of them is the transportation cost. While determining the transportation cost, the costs of the vehicles that meet the cold chain requirements are taken into account. There is a transportation cost of one km for one dose of vaccine for three types of vehicles. As expected, the transportation cost of the vehicle with a larger transportation capacity is higher.

We do not have any information about holding costs. For this reason, the holding cost is determined by considering a previous study on influenza vaccines (Hovav & Tsadikovich, 2015) with storage conditions similar to those for COVID-19 vaccines. The cost of losing a vaccine dose is directly equal to its cost, and the cost of administering a dose of vaccine is determined by the average monthly salary of the healthcare personnel. Since medical personnel work 16,200 hours per month and can administer six vaccines per hour (one vaccine in 10 minutes), $1/97,200$ of their monthly salary is equal to the cost of one dose. The waste treatment costs are determined according to the method of disposal collected from the municipality of Izmir (IMM, 2019). Collection and transportation costs are also included in the waste processing cost.

The cost of not transporting and treating waste is presumed to be subsidized by an external service. For this reason, it is accepted that the cost of not transporting 1 kg of medical waste is equal to 1.5 times the current medical waste transportation, collection, and processing costs. All mentioned cost types and corresponding cost amounts are presented in Table 4.3.

Table 4.3 Cost types and corresponding costs

Cost Type	Cost (₺)		
Transportation (₺/dose)	<i>Vehicle Type-1</i> 0,00088235	<i>Vehicle Type-2</i> 0,00013235	<i>Vehicle Type-3</i> 0,00011765
Inventory (₺/dose)	<i>CHC</i> 1,494	<i>FHC</i> 1,718	
Waste Processing (₺/kg)	<i>SC</i> 3,1	<i>IC</i> 9,41	
Untransported Waste (₺/kg)	14,115		
Vaccine Loss (₺/dose)	90,04		
Unsatisfied Demand (₺/dose)	<i>Patient Type-1</i> 691,1	<i>Patient Type-2</i> 345,6	
Service (₺/dose)	2,20987654		

4.1.5 Distances

We only have coordinated information for the provincial warehouse, health centers, waste collection centers, and disposal centers. These data can be accessed through the Izmir Metropolitan Municipality Open Data Portal. The distance between the centers is calculated as in Fazli-Khalaf et al.'s study (2019). Accordingly, the following formula is used to calculate the distance between two centers:

$$\begin{aligned}
 Dist_{i,j} = & \text{Arccos}(\sin(\text{Latitude}_i) * \sin(\text{Latitude}_j) + \cos(\text{Latitude}_i) \\
 & * \cos(\text{Latitude}_j) * \cos(\text{Longitude}_j - \text{Longitude}_i)) \\
 & * 6371.1
 \end{aligned} \quad (4.3)$$

where 6371.1 is the earth's radius and Latitude and Longitude are the geographic coordinates of the facilities multiplied by $\pi/180$.

4.1.6 Medical Waste Rates

Different kinds of medical waste may occur in different centers as part of the vaccine distribution. One of these is the waste generated after vaccination and includes medical waste such as syringes, medical needles, and cotton. This type of waste emerges in health centers where vaccines are administered. Another type is due to the

deterioration of vaccines to heat change. This type of medical waste may occur in the provincial warehouse, health center storage areas, and during transportation. Medical waste generated in all centers is first transported to waste collection centers and then sent to sterilization or incineration centers for disposal. According to the Turkish Statistical Institute data, the sharing between these two centers is determined as 91.3% Sterilization and 8.7% Incineration (Çivit, 2020).

In the developed model, vaccines are handled on a unit basis, while medical waste is handled in kg. For vaccines, one unit corresponds to one dose box of vaccines. For this reason, there is a need for conversion from unit to kg unit in the model. The estimated weight of one vaccine waste is 50 grams. That is, a value of 0.05 kg is used for conversion.

4.2 Results for Deterministic Data

The proposed model is coded and solved in CPLEX Studio IDE 12.10.0 using the data described above. Model codes are presented in Appendix 3.1. It is run on a PC with an Intel Core i5-7200U CPU 2.50 GHz processor and 8.00 GB RAM. As mentioned earlier, the model is run separately for two objectives defined in Chapter 3: minimizing total cost and maximizing the total number of FIPs. While there are 55506 constraints in the model, there are 52362 variables, 41417 of which are integers. The results are compared in terms of both objectives and solution time. Since the objective values will be in millions, the deviation from the optimal value is more tolerable. Because of this, the relative tolerance gap value in the CPLEX Optimizer is taken as one per thousand to prevent the model from running too long. The results of the study are summarized in Table 4.4.

Table 4.4 Deterministic model results

OBJECTIVE	TOTAL COST	TOTAL NUMBER OF FIPs	SOLVE TIME
MIN COST	3,340,382.673 ₺	0 patient	34.48 sec.
MAX FIP	1,121,100,000 ₺	3,325,616 patients	163.98 sec.

Based on these results, the cost-minimization objective does not permit vaccine administration to avoid all costs associated with vaccine administration. Therefore, the

cost remains at a very low level. When we examine the results of the FIP maximization objective, we see that the entire population is fully vaccinated. (The fact that the total FIP value is above the target population is due to rounding in the demand calculations). However, this time, the resulting cost is more than 300 times of minimizing the cost objective. As the primary objective of our problem is to guarantee social immunity, the objective of maximizing FIPs should be used. However, this level of cost is also unacceptable. For this reason, multi-objective optimization methods that take both objectives into account should be used.

Multi-objective optimization methods are used in problems with more than one objective. These methods aim to find acceptable solutions by considering the different objectives defined for the problem simultaneously. Some methods ultimately yield a single solution. Lexicographic method and Fuzzy goal programming are examples of these methods. On the other hand, some methods provide different solutions when all objectives are addressed at different levels, giving the decision-maker a wide choice of area. All solutions presented by these methods are called Pareto optimal solutions and do not dominate each other. The ε -constraint method can be given as an example of these methods.

The ε -constrained method was developed by Haimes et al. (1971). The method's advantages are that it can be used for convex and non-convex problems and is easy to apply. The logic behind the method is to determine an objective as the main objective and then to reach a solution by restricting other objectives to certain levels. The most important point to be considered here and the disadvantage of the method is the determination of the ε -level, which is the level at which other objectives will be constrained. This level is determined between the best and worst values of the constrained objective function value. The problem is solved over and over again by dividing this interval into equal parts. All of the feasible solutions obtained are Pareto optimal solutions, and by showing them on a Pareto curve, a wide range of options is offered to the decision-maker (Mavrotas, 2009).

In our study, the cost is minimized under the number of FIPs constraint. We calculate the range value using the upper and lower limits corresponding to the worst and best objective values. The ε -level values are calculated by dividing the range value

of the FIP objective function into 100 equal parts. Then, the constraint given in Equation (4.4) is added to the model, and the model is solved successively.

$$\sum_{n \in N} \sum_{h \in H} FIP_{n,h} \geq \varepsilon_l \quad \forall l \in 1..100 \quad (4.4)$$

The pareto optimal solutions obtained are given in Figure 4.1. Note that values do not dominate each other. The model is limited to 1800 seconds per run. The results presented in the figure include only the solutions found in 1800 seconds. For the runs, which cannot obtain results within the specified time, no results have been obtained even if the runs without the time limit were carried out later.

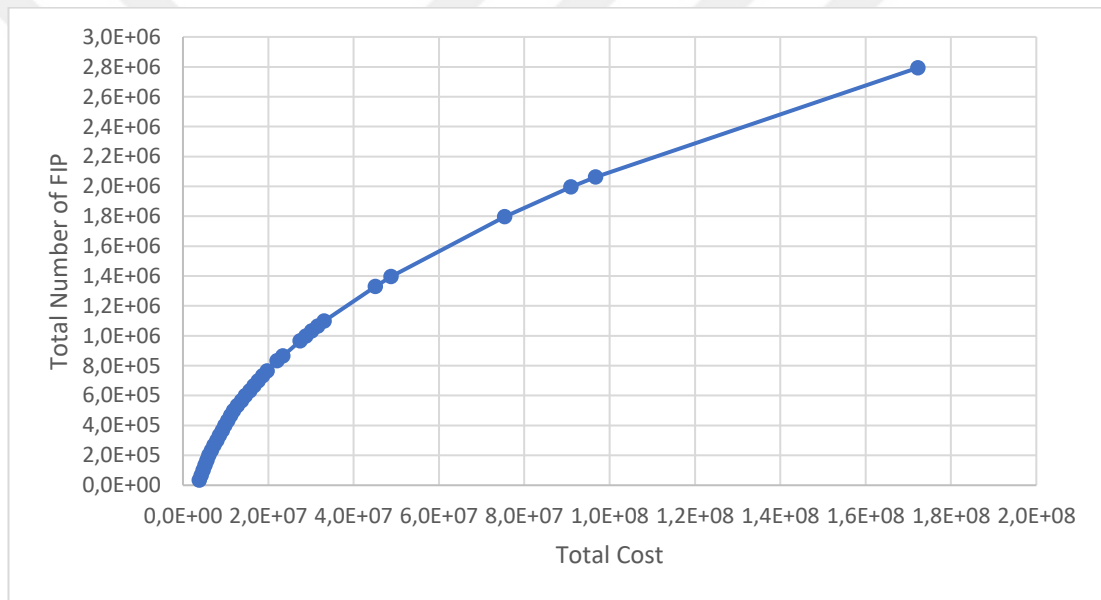


Figure 4.1 Pareto optimal solutions corresponding to ε values

The solution in which the highest number of people vaccinated among the solutions was obtained that represented by the dot in the upper right corner of the graph is shown in Table 4.5. Since a solution cannot be obtained within the time limit determined for higher ε values, the solution with the highest total FIP number is reported, among the results obtained. As can be seen from the table, although the total cost and the total number of FIPs are beginning to stabilize, the entire population is still not vaccinated.

Table 4.5 Pareto optimal solution chosen according to the results of the ε -constraint method

EPSILON	TOTAL COST	TOTAL NUMBER OF FIPs	SOLVE TIME
2793501.48	172,230,701.399 ₺	2,793,502 patient	751.079 sec.

Another way to address different objectives is to add penalty costs to one of the objectives. In our problem, this can be achieved by setting a penalty cost for the unsatisfied demand. Such an application was made in the study of Hovav and Tsadikovich (2015).

The high vaccination rate can be achieved by adding the cost of unsatisfied demand to other costs. For this, the CD_h parameter is defined as “the cost of not vaccinating a type h patient (Unsatisfied demand).” The objective function formed by the addition of the new cost is given in Equation (4.5).

$$\begin{aligned}
 \text{Min } Z_3 = & \sum_{i \in I} \sum_{k \in K_1} \sum_{t \in T, t \neq 0} C_k * \text{Dist}_{0,i} * A_{0,i,k,t} \\
 & + \sum_{i \in I} \sum_{j \in VF_i} \sum_{k \in K_2} \sum_{t \in T, t \neq 0} C_k * \text{Dist}_{i,j} * A_{i,j,k,t} \quad \{\text{Transportation Cost}\} \\
 & + \sum_{c \in C} \sum_{s \in WF5_c} \sum_{t \in T, t \neq 0} CW_s * WF_{c,s,t} \\
 & + \sum_{c \in C} \sum_{f \in WF6_c} \sum_{t \in T, t \neq 0} CW_f * WF_{c,f,t} \quad \{\text{Waste Processing Cost}\} \\
 & + CWD \\
 & * \sum_{c \in C} \sum_{t \in T, t \neq 0} \left(DDW_{o,c,t} + \sum_{n \in WF3_c} DDW_{n,c,t} + \sum_{s \in WF5_c} DDW_{c,s,t} \right. \\
 & \left. + \sum_{f \in WF6_c} DDW_{c,f,t} \right) \quad \{\text{The Cost of not Transporting Medical Waste}\} \\
 & + \sum_{n \in N} \sum_{t \in T, t \neq 0} C_n * \text{Inv}_{n,t} \quad \{\text{Inventory Holding Cost}\}
 \end{aligned}$$

$$\begin{aligned}
& +CB * \sum_{t \in T, t \neq 0} \left(B_0 * Inv_{0,t} + \sum_{n \in N} B_n * Inv_{n,t} + \sum_{i \in I} \sum_{k \in K_1} B_{0,i,k} * A_{0,i,k,t} \right. \\
& \quad + \sum_{i \in I} \sum_{j \in J} \sum_{k \in K_2} B_{i,j,k} * A_{i,j,k,t} + \sum_{n \in N} \sum_{h \in H} BO * Con1_{n,h,t} \\
& \quad \left. + \sum_{n \in N} \sum_{h \in H} BO * Con2_{n,h,t} \right) \{Vaccine Loss Cost\} \\
& + \sum_{n \in N} \sum_{h \in H} \sum_{t \in T, t \neq 0} CD_h * DD_{n,h,t} \{The Cost of Unsatisfied Demand\} \\
& + CS * \sum_{n \in N} \sum_{h \in H} \sum_{t \in T, t \neq 0} (Con1_{n,h,t} + Con2_{n,h,t}) \{Service Cost\} \tag{4.5}
\end{aligned}$$

The determination method used in Hovav & Tsadikovich (2015) calculates the cost of unsatisfied demand. It is assumed that this is the cost of treatment if a non-vaccinated person is infected. The following formula is used for calculation:

$$CD_h = TC_h * p - TC_h * p', \quad \forall h \in H \tag{4.6}$$

Here, TC_h is the average treatment cost of the h -type patient. Since patients aged 60 and over are more likely to be treated in intensive care, treatment costs are also higher. The p -value is the probability of the unvaccinated individual being infected, while the p' value indicates the probability of the vaccinated individual. The probability of the unvaccinated individual being infected is currently determined by the ratio of the number of COVID-19 positive cases to the total number of tests. The probability of a vaccinated individual being infected is equal to the probability of an unvaccinated individual being infected multiplied by the value (1 - the effectiveness of the vaccine). The effectiveness of the administered vaccine was reported as 83.5% (Tanriover et al., 2021).

The results obtained from the solution of the model according to this new objective function are given in Table 4.6.

Table 4.6 The solution obtained by cost minimization with the cost of unsatisfied demand

OBJECTIVE	TOTAL COST	TOTAL NUMBER OF FIPs	SOLVE TIME
MIN COST	244,678,641.96 ₺	3,325,939 patients	29.05 sec.

As can be seen from the table, the cost minimization objective with unsatisfied demand cost gives more effective results in all indicators than the FIP maximization objective and ϵ -constraint method. The total cost value obtained here is higher than the result in Table 4.5, but the entire population can be vaccinated in return. Additionally, it should not be noted that the cost of unsatisfied demand is included in the total cost value obtained here. When the unsatisfied demand cost of 38,702.67 TL is subtracted, the total cost is obtained as 244,639,939.285873. The difference of 72,409,237.89 TL between the total cost reported in Table 4.5 and the total cost here is due to the vaccination of 532,437 additional patients. In other words, while the number of vaccinated patients increased by 19.06%, the cost increases by 42.042%. This cost increase is quite tolerable compared to the solution obtained to maximize the total number of FIPs reported in Table 4.4. For this reason, the analysis made in the following sections is based on the results obtained using the objective function (4.5).

Important decisions are made using the proposed model when achieving these objective values. The values of these decision variables provide important insights as to the adequacy of the existing system. The analysis is made according to the model's results for the cost minimization objective function with unsatisfied demand cost. When examining vaccine flow variables showing the amount of vaccine transported between centers, type 3 vehicles are more widely used for transportation from the provincial warehouse to CHCs, and type-2 vehicles are more widely used from CHCs to FHCs. As more vaccines are transported simultaneously with these vehicles, the unit cost of transporting the vaccines is lower than type-1 vehicles. In addition, it is more reasonable to transport enough vaccines to meet demand with larger capacity vehicles.

When examining the inventory amounts, the model meets the demand for each period, with the vaccines reaching the center at the beginning of that period to avoid the holding cost. For this reason, the inventory amount is zero or close to zero in all periods except the first period. When the inventory amount of the provincial warehouse is examined, it is noted that it decreases in each period and becomes zero in the 11th period. The amount of decrease in inventory shows a downward trend. While the difference in the inventory amount in the first two periods is over one

million, the difference in the tenth and 11th periods remains at the level of eighteen thousand.

When we look at the consumption variables showing the number of vaccines and the unsatisfied demand variables, the demand is essentially satisfied. When we look at the capacities in each period, we see that they are adequate. Only a small amount of unsatisfied demand situation arises due to deterioration. Where the demand cannot be met, priority for vaccination is given to type-1 patients aged 60 and over.

