REDUCING OPEN VIAL WASTAGE WITH LATERAL TRANSSHIPMENT IN COVID-19 VACCINE ADMINISTRATION

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REDUCING OPEN VIAL WASTAGE WITH LATERAL TRANSSHIPMENT IN COVID-19 VACCINE ADMINISTRATION

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To healthcare professionals, the true heroes of our time...

ABSTRACT

After the discovery and production of vaccines for the immunization against COVID-19 pandemic, mass vaccination programs are launched across the world. One of the main challenges faced during the COVID-19 mass vaccination programs is vaccine wastage. In a preliminary and empirical work conducted with healthcare professionals working at family health centers, we identify that using multi-dose vaccine vials is one of the significant factors causing the wastage. Some COVID-19 vaccines are preserved in multi-dose vials, and once a vial is opened, doses inside perish and go to waste in a few hours if not used. In this study, we analyze the lateral transshipment strategies in which open vials are transferred between vaccination points to decrease vaccine wastage. Besides making operational decisions regarding the vaccination process, we also examine the demand uncertainty issue due to the appointment no-shows. The problem is formulated as a 2-stage stochastic programming model. We solve the problem by developing a heuristic approach in which we cluster the vaccination points to form alliances using a mathematical model and utilizing the second stage of the 2-stage stochastic programming model. We validate our work by conducting a case study with family health centers in Tuzla, İstanbul and provide valuable insights for the case. The results show that our heuristic approach can be relied on its reasonable solution time, and provide quality solutions.

ÖZETÇE

COVID-19 pandemisine karşı bağışıklık kazandıran aşıların keşfi ve üretimi ardından tüm dünyada kitle aşılama süreçleri başlatılmıştır. COVID-19 aşılama sürecinde karşılaşılan en önemli sorunlardan biri ise aşı israfıdır. Aile sağlığı merkezlerinde çalışan sağlık personelleri ile gerçekleştirilen deneysel ön çalışmada, israfa yol açan önemli faktörlerden birinin çok dozlu flakonların kullanılması olduğu belirlenmiştir. Bazı COVID-19 aşıları çok dozlu flakonlarda saklanır ve flakonların kullanım için açılmasının ardından saat bazında kısa bir raf ömrüne sahiptir ve bu süreç içerisinde kullanılmazlarsa aşı israfı ortaya çıkmaktadır. Bu çalışmada, aşı israfını azaltmak için aşılama noktaları arasında gerçekleşen, açılmış flakonların taşındığı yanal aktarma stratejileri analiz edilmiştir. Problemde, aşılama sürecini temsil eden günlük operasyonel kararlar vermenin yanı sıra aşı rezervasyonuna katılım göstermeme durumundan dolayı talep belirsizliği durumunu da ele alınmıştır. Problem iki aşamalı olasılıksal programlama kullanılarak modellenmiştir. Çözüm yöntemi olarak matematiksel model kullanılarak birlikler oluşturmak için aşılama noktalarının kümelendiği ve iki aşamalı olasılıksal programlama modelinin ikinci aşamasından yararlanılan bir sezgisel yöntem geliştirilmiştir. İstanbul'un Tuzla ilçesinde yer alan aile sağlığı merkezlerinin yer aldığı bir vaka çalışması ile çalışmanın geçerliliği test edilmiştir ve vaka için değerli içgörüler sunulmuştur. Elde edilen sonuçlara göre geliştirdiğimiz sezgisel yöntem makul bir sürede iyi çözümler üretmektedir.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER I

INTRODUCTION

On March 11, 2020, World Health Organization (WHO) declared COVID-19 as a pandemic [1]. Since that date, the pandemic has threatened the health and life of human beings worldwide. As of May 22, 2022, 521,920,560 positive cases and 6,274,323 deaths have been detected [2]. During this period, the severity of the pandemic and rate of change in positive cases are affected by several factors such as new variants, lock-downs, seasonal changes, and incautiousness [3]. As the pandemic continued, the virus started to circulate more widely among the population and this has been causing new variants due to the mutation [4]. Now, it is understood that the vaccines, along with other practiced measures, are a critical tool to prevent the further spread of the pandemic and take it under control [5]. Currently, several different vaccines of different vaccine types have been administrated to the world population. For example, Pfizer-BioNTech is an m-RNA vaccine and Janssen is a viral vector-based vaccine [6].

The whole process of vaccination can be viewed in three main parts. First one is the production of the vaccines by the vaccine manufacturers or sometimes the government. The second is the embracive process, including purchasing from manufacturers, transportation, storage, and distribution of vaccines until the point of administration which is conducted by authorities with no-profit or profit-oriented intentions. This part can be achieved successfully by adequate vaccine supply chain resources such as vaccine cold chain equipment (refrigerators, freezers, and trucks with cold chain capacity). On the other hand, especially for developing countries, this process can be challenging due to the scarcity of budget and necessary resources. As a result, there are several studies in the literature addressing these processes [7, 8, 9, 10]. The third part, which is the endpoint, is the administration of vaccines to the individuals at certain capable centers such as hospitals, clinics, pharmacies, or administration points built for this specific reason. This process contains short-term operational level actions which should be taken in detail, such as administration scheduling, vaccine vial allocation, periodic controls, and inventory management. However, few studies in the literature address the problems faced at this level, especially during pandemics.

In the context of the COVID-19 vaccine administration, some problems should be dealt, carefully. For example, COVID-19 differs from other vaccines in terms of target population, because it is estimated that around % 67 of a population should be vaccinated to control the spread of the virus by gaining herd immunity [11]. Therefore, each dose of the vaccine is significant due to the enormity of the target population. As a consequence of this excessive demand, some COVID-19 vaccines are carried in small, air-tight tubes called multi-dose vials to ease the supply chain processes (transportation, storage, etc.) and each dose in a vial is administrated to a person by shared consumption. Although using a multi-dose vial is economically more viable, it should be consumed quickly after the extraction of the first dose from the vial by opening it. For instance, the duration is 6 hours for Pfizer-BioNTech COVID-19 vaccine [12]. This short shelf-life of an opened vial is called open vial lifetime (OVL), and the remaining doses inside a vial should be discarded after its OVL. If a vial is discarded with the remaining doses due to OVL, open vial wastage (OVW) occurs [13]. The main reason for OVW is being unable to consume all doses inside an open vial in the pre-specified OVL, which is related to the low demand rate that fails to meet the number of doses inside an open vial. Waiting for the sufficient demand to accumulate or rejecting or postponing a demand that cannot consume a whole vial can be practiced as a solution for this problem, however, this may contradict the goal of a vaccination program during a pandemic such as COVID-19, in which gaining herd immunity by vaccinating as many people as possible is critical. Additionally, as mentioned before, since each dose of vaccine is significant in COVID-19 vaccination, some actions should be taken to prevent OVW.

There are two driving factors for OVW during vaccine administration. The first one is the uneven number of individuals who showed up for vaccination and the number of doses inside a multi-dose vial, and the second one is the uncertainty of the demand at the vaccination points. For instance, if four people show up during the OVL of a multi-dose vial containing six doses, then two doses are wasted.

In our study, we present a multi-clinic network in which each clinic performs vaccine administration. We focus on a period of one working day for the network and give transshipment decisions among clinics to reduce OVW. The logic behind the transshipment is that the clinics which cannot fully consume an open vial before the expiration will transfer the vial to a clinic that can reduce its OVW, which also leads to fewer vial openings and OVW in the receiving clinic. We formulate the problem as a 2-stage stochastic programming model because the demand is uncertain due to the no show probability, and solve it with a particular heuristic approach. Based on our results, we achieve substantial savings in terms of OVW.

The rest of the study is organized as follows. Chapter 2 describes the system of interest and presents our empirical study, which motivates this research. In Chapter 3, we review the related literature. In Chapter 4, we define and formulate the problem. Chapter 5 describes the developed solution methodology. Chapter 6 introduces the case study, and represent our numerical analysis. Finally, in Chapter 7, we conclude our work and provide our ideas for future work.

CHAPTER II

SYSTEM DESCRIPTION AND EMPIRICAL STUDY

To understand the process and challenges of the COVID-19 mass vaccination efforts in detail, we analyze the system implemented in Turkey and conduct an empirical study with health care professionals, which are discussed next.

2.1 System Description

In Turkey, COVID-19 vaccine administration is conducted at family health centers and public hospitals under government provision, and a substantial portion of vaccines are administered at family health centers. These centers are small-scaled compared to hospitals and composed of examination rooms called units in which a physician is working. According to 2020 statistics from the Ministry of Health, a family health center has 3.32 units, on average. Moreover, there are 8,015 family health centers, and, 26,594 units, in total, in Turkey. They have a wide geographical spread across all cities of Turkey providing health services to the entire population. While the most crowded city has 4,694 family health centers, the least crowded city has 31. On overage, a unit of a family health center is responsible for 3,144 individuals [14].

A person living in Turkey and eligible for COVID-19 vaccination, can make an appointment at any time for any of the family health centers, if there is available capacity, through an online booking system. Additionally, a physician working at a family health center has access to valuable information to conduct the administration efficiently. At any time of a working day, a physician knows the amount and timing of upcoming appointments, vaccine stock at hand, the number of remaining doses inside an open vial, and the expiration time of these remaining doses through the online Vaccination Tracking System (VTS). With VTS, physicians try to implement practical measures to avoid OVW and vaccinate as many individuals as possible.

In Turkey, three types of COVID-19 vaccine is being used, which are Pfizer-BioNTech, CoronaVac, and TURKOVAC. First doses for CoronaVac and Pfizer-BioNTech are administered on January 14, 2021, and April 2, 2021, respectively [15, 16]. Whereas, more recently, the first dose of TURKOVAC is administered on December 30, 2021 [17]. During the period that we had conducted our empirical study TURKOVAC vaccine was not in use. Additionally, CoronaVac vaccine is preserved in single-dose vials that do not cause OVW. Therefore, we examine the system regarding the usage of Pfizer-BioNTech vaccine. Pfizer-BioNTech vaccine used in Turkey, also known as BNT162b2, is a multi-dose vaccine containing six doses inside a vial. Once a vial is opened, the doses inside expire after 6 hours and are wasted if not used [12]. A 2D barcode system, as presented in Figure 1, containing seven stickers is practiced to keep track of the number of doses inside open vials and their expiration time information on VTS. As shown by Daily et al. [18], using 2D barcode systems increases the data accuracy in vaccination sites and improves the vaccine logistics. In this system, one main 2D barcode sticker represents the vial, and each of the other six 2D barcode stickers represents one dose inside the vial. After the vaccination, physicians enter the 2D barcode information into the VTS. By this means, VTS contains all of the necessary information for tracking the number of doses inside an open vial and their expiration time. Since keeping track of these two pieces of information is crucial for our solution method developed for solving the problem, the system compromises with the problem.

Over the COVID-19 vaccination horizon, physicians have practiced the method of rejecting or postponing a demand that cannot consume a whole vial, or waiting for six people to open a vaccine vial to ensure the prevention of OVW. However, waiting for six people can be an issue due to appointment no-shows or the number of appointments not being a multitude of six. In this kind of situation, physicians

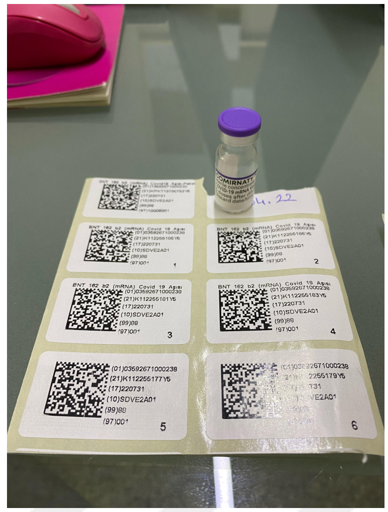

Figure 1: 2D barcode system implemented for BioNTech vials

and individuals who showed up might wait for a long time, or even appointments can be postponed to a later date. Since this might lead to a loss in vaccination demand for an administration process with herd immunity goal, it becomes one of the most serious challenges. Moreover, there are also several additional challenges faced in the COVID-19 vaccine administration process. To analyze and evaluate the challenges and practical solutions implemented in family health centers, we conducted an empirical study with health care practitioners working at a family health center in Turkey.