When looking at the variables related to waste management resulting from vaccination applications and deterioration, there is no situation where waste is not transported. It demonstrates that Izmir province has sufficient capacity to manage medical waste.

As the analysis of the results shows, it is possible to vaccinate the whole population over a one-year planning horizon. Since vaccination is also in a race with epidemic disease, it is also important to know when community immunity can be gained. The model is solved again by using the same data but narrowing the planning horizon to analyze this situation. The results obtained are presented in Table 4.7.

Table 4.7 Results obtained according to the planning horizon contraction

PLANNING HORIZON	TOTAL COST (₺)	TOTAL NUMBER OF FIPs	SOLVE TIME (SEC.)
12 MONTHS	244,678,641.96	3,325,939 patients	29.05
11 MONTHS	222,385,991.404	3,325,376 patients	1114.44
10 MONTHS	204,196,275.666	3,310,332 patients	31.39
9 MONTHS	192,881,022.355	3,282,563 patients	3469.88
8 MONTHS	220,874,634.706	3,113,848 patients	2026.48

The table shows that the total cost with unsatisfied demand decreases while the planning horizon narrows to nine months. This situation can be considered normal, as the types of costs also depend on the time frame. However, when the planning horizon narrows from nine months to eight months, the total cost becomes higher than the nine-month planning horizon as the cost of unsatisfied demand increases. Thus, it is not possible to vaccinate the entire population in eight months.

Given the total number of FIPs, we can observe not much difference between the 12-month and 11-month planning horizons, and the overall population is still vaccinated. For the 10-month planning horizon, approximately 15,000 persons cannot be vaccinated, and approximately 40,000 persons cannot be vaccinated for the nine-month planning horizon. Finally, more than 100 thousand individuals cannot be vaccinated for the 8-month planning horizon. The eight-month planning horizon can be considered a limit because the cost increases compared to the previous option, and the number of people who could not be vaccinated exceeds 100 thousand. Therefore, it can be asserted that, with the available resources, the fastest vaccination at the most affordable cost can be achieved with a nine-month planning horizon. However, since vaccinating the entire population is the main goal, the analysis in the following sections is made for the 12-month planning horizon.

The Robust Optimization approach used to handle uncertainties is explained in detail in the next chapter.

CHAPTER 5

ROBUST OPTIMIZATION APPROACH

Necessary definitions about Robust optimization were made in Section 2.5. This chapter focuses on choosing the appropriate approach to the problem under consideration, creating the model, and its application.

The vaccine distribution problem involves uncertainties. In particular, demand, capacity, and deterioration rate parameters are often not known with certainty in real-life applications. Since the distribution of vaccines is a major public health problem, it is crucial to encompass these uncertainties to produce viable solutions in all conditions. In this thesis, the Robust optimization approach is used to ensure that the model meets these requirements. To create a robust model, the parameters to be considered uncertain are initially identified, and from which interval set these parameters will take values is determined. Then, the most suitable model is selected according to the uncertainty type among the proposed modeling approaches, and the robust model is created. The results obtained based on the different values of the special model performance parameters defined for the robust model are examined. The results obtained are presented on a trade-off curve, considering the decision-maker's risk-taking level.

In our problem, three parameters are taken as uncertain: the demand of each period, the health centers' storage capacities, and the deterioration rate. The presumed deterioration during vaccine administration (OVW) is not included in the uncertain parameters. Since we have no expert opinion or historical data on these parameters, the type of our uncertain parameters is determined as deep uncertainty. Therefore, a robust convex programming modeling approach is used.

There are different modeling approaches developed for Robust convex programming. The advantages and disadvantages of these approaches are described in Section 2.5. Based on this information, the modeling approach of Bertsimas and Sim (2004) is used in this study to avoid non-linear modeling and overcome pessimistic situations where all parameters have the worst-case value. Before presenting our robust

model, information about how the modeling approach used works is explained in the next section.

5.1 Robust Convex Optimization

The approach used for creating the robust model is to obtain the robust counterpart form of the existing model by expressing the uncertain parameters linearly. The modeling approach of Bertsimas and Sim (2004) consists of three stages. In these stages, respectively, 1) The required protection level on the relevant constraint is expressed by ignoring the uncertainty in the parameters, 2) The linear optimization formula where the protection function corresponds to the objective function is written, and 3) The dual form of the model is taken, and its constraint is added. These steps are applied for each constraint where uncertain parameters are used, and as a result, a robust counterpart model is obtained.

Suppose the following linear optimization model is given. In the model, c is the objective function coefficient, x is the decision variable, A is the coefficient matrix, and b is the right-hand side value. The K_j value represents the uncertainty set and is convex.

$$\begin{aligned}
 & \text{Max } c * x \\
 & \text{subject to; } \sum_j^n A_j * x_j \leq b, \quad \forall A_j \in K_j, j = 1, \dots, n \quad (5.1) \\
 & x \geq 0
 \end{aligned}$$

If the coefficient matrix A is assumed to be uncertain, the model turns into the following form;

$$\begin{aligned}
 & \text{Max } c * x \\
 & \text{subject to; } \sum_j^n \tilde{a}_j * x_j \leq b, \quad \forall A_j \in K_j, j = 1, \dots, n \quad (5.2)
 \end{aligned}$$

$$x \geq 0$$

Then, according to the first step of the modeling approach of Bertsimas and Sim (2004), a model as follows is obtained;

$$\begin{aligned}
 & \text{Max } c * x \\
 & \text{subject to } \sum_j^n a_{i,j} * x_j \\
 & \quad + \max_{\{S_i \cup \{t_i\} | S_i \subseteq J_i, |S_i| = \lfloor \Gamma_i \rfloor, t_i \in J_i \setminus S_i\}} \left\{ \sum_{j \in S_i} \hat{a}_{i,j} * y_j + (\Gamma_i - \lfloor \Gamma_i \rfloor) \right. \\
 & \quad \left. * a_{i,t_i} * y_{t_i} \right\} \leq b_i, \quad \forall i \\
 & \quad -y_j \leq x_j \leq y_j \quad \forall j \\
 & \quad l \leq x \leq u \\
 & \quad y \geq 0
 \end{aligned} \tag{5.3}$$

In the above formulation, J_i denotes the set of coefficients of $a_{i,j}$. The uncertain parameter $a_{i,j}$ takes a value in the range $[a_{i,j} - \hat{a}_{i,j}, a_{i,j} + \hat{a}_{i,j}]$. Parameter Γ_i is defined for each constraint that includes uncertain parameters. This parameter, which is defined as the budget of uncertainty, takes a value in the interval $[0, |J_i|]$ and it does not need to be an integer. The function of this parameter is to set the level of conservatism of the solution. When the value of this parameter is $\Gamma_i = 0$, the uncertain parameter takes its nominal value, and the model is solved deterministically. When the parameter takes the value of $\Gamma_i = |J_i|$, which is the other extreme point, the uncertain parameter takes the worst-case value. In this case, the modeling approach of Soyster (1973) is obtained. The model is still a non-linear optimization model in this form. Bertsimas and Sim (2004) propose that the part that makes the model nonlinear, $\beta_i = \max_{\{S_i \cup \{t_i\} | S_i \subseteq J_i, |S_i| = \lfloor \Gamma_i \rfloor, t_i \in J_i \setminus S_i\}} \{\sum_{j \in S_i} \hat{a}_{i,j} * |x_j^*| + (\Gamma_i - \lfloor \Gamma_i \rfloor) * \hat{a}_{i,t_i} * |x_{t_i}^*|\}$, is the same as the objective function of a linear optimization problem given below:

$$\begin{aligned}
\beta_i &= \max \sum_{j \in S_i} \hat{a}_{i,j} * |x_j^*| * z_{i,j} \\
\text{subject to } \sum_{j \in J_i} z_{i,j} &\leq \Gamma_i, \quad (q_i) \\
0 \leq z_{i,j} &\leq 1, \quad \forall j \in J_i, \quad (r_{i,j})
\end{aligned} \tag{5.4}$$

The q_i and $r_{i,j}$ expressions next to the constraints of this linear optimization model represent dual variables corresponding to the constraints. The linear robust counterpart form of the model is written using these dual variables with the help of duality.

$$\begin{aligned}
&\max c * x \\
\text{subject to } \sum_j a_{i,j} * x_j + z_i * \Gamma_i + \sum_{j \in J_i} p_{i,j} &\leq b_i, \quad \forall i \\
z_i + p_{i,j} &\geq \hat{a}_{i,j} * y_j, \quad \forall i, j \in J_i \\
-y_j &\leq x_j \leq y_j, \quad \forall j \\
l_j &\leq x_j \leq u_j, \quad \forall j \\
z_i, p_{i,j}, y_j &\geq 0, \quad \forall i, j \in J_i
\end{aligned} \tag{5.5}$$

In the study of Bertsimas and Sim (2004), an approach is presented only for cases where the coefficient matrix contains uncertainty. However, uncertainty can also occur in right-hand side values. For this reason, Najafi et al. (2013) proposed a modeling approach that handles situations where right-sided values contain uncertainty. The approach includes the same steps as the work of Bertsimas and Sim (2004), only the uncertain parameter's position changes. Assuming that the b value is uncertain in the model (5.1), the model formed according to the Najafi et al.'s (2013) approach is as follows;

$$\begin{aligned}
& \text{Max } c * x \\
& \text{subject to } \sum_j a_{i,j} * x_j + z_i * \Gamma_i + \sum_{j \in J_i} p_{i,j} \leq b_i, \quad \forall i \\
& z_i + p_{i,j} \geq \hat{b}_{i,j}, \quad \forall i, j \in J_i \\
& z_i, p_{i,j}, x_j \geq 0, \quad \forall i, j \in J_i
\end{aligned} \tag{5.6}$$

In another study, the uncertainty in the right-hand value was modeled differently. Hatefi and Jolai (2014) handled this situation more simply in their study and formed the robust counterpart problem of the same model. The model is similar to the robust modeling approach proposed by Ben Tal and Nemirovski (2009).

$$\begin{aligned}
& \text{Max } c * x \\
& \text{subject to } \sum_j a_{i,j} * x_j \leq b_i - \Gamma_i * \hat{b}_i, \quad \forall i \\
& x_j \geq 0, \quad \forall i, j \in J_i
\end{aligned} \tag{5.7}$$

The robust optimization approach can only manage constraints of the type “less than or equal to” (H. Sun et al., 2021). However, Hatefi and Jolai (2014) suggested an approach similar to (5.7) to handle constraints involving equality. If we have a model like the following;

$$\begin{aligned}
& \text{Max } c * x \\
& \text{subject to; } \sum_j^n A_j * x_j = \tilde{b}, \quad \forall A_j \in K_j, j = 1, \dots, n \\
& x \geq 0
\end{aligned} \tag{5.8}$$

According to Hatefi and Jolai (2014)’s approach, the robust counterpart form of this model is obtained as follows;

$$\begin{aligned}
& \text{Max } c * x \\
& \text{subject to; } b_i - \Gamma_i * \hat{b}_i \leq \sum_j^n A_j * x_j \leq b_i + \Gamma_i * \hat{b}_i, \quad \forall A_j \in K_j, j = 1, \dots, n \quad (5.9) \\
& x \geq 0
\end{aligned}$$

As can be expected, the most important point of this modeling approach is determining the budget of uncertainty value. Different methods are suggested in different studies to determine this value. Bertsimas and Sim (2004) proposed the modeling approach and offered suggestions for determining the budget of uncertainty value. The authors examined the effect of the change in Γ_i value at different bounds on the objective function, showing appropriate values where the constraint violation is less than 1% for different $|J_i|$ values. Similarly, in subsequent studies, the approach of examining the objective function values according to the variation of the Γ_i value at certain intervals was frequently used. With the trade-off curves created by this approach, a selection area can be revealed for the decision-maker to choose the appropriate result according to the level of risk-taking.

In some studies, formulations have been developed to determine the problem-specific Γ_i value. For example, Ahabchane et al. (2021), in their study dealing with a routing problem, calculated the Γ_i value with a formulation containing the driver's scattering level reflecting the vehicle's behavior compared to the average dispersion of all drivers. Najafi et al. (2013) and Modarres and Izadpanahi (2016) stated that the Γ_i value can be expressed as a time-dependent function.

5.2 Robust Counterpart Model

In this section, the model that includes the uncertainties and the robust counterpart model, which is created using the modeling approaches described above, are presented, respectively. The Z_3 objective function is used in the same way in the models. Accordingly, the model including the uncertainties is given as follows;

Demand Calculation Constraints:

$$DD_{n,h,t} \geq \tilde{D}_{n,h,t} - Con1_{n,h,t}, \quad \forall n \in N, h \in H, t \in \{1..1\} \quad (5.10)$$

$$DD_{n,h,t} \geq \tilde{D}_{n,h,t} + Con1_{n,h,t-1} - Con1_{n,h,t} - Con2_{n,h,t}, \quad \forall n \in N, h \in H, t \in \{2..|T|\} \quad (5.11)$$

$$Con2_{n,h,t} \leq 0, \quad \forall n \in N, h \in H, t \in \{1..1\} \quad (5.12)$$

$$Con1_{n,h,t} \leq \tilde{D}_{n,h,t}, \quad \forall n \in N, h \in H, t \in \{1..|T|\} \quad (5.13)$$

$$Con2_{n,h,t} \leq Con1_{n,h,t-1}, \quad \forall n \in N, h \in H, t \in \{2..|T|\} \quad (5.14)$$

Capacity Limitation Constraints:

$$Inv_{i,t} + \sum_{k \in K_1} (1 - \tilde{B}_{0,i,k}) * A_{0,i,k,t} \leq \tilde{Cap}_i, \quad \forall i \in I, t \in \{1..|T|\} \quad (5.15)$$

$$Inv_{j,t} + \sum_{k \in K_2} (1 - \tilde{B}_{i,j,k}) * A_{i,j,k,t} \leq \tilde{Cap}_j, \quad \forall i \in I, j \in VF_i, t \in \{1..|T|\} \quad (5.16)$$

$$A_{0,i,k,t} \leq Cap_k, \quad \forall i \in I, k \in K_1, t \in \{1..|T|\} \quad (5.17)$$

$$A_{i,j,k,t} \leq Cap_k, \quad \forall i \in I, j \in VF_i, k \in K_2, t \in \{1..|T|\} \quad (5.18)$$

$$Inv_{0,0} = Cap_0 \quad (5.19)$$

$$Inv_{n,0} = \tilde{Cap}_n, \quad \forall n \in N \quad (5.20)$$

$$\sum_{h \in H} Ap * (Con1_{n,h,t} + Con2_{n,h,t}) \leq G_{n,t}, \quad \forall n \in N, t \in \{1..|T|\} \quad (5.21)$$

Inventory Balance Constraints:

$$Inv_{0,t} \leq (1 - \tilde{B}_0) * Inv_{0,t-1} - \sum_{i \in I} \sum_{k \in K_1} A_{0,i,k,t}, \quad \forall t \in \{1 \dots |T|\} \quad (5.22)$$

$$Inv_{i,1} \leq (1 - \tilde{B}_i) * Inv_{i,0} - \sum_{j \in VF_i} \sum_{k \in K_2} A_{i,j,k,1} - \frac{\sum_{h \in H} Con1_{i,h,1}}{(1 - BO)} - \frac{\sum_{h \in H} Con2_{i,h,1}}{(1 - BO)}, \quad \forall i \in I \quad (5.23)$$

$$\begin{aligned}
Inv_{i,t} \leq & (1 - \tilde{B}_i) * Inv_{i,t-1} + \sum_{k \in K_1} (1 - \tilde{B}_{0,i,k}) * A_{0,i,k,t-1} \\
& - \sum_{j \in VF_i} \sum_{k \in K_2} A_{i,j,k,t} - \frac{\sum_{h \in H} Con1_{i,h,t}}{(1 - BO)} \\
& - \frac{\sum_{h \in H} Con2_{i,h,t}}{(1 - BO)}, \quad \forall i \in I, t \in \{2 \dots |T|\}
\end{aligned} \tag{5.24}$$

$$\begin{aligned}
Inv_{j,1} \leq & (1 - \tilde{B}_j) * Inv_{j,0} - \frac{\sum_{h \in H} Con1_{j,h,1}}{(1 - BO)} - \frac{\sum_{h \in H} Con2_{j,h,1}}{(1 - BO)}, \quad \forall j \\
& \in J
\end{aligned} \tag{5.25}$$

$$\begin{aligned}
Inv_{j,t} \leq & (1 - \tilde{B}_j) * Inv_{j,t-1} + \sum_{k \in K_2} (1 - \tilde{B}_{i,j,k}) * A_{i,j,k,t-1} \\
& - \frac{\sum_{h \in H} Con1_{j,h,t}}{(1 - BO)} - \frac{\sum_{h \in H} Con2_{j,h,t}}{(1 - BO)}, \\
& \forall i \in I, j \in VF_i, t \in \{2 \dots |T|\}
\end{aligned} \tag{5.26}$$