2.2 Motivation: Empirical Study

To motivate this research with empirical evidence, we designed and carried out an online survey under the supervision of family health practitioners. The only condition to participate in the survey is being a health care professional working at a family health center.

In total, 124 participants responded to our survey. The survey is conveyed to the participants through Google Forms between July and September 2021, during a period in which high vaccination rates are observed in Turkey. The study aims to uncover the challenges affecting vaccine administration efficiency, practical approaches

Table 1: Questions 1-7 from the survey

Q1	Please identify your job description.
Q2	In which city you are working?
Q3	How many units are there in your family health center?
Q4	Which vaccines are still administered in your family health center?
Q5	In which date you started administering Pfizer-BioNTech vaccine in your family health center ?
Q6	How many doses, on average, are administered on a busy day in your family health center ?
Q7	On a scale of 1 to 5, what is the rate of people who are not enrolled in your family health center but show up for vaccination?

adopted by health care practitioners and their needs, and recommendations.

Questions 1-7 are allocated for facts regarding the participant and the family health center in which the participant works. The first two questions are asked to learn the participant's occupation and residence, and the remaining five questions of the first part gather the facts about the family health center where the participant works. These facts include information about the number of units in the center, daily vaccination rate, and vaccine types used in administration. We provide these questions in Table 1.

In question 8, we aim to learn about factors that decrease vaccine administration efficiency and effectiveness. Figure 2 depicts the result of this question with the five most checked options by the participants. The two most checked options which are "Waiting for six people to open a vial" and "Appointment no shows" highlight the need for abandoning the practice of waiting for six people and indicate that the demand uncertainty issue should also be handled, which is a reason for waiting for six people. The third best option concerns the vaccine shortage problem which must be addressed with good resource allocation decisions. This problem requires making decisions for multiple periods at the tactical level. The last two options also support the claim of taking measures for the waiting for six people policy, because late-show and early-show is similar to a no-show due to not showing up at the designated appointment time, leading to the same demand uncertainty issue. According to the results obtained for challenges that decrease efficiency, we observe that the most critical challenges are faced at the operational level caused by demand uncertainty. As a practical approach, health care professionals have been practicing the policy of waiting for six people but the results demonstrate that this policy should be abandoned. Therefore, we aim to develop an approach that will replace the previous policy. Since leaving the previous policy will trigger the potential for OVW, measures to prevent vaccine wastage must also be taken.

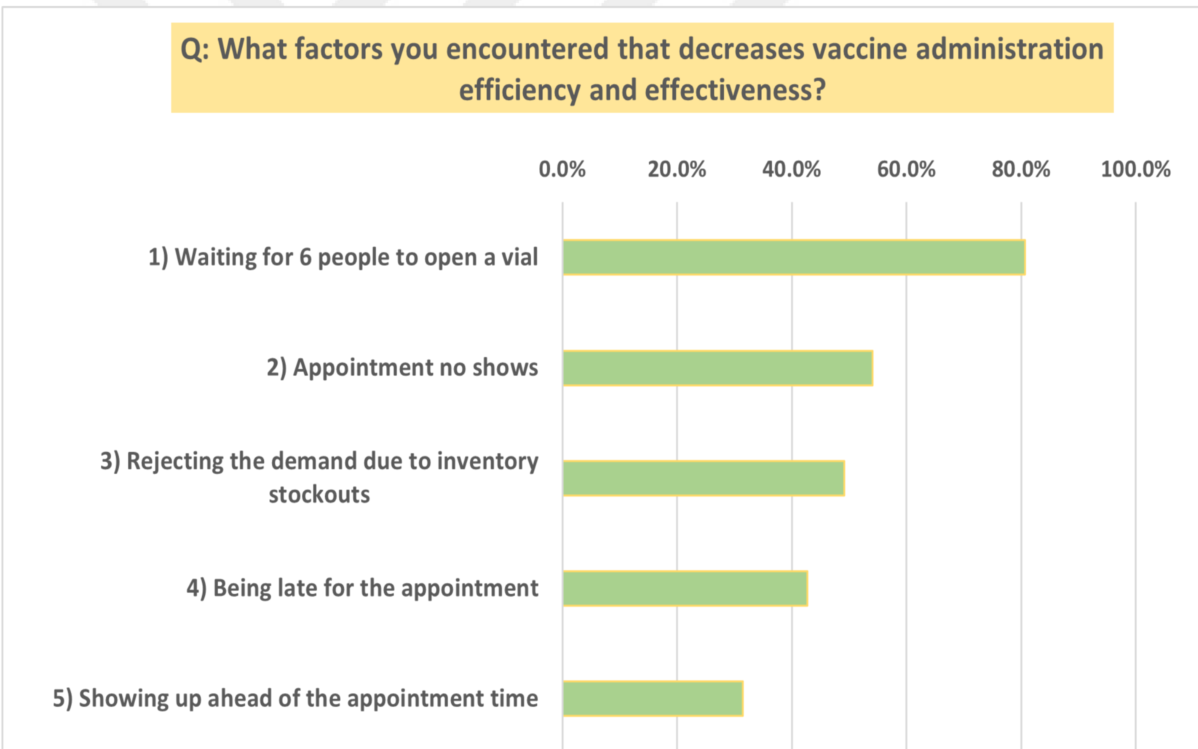

Figure 2: Factors that decreases vaccine administration efficiency and effectiveness

Question 10 asks for practices that would increase resource efficiency and effectiveness. Figure 3 represents the six most checked options for the question. The three most checked options highlight the managerial solutions that address the healthcare professionals' concerns on the workload and abilities of a family health center, which would not solve the demand uncertainty and waiting for six people issues. The least checked option is related to the previously specified demand uncertainty issue and the need for finding an alternative for the waiting for six people policy. However, this practice can create an additional challenge of vaccine shortage if everybody, even the overbooked demand, shows up. Since the presence of all demand would lead to an increase in vial openings, it might even cause an increase in OVW. However, the fourth and fifth most checked options indicate operational level measures that can be incorporated into the current system and seem suitable practices to respond to the previously mentioned challenges. The fourth most checked option suggests transferring the present patients to nearby centers if less than six people show up for vaccination. This option might seem reasonable, however, there is a non-negligible chance that the transferred patients might not follow the transfer decision and not show up at the designated nearby center or cannot be there on time due to some personal or logistic issues. On the other hand, the fifth most checked option suggests opening the vial regardless of the number of people who showed up and transshipping the possible unused doses inside the vial to a nearby center that can use them before they expire. Luckily, this approach can be practiced by integrating it into the current system if a suitable collaboration environment between family health centers and an adequate cold-chain transshipment system is established. A collaboration environment can be easily created with the previously introduced VTS that tracks all the necessary information for each family health center and by training the healthcare professional to practice the transshipment of vials. Moreover, an adequate cold-chain system can be implemented by hiring dedicated motorcycle couriers that drive motorcycles having a tail bag that provides the suitable temperature and transportation conditions for open vials. Thus, in this study, we investigate the benefit of lateral transshipment of unused doses inside open vials between centers. The practice aims to decrease OVW while every present individual is being vaccinated without any delay, postponement, or loss in demand. In this way, we can be one step closer to the goal of vaccinating as many people as possible to gain herd immunity.

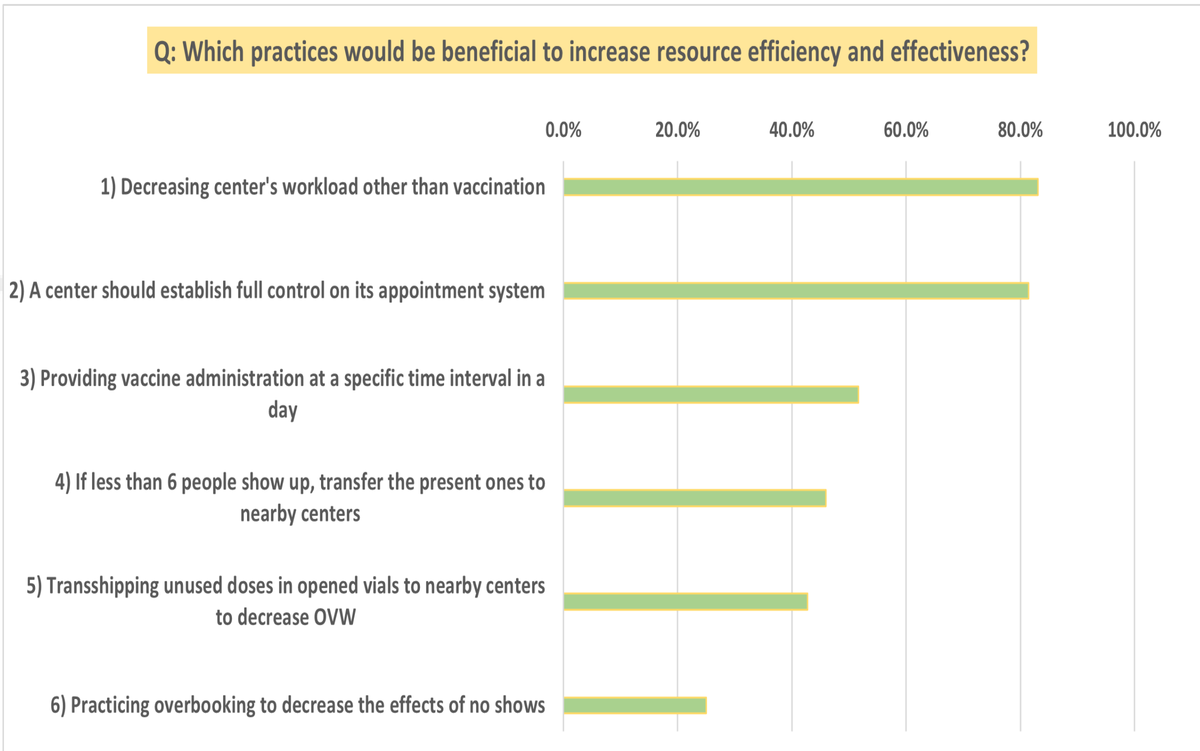

Figure 3: Practices that would increase resource efficiency and effectiveness

CHAPTER III

LITERATURE REVIEW

The related literature is discussed in three categories. The first category of literature focuses on vaccine logistics addressing the problems which occur during its transportation from the supplier to the endpoint, and the second category analyzes vaccine administration and wastage problems. Whereas the last category digresses from the vaccine literature and discuss the lateral transshipment of perishable items.

3.1 Vaccine Logistics Problems

Many works in the literature focus on vaccine logistics. These works generally combine several problem topics such as transportation, distribution, inventory management, and resource allocation. These works discuss the logistics process until the vaccine usage point. Chen et al. [7] study the distribution of WHO-EPI vaccines in a multi-level supply chain for developing countries. They consider vaccine wastage during the transportation, storage, and administration, cold chain and refrigerator capacity, and multi-dose vaccines. Their problem is solved with a special meta-heuristic algorithm. Another study that focuses on WHO-EPI vaccines belongs to Yang et al. [8]. They address a distribution network design problem in a four-tier network in which different replenishment periods and storage device options are evaluated. Their problem is formulated as a MIP model and solved with a disaggregation-and-merging algorithm, which is a mathematical programming-based heuristic. Hovav and Tsadikovich [19] propose an IP model for the distribution and inventory management of flu vaccine through a multi-level supply chain. The problem contains several aspects, such as manufacturer selection and cost factors throughout the supply chain. Rastegar et al. [10] focus on equitable influenza vaccine distribution in developing countries during a pandemic. They place a strong emphasis on equity with a delivery-to-demand ratio and by considering the prioritization of risk groups. Their problem addresses locating distribution centers and their capacities, vaccine shortage, and budget constraints in a two-level multi-period supply chain.