Objective Function Constraints:

$$FIP_{n,h} = \sum_{t \in T} Con2_{n,h,t}, \forall n \in N, h \in H \tag{5.27}$$

Medical Waste Management Constraints:

$$\sum_{c \in WF1_0} (WF_{0,c,t} - DDW_{0,c,t}) \geq M * (\tilde{B}_0 * Inv_{0,t}), \quad \forall t \in \{1..|T|\} \tag{5.28}$$

$$\begin{aligned}
& \sum_{c \in WF2_i} (WF_{i,c,t} - DDW_{i,c,t}) \\
& \geq M \\
& * \left(\sum_{h \in H} \frac{Con1_{i,h,t}}{(1 - BO)} + \sum_{h \in H} \frac{Con2_{i,h,t}}{(1 - BO)} + \tilde{B}_i * Inv_{i,t} \right. \\
& \quad \left. + \sum_{k \in K_1} \tilde{B}_{0,i,k} * A_{0,i,k,t} \right), \quad \forall i \in I, t \in \{1..|T|\}
\end{aligned} \tag{5.29}$$

$$\begin{aligned}
& \sum_{c \in WF2_j} (WF_{j,c,t} - DDW_{j,c,t}) \\
& \geq M \\
& * \left(\sum_{h \in H} \frac{Con1_{j,h,t}}{(1 - BO)} + \sum_{h \in H} \frac{Con2_{j,h,t}}{(1 - BO)} + \tilde{B}_j * Inv_{j,t} \right. \\
& \quad \left. + \sum_{k \in K_2} \tilde{B}_{i,j,k} * A_{i,j,k,t} \right), \forall i \in I, j \in VF_i, t \in \{1..|T|\}
\end{aligned} \tag{5.30}$$

$$\sum_{s \in WF5_c} (WF_{c,s,t} - DDW_{c,s,t}) \geq SC * \left(WF_{0,c,t} + \sum_{n \in WF3_c} WF_{n,c,t} \right), \quad \forall c \in C, t \in \{1..|T|\} \quad (5.31)$$

$$\sum_{f \in WF6_c} (WF_{c,f,t} - DDW_{c,f,t}) \geq IC * \left(WF_{0,c,t} + \sum_{n \in WF3_c} WF_{n,c,t} \right), \quad \forall c \in C, t \in \{1..|T|\} \quad (5.32)$$

$$WF_{0,c,t} + \sum_{n \in WF3_c} WF_{n,c,t} \leq Cap_c, \quad \forall c \in C, t \in \{1..|T|\} \quad (5.33)$$

$$\sum_{c \in WF7_p} WF_{c,p,t} \leq Cap_p, \quad \forall p \in P, t \in \{1..|T|\} \quad (5.34)$$

Bounds of Decision Variables:

$$\begin{aligned} FIP_{n,h}, A_{0,i,k,t}, A_{i,j,k,t}, Inv_{n,t}, Con1_{n,h,t}, Con2_{n,h,t}, DD_{n,h,t}, UD_{n,h,t}, WF_{n,c,t}, \\ WF_{c,p,t}, DDW_{n,c,t}, DDW_{c,p,t} \geq 0 \\ \forall i \in I, j \in J, n \in N, k \in K, t \in T, h \in H, c \in C, p \in P \end{aligned} \quad (5.34)$$

In the model, $\bar{D}_{n,h,t}$, $\bar{Cap}_n$, $\bar{B}_n$, $\bar{B}_{0,i,k}$ ve $\bar{B}_{i,j,k}$ represent our uncertain parameters. These parameters take values in $[\bar{D}_{n,h,t} - \hat{D}_{n,h,t}, \bar{D}_{n,h,t} + \hat{D}_{n,h,t}]$, $[\bar{Cap}_n - \hat{Cap}_n, \bar{Cap}_n + \hat{Cap}_n]$, $[\bar{B}_n - \hat{B}_n, \bar{B}_n + \hat{B}_n]$, $[\bar{B}_{0,i,k} - \hat{B}_{0,i,k}, \bar{B}_{0,i,k} + \hat{B}_{0,i,k}]$ and $[\bar{B}_{i,j,k} - \hat{B}_{i,j,k}, \bar{B}_{i,j,k} + \hat{B}_{i,j,k}]$ symmetric intervals, respectively. $\bar{D}_{n,h,t}$, $\bar{Cap}_n$, $\bar{B}_n$, $\bar{B}_{0,i,k}$ and $\bar{B}_{i,j,k}$ values represent the nominal values of the parameters, while $\hat{D}_{n,h,t}$, $\hat{Cap}_n$, $\hat{B}_n$, $\hat{B}_{0,i,k}$, and $\hat{B}_{i,j,k}$ values represent the maximum deviation from the nominal value. The robust model created according to the specified parameters is given below.

Demand Calculation Constraints:

$$\bar{D}_{n,h,t} - DD_{n,h,t} - Con1_{n,h,t} + q_{n,h,t}^{(1)} * \Gamma_{n,h,t}^{(1)} + r_{n,h,t}^{(1)} \leq 0, \quad \forall n \in N, h \in H, t \in \{1..1\} \quad (5.35)$$

$$q_{n,h,t}^{(1)} + r_{n,h,t}^{(1)} \geq \hat{D}_{n,h,t}, \quad \forall n \in N, h \in H, t \in \{1..1\} \quad (5.36)$$

$$\begin{aligned} \bar{D}_{n,h,t} - DD_{n,h,t} + Con1_{n,h,t-1} - Con1_{n,h,t} - Con2_{n,h,t} + q_{n,h,t}^{(2)} * \Gamma_{n,h,t}^{(2)} \\ + r_{n,h,t}^{(2)} \leq 0, \quad \forall n \in N, h \in H, t \in \{2..|T|\} \end{aligned} \quad (5.37)$$

$$q_{n,h,t}^{(2)} + r_{n,h,t}^{(2)} \geq \widehat{D}_{n,h,t}, \quad \forall n \in N, h \in H, t \in \{2..|T|\} \quad (5.38)$$

$$Con2_{n,h,t} \leq 0, \quad \forall n \in N, h \in H, t \in \{1..1\} \quad (5.39)$$

$$Con1_{n,h,t} - \bar{D}_{n,h,t} - \widehat{D}_{n,h,t} * \Gamma_{n,h,t}^{(3)} \leq 0, \quad \forall n \in N, h \in H, t \in \{1..|T|\} \quad (5.40)$$

$$Con2_{n,h,t} \leq Con1_{n,h,t-1}, \quad \forall n \in N, h \in H, t \in \{2..|T|\} \quad (5.41)$$

Capacity Limitation Constraints:

$$Inv_{i,t} + \sum_{k \in K_1} A_{0,i,k,t} - \sum_{k \in K_1} \bar{B}_{0,i,k} * A_{0,i,k,t} + q_i^{(4)} * \Gamma_i^{(4)} + \sum_{k \in K_1} r_{i,k}^{(4)} - \bar{Cap}_i \quad (5.42)$$

$$+ q_i^{(5)} * \Gamma_i^{(5)} + r_i^{(5)} \leq 0, \quad \forall i \in I, t \in \{1..|T|\}$$

$$q_i^{(4)} + r_{i,k}^{(4)} \geq \widehat{B}_{0,i,k} * A_{0,i,k,t}, \quad \forall i \in I, k \in K_1, t \in \{1..|T|\} \quad (5.43)$$

$$q_i^{(5)} + r_i^{(5)} \geq \widehat{Cap}_i, \quad \forall i \in I \quad (5.44)$$

$$Inv_{j,t} + \sum_{k \in K_2} A_{i,j,k,t} - \sum_{k \in K_2} \bar{B}_{i,j,k} * A_{i,j,k,t} + q_{i,j}^{(6)} * \Gamma_{i,j}^{(6)} + \sum_{k \in K_1} r_{i,j,k}^{(6)} - \bar{Cap}_j \quad (5.45)$$

$$+ q_j^{(7)} * \Gamma_j^{(7)} + r_j^{(7)} \leq 0, \quad \forall i \in I, j \in VF_i, t \in \{1..|T|\}$$

$$q_{i,j}^{(6)} + r_{i,j,k}^{(6)} \geq \widehat{B}_{i,j,k} * A_{i,j,k,t}, \quad \forall i \in I, j \in VF_i, k \in K_2, t \in \{1..|T|\} \quad (5.46)$$

$$q_j^{(7)} + r_j^{(7)} \geq \widehat{Cap}_j, \quad \forall j \in J \quad (5.47)$$

$$A_{0,i,k,t} \leq Cap_k, \quad \forall i \in I, k \in K_1, t \in \{1..|T|\} \quad (5.48)$$

$$A_{i,j,k,t} \leq Cap_k, \quad \forall i \in I, j \in VF_i, k \in K_2, t \in \{1..|T|\} \quad (5.49)$$

$$Inv_{0,0} = Cap_0 \quad (5.50)$$

$$\bar{Cap}_n - \widehat{Cap}_n * \Gamma_n^{(8)} \leq Inv_{n,0} \leq \bar{Cap}_n + \widehat{Cap}_n * \Gamma_n^{(8)}, \quad \forall n \in N \quad (5.51)$$

$$\sum_{h \in H} Ap * (Con1_{n,h,t} + Con2_{n,h,t}) \leq G_{n,t}, \quad \forall n \in N, t \in \{1..|T|\} \quad (5.52)$$

Inventory Balance Constraints:

$$Inv_{0,t} - Inv_{0,t-1} + \sum_{i \in I} \sum_{k \in K_1} A_{0,i,k,t} + \bar{B}_0 * Inv_{0,t-1} + q_0^{(9)} * \Gamma_0^{(9)} + r_0^{(9)} \quad (5.53)$$

$$\leq 0, \quad \forall t \in \{1 \dots |T|\}$$

$$q_0^{(9)} + r_0^{(9)} \geq \widehat{B}_0 * Inv_{0,t-1}, \quad \forall t \in \{1 \dots |T|\} \quad (5.54)$$

$$\begin{aligned}
& Inv_{i,1} - Inv_{i,0} + \bar{B}_i * Inv_{i,0} + \sum_{j \in VF_i} \sum_{k \in K_2} A_{i,j,k,1} + \frac{\sum_{h \in H} Con1_{i,h,1}}{(1 - BO)} \\
& + \frac{\sum_{h \in H} Con2_{i,h,1}}{(1 - BO)} + q_i^{(10)} * \Gamma_i^{(10)} + r_i^{(10)} \leq 0, \quad \forall i \in I
\end{aligned} \tag{5.55}$$

$$q_i^{(10)} + r_i^{(10)} \geq \hat{B}_i * Inv_{i,0}, \quad \forall i \in I \tag{5.56}$$

$$\begin{aligned}
& Inv_{i,t} - Inv_{i,t-1} + \bar{B}_i * Inv_{i,t-1} + q_i^{(11)} * \Gamma_i^{(11)} + r_i^{(11)} - \sum_{k \in K_1} A_{0,i,k,t-1} \\
& + \sum_{k \in K_1} \bar{B}_{0,i,k} * A_{0,i,k,t-1} + q_{0,i}^{(12)} * \Gamma_{0,i}^{(12)} + \sum_{k \in K_1} r_{0,i,k}^{(12)}
\end{aligned} \tag{5.57}$$

$$\begin{aligned}
& + \sum_{j \in VF_i} \sum_{k \in K_2} A_{i,j,k,t} + \frac{\sum_{h \in H} Con1_{i,h,t}}{(1 - BO)} + \frac{\sum_{h \in H} Con2_{i,h,t}}{(1 - BO)} \\
& \leq 0, \quad \forall i \in I, t \in \{2 \dots |T|\}
\end{aligned}$$

$$q_i^{(11)} + r_i^{(11)} \geq \hat{B}_i * Inv_{i,t-1}, \quad \forall i \in I, t \in \{2 \dots |T|\} \tag{5.58}$$

$$q_{0,i}^{(12)} + r_{0,i,k}^{(12)} \geq \hat{B}_{0,i,k} * A_{0,i,k,t-1}, \quad \forall i \in I, k \in K_1, t \in \{2 \dots |T|\} \tag{5.59}$$

$$\begin{aligned}
& Inv_{j,1} - Inv_{j,0} + \bar{B}_j * Inv_{j,0} + q_j^{(13)} * \Gamma_j^{(13)} + r_j^{(13)} + \frac{\sum_{h \in H} Con1_{j,h,1}}{(1 - BO)} \\
& + \frac{\sum_{h \in H} Con2_{j,h,1}}{(1 - BO)} \leq 0, \quad \forall j \in J
\end{aligned} \tag{5.60}$$

$$q_j^{(13)} + r_j^{(13)} \geq \hat{B}_j * Inv_{j,0}, \quad \forall j \in J \tag{5.61}$$

$$\begin{aligned}
& Inv_{j,t} - Inv_{j,t-1} + \bar{B}_j * Inv_{j,t-1} + q_j^{(14)} * \Gamma_j^{(14)} + r_j^{(14)} - \sum_{k \in K_2} A_{i,j,k,t-1} \\
& + \sum_{k \in K_2} \bar{B}_{i,j,k} * A_{i,j,k,t-1} + q_{i,j}^{(15)} * \Gamma_{i,j}^{(15)} + \sum_{k \in K_2} r_{i,j,k}^{(15)}
\end{aligned} \tag{5.62}$$

$$+ \frac{\sum_{h \in H} Con1_{j,h,t}}{(1 - BO)} + \frac{\sum_{h \in H} Con2_{j,h,t}}{(1 - BO)} \leq 0,$$

$$\forall i \in I, j \in VF_i, t \in \{2 \dots |T|\}$$

$$q_j^{(14)} * \Gamma_j^{(14)} + r_j^{(14)} \geq \hat{B}_j * Inv_{j,t-1}, \quad \forall j \in J, t \in \{2 \dots |T|\} \tag{5.63}$$

$$\begin{aligned}
& q_{i,j}^{(15)} * \Gamma_{i,j}^{(15)} + \sum_{k \in K_2} r_{i,j,k}^{(15)} \geq \hat{B}_{i,j,k} * A_{i,j,k,t-1}, \quad \forall i \in I, j \in VF_i, k \in K_2, t \\
& \in \{2 \dots |T|\}
\end{aligned} \tag{5.64}$$

Objective Function Constraints:

$$FIP_{n,h} = \sum_{t \in T} Con2_{n,h,t}, \forall n \in N, h \in H \quad (5.65)$$

Medical Waste Management Constraints:

$$M * (\bar{B}_0 * Inv_{0,t}) - \sum_{c \in WF1_0} (WF_{0,c,t} - DDW_{0,c,t}) + q_0^{(16)} * \Gamma_0^{(16)} + r_0^{(16)} \leq 0, \quad \forall t \in \{1..|T|\} \quad (5.66)$$

$$q_0^{(16)} + r_0^{(16)} \geq M * (\hat{B}_0 * Inv_{0,t}), \quad \forall t \in \{1..|T|\} \quad (5.67)$$

$$M * \left(\sum_{h \in H} \frac{Con1_{i,h,t}}{(1-BO)} + \sum_{h \in H} \frac{Con2_{i,h,t}}{(1-BO)} \right) - \sum_{c \in WF2_i} (WF_{i,c,t} - DDW_{i,c,t}) + M * \bar{B}_i * Inv_{i,t} + q_i^{(17)} * \Gamma_i^{(17)} + r_i^{(17)} + M * \sum_{k \in K_1} \bar{B}_{0,i,k} * A_{0,i,k,t} + q_{0,i}^{(18)} * \Gamma_{0,i}^{(18)} + \sum_{k \in K_1} r_{0,i,k}^{(18)} \leq 0, \quad \forall i \in I, t \in \{1..|T|\} \quad (5.68)$$

$$q_i^{(17)} + r_i^{(17)} \geq M * \hat{B}_i * Inv_{i,t}, \quad \forall i \in I, t \in \{1..|T|\} \quad (5.69)$$

$$q_{0,i}^{(18)} + r_{0,i,k}^{(18)} \geq M * \hat{B}_{0,i,k} * A_{0,i,k,t}, \quad \forall i \in I, k \in K_1, t \in \{1..|T|\} \quad (5.70)$$

$$M * \left(\sum_{h \in H} \frac{Con1_{j,h,t}}{(1-BO)} + \sum_{h \in H} \frac{Con2_{j,h,t}}{(1-BO)} \right) - \sum_{c \in WF2_j} (WF_{j,c,t} - DDW_{j,c,t}) + M * \bar{B}_j * Inv_{j,t} + q_j^{(19)} * \Gamma_j^{(19)} + r_j^{(19)} + M * \sum_{k \in K_2} \bar{B}_{i,j,k} * A_{i,j,k,t} + q_{i,j}^{(20)} * \Gamma_{i,j}^{(20)} + \sum_{k \in K_2} r_{i,j,k}^{(20)} \leq 0, \quad \forall i \in I, j \in VF_i, t \in \{1..|T|\} \quad (5.71)$$

$$q_j^{(19)} + r_j^{(19)} \geq M * \hat{B}_j * Inv_{j,t}, \quad \forall j \in J, t \in \{1..|T|\} \quad (5.72)$$

$$q_{i,j}^{(20)} + r_{i,j,k}^{(20)} \geq M * \hat{B}_{i,j,k} * A_{i,j,k,t}, \quad \forall i \in I, j \in VF_i, k \in K_2, t \in \{1..|T|\} \quad (5.73)$$

$$\sum_{s \in WF5_c} (WF_{c,s,t} - DDW_{c,s,t}) \geq SC * \left(WF_{0,c,t} + \sum_{n \in WF3_c} WF_{n,c,t} \right), \forall c \in C, t \in \{1..|T|\} \quad (5.74)$$

$$\sum_{f \in WF6_c} (WF_{c,f,t} - DDW_{c,f,t}) \geq IC * \left(WF_{0,c,t} + \sum_{n \in WF3_c} WF_{n,c,t} \right), \forall c \in C, t \in \{1..|T|\} \quad (5.75)$$

$$WF_{0,c,t} + \sum_{n \in WF3_c} WF_{n,c,t} \leq Cap_c, \forall c \in C, t \in \{1..|T|\} \quad (5.76)$$

$$\sum_{c \in WF7_p} WF_{c,p,t} \leq Cap_p, \forall p \in P, t \in \{1..|T|\} \quad (5.77)$$

Bounds of Decision Variables:

$$FIP_{n,h}, A_{0,i,k,t}, A_{i,j,k,t}, Inv_{n,t}, Con1_{n,h,t}, Con2_{n,h,t}, DD_{n,h,t}, UD_{n,h,t}, WF_{n,c,t}, \\ WF_{c,p,t}, DDW_{n,c,t}, DDW_{c,p,t} \geq 0 \quad (5.78) \\ \forall i \in I, j \in J, n \in N, k \in K, t \in T, h \in H, c \in C, p \in P$$

As stated before, the robust model is written according to the approach of Bertsimas and Sim (2004). However, in the constraints (5.13) and (5.20), the approach of Hatefi and Jolai (2014) is used. The reason for this is that the demand parameter in the constraint (5.13) moves inversely to the demand parameters in other constraints when Bertsimas and Sim's (2004) approach is applied.; it decreases while the others increase. The fact that constraint (5.20) is an equality constraint requires using Hatefi and Jolai's (2014) approach.

The developed robust model is also coded in the IBM ILOG CPLEX Optimization Studio 12.10.0 environment and solved with CPLEX. Model codes are presented in Appendix 5.1.

5.3 Robust Model Implementation

For implementing the robust model, it is necessary to determine the intervals from which the uncertain parameters will take their values and the budget of uncertainty values. Initially, the intervals for uncertain parameters are determined. For the demand parameter, the data considered in the deterministic model are taken as the nominal value. The variability value is determined according to the increase in seasonal demand. Since the nominal values for the demand parameter include the entire population targeted to be vaccinated, no increase in demand is expected. However, only individuals 18 years of age or older are part of the target population. The variability of the demand parameter ($\hat{D}_{n,h,t}$) is determined by considering a situation where individuals younger than 18 are also involved in the vaccination process. In other words, 1,073,740 people participate in this process.

The variability of storage capacities in health centers is determined by considering that different vaccines can be found in vaccine cabinets or stores. As explained earlier in Section 3.2, the net capacities of the vaccine cabinets are specified by taking three-quarters of the gross capacity. Variability is determined by considering situations where one-quarter of gross capacity cannot be used. In other words, whereas net capacity amounts are taken as nominal value, the amount of variability for storage capacities ($\widehat{Cap}_n$) is determined as one-quarter of gross capacity.

The deteriorations are divided into two parts: the deterioration caused by heat exchange in the provincial warehouse and health centers and the deterioration caused by heat exchange during transport. As in the other two parameters, the values used in the deterministic model are taken as nominal values. Variability is accepted as 2% for the provincial warehouse ($\hat{B}_0$) and CHCs ($\hat{B}_i$) and 1.5% for FHCs ($\hat{B}_j$), and 1% for deterioration during transportation ($\hat{B}_{i,j,k}$). Since no deterioration is assumed between centers with a distance of less than five km during transportation, there is no variability here.

After determining the amount of variability of uncertain parameters, the most important value for the modeling approach of Bertsimas and Sim (2004) is the value of the budget of uncertainty (Γ) parameter. The value of this parameter directly affects

the level at which the uncertainties are handled. The behavior of the robust model with different values of this parameter is important to see how the distribution problem we are looking at will give results under different conditions. When literature studies are reviewed, the model is solved for each Γ parameter value, and the results are compared. The value of the Γ parameter is obtained by dividing the interval into equal parts (José Alem and Morabito, 2012; Hatefi and Jolai, 2014; Modarres and Izadpanahi, 2016; Zokaee et al., 2017; Liu et al., 2019; H. Sun et al., 2021). In this study, the robust model is run separately for each value by dividing the Γ value into ten equal parts from its interval.

As mentioned before, the value of Γ takes a value in the range of $[0, |J|]$. Although 20 separate Γ parameters are defined for the robust model discussed here, their value depends on the uncertain parameter with which they are associated. Therefore, the $\Gamma^{(1)}$, $\Gamma^{(2)}$ and $\Gamma^{(3)}$ parameters depending on the demand parameter take values in the range of $[0,1]$. It is the same for Γ parameters for storage capacities in health centers and deterioration due to heat exchange in health centers. In other words, these Γ parameters also take values in the range of $[0,1]$. The $\Gamma^{(4)}$, $\Gamma^{(6)}$, $\Gamma^{(12)}$, $\Gamma^{(15)}$, $\Gamma^{(18)}$ and $\Gamma^{(20)}$ parameters only take values in the range of $[0,2]$ for the deterioration experienced during transportation since they also depend on the vehicle type. After all the parameter values are determined, the results can be examined by running the model separately for different values.

5.4 Experimental Results

The robust model is first run separately for all uncertain parameters, as in other studies in the literature. We solve the model for the demand parameter initially. Therefore, the $\Gamma^{(1)}$, $\Gamma^{(2)}$ and $\Gamma^{(3)}$ parameters take values within the interval $[0,1]$, while the other Γ parameters are set to 0. When the value of the Γ parameter is 0, the model behaves like deterministic, and when it takes the value of 1, it produces a solution under the worst-case scenario where the demand parameters are handled with the highest level of variability. The model is run with a time limit of 7200 seconds with a MIP relative gap value set to 0.001 as in the deterministic model. The number of constraints in the robust model has almost doubled compared to the deterministic

model and has become 100297. There was also an increase in the number of variables, and 76980 variables, of which 66028 were integers, emerged. The corresponding solutions are presented in Table 5.1.

Table 5.1 The results of the robust model for demand uncertainty

$\Gamma^{(1)} = \Gamma^{(2)} = \Gamma^{(3)}$	Total Cost (£)	Total Number of FIPs (patient)	Optimality Gap (%)	Solve Time (sec.)
0	244678642	3325939	0.0159	28.984
0.1	254614477.2	3431570	0.0330	1555.062
0.2	265304516.3	3538832	0.0943	2584.86
0.3	278576740.3	3634526	0.1280	7200
0.4	301721427.9	3661141	0.0998	6605.203
0.5	1442866083	336211	77.3787	7200
0.6	353019488.9	3705191	0.1136	7200
0.7	379286950.8	3725952	0.0999	3090.687
0.8	405734674.2	3746339	0.0999	1522.391
0.9	433496022.6	3764403	0.0998	3235.5
1	1633436973	339560	71.7999	7200

As shown in Table 5.1, the total cost value increases as the budget of uncertainty value, or in other words, the uncertainty level increases. A similar upward trend is also seen in the total number of FIPs. The increase in demand increases the cost, but the total number of FIPs increases as demand can still be met. Although the solution time is not regular, it increases depending on the Γ value. Solutions with large optimality gap values found within 7200 seconds in the results reveal uninterpretable solutions. Therefore, interpretations are made by excluding these solutions. The graph showing the percent increase in the robust model solution values concerning the deterministic model solution values is shown in Figure 5.1.

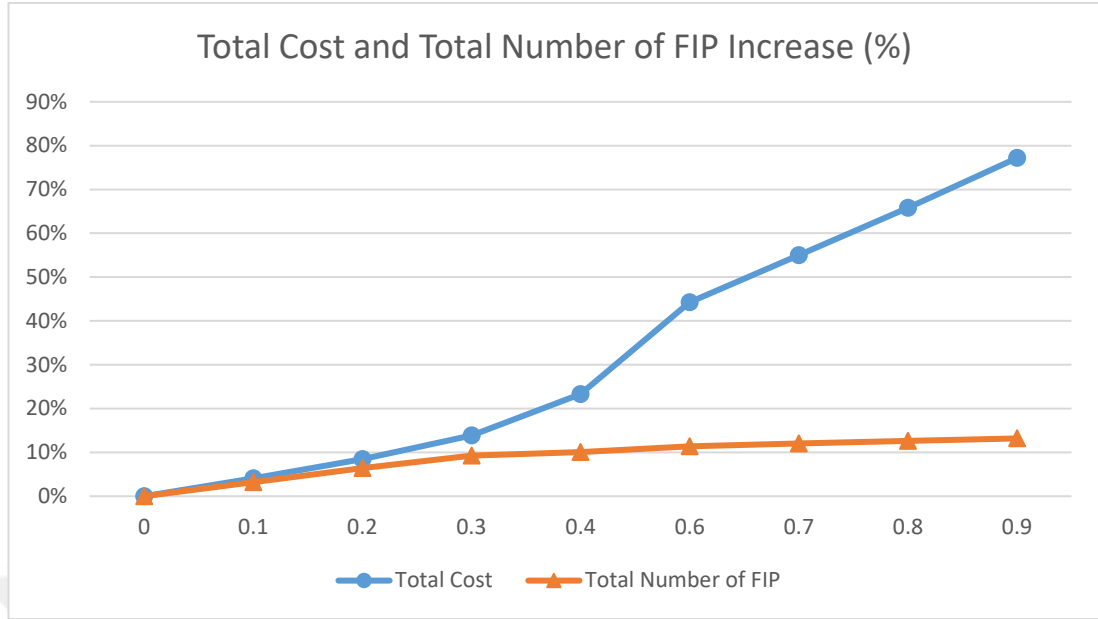


Figure 5.1 The effect of the budget of uncertainty on total cost and the total number of FIPs for demand uncertainty

The gap value between the results of the deterministic model and the robust model is known as the price of robustness (Ahabchane et al., 2021). Here, Figure 5.1 shows us the cost of the increase in demand. It is possible to meet the increasing demand, but the cost increases by about 80%. Here, it is up to the decision-maker to decide on the position to be held. For instance, since the upward trend in total cost increases after the Γ value exceeds 0.3, this point can be chosen because it satisfies a larger demand, and the total cost is at an acceptable level. The worst-case scenario point is not always appropriate, as handling this point increases costs considerably. Figure 5.2 illustrates the effects of the change in the budget of uncertainty parameter value on different cost types.

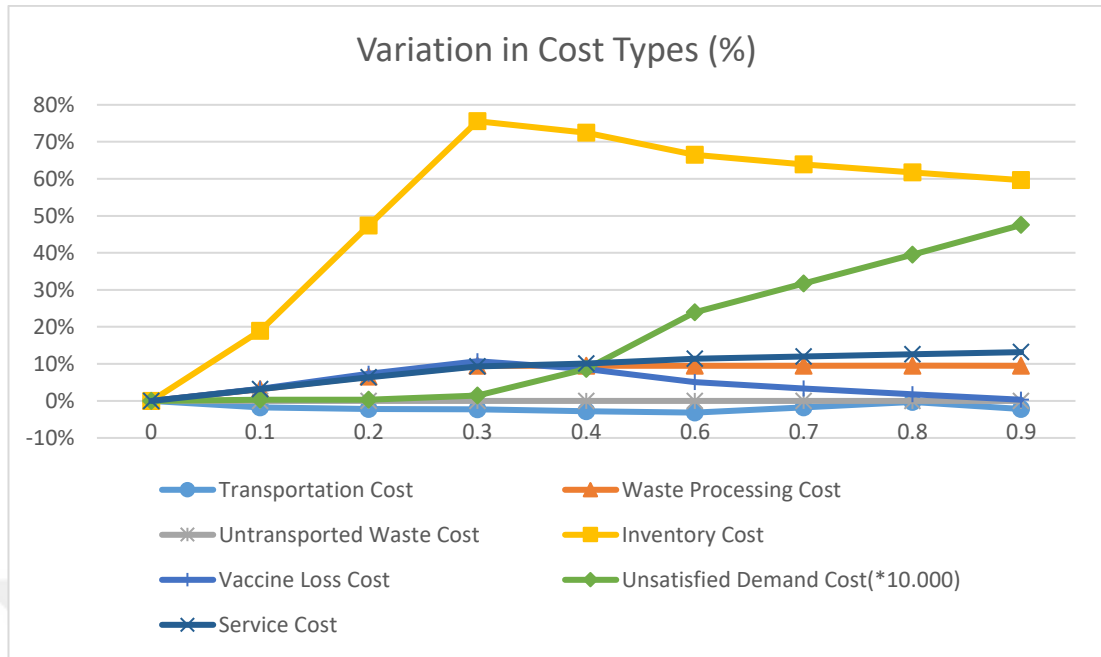


Figure 5.2 The effect of the budget of uncertainty on different types of costs for demand uncertainty

As seen in Figure 5.2, there is a continuous increase in unsatisfied demand and service costs. It shows that as demand increases, vaccine administration also increases, but simultaneously, the amount of unsatisfied demand also increases. Additionally, the cost of non-transportable waste does not change and is zero for all different Γ values; that is, the capacity to manage medical waste is sufficient, even in the worst-case scenario. An unexpected result is that the cost of transportation shows a decreasing trend. When the results of the deterministic model are examined, we see that the demand is often tempted to be satisfied with the quantity transported for that period to avoid the cost of inventories. In situations where demand cannot be met solely by transportation, the tendency to meet demand from inventory accounts for the reduction in transportation costs. The increase in inventory cost also supports this situation. Another striking point in the chart is that when the Γ value is 0.3, other cost types, inventory, waste processing, and vaccine loss cost, see the highest level, and after this point, they tend to decrease or remain stable. The main reason for this situation is the balance between the cost of inventory and unsatisfied demand. In this way, the inventory cost decreases in the amount of the total cost that increases with the cost of the unmet demand, and this situation directly downward affects the cost types such as waste treatment and vaccine loss cost.

In summary, as uncertainty in demand increases, the model tries to meet demand by using inventory rather than transportation. However, because demand cannot be met after a certain level, unsatisfied demand is allowed to increase, and its costs increase. Since the costs of waste processing and vaccine loss are directly related to inventory and unsatisfied demand costs, both of these costs are also reduced.

Second, the situation where vaccine storage capacities in health centers are considered uncertain is discussed. Here, the approach applied for the case of demand parameter is implemented similarly. The interval in which the Γ parameter takes value is also the same. Accordingly, the results are given in Table 5.2. A solution can be reached at all uncertainty levels within the specified time and optimality gap value. Although the solution time is not regular, it increases as the uncertainty level increases.