Vaccine logistics literature also addresses problems faced during the COVID-19 pandemic. For instance, Sujaree and Samattapapong [20] study capacitated vehicle routing problem for a multi-level vaccine cold chain network. They concentrate on transportation with capacitated vehicles and attain solutions with Hybrid Artificial Chemical Reaction Optimization Algorithm (HACROA). Tavana et al. [9] present a location-inventory MILP model for the equitable COVID-19 vaccine distribution in developing countries. They refer to prioritizing risk groups, vaccine order and lead times, and manufacturer selection. Vaccine logistic works mentioned until here do not practice the transshipment. However, in our work, in terms of vaccine logistics, we focus on the transshipment of vaccines after they arrive at the vaccination point. The closest study to ours, in terms of vaccine logistics, is presented by Abbasi et al. [21], which addresses the lateral transshipment of COVID-19 vaccines between medical centers in a vaccine allocation and distribution problem. In this problem, vaccines are first allocated and distributed to each medical center from the main distribution center considering factors such as prioritization of risk groups, demand information obtained from an online booking system, capacity of the medical centers, and the transshipment capacity, and limited vaccine stocks. After the allocation of vaccines to the medical centers, they practice lateral vaccine transshipment. However, unlike our problem, they focus on performing a transshipment to prevent shortages in centers. That is, when a center faces a shortage under excessive demand, another center having vaccine surplus transships some of its vaccine stock to the center which is facing the vaccine shortage. Another distinction of this problem from ours is that the vials transshipped are not opened, so there is no consideration of OVW. Differently, we focus on the lateral transshipment of opened vaccine vials between vaccination points to reduce OVW. To the best of our knowledge, no vaccine logistics study focuses on this matter.

3.1.1 Vaccine Administration and Wastage

Studies that address problems regarding the vaccine administration, and OVW occurring at the vaccination points are fewer in number compared to vaccine logistics studies. The studies focusing on vaccine administration usually address a combination of the topics such as scheduling, inventory management, resource allocation, location, and OVW. For instance, the study presented by Li et al. [22] couples locating vaccination stations, assignment and scheduling of health care professionals, order replenishment problems for an efficient vaccine administration system. In this study, stations are located considering the distance to demand points, workforce assignment, and operational cost. Unlike our study, Li et al. [22] do not consider OVW. However, there are studies in the literature that resemble ours in terms of emphasizing OVW. For example, Wedlock et al. [23] address the problem of deciding on the vial opening threshold and vial presentation (number of doses inside a vial) for a measles-containing vaccine. The authors aim to maximize coverage and minimize OVW, and for that, they evaluate the performance of different thresholds and presentations through HERMES simulation software. Abrahams and Ragsdale [24] study a travel vaccine administration system in which different combinations of vaccine types are administered to individuals. Similar to our work, they aim to satisfy all demands. However, this study proposes a zero wastage system by making the main decision: for a specific demand, open a single-dose or multi-dose vial for a specific vaccine type. Differently, we focus on a mass vaccination system where a single type of vaccine carried in multi-dose vials is used. Mofrad et al. [25] focus on a vaccine administration clinic thorough multiple periods in which they evaluate different session sizes and replenishment schedules under random patient arrival with a fixed mean daily demand rate. Distinctively, the main decision is whether to end or continue the current vaccination session in case of present demand, meaning that the demand might be unsatisfied. The reason behind this decision is to prevent opening a vial in the final hours of a vaccination day for a small demand which will lead to OVW. They develop a Markov Decision Process (MDP), which provides the optimal policy for the main decision. Mofrad et al. [26] evaluate the performance of the MDP developed in the work of Mofrad et al. [25] and two heuristic policies by utilizing simulation. Additionally, they conduct a sensitivity analysis on the effect of controllable and non-controllable parameters on the success of the MDP mentioned above. Mofrad et al. [27] extend the work of Mofrad et al. [25] by considering a more realistic demand pattern which the mean daily demand and arrival rate at each session varies. Another study that makes a similar main decision, which is either satisfying or rejecting a present demand, belongs to Azadi et al. [28]. The authors discuss vaccine administration and inventory replenishment policies for an immunization outreach session of childhood vaccines in which a single session of a single clinic is analyzed under uncertain patient arrival. Unlike our work, the main decision is opening a vial or not in presence of a demand and the size of the vial to be opened. Thus, after examining the existing studies that address vaccine administration and OVW, we can say that no other study addresses the vaccine administration in a multi-clinic network during mass vaccination by satisfying all demand and reducing OVW through lateral transshipment. Since we focus on a vaccine administration problem and address OVW, we provide Table 2 to better illustrate the difference between other vaccine administration studies that discuss OVW and our problem under significant distinctions.