Table 5.2 The results of the robust model for capacity uncertainty

$\Gamma^{(5)} = \Gamma^{(7)} = \Gamma^{(8)}$	Total Cost (₺)	Total Number of FIPs (patient)	Optimality Gap (%)	Solve Time (sec.)
0	244678642	3325939	0,0159	28,047
0.1	244573641,7	3325945	0,0116	1606,156
0.2	244496694,3	3325923	0,02	30,797
0.3	244803897,7	3325569	0,0704	250,766
0.4	245156946,1	3324340	0,0508	51,641
0.5	246029602	3319200	0,0586	111,985
0.6	247409297,4	3312860	0,0539	105,953
0.7	249495923,8	3304232	0,0763	35,235
0.8	251742343	3295131	0,0558	92,531
0.9	254425501,6	3285099	0,0857	3385,797
1	259999279,3	3265819	0,0996	4067,891

The table shows that as the value of the Γ parameter increases, the total cost first decreases and then increases. On the other hand, the total number of FIPs first remains more stable and then declines. The increase in unsatisfied demand can explain the increase in the total cost amount. Figure 5.3 shows the robustness price, reflecting the difference between the total number of FIPs and the total cost obtained at different Γ values from the deterministic model results.

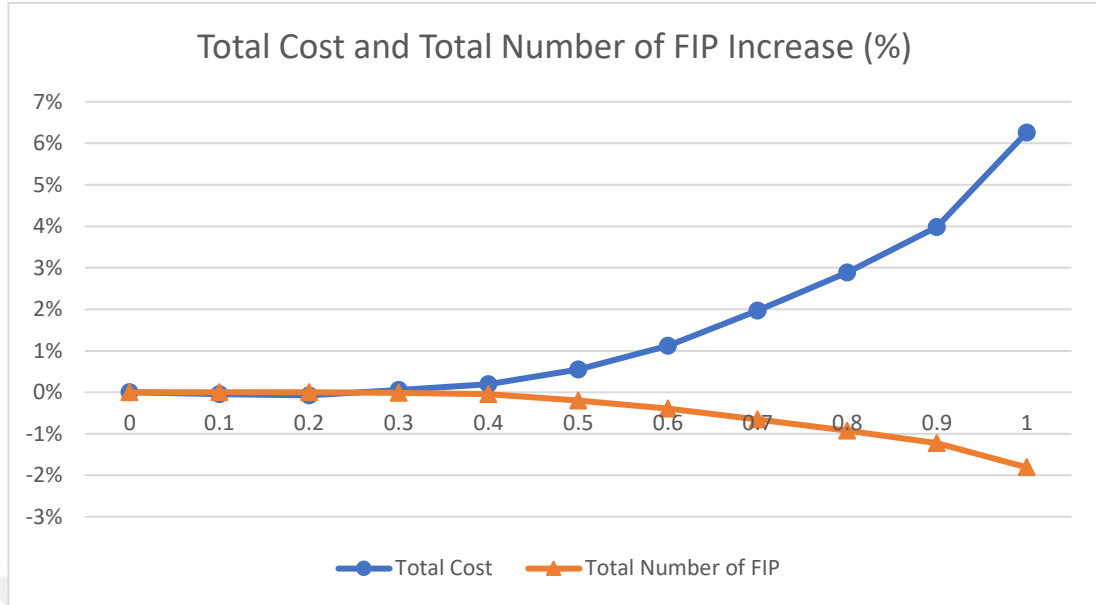


Figure 5.3 The effect of the budget of uncertainty on total cost and the total number of FIP for capacity uncertainty

As the uncertainty level or the budget of uncertainty increases, we see more clearly in the graph that the total cost increases and the total number of FIPs decreases. Here, we notice that the deviations according to the deterministic model increase after the critical threshold for the budget of the uncertainty value of 0.3. However, the percentage change from the deterministic model is considerably lower than the percentage change due to the demand variability. It can therefore be interpreted that uncertainty in demand is much more effective than uncertainty in storage capacity.

The increasing uncertainty in storage capacity results in a significant decrease in the number of people vaccinated, increasing the total cost as unsatisfied demand increases. However, as there is no addition to existing demand, the upward effect of this uncertainty in total cost is much smaller than the uncertainty in demand. Nevertheless, the uncertainty in storage capacity means that demand is not being met, which reveals an important management outcome. Based on these results, a decision can be made to increase storage capacities.

To determine the reason for the reduced costs and the stability of the total number of FIPs up to a certain level of uncertainty, the behavior of the cost types according to

different Γ values should be examined. Figure 5.4 illustrates the values of cost types according to different Γ values.

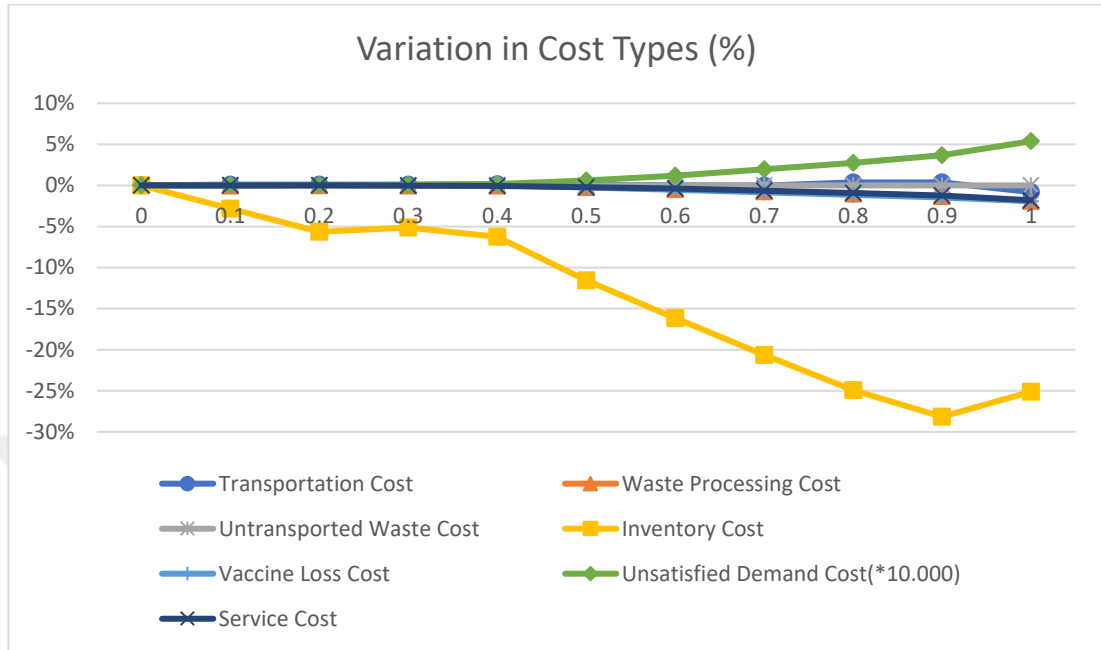


Figure 5.4 The effect of the budget of uncertainty on different types of costs for capacity uncertainty

The graph shows that the greatest change is in the cost of inventory, which is in a downward trend. The reason for the decrease in the inventory cost is that the initial inventory values are taken as the capacity amount in the model. As the capacity decreases, the initial inventory value decreases, so the inventory cost also decreases. However, after a certain level, since the demand cannot be met, the cost of the unsatisfied demand increases, so the total cost also increases. As inventories decrease, vaccine loss and waste processing costs, directly linked to inventories, also decrease. Also, the increase in unsatisfied demand indicates that fewer patients are vaccinated, resulting in a lower cost of service.

In summary, increased uncertainty in storage capacity leads to lower total cost until demand can be met. However, after the level at which demand cannot be met, the total cost increases under the cost of unsatisfied demand. The reduction in inventory and associated costs is not sufficient to reduce the total cost.

Third, the situation where the deterioration due to heat exchange in health center warehouses and vaccine storage cabinets is handled as uncertain is considered. Here,

the behavior of the model and the results are analyzed against the increase in Γ value. The results obtained are presented in Table 5.3.

Table 5.3 The results of the robust model for deterioration in storage uncertainty

$\Gamma^{(9)} = \Gamma^{(10)} = \Gamma^{(11)}$ $= \Gamma^{(13)} = \Gamma^{(14)}$ $= \Gamma^{(16)} = \Gamma^{(17)}$ $= \Gamma^{(19)}$	Total Cost (₺)	Total Number of FIPs (patient)	Optimality Gap (%)	Solve Time (sec.)
0	244678642	3325939	0,0159435	28,266
0.1	250202278,9	3326015	2,52E-04	8,031
0.2	257340944,9	3326015	5,03E-04	11,703
0.3	265902194,5	3326015	0,0020754	26,406
0.4	278634754,7	3300338	7,33E-04	32,672
0.5	296535510,1	3235999	8,72E-04	44,609
0.6	315818288	3169098	3,40E-04	295,438
0.7	335377884,1	3101636	2,81E-04	121,671
0.8	355109376,7	3033838	0,0011862	29,828
0.9	375651070,3	2964534	0,001107	28,75
1	396946498,7	2893742	8,44E-04	1056,563

As shown in the table, the total cost increases, and the total number of FIPs decreases as the budget of uncertainty value increases. There is a decline in the number of FIPs as demand is not fully met due to the deterioration. Furthermore, the cost of unsatisfied demand also increases the total cost. According to the deterministic model result, the total cost and the total FIP number can be seen more clearly from the Figure 5.5.

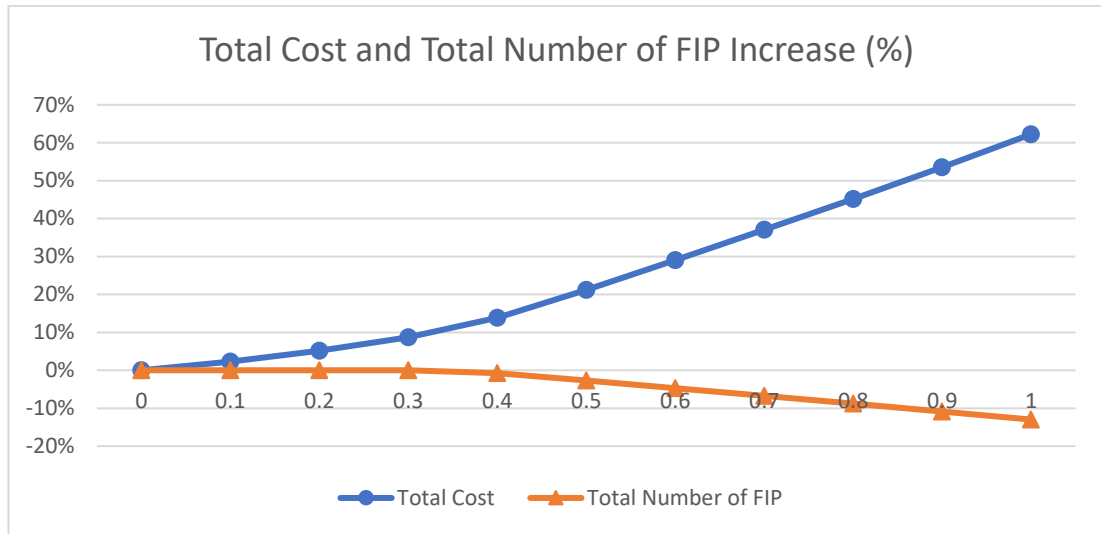


Figure 5.5 The effect of the budget of uncertainty on total cost and the total number of FIPs for deterioration in storage uncertainty

The amount of increase in the total cost is almost 70%. This result shows that the deterioration in health center warehouses is as important as the uncertainty in demand. Figure 5.6 shows the types of costs from which this increase in total cost occurs.

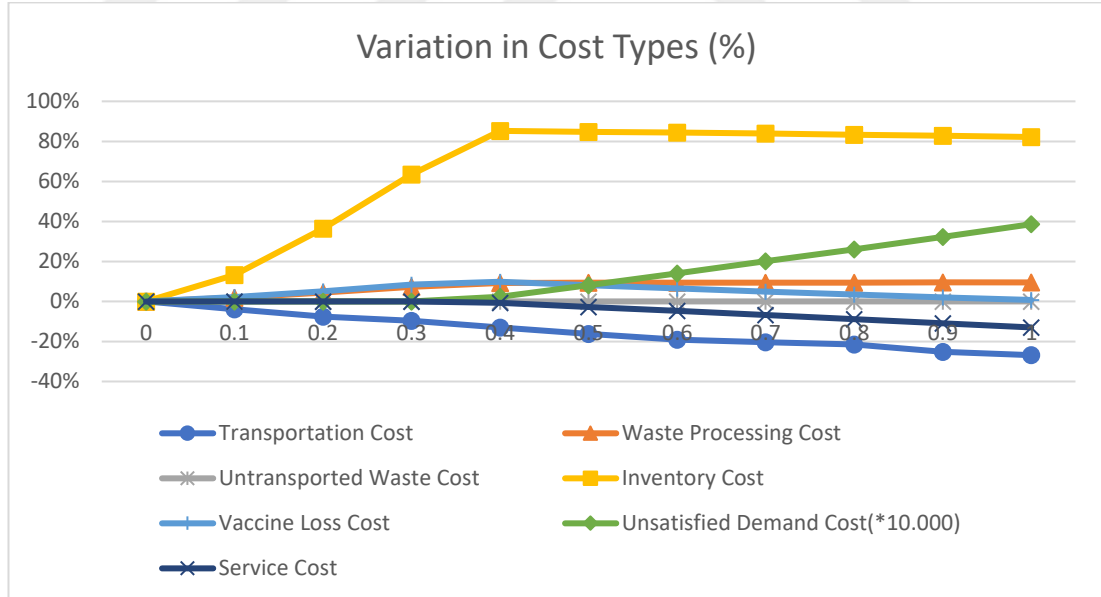


Figure 5.6 The effect of the budget of uncertainty on total cost and the total number of FIP for deterioration in storage uncertainty

As shown in the figure, as transportation and service costs decrease relative to the deterministic model, inventory, vaccine loss, and waste processing costs increase. The

cost of untransported waste is observed to be zero. The inability to properly respond to demand results in a decrease in the number of people vaccinated, which reduces the cost of service. For the same reason, the quantity of vaccines transported is also reduced. Deteriorated vaccines directly cause vaccine loss, and these losses result in medical waste. An increase follows this in the cost of vaccine loss and waste processing costs. Due to the deterioration suffered, the inventory increases, and the model attempts to meet the demand from here, increasing the inventory cost. However, as shown in Figure 5.6, this increase remains constant after a level since the storage capacities are fully utilized.

Lastly, the deterioration due to heat exchange during the transportation is handled as uncertain. Here, differently, the Γ parameter takes a value in the interval $[0,2]$. This interval is also divided into ten equal parts, and the results are examined. The results obtained are given in Table 5.4.

Table 5.4 The results of the robust model for deterioration during transportation uncertainty

$\Gamma^{(4)} = \Gamma^{(6)} = \Gamma^{(12)}$ $= \Gamma^{(15)} = \Gamma^{(18)}$ $= \Gamma^{(20)}$	Total Cost (₺)	Total Number of FIPs (patient)	Optimality Gap (%)	Solve Time (sec.)
0	244678642	3325939	0,0159	28,719
0.2	245472389,6	3325794	0,0555	33,844
0.4	246234314,1	3325711	0,0716	33,313
0.6	247012301,7	3325648	0,0887	37,547
0.8	247672273,8	3325828	0,0377	2164,609
1	248535502,7	3325280	0,092	2291,406
1.2	1178562867	550986	78,9304	7200
1.4	248611342,1	3325209	0,1137	7200
1.6	248582861,9	3325528	0,0981	1519,234
1.8	248567615,4	3325625	0,0986	51,11
2	1213402973	456203	79,5319	7200

As the table illustrates, while the level of uncertainty increases, the total cost increases, and the total number of FIPs decreases. Additionally, the solution time generally increases depending on the value of Γ . Within the time limit of 7200 seconds, the optimality gap values of all solutions, except three solutions, are within the determined optimality gap value. Since the gap value of one of these solutions ($\Gamma=1.4$)

is very close to the determined optimality gap value, it is included in the interpretation part. Other solutions are left out, and the results are interpreted. Accordingly, the price of the robustness graph is presented in Figure 5.7.

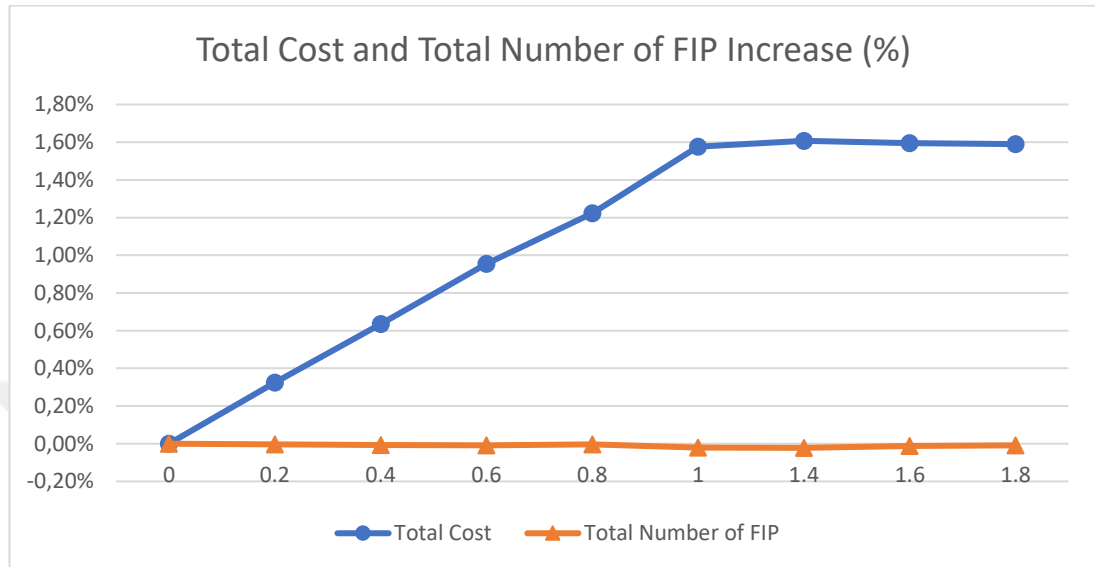


Figure 5.7 The effect of the budget of uncertainty on total cost and the total number of FIP for deterioration during transportation uncertainty

As seen in the figure, while the total cost increases, there is a slight decrease in the total number of FIPs. For the budget of uncertainty values greater than one, the increasing trend of the total cost value decreases. This graph shows that the percentage change from the deterministic model did not exceed 2% of the total cost and 0.2% for the total number of FIPs. The uncertain handling of deterioration due to heat exchange during transportation affects the value of the objective function much less than the uncertainty of capacity and demand parameters. To see from which cost type this effect arises, the values of different cost types according to different Γ values should be examined. The related graphic is presented in Figure 5.8.

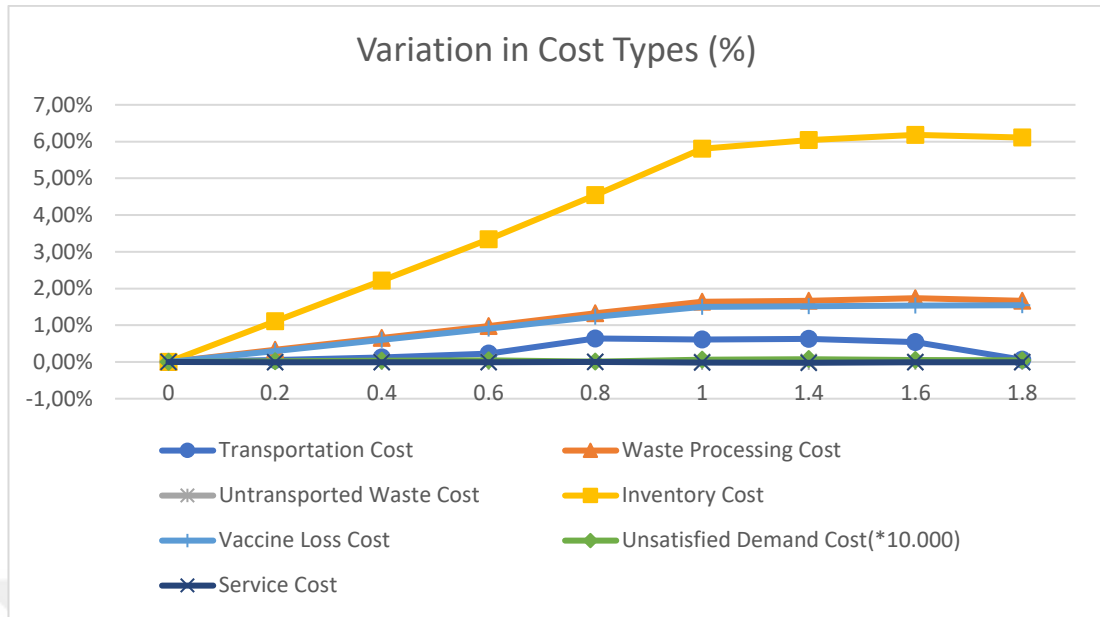


Figure 5.8 The effect of the budget of uncertainty on different types of costs for deterioration during transportation uncertainty

The graph shows that the cost of inventory causes the biggest impact after the cost of unsatisfied demand. Apart from the service cost, all other costs also increase according to the deterministic model. The decrease in the service cost is due to the decrease in the number of vaccinated individuals, increasing the cost of the unsatisfied demand.

Increasing uncertainty in the deterioration experienced during transportation causes a decrease in the number of patients vaccinated. Therefore, the number of unmet demand increases, and the total cost increases. However, this upside effect is quite small compared to the uncertainty in demand or storage capacity. Nevertheless, this uncertainty increase that causes the demand not to be met reveals an important result in terms of management. By analyzing these results, a decision can be made to maintain a higher inventory level or allocate a safety stock.

In summary, it is observed that the objective function value worsens as the uncertainty level increases. Different cost types may cause this effect according to different uncertain parameters. Although the total cost value worsens, solutions handled at a higher budget of uncertainty-level appear as conservative solutions closer to the worst-case scenario.

The parameter that affects the objective function value the most is the demand parameter. Considering the demand parameter as uncertain causes the total cost to increase by approximately 80% compared to the deterministic model. Among the cost types, the biggest impact is the cost of the unsatisfied demand. Then, the inventory cost follows it, and other cost types vary depending on these two cost types. Only the cost of untransported medical waste is seen as zero in all conditions discussed. From this, it can be seen that the medical waste management capacity is sufficient even for the worst-case scenario.

The results obtained for each uncertain parameter give an idea of the policies to be followed by the decision-makers:

- In response to the uncertainty in demand, storage and workforce capacities should be increased, and measures should be taken against the deterioration experienced,
- Against the uncertainty in storage capacities, storage capacities should be increased. However, in an environment without demand uncertainty, capacities can be reduced to reduce costs,
- Countermeasures should be taken because the deterioration has been shown to result in the demand not being met. Even if these measures cannot be taken, it is possible to ensure that the demand can be met by maintaining a safety stock.

The trade-off curves presented between the budget of uncertainty and the objective function for each uncertain parameter offer a choice area to the decision-maker. After this stage, it is up to the decision-maker to decide which level of conservatism will be achieved and how much it will cost.

CHAPTER 6

CONCLUSION AND FUTURE RESEARCH

The vaccine is our strongest weapon against epidemics for public health. For ending the COVID-19 pandemic that affects the whole world, it is necessary to provide community immunity. For this reason, vaccination studies have started in the first days of the epidemic. Following a challenging production and development process, COVID-19 vaccines were made available to the public and approved for immediate use by the WHO. However, the distribution of COVID-19 vaccines is a challenging process as the entire world population needs to be vaccinated.

Vaccines must be kept within certain temperature ranges and time periods because of their structural characteristics. Therefore, the vaccine distribution process requires cold chain logistics applications. Additionally, vaccines' perishable structure causes any break in the cold chain to damage the product directly.

Besides spoiling and wasted vaccines, waste such as injectors, needles, etc., will result in a large quantity of medical waste. Medical waste has more limited disposal options than other types of waste. They must either be sterilized or incinerated. Therefore, the vaccine distribution process cannot be considered without considering medical waste management.

This thesis focuses on optimizing the COVID-19 cold chain vaccine distribution network with medical waste management to get through all these difficult processes and help end the pandemic as soon as possible. The study uses MILP to model the distribution problem and a robust optimization approach to addresses uncertainties. The validity and effectiveness of the developed models are tested in a case study conducted in Izmir, Turkey.

To reveal the study's originality and determine its place in the literature; first, a literature review is performed. For this purpose, the literature is examined in four stages depending on the relevant subject. Due to the structural features of vaccines, first, cold chain logistics applications and then studies on the perishable supply chain are examined. Next, the vaccine supply chain literature is reviewed, and finally, studies

on vaccine distribution optimization are analyzed in detail. The literature review shows that this is the first study that focuses on the direct distribution of COVID-19 vaccines. It is also the first study in which vaccine distribution and medical waste management are considered together.

The robust optimization literature reveals that only one study uses a robust optimization modeling approach in vaccine distribution (Sadjadi et al., 2019). However, this thesis uses a different modeling method than this study, and different parameters are handled as uncertain. In Sadjadi et al. 's (2019) study, only demand and cost of opening are considered uncertain, whereas, in our study, demand, capacity, and deterioration parameters together are considered uncertain.

As we model the distribution problem, we consider that COVID-19 vaccines are administered in two doses. Since the perishable nature of the vaccines is also considered, deterioration from heat exchange in the provincial warehouse, health centers, and during transport and deterioration that may occur during vaccine administration are included in the model.

While the main objective of the proposed model is to provide community immunity, it is also important to do so at the least cost. For this reason, two objectives are determined for the model: minimizing the total cost and maximizing the total number of FIPs. Since these objectives conflict with each other, the ϵ -constraint method, which is a multi-objective optimization method, is used in the solution of the model. In the resulting solutions, any solution where the entire population is vaccinated could not be achieved. For this reason, the penalty cost method, which is another method used to handle different objectives simultaneously, was used. For this method, the cost of unsatisfied demand is added to the cost minimization objective as a penalty cost, thus minimizing the cost and ensuring that the entire population is vaccinated.

As with all real-life problems, the distribution process of COVID-19 vaccines also contains uncertainties. Since COVID-19 vaccines are new products, we do not have sufficient historical data or expert opinions. Here, the most suitable method to encompass the parameter uncertainty is robust convex optimization, one of the robust optimization methods. Although there are different modeling approaches for this

method, the modeling approach of Bertsimas and Sim (2004) was used in this thesis because it provides both linearities and avoids focusing on the worst-case scenario.

First, the intervals in which the uncertain parameters were determined to use this modeling approach. Then, the value of the budget of uncertainty parameter, the only parameter of the approach, was determined. The robust model was operated according to different values of the budget of uncertainty parameter for each uncertain parameter. The trade-off curves obtained from these analyses assist the decision-maker in deciding which position to take. Additionally, the behavior of cost types according to the budget of uncertainty value for different uncertain parameters was analyzed in the results obtained.

The results show that the capacity of Izmir province is sufficient in terms of both meeting the total demand and eliminating medical wastes, according to deterministic model solutions. It has been found that the vaccination process can be completed in 11 months, whereas the capacity is insufficient to vaccinate the entire target population over shorter time frames.

When the problem is considered with uncertain parameters, we find that the most important effect accrues from the demand parameter. In a scenario where the population under 18 is included in the immunization process, whereas total demand can still be met, the total cost increases by almost 80%. This effect remains at 8% and 2% for uncertainty in health centers' storage capacity and deterioration during transportation, respectively. Concerning the types of costs, the biggest impact is related to the cost of unsatisfied demand and then the cost of inventory. In all scenarios discussed, the cost of untransported medical waste is zero, meaning that medical waste management capacity is adequate, even in the worst-case scenario.

Since COVID-19 vaccines are new products, authorities are constantly making new decisions, making a difference. As a result, future studies should optimize the distribution process, which has become more stable. Additionally, since new vaccines are being developed, including multiple products will make the problem even more difficult. Adding vehicle routing decisions to the model can be another extension to the problem. Lastly, with the increase in the amount of data to handle uncertainty,

hybrid robust optimization methods can be used by considering different types of uncertainties.



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APPENDICES

APPENDIX 1: Mixed-Integer Linear Programming Model

```
int nbCHCs = ...;
int nbFHCs = ...;
int nbHnodes = nbCHCs + nbFHCs;
int nbCCs = ...;
int nbSCs = ...;
int nbICs = ...;
int nbPnodes = nbSCs + nbICs;
int nbTimePeriods = ...;
int nbVehicleTypes = ...;
int nbPatientTypes = ...;

range CHCs = 1..nbCHCs;
range FHCs = nbCHCs + 1..nbCHCs + nbFHCs;
range Hnodes = 1..nbHnodes;
range CCs = 1..nbCCs;
range SCs = 1..nbSCs;
range ICs = nbSCs + 1..nbSCs + nbICs;
range Pnodes = 1..nbPnodes;
range Periods = 0..nbTimePeriods;
range Vehicles = 1..nbVehicleTypes;
range Vehicles1 = 2..nbVehicleTypes;
range Vehicles2 = 1..nbVehicleTypes-1;
range Patients = 1..nbPatientTypes;

tuple V {
    int fromCHC;
    int toFHC;
}

{V} V_Flow = ...;

tuple W {
    int fromCHC;
    int toCC;
}

{W} W_Flow = ...;

tuple CW {
    int fromFHC;
    int toCC;
}

{CW} CW_Flow = ...;

tuple CSC {
    int fromCC;
    int toSC;
}

{CSC} CW_SC_Flow = ...;
```

```

tuple CIC {
    int fromCC;
    int toIC;
}

{CIC} CW_IC_Flow = ...;

tuple TWF {
    int fromHC;
    int toCC;
}

{TWF} TW_Flow = ...;

tuple PWF {
    int fromCC;
    int toPC;
}

{PWF} PW_Flow = ...;
//Demands:
int D2 [1..nbHnodes, 1..nbPatientTypes*nbTimePeriods] = ...;
int D[n in Hnodes][h in Patients][t in 1..nbTimePeriods] =
D2[n,t+nbTimePeriods*(h-1)];

//Capacities:
int Ware_Cap [0..0] = ...;
int HC_Cap [n in Hnodes] = ...;
int CC_Cap [c in CCs] = ...;
int PC_Cap [p in Pnodes] = ...;
int V_Cap [k in Vehicles] = ...;
int HC_N [n in Hnodes][t in 1..nbTimePeriods]=...;
int Ap = ...;

//Deteriorations:
float BO =...;
float Ware_B [0..0]=...;
float B [n in Hnodes]=...;
float CHC_Trans_B [i in CHCs][k in Vehicles]=...;
float FHC_Trans_B2 [1..nbCHCs, 1..nbHnodes*nbVehicleTypes] = ...;
float FHC_Trans_B [i in CHCs][j in FHCs][k in Vehicles] =
FHC_Trans_B2[i,k+nbVehicleTypes*(j-1)];

//Costs:
float Trans_cost [k in Vehicles]=...;
float Inv_cost [n in Hnodes]=...;
float CB =...;
float CD [h in Patients]=...;
float CS =...;
float PC_CW [p in Pnodes]=...;
float TransW_cost =...;
float CWD = ...;

//Distances:
float Ware_CHC_dist [0..0][i in CHCs]=...;
float CHC_FHC_dist [i in CHCs][j in FHCs]=...;

```

```

float Ware_CC_dist [0..0][c in CCs]=...;
float CHC_CC_dist [i in CHCs][c in CCs]=...;
float FHC_CC_dist [j in FHCs][c in CCs]=...;
float CC_SC_dist [c in CCs][s in SCs]=...;
float CC_IC_dist [c in CCs][f in ICs]=...;

//Rates
float SC_Rate = ...;
float IC_Rate = ...;
float M = ...;

//Fully Immunized Patient (FIP):
dvar int+ FIP[n in Hnodes][h in Patients];

//Vaccine Flow:
dvar int+ CHC_A[0..0][i in CHCs][k in Vehicles][t in 1..nbTimePeriods];
dvar int+ FHC_A[i in CHCs][j in FHCs][k in Vehicles][t in
1..nbTimePeriods];

//Inventory:
dvar int+ Ware_Inv[0..0][t in Periods];
dvar int+ Inv[n in Hnodes][t in Periods];

//Consumption:
dvar int+ Con1[n in Hnodes][h in Patients][t in 1..nbTimePeriods];
dvar int+ Con2[n in Hnodes][h in Patients][t in 1..nbTimePeriods];

//Unsatisfied Demand:
dvar int+ DD[n in Hnodes][h in Patients][t in 1..nbTimePeriods];

//Waste Flow:
dvar float+ Ware_WF[0..0][c in CCs][t in 1..nbTimePeriods];
dvar float+ HC_WF[n in Hnodes][c in CCs][t in 1..nbTimePeriods];
dvar float+ PC_CWF[c in CCs][p in Pnodes][t in 1..nbTimePeriods];

//Untransported Waste:
dvar float+ Ware_DDW[0..0][c in CCs][t in 1..nbTimePeriods];
dvar float+ HC_DDW[n in Hnodes][c in CCs][t in 1..nbTimePeriods];
dvar float+ PC_DDW[c in CCs][p in Pnodes][t in 1..nbTimePeriods];

//Objectives
dvar int+ TotalFIP;
dvar float+ Cost;

//Maximization total number of FIPs:
maximize TotalFIP;

//Minimization of total cost with the cost of unsatisfied demand:
minimize Cost;

subject to{
    //Objective Function (1)
    TotalFIP == sum(n in Hnodes, h in Patients) FIP[n][h];

    //Objective Function (2)
    Cost == sum(i in CHCs,k in Vehicles1,t in 1..nbTimePeriods)
    Trans_cost[k]*Ware_CHC_dist[0][i]*CHC_A[0][i][k][t]