3.2 Transshipment of Perishable Items

To the best of our knowledge, no study in the literature studies the lateral transshipment of open vaccine vials, which is a perishable item. However, several studies address the lateral transshipment of perishable items. Cheong [29] discusses the transshipment of perishable food items having a two-period lifetime between retail stores facing uncertain demand for the period between two inventory control points. By practicing the transshipment in the same echelon, the authors aim to reduce wastage and related costs and solve the problem with a decomposition-based iterative solution approach. A similar work is presented by Nakandala et al. [30] in which the objective is to minimize the perishable inventory costs by applying lateral transshipment between supermarkets, but different from our study, the authors address the issue in a multi-period inventory control system. The problem is solved by a discrete-time decision model and validated with Monte Carlo simulation. Dehghani and Abbasi [31] study the transshipment of blood units between hospitals to decrease shortage rates by implementing an age-based and reactive policy. In this policy, when a hospital faces a shortage and there are blood units in another hospital older than a specific threshold, a lateral transshipment is performed towards to hospital that is out of stock. Otherwise, the shortage is prevented by an emergency shipment from the supplier. Dehghani et al. [32] focus on a proactive transshipment and aim to decrease both the shortage and wastage of blood units in a network of multiple hospitals. The authors tackle the problem with a 2-stage stochastic programming model integrated with a rolling horizon approach. With the mentioned literature, we witness the applicability of lateral transshipment for the movement of perishable goods. Especially with the works of Dehghani and Abbasi [31] and Dehghani et al. [32], we understand that lateral transshipment can be practiced in healthcare systems which concerns the perishability of the items. Although we provide studies that show the applicability of lateral transshipment for perishable items, we cannot utilize the transshipment models presented in them. The reason for that is we focus on a perishable item, doses inside open vials, which has different characteristics from the items considered in these studies. The differences are four-fold. First, unlike other perishable items, a vaccine vial's perishability can be discussed if it is opened. Otherwise, they can be stored under suitable temperatures for months. Second, there are certain characteristic transshipment conditions which will be explained in the next section. Third, sending an open vial means sending the doses inside. Since a clinic can only send the doses inside open vials, the quantity of perishable items to send is limited and it is not under our control. Lastly, for the systems considering other perishable items, as the demand increases, less perishable items are sent to other points. However, in the vaccine vial case, more demand can decrease or increase the transshipment quantity, because more demand can cause more vial openings, which results in more doses inside open vials.

Table 2: Comparison with other vaccine administration studies that discuss OVW

Work	System description	Demand	Coverage	Main decision
Abrahams and Ragsdale(2012)	One clinic	Known	Satisfy all demand	Open a single or multi – dose vial
Wedlock et al.(2019)	One clinic	Uncertain	Unsatisfied demand	Vial opening threshold, vial presentation
Mofrad et al.(2014)	One clinic	Uncertain	Unsatisfied demand	Whether to end current vaccination session
Azadi et al.(2020)	One clinic	Uncertain	Unsatisfied demand	Open the vial now or save it for future demand
Our contribution	Multiple clinics	Uncertain	Satisfy all demand	Lateral transshipment of doses inside open vials

To conclude, after examining the related literature, we can state that there is no other study in the literature that addresses the OVW issue in a multi-clinic vaccine administration network facing uncertain demand during a mass vaccination process by performing lateral transshipment of open vials between clinics and satisfying all present demand.

CHAPTER IV

PROBLEM DEFINITION

We define the Vaccine Transshipment Problem (VTP), which focuses on a network of clinics that corresponds to the family health centers in the described system. All clinics use the same vaccine type which is carried in multi-dose vials, and the number of doses inside a vial is represented with v. Moreover, the problem is solved for one working day, and it is assumed that all clinics follow the same session structure, throughout the day, by starting and ending the vaccination simultaneously, and conducting the same number of sessions, which is $|S|$. Figure 4 illustrates the logic of the session structure implemented by all clinics.

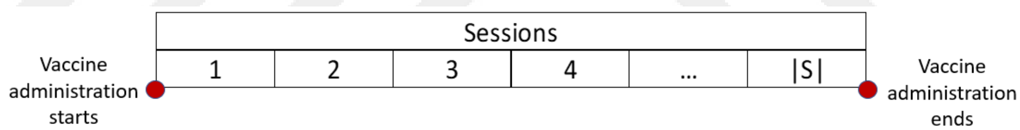

Figure 4: Session structure

There is an online booking system from which individuals can make an appointment for a specific session of a day if there is remaining capacity in that session. Determining the session capacity of clinics and workforce scheduling is out of the scope of the problem. Through the online booking system, the number of appointments for each session of a clinic is known before the day starts. However, we consider the probability of no shows caused by appointment breaks. Since the number of no shows is uncertain for a session, demand also becomes uncertain. To handle the demand uncertainty, we formulate the problem as a 2-stage stochastic programming model and represent the demand uncertainty by multiple scenarios. Thus, the demand realized for session s of clinic i in scenario k is determined by the formula $d_{isk} =$ (Number of appointments for session s of clinic i) - (Number of no shows for sessions s of clinic i in scenario k). Additionally, we assume that early and late arrivals to a session and walk-ins (individuals showing up without an appointment) are not observed, which means that an individual either shows up for the appointment on time or does not show up at all.

If a vial is opened at a clinic, doses inside can either be used in the same clinic until the expiration, transshipped to another clinic, or wasted. Figure 5 represents the possibilities for doses inside an opened vial. Moreover, we have some further assumptions regarding the vial openings and transshipment. We assume when a vial is opened, doses inside should be consumed in consecutive sessions that have demand. That is, there can be no session gap in which doses inside are not consumed unless there is no demand in that session. Also, a new vial should be opened upon the complete consumption of the previous one. We also assume that transshipment can only be made at specific sessions, meaning that the number of sessions in which transshipment is permitted is limited with parameter c over a day. In addition, transshipment duration is taken into account, and we assumed that a fixed lead time of lt sessions should be elapsed before the receiver clinics start to consume the received vials.

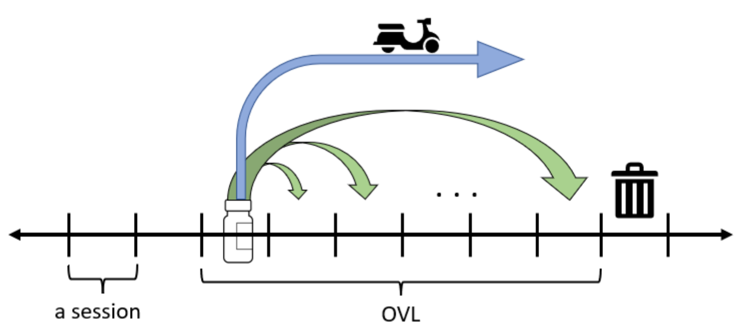

Figure 5: Vial usage

Moreover, in this system, in terms of practicality, a clinic cannot send its remaining doses in a transshipment session if its demand in the remaining OVL is greater than or equal to its remaining doses. The reason for that is a clinic would not want to send its doses if it can fully consume them in the following sessions.