```

```

+ sum(<i,j> in V_Flow,k in Vehicles2,t in 1..nbTimePeriods)
Trans_cost[k]*CHC_FHC_dist[i][j]*FHC_A[i][j][k][t]
//Waste Processing Cost
+ sum(<c,s> in CW_SC_Flow,t in 1..nbTimePeriods)
PC_CW[s]*PC_CWF[c][s][t]
+ sum(<c,f> in CW_IC_Flow,t in 1..nbTimePeriods)
PC_CW[f]*PC_CWF[c][f][t]
//The cost of not transporting one unit of medical waste
+ CWD*sum(c in CCs, t in 1..nbTimePeriods) (Ware_DDW[0][c][t]
+ sum(<n,c> in TW_Flow) HC_DDW[n][c][t]
+ sum(<c,s> in CW_SC_Flow) PC_DDW[c][s][t]
+ sum(<c,f> in CW_IC_Flow) PC_DDW[c][f][t])
//Inventory Holding Cost
+ sum(n in Hnodes,t in Periods) Inv_cost[n]*Inv[n][t]
//Vaccine Loss Cost
+ CB*sum(t in 1..nbTimePeriods) (Ware_B[0]*Ware_Inv[0][t]
+ sum(n in Hnodes) B[n]*Inv[n][t]
+ sum(i in CHCs, k in Vehicles1)
CHC_Trans_B[i][k]*CHC_A[0][i][k][t]
+ sum(<i,j> in V_Flow,k in Vehicles2)
FHC_Trans_B[i][j][k]*FHC_A[i][j][k][t]
+ sum(n in Hnodes, h in Patients) BO*(Con1[n][h][t])
+ sum(n in Hnodes, h in Patients) BO*Con2[n][h][t])
//The Cost of Unsatisfied Demand
+ sum(h in Patients,n in Hnodes,t in 1..nbTimePeriods)
DD[n][h][t]*CD[h]
//Service Cost
+ CS * sum(h in Patients,n in Hnodes,t in 1..nbTimePeriods)
(Con1[n][h][t] + Con2[n][h][t]);

//Amount of unsatisfied demand (3-4)
forall (h in Patients,n in Hnodes,t in 1..1) DD[n][h][t] >= D[n][h][t] -
Con1[n][h][t];
forall (h in Patients,n in Hnodes,t in 2..nbTimePeriods) DD[n][h][t] >=
D[n][h][t] + Con1[n][h][t-1] - Con1[n][h][t] - Con2[n][h][t];

//Second dose consumption constraint (5)
forall (h in Patients,n in Hnodes,t in 1..1) Con2[n][h][t] <= 0;

//Amount of vaccine used for each patient type can not exceed the total
demand (6-7)
forall (h in Patients,n in Hnodes,t in 1..nbTimePeriods) Con1[n][h][t]
<= D[n][h][t];
forall (h in Patients,n in Hnodes,t in 2..nbTimePeriods) Con2[n][h][t]
<= Con1[n][h][t-1];

//Storage capacity constraints (8-9)
forall (i in CHCs,t in 1..nbTimePeriods)
Inv[i][t] + sum(k in Vehicles1) (1-
CHC_Trans_B[i][k])*CHC_A[0][i][k][t] <= HC_Cap[i];

forall (<i,j> in V_Flow,t in 1..nbTimePeriods)
Inv[j][t] + sum(k in Vehicles2) (1-
FHC_Trans_B[i][j][k])*FHC_A[i][j][k][t] <= HC_Cap[j];

//Capacity constraints (10-11)

```

```

forall (i in CHCs,k in Vehicles1,t in 1..nbTimePeriods)
CHC_A[0][i][k][t] <= V_Cap[k];
forall (<i,j> in V_Flow,k in Vehicles2,t in 1..nbTimePeriods)
FHC_A[i][j][k][t] <= V_Cap[k];

//First time inventory constraints (12-13)
Ware_Inv[0][0] == Ware_Cap[0];
forall (n in Hnodes) Inv[n][0] == HC_Cap[n];

//Administration capacity constraints (14)
forall(n in Hnodes, t in 1..nbTimePeriods) sum(h in Patients)
Ap*(Con1[n][h][t] + Con2[n][h][t]) <= HC_N[n][t];

//Inventory balance constraints (15-19)
forall (t in 1..nbTimePeriods) Ware_Inv[0][t] <=
(1-Ware_B[0])*Ware_Inv[0][t-1] - sum(i in CHCs,k in Vehicles1)
CHC_A[0][i][k][t];

forall (i in CHCs,t in 1..1) Inv[i][t] <=
(1 - B[i])*Inv[i][t-1] - sum(<i,j> in V_Flow,k in Vehicles2)
FHC_A[i][j][k][t]
- sum(h in Patients) Con1[i][h][t]/(1 - BO) - sum(h in Patients)
Con2[i][h][t]/(1 - BO);

forall (i in CHCs,t in 2..nbTimePeriods) Inv[i][t] <=
(1 - B[i])*Inv[i][t-1] + sum(k in Vehicles1) (1-
CHC_Trans_B[i][k])*CHC_A[0][i][k][t-1]
- sum(<i,j> in V_Flow,k in Vehicles2) FHC_A[i][j][k][t]
- sum(h in Patients) Con1[i][h][t]/(1 - BO) - sum(h in Patients)
Con2[i][h][t]/(1 - BO);

forall (j in FHCs,t in 1..1) Inv[j][t] <=
(1 - B[j])*Inv[j][t-1] - sum(h in Patients) Con1[j][h][t]/(1 - BO) -
sum(h in Patients) Con2[j][h][t]/(1 - BO);

forall (<i,j> in V_Flow,t in 2..nbTimePeriods) Inv[j][t] <=
(1 - B[j])*Inv[j][t-1] + sum(k in Vehicles2) (1-
FHC_Trans_B[i][j][k])*FHC_A[i][j][k][t-1]
- sum(h in Patients) Con1[j][h][t]/(1 - BO) - sum(h in Patients)
Con2[j][h][t]/(1 - BO);

//Number of FIPs (20)
forall(n in Hnodes, h in Patients) FIP[n][h] == (sum(t in
1..nbTimePeriods) Con2[n][h][t]);

//Total amount of waste calculations (21-23)
forall(t in 1..nbTimePeriods)
Ware_WF[0][1][t] - Ware_DDW[0][1][t] >= M *
(Ware_B[0]*Ware_Inv[0][t]);

forall(i in CHCs,t in 1..nbTimePeriods)
sum (<i,c> in W_Flow) (HC_WF[i][c][t] - HC_DDW[i][c][t]) >=
M * (sum(h in Patients) Con1[i][h][t]/(1-BO) + sum(h in
Patients) Con2[i][h][t]/(1-BO) + B[i]*Inv[i][t] +
sum(k in Vehicles1) CHC_Trans_B[i][k]*CHC_A[0][i][k][t]);

forall(<i,j> in V_Flow,t in 1..nbTimePeriods)

```

```

sum (<j,c> in CW_Flow) (HC_WF[j][c][t] - HC_DDW[j][c][t]) >=
    M * (sum(h in Patients) Con1[j][h][t]/(1-B0) + sum(h in
Patients) Con2[j][h][t]/(1-B0) + B[j]*Inv[j][t] +
    sum(k in Vehicles2) FHC_Trans_B[i][j][k]*FHC_A[i][j][k][t]);

//Waste Flow Constraints (24-25)
forall(c in CCs,t in 1..nbTimePeriods) sum (<c,s> in CW_SC_Flow)
(PC_CWF[c][s][t] - PC_DDW[c][s][t]) >=
    SC_Rate*(Ware_WF[0][c][t] + sum(<n,c> in TW_Flow) HC_WF[n][c][t]);

forall(c in CCs,t in 1..nbTimePeriods) sum (<c,f> in CW_IC_Flow)
(PC_CWF[c][f][t] - PC_DDW[c][f][t]) >=
    IC_Rate*(Ware_WF[0][c][t] + sum(<n,c> in TW_Flow) HC_WF[n][c][t]);

//Waste capacity constraints (26-27)
forall(c in CCs,t in 1..nbTimePeriods)
    Ware_WF[0][c][t] + sum (<n,c> in TW_Flow) HC_WF[n][c][t] <=
CC_Cap[c];

forall(t in 1..nbTimePeriods, p in Pnodes) sum(<c,p> in PW_Flow)
PC_CWF[c][p][t] <= PC_Cap[p];
}

```

APPENDIX 2: Robust Model

```
int nbCHCs = ...;
int nbFHCs = ...;
int nbHnodes = nbCHCs + nbFHCs;
int nbCCs = ...;
int nbSCs = ...;
int nbICs = ...;
int nbPnodes = nbSCs + nbICs;
int nbTimePeriods = ...;
int nbVehicleTypes = ...;
int nbPatientTypes = ...;

range CHCs = 1..nbCHCs;
range FHCs = nbCHCs + 1..nbCHCs + nbFHCs;
range Hnodes = 1..nbHnodes;
range CCs = 1..nbCCs;
range SCs = 1..nbSCs;
range ICs = nbSCs + 1..nbSCs + nbICs;
range Pnodes = 1..nbPnodes;
range Periods = 0..nbTimePeriods;
range Vehicles = 1..nbVehicleTypes;
range Vehicles1 = 2..nbVehicleTypes;
range Vehicles2 = 1..nbVehicleTypes-1;
range Patients = 1..nbPatientTypes;

tuple V {
    int fromCHC;
    int toFHC;
}

{V} V_Flow = ...;

tuple W {
    int fromCHC;
    int toCC;
}

{W} W_Flow = ...;

tuple CW {
    int fromFHC;
    int toCC;
}

{CW} CW_Flow = ...;

tuple CSC {
    int fromCC;
    int toSC;
}

{CSC} CW_SC_Flow = ...;

tuple CIC {
    int fromCC;
```

```

    int toIC;
}

{CIC} CW_IC_Flow = ...;

tuple TWF {
    int fromHC;
    int toCC;
}

{TWF} TW_Flow = ...;

tuple PWF {
    int fromCC;
    int toPC;
}

{PWF} PW_Flow = ...;

//Demands:
int D2 [1..nbHnodes, 1..nbPatientTypes*nbTimePeriods] = ...;
int D[n in Hnodes][h in Patients][t in 1..nbTimePeriods] =
D2[n,t+nbTimePeriods*(h-1)];

//Capacities:
int Ware_Cap [0..0] = ...;
int HC_Cap [n in Hnodes] = ...;
int CC_Cap [c in CCs] = ...;
int PC_Cap [p in Pnodes] = ...;
int V_Cap [k in Vehicles] = ...;
int HC_N [n in Hnodes][t in 1..nbTimePeriods]=...;
int Ap = ...;

//Deteriorations:
float BO =...;
float Ware_B [0..0]=...;
float B [n in Hnodes]=...;
float CHC_Trans_B [i in CHCs][k in Vehicles]=...;
float FHC_Trans_B2 [1..nbCHCs, 1..nbHnodes*nbVehicleTypes] = ...;
float FHC_Trans_B [i in CHCs][j in FHCs][k in Vehicles] =
FHC_Trans_B2[i,k+nbVehicleTypes*(j-1)];

//Costs:
float Trans_cost [k in Vehicles]=...;
float Inv_cost [n in Hnodes]=...;
float CB =...;
float CD [h in Patients]=...;
float CS =...;
float PC_CW [p in Pnodes]=...;
float TransW_cost =...;
float CWD = ...;

//Distances:
float Ware_CHC_dist [0..0][i in CHCs]=...;
float CHC_FHC_dist [i in CHCs][j in FHCs]=...;
float Ware_CC_dist [0..0][c in CCs]=...;
float CHC_CC_dist [i in CHCs][c in CCs]=...;

```

```

float FHC_CC_dist [j in FHCs][c in CCs]=...;
float CC_SC_dist [c in CCs][s in SCs]=...;
float CC_IC_dist [c in CCs][f in ICs]=...;

//Rates
float SC_Rate = ...;
float IC_Rate = ...;
float M = ...;

//Maximum Variation of Uncertain Parameters
int HC_Cap_U[n in Hnodes]=...;
int D_U2 [1..nbHnodes, 1..nbPatientTypes*nbTimePeriods] = ...;
int D_U[n in Hnodes][h in Patients][t in 1..nbTimePeriods] =
    D_U2[n,t+nbTimePeriods*(h-1)];
float FHC_Trans_B_U2 [1..nbCHCs, 1..nbHnodes*nbVehicleTypes] = ...;
float FHC_Trans_B_U [i in CHCs][j in FHCs][k in Vehicles] =
    FHC_Trans_B_U2[i,k+nbVehicleTypes*(j-1)];
float CHC_Trans_B_U [i in CHCs][k in Vehicles]=...;
float Ware_B_U [0..0]=...;
float B_U [n in Hnodes]=...;

//Budget of Uncertainty Parameters
float R1_2 [1..nbHnodes, 1..nbPatientTypes*1] = ...;
float R1[n in Hnodes][h in Patients][t in 1..1] = R1_2[n,t+1*(h-1)];
float R2_2 [1..nbHnodes, 1..nbPatientTypes*nbTimePeriods] = ...;
float R2[n in Hnodes][h in Patients][t in 1..nbTimePeriods] =
    R2_2[n,t+nbTimePeriods*(h-1)];
float R3_2 [1..nbHnodes, 1..nbPatientTypes*nbTimePeriods] = ...;
float R3[n in Hnodes][h in Patients][t in 1..nbTimePeriods] =
    R3_2[n,t+nbTimePeriods*(h-1)];
float R4[i in CHCs]=...;
float R5[i in CHCs]=...;
float R6[i in CHCs][j in FHCs]=...;
float R7[j in FHCs]=...;
float R8[n in Hnodes]=...;
float R9=...;
float R10[i in CHCs]=...;
float R11[i in CHCs]=...;
float R12[0..0][i in CHCs]=...;
float R13[j in FHCs]=...;
float R14[j in FHCs]=...;
float R15[i in CHCs][j in FHCs]=...;
float R16[0..0]=...;
float R17[i in CHCs]=...;
float R18[0..0][i in CHCs]=...;
float R19[j in FHCs]=...;
float R20[i in CHCs][j in FHCs]=...;

//Fully Immunized Patient (FIP):
dvar int+ FIP[n in Hnodes][h in Patients];

//Vaccine Flow:
dvar int+ CHC_A[0..0][i in CHCs][k in Vehicles][t in 1..nbTimePeriods];
dvar int+ FHC_A[i in CHCs][j in FHCs][k in Vehicles][t in
1..nbTimePeriods];

//Inventory:

```

```

dvar int+ Ware_Inv[0..0][t in Periods];
dvar int+ Inv[n in Hnodes][t in Periods];

//Consumption:
dvar int+ Con1[n in Hnodes][h in Patients][t in 1..nbTimePeriods];
dvar int+ Con2[n in Hnodes][h in Patients][t in 1..nbTimePeriods];

//Unsatisfied Demand:
dvar int+ DD[n in Hnodes][h in Patients][t in 1..nbTimePeriods];

//Waste Flow:
dvar float+ Ware_WF[0..0][c in CCs][t in 1..nbTimePeriods];
dvar float+ HC_WF[n in Hnodes][c in CCs][t in 1..nbTimePeriods];
dvar float+ PC_CWF[c in CCs][p in Pnodes][t in 1..nbTimePeriods];

//Untransported Waste:
dvar float+ Ware_DDW[0..0][c in CCs][t in 1..nbTimePeriods];
dvar float+ HC_DDW[n in Hnodes][c in CCs][t in 1..nbTimePeriods];
dvar float+ PC_DDW[c in CCs][p in Pnodes][t in 1..nbTimePeriods];

//Dual Variables
dvar int+ q1[n in Hnodes][h in Patients][t in 1..1];
dvar int+ q2[n in Hnodes][h in Patients][t in 2..nbTimePeriods];
dvar int+ q4[i in CHCs];
dvar int+ q5[i in CHCs];
dvar int+ q6[i in CHCs][j in FHCs];
dvar int+ q7[j in FHCs];
dvar int+ q9[0..0];
dvar int+ q10[i in CHCs];
dvar int+ q11[i in CHCs];
dvar int+ q12[0..0][i in CHCs];
dvar int+ q13[j in FHCs];
dvar int+ q14[j in FHCs];
dvar int+ q15[i in CHCs][j in FHCs];
dvar int+ q16[0..0];
dvar int+ q17[i in CHCs];
dvar int+ q18[0..0][i in CHCs];
dvar int+ q19[j in FHCs];
dvar int+ q20[i in CHCs][j in FHCs];

dvar int+ r1[n in Hnodes][h in Patients][t in 1..1];
dvar int+ r2[n in Hnodes][h in Patients][t in 2..nbTimePeriods];
dvar int+ r4[i in CHCs][k in Vehicles];
dvar int+ r5[i in CHCs];
dvar int+ r6[i in CHCs][j in FHCs][k in Vehicles];
dvar int+ r7[j in FHCs];
dvar int+ r9[0..0];
dvar int+ r10[i in CHCs];
dvar int+ r11[i in CHCs];
dvar int+ r12[0..0][i in CHCs][k in Vehicles];
dvar int+ r13[j in FHCs];
dvar int+ r14[j in FHCs];
dvar int+ r15[i in CHCs][j in FHCs][k in Vehicles];
dvar int+ r16[0..0];
dvar int+ r17[i in CHCs];
dvar int+ r18[0..0][i in CHCs][k in Vehicles];
dvar int+ r19[j in FHCs];

```

```

dvar int+ r20[i in CHCs][j in FHCs][k in Vehicles];

//Objectives
dvar int+ TotalFIP;
dvar float+ Cost;

//Minimization of total cost with the cost of unsatisfied demand:
minimize Cost;

subject to{
    //Objective Function
    Cost == sum(i in CHCs,k in Vehicles1,t in 1..nbTimePeriods)
    Trans_cost[k]*Ware_CHC_dist[0][i]*CHC_A[0][i][k][t]
        + sum(<i,j> in V_Flow,k in Vehicles2,t in 1..nbTimePeriods)
    Trans_cost[k]*CHC_FHC_dist[i][j]*FHC_A[i][j][k][t]
    //Waste Processing Cost
        + sum(<c,s> in CW_SC_Flow,t in 1..nbTimePeriods)
    PC_CW[s]*PC_CWF[c][s][t]
        + sum(<c,f> in CW_IC_Flow,t in 1..nbTimePeriods)
    PC_CW[f]*PC_CWF[c][f][t];
    //The cost of not transporting one unit of medical waste
        + CWD*sum(c in CCs, t in 1..nbTimePeriods) (Ware_DDW[0][c][t]
        + sum(<n,c> in TW_Flow) HC_DDW[n][c][t]
        + sum(<c,s> in CW_SC_Flow) PC_DDW[c][s][t]
        + sum(<c,f> in CW_IC_Flow) PC_DDW[c][f][t]);
    //Inventory Holding Cost
        + sum(n in Hnodes,t in Periods) Inv_cost[n]*Inv[n][t];
    //Vaccine Loss Cost
        + CB*sum(t in 1..nbTimePeriods) (Ware_B[0]*Ware_Inv[0][t]
        + sum(n in Hnodes) B[n]*Inv[n][t]
        + sum(i in CHCs, k in Vehicles1)
    CHC_Trans_B[i][k]*CHC_A[0][i][k][t]
        + sum(<i,j> in V_Flow,k in Vehicles2)
    FHC_Trans_B[i][j][k]*FHC_A[i][j][k][t]
        + sum(n in Hnodes, h in Patients) B0*(Con1[n][h][t])
        + sum(n in Hnodes, h in Patients) B0*Con2[n][h][t]);
    //The Cost of Unsatisfied Demand
        + sum(h in Patients,n in Hnodes,t in 1..nbTimePeriods)
    DD[n][h][t]*CD[h];
    //Service Cost
        + CS * sum(h in Patients,n in Hnodes,t in 1..nbTimePeriods)
    (Con1[n][h][t] + Con2[n][h][t]);

    //Amount of unsatisfied demand
    forall (h in Patients,n in Hnodes,t in 1..1)
        D[n][h][t] - DD[n][h][t] - Con1[n][h][t] + q1[n][h][t]*R1[n][h][t] +
    r1[n][h][t] <= 0;

    forall (h in Patients,n in Hnodes,t in 1..1) q1[n][h][t] + r1[n][h][t]
    >= D_U[n][h][t];

    forall (h in Patients,n in Hnodes,t in 2..nbTimePeriods)
        D[n][h][t] - DD[n][h][t] + Con1[n][h][t-1] - Con1[n][h][t] -
    Con2[n][h][t] + q2[n][h][t]*R2[n][h][t] + r2[n][h][t] <= 0;

    forall (h in Patients,n in Hnodes,t in 2..nbTimePeriods) q2[n][h][t] +
    r2[n][h][t] >= D_U[n][h][t];

```

```

forall (h in Patients,n in Hnodes,t in 1..1) Con2[n][h][t] <= 0;

forall (h in Patients,n in Hnodes,t in 1..nbTimePeriods)
    Con1[n][h][t] - D[n][h][t] - D_U[n][h][t]*R3[n][h][t] <= 0;

forall (h in Patients,n in Hnodes,t in 2..nbTimePeriods) Con2[n][h][t]
<= Con1[n][h][t-1];

//Storage capacity constraints
forall (i in CHCs,t in 1..nbTimePeriods)
    Inv[i][t] + sum(k in Vehicles1) CHC_A[0][i][k][t] - sum(k in
Vehicles1) CHC_Trans_B[i][k] * CHC_A[0][i][k][t]
    + q4[i]*R4[i] + sum(k in Vehicles1) r4[i][k] - HC_Cap[i] +
q5[i]*R5[i] + r5[i] <= 0;

forall (i in CHCs) q5[i] + r5[i] >= HC_Cap_U[i];
forall (i in CHCs, k in Vehicles1, t in 1..nbTimePeriods) q4[i] +
r4[i][k] >= CHC_Trans_B_U[i][k] * CHC_A[0][i][k][t];

forall (<i,j> in V_Flow,t in 1..nbTimePeriods)
    Inv[j][t] + sum(k in Vehicles2) FHC_A[i][j][k][t] - sum(k in
Vehicles2) FHC_Trans_B[i][j][k] * FHC_A[i][j][k][t]
    + q6[i][j]*R6[i][j] + sum(k in Vehicles2) r6[i][j][k] - HC_Cap[j] +
q7[j]*R7[j] + r7[j] <= 0;

forall (j in FHCs) q7[j] + r7[j] >= HC_Cap_U[j];
forall (<i,j> in V_Flow, k in Vehicles2, t in 1..nbTimePeriods) q6[i][j]
+ r6[i][j][k] >= FHC_Trans_B_U[i][j][k] * FHC_A[i][j][k][t];

//Vehicle Capacity constraints
forall (i in CHCs,k in Vehicles1,t in 1..nbTimePeriods)
CHC_A[0][i][k][t] <= V_Cap[k];
forall (<i,j> in V_Flow,k in Vehicles2,t in 1..nbTimePeriods)
FHC_A[i][j][k][t] <= V_Cap[k];

//First time inventory constraints
Ware_Inv[0][0] == Ware_Cap[0];

forall (n in Hnodes) Inv[n][0] <= HC_Cap[n] - HC_Cap_U[n]*R8[n];
forall (n in Hnodes) Inv[n][0] >= HC_Cap[n] - HC_Cap_U[n]*R8[n];

//Administration capacity constraints
forall(n in Hnodes, t in 1..nbTimePeriods) sum(h in Patients)
Ap*(Con1[n][h][t] + Con2[n][h][t]) <= HC_N[n][t];

//Inventory balance constraints
forall (t in 1..nbTimePeriods) Ware_Inv[0][t] - Ware_Inv[0][t-1] + sum(i
in CHCs,k in Vehicles1) CHC_A[0][i][k][t]
    + Ware_B[0] * Ware_Inv[0][t-1] + q9[0]*R9 + r9[0] <= 0;

forall (t in 1..nbTimePeriods) q9[0] + r9[0] >= Ware_B_U[0] *
Ware_Inv[0][t-1];

forall (i in CHCs,t in 1..1) Inv[i][t] - Inv[i][t-1] + B[i]*Inv[i][t-1]
    + sum(<i,j> in V_Flow,k in Vehicles2) FHC_A[i][j][k][t] + sum(h in
Patients) Con1[i][h][t]/(1 - B0)

```

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+ sum(h in Patients) Con2[i][h][t]/(1 - BO) + q10[i]*R10[i] + r10[i]
<= 0;

forall (i in CHCs,t in 1..1) q10[i] + r10[i] >= B_U[i] * Inv[i][t-1];

forall (i in CHCs,t in 2..nbTimePeriods) Inv[i][t] - Inv[i][t-1] +
B[i]*Inv[i][t-1] + q11[i]*R11[i] + r11[i]
- sum(k in Vehicles1) CHC_A[0][i][k][t-1] + sum(k in Vehicles1)
CHC_Trans_B[i][k] * CHC_A[0][i][k][t-1]
+ q12[0][i]*R12[0][i] + sum(k in Vehicles1) r12[0][i][k]
+ sum(<i,j> in V_Flow,k in Vehicles2) FHC_A[i][j][k][t]
+ sum(h in Patients) Con1[i][h][t]/(1 - BO) + sum(h in Patients)
Con2[i][h][t]/(1 - BO) <= 0;

forall (i in CHCs,t in 2..nbTimePeriods) q11[i] + r11[i] >= B_U[i] *
Inv[i][t-1];
forall (i in CHCs,k in Vehicles1,t in 2..nbTimePeriods) q12[0][i] +
r12[0][i][k] >= CHC_Trans_B_U[i][k] * CHC_A[0][i][k][t-1];

forall (j in FHCs,t in 1..1) Inv[j][t] - Inv[j][t-1] + B[j]*Inv[j][t-1]
+ q13[j]*R13[j] + r13[j]
+ sum(h in Patients) Con1[j][h][t]/(1 - BO) + sum(h in Patients)
Con2[j][h][t]/(1 - BO) <= 0;

forall (j in FHCs,t in 1..1) q13[j] + r13[j] >= B_U[j] * Inv[j][t-1];

forall (<i,j> in V_Flow,t in 2..nbTimePeriods) Inv[j][t] - Inv[j][t-1] +
B[j]*Inv[j][t-1] + q14[j]*R14[j] + r14[j]
- sum(k in Vehicles2) FHC_A[i][j][k][t-1] + sum(k in Vehicles2)
FHC_Trans_B[i][j][k]*FHC_A[i][j][k][t-1]
+ q15[i][j]*R15[i][j] + sum(k in Vehicles1) r15[i][j][k]
+ sum(h in Patients) Con1[j][h][t]/(1 - BO) + sum(h in Patients)
Con2[j][h][t]/(1 - BO) <= 0;

forall (j in FHCs,t in 2..nbTimePeriods) q14[j] + r14[j] >= B_U[j] *
Inv[j][t-1];
forall (<i,j> in V_Flow,k in Vehicles2,t in 2..nbTimePeriods) q15[i][j]
+ r15[i][j][k] >=
FHC_Trans_B_U[i][j][k]*FHC_A[i][j][k][t-1];

//Number of FIPs
forall(n in Hnodes, h in Patients) FIP[n][h] == (sum(t in
1..nbTimePeriods) Con2[n][h][t]);

//Total amount of waste calculations
forall(t in 1..nbTimePeriods)
- Ware_WF[0][1][t] + Ware_DDW[0][1][t] + M *
(Ware_B[0]*Ware_Inv[0][t])
+ q16[0]*R16[0] + r16[0] <= 0;

forall (t in 1..nbTimePeriods) q16[0] + r16[0] >= M * Ware_B_U[0] *
Ware_Inv[0][t-1];

forall(i in CHCs,t in 1..nbTimePeriods)
- sum (<i,c> in W_Flow) (HC_WF[i][c][t] - HC_DDW[i][c][t])
+ M * (sum(h in Patients) Con1[i][h][t]/(1-BO) + sum(h in Patients)
Con2[i][h][t]/(1-BO))

```

```

+ M * B[i]*Inv[i][t] + q17[i]*R17[i] + r17[i]
+ M * sum(k in Vehicles1) CHC_Trans_B[i][k]*CHC_A[0][i][k][t]
+ q18[0][i]*R18[0][i] + sum(k in Vehicles1) r18[0][i][k] <= 0;

forall(i in CHCs,t in 1..nbTimePeriods) q17[i] + r17[i] >= M * B_U[i] *
Inv[i][t];
forall(i in CHCs,k in Vehicles1,t in 1..nbTimePeriods)
q18[0][i] + r18[0][i][k] >= M *
CHC_Trans_B_U[i][k]*CHC_A[0][i][k][t];

forall(<i,j> in V_Flow,t in 1..nbTimePeriods)
- sum (<j,c> in CW_Flow) (HC_WF[j][c][t] - HC_DDW[j][c][t])
+ M * (sum(h in Patients) Con1[j][h][t]/(1-B0) + sum(h in Patients)
Con2[j][h][t]/(1-B0))
+ M * B[j]*Inv[j][t] + q19[j]*R19[j] + r19[j] + M * sum(k in
Vehicles2) FHC_Trans_B[i][j][k]*FHC_A[i][j][k][t]
+ q20[i][j]*R20[i][j] + sum(k in Vehicles2) r20[i][j][k] <= 0;

forall(j in FHCs,t in 1..nbTimePeriods) q19[j] + r19[j] >= M * B_U[j] *
Inv[j][t];
forall(<i,j> in V_Flow,k in Vehicles2,t in 1..nbTimePeriods)
q20[i][j] + r20[i][j][k] >= M * FHC_Trans_B_U[i][j][k] *
FHC_A[i][j][k][t];

//Waste Flow Constraints
forall(c in CCs,t in 1..nbTimePeriods) sum (<c,s> in CW_SC_Flow)
(PC_CWF[c][s][t] - PC_DDW[c][s][t]) >=
SC_Rate*(Ware_WF[0][c][t] + sum(<n,c> in TW_Flow) HC_WF[n][c][t]);

forall(c in CCs,t in 1..nbTimePeriods) sum (<c,f> in CW_IC_Flow)
(PC_CWF[c][f][t] - PC_DDW[c][f][t]) >=
IC_Rate*(Ware_WF[0][c][t] + sum(<n,c> in TW_Flow) HC_WF[n][c][t]);

//Waste capacity constraints
forall(c in CCs,t in 1..nbTimePeriods)
Ware_WF[0][c][t] + sum (<n,c> in TW_Flow) HC_WF[n][c][t] <=
CC_Cap[c];

forall(t in 1..nbTimePeriods, p in Pnodes) sum(<c,p> in PW_Flow)
PC_CWF[c][p][t] <= PC_Cap[p];
}

```

APPENDIX 3: List of Abbreviations

WHO	World Health Organization
HSGM	Halk Sağlığı Genel Müdürlüğü
OR/MS	Operations Research/Management Science
UNICEF	United Nations International Children's Emergency Found
GAVI	Global Alliance for Vaccines and Immunization
EPI	Expanded Program on Immunization
SCND	Supply Chain Network Design
IP	Integer Programming
MIP	Mixed-integer Programming
MILP	Mixed-integer Linear Programming
SCD	Supply Chain Design
HERMES	Highly Extensible Resource for Modeling Event-Driven Supply Chains
LP	Linear Programming
FIC	Fully Immunized Children
FIP	Fully Immunized Patient
RPP	Robust Possibilistic Programming
CHC	Community Health Center
FHC	Family Health Center
OVW	Open Vial Wastage
RTMH	Republic of Turkey Ministry of Health
IMM	Izmir Metropolitan Municipality