The decisions made in the VTP are split into two stages to implement 2-stage stochastic programming. The first stage decisions apply to all scenarios, and the second stage decisions vary based on each scenario, as practiced in scenario-based stochastic programming. There is only one first-stage decision variable which is the sessions in which transshipment must be performed over a day and it is represented as C_s. This decision must be given at the beginning of the day and it will be valid for all scenario realizations throughout the day. There are three main second-stage decisions. The first one, $Y_{iss'k}$, decides how many doses will be used at session s' from the vials opened at s. This decision helps keeping track of the remaining doses inside an open vial and when they will be expired. The second one, $T_{ii'ss's''k}$, defines the direction, timing, and quantity of the transshipment, and utilization times of the transshipped doses. The direction of the transshipment is from the sender clinic to the receiver clinic. The sender clinic sends its doses inside open vials to the receiver clinic which will start consuming the received doses after the transshipment is performed. It decides on the number of doses used at session s'' in clinic i' from the vials opened at session s in clinic i via transshipment at session s'. This decision is demonstrated in Figure 6. The final one, W_{isk}, records the wastage by deciding the number of doses wasted from the vials opened at session s in clinic i. We also utilize some second-stage auxiliary decision variables to represent the vial openings and basic transshipment decisions.

Finally, there is one primary and one secondary objective of the VTP. The primary objective is to minimize the expected number of doses wasted over a day in the network. Based on our initial experiments, we find that number of doses wasted and the number of opened vials are positively correlated. That is, as the expected number of doses wasted decreases, the expected number of vials opened also decreases, which is

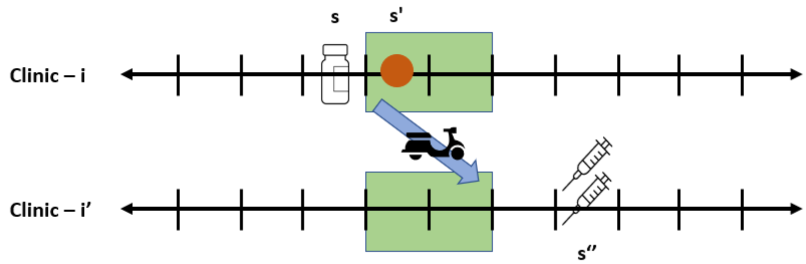

Figure 6: Transshipment decision

also desired because reducing the number of opened vials by one means saving v doses inside the vial from wastage. Therefore, we do not set any objective regarding the minimizing expected number of vials opened since minimizing the expected number of doses wasted inherently provides it. The secondary objective is minimizing the expected number of transshipments over a day in the network, which ensures that there is no redundant transshipment and removes alternative optima.

Sets:

I: set of clinics, $i \in I$

S: set of sessions, $s \in S$

K: set of scenarios, $k \in K$

Parameters:

v: vial size

ovl: session-wise open vial lifetime

lt: session-wise lead time

c: maximum number of sessions in which transshipment are permitted

d_{isk}: demand of clinic i at session s for scenario k

u_{isk}: limit for number of opened vials in clinic i at session s for scenario k

$u_{isk} = roundup(d_{isk}/v)$

p_k: probability of scenario k

Decision Variables:

C_s: 1, if transshipment are permitted at session s; 0, otherwise

O_{isk}: number of vials opened at session s in clinic i for scenario k

$Z_{ii'ss'k}$: 1, if a transshipment is made from clinic i to i' at session s' from the vial opened at session s for scenario k 0, otherwise

$T_{ii'ss's''k}$: number of doses used at session s'' in clinic i' from the vials opened at session s in clinic i, which have been transshipped from clinic i to i' at session s' for scenario k

W_{isk}: number of doses wasted from the vials opened at session s in clinic i for scenario k

$Y_{iss'k}$: number of doses used at session s' from the vials opened at session s in clinic i for scenario k

$B_{iss'k}$: 1, if any number of doses used at session s' from the vials opened at session s in clinic i for scenario k; 0, otherwise

We provide the problem formulation in the following.

$$\min \qquad \sum_{k\in K} p_k(\theta_1 \sum_{i\in I}\sum_{s\in S} W_{isk} + \theta_2 \sum_{i\in I}\sum_{i'\in I}\sum_{s\in S} Z_{ii'sk}) \tag{1}$$

s.t.

$$\sum_{s\in S} C_s \leq c \tag{2}$$

$$\sum_{s=1}^{s'-1} Z_{ii'ss'k} \leq C_{s'} \qquad \forall i, i' \in I, s' \in S, k \in K \tag{3}$$

$$T_{ii'ss's''k} \leq M(Z_{ii'ss'k}) \tag{4}$$

$$\forall i, i' \in I, s, s', s'' \in S, s' > s, \text{ and } s'' \geq s' + ls, \text{ and } s'' < s + ovl, k \in K$$

$$T_{ii'ss's''k} \leq 0 \tag{5}$$

$$\forall i, i' \in I, s, s', s'' \in S, s' \leq s, \text{ or } s'' < s' + ls, \text{ or } s'' \geq s + ovl, k \in K$$

$$vO_{isk} = \sum_{s'=s}^{s+ovl-1} Y_{iss'k} + \sum_{i'\in I} \sum_{s'=s+1}^{(s+ovl-lt-1)} \sum_{s''=s'+lt}^{(s+ovl-1)} T_{ii'ss's''k} + W_{isk} \tag{6}$$

$$\forall i \in I, s \in S, s \leq |S| - ovl, k \in K$$

$$vO_{isk} = \sum_{s'=s}^{|S|} Y_{iss'k} + \sum_{i' \in I} \sum_{s'=(s+1)}^{|S|-lt} \sum_{s''=(s'+lt)}^{|S|} T_{ii'ss's''k} + W_{isk} \tag{7}$$

$\forall i \in I, s \in S, |S| - ovl < s < |S| - lt, k \in K$

$$vO_{isk} = \sum_{s'=s}^{|S|} Y_{iss'k} + W_{isk} \qquad \forall i \in I, s \in S, s \geq |S| - lt, k \in K \tag{8}$$

$$d_{isk} = \sum_{s'=s-ovl+1}^{s} Y_{is'sk} + \sum_{i' \in I} \sum_{s'=(s-ovl+1)}^{(s-lt-1)} \sum_{s''=(s'+1)}^{(s-lt)} T_{i'is's''sk} \tag{9}$$

$\forall i \in I, s \in S, s \geq ovl, k \in K$

$$d_{isk} = \sum_{s'=1}^{s} Y_{is'sk} + \sum_{i' \in I} \sum_{s'=1}^{(s-lt-1)} \sum_{s''=s'+1}^{(s-lt)} T_{i'is's''sk} \qquad \forall i \in I, s \in S, s < ovl, k \in K \tag{10}$$

$$O_{isk} \leq u_{isk} \qquad \forall i \in I, s \in S, k \in K \tag{11}$$

$$Y_{iss'k} \leq M(O_{isk}) \qquad \forall i \in I, s, s' \in S, k \in K \tag{12}$$

$$T_{ii'ss's''k} \leq M(O_{isk}) \qquad \forall i, i' \in I, s, s', s'' \in S, k \in K \tag{13}$$

$$Y_{iss'k} \leq M(B_{iss'k}) \qquad \forall i \in I, s, s' \in S, k \in K \tag{14}$$

$$B_{iss'k} \leq Y_{iss'k} \qquad \forall i \in I, s, s' \in S, k \in K \tag{15}$$

$$O_{is'k} \leq M(1 - B_{iss''k}) \tag{16}$$

$\forall i \in I, s, s' \in S, s < s', s' \leq |S| - 1, s' < s'' \leq |S|, k \in K$

$$\sum_{i' \in I} z_{ii'ss''k} \leq 1 - B_{is's'k} \qquad \forall i \in I, s, s' \in S, k \in K \tag{17}$$

$$O_{isk} \leq M(B_{issk}) \qquad \forall i \in I, s \in S, k \in K \tag{18}$$

$$\sum_{i' \in I} Z_{ii'ss'k} \leq 1 \qquad \forall i \in I, s, s' \in S, k \in K \tag{19}$$

$$\sum_{i' \in I} Z_{i'iss'k} \leq M(1 - \sum_{i' \in I} Z_{ii'ss'k}) \qquad \forall i \in I, s, s' \in S, k \in K \tag{20}$$

$$Z_{ii'ss'k} \leq 0 \qquad \forall i, i' \in I, s, s' \in S, s' \geq |S| - lt, k \in K \tag{21}$$

$$Z_{iiss'k} \leq 0 \qquad \forall i \in I, s, s' \in S, k \in K \tag{22}$$

$$\sum_{s''=s'}^{s+ovl-1} d_{is''k} \leq vO_{isk} + \sum_{i' \in I} \sum_{s''' \in S} \sum_{s'''' \in S} \sum_{s''=s}^{s'-1} T_{i'is'''s''''s''k} - \sum_{s''=s}^{s'-1} Y_{iss''k} + M(1 - \sum_{i' \in I} Z_{ii'ss'k}) \tag{23}$$

$\forall i \in I, s, s' \in S, s \leq |S| - ovl, k \in K$

$$\sum_{s''=s'}^{|S|} d_{is''k} \leq vO_{isk} + \sum_{i' \in I} \sum_{s''' \in S} \sum_{s'''' \in S} \sum_{s''=s}^{s'-1} T_{i'is'''s''''s''k} - \sum_{s''=s}^{s'-1} Y_{iss''k} + M(1 - \sum_{i' \in I} Z_{ii'ss'k}) \tag{24}$$

$\forall i \in I, s, s' \in S, s > |S| - ovl, k \in K$

$$C_s \in \{0,1\} \qquad \forall s \in S \tag{25}$$

$$O_{isk}, W_{isk} \in \mathbb{Z}^+ \qquad \forall i \in I, s \in S, k \in K \tag{26}$$

$$B_{iss'k} \in \{0,1\} \qquad \forall i \in I, s, s' \in S, k \in K \tag{27}$$

$$Y_{iss'k} \in \mathbb{Z}^+ \qquad \forall i \in I, s, s' \in S, k \in K \tag{28}$$

$$Z_{ii'ss'k} \in \{0,1\} \qquad \forall i, i' \in I, s, s' \in S, k \in K \tag{29}$$

$$T_{ii'ss's''k} \in \mathbb{Z}^+ \qquad \forall i, i' \in I, s, s', s'' \in S, k \in K \tag{30}$$

The objective function (1) minimizes the expected number of doses wasted and the expected number of transshipment over a day across all clinics. θ_2 takes a significantly small value compared to θ_1 because reducing transshipment rates is only for preventing unnecessary transshipment and alternative optima.

Following constraints assess the effect of the first-stage decision on the system. Constraint (2) restricts the number of sessions in which transshipment is permitted. Thus, there can be at most c sessions in which transshipment can be made. Constraint (3) states if there is no permission for transshipment at session s, then no transshipment can be made at that session.

Next, we provide the link between transshipment decisions. Constraint (4) links decision variables $Z_{ii'sk}$ and $T_{ii'ss's''k}$. Constraint (5) states the conditions in which transshipment cannot be made.

Succeeding constraints specifies what happens to doses inside open vials. Constraint (6) shows the usage of doses inside vials opened at session s in clinic i if $s \leq |S| - ovl$. Doses inside opened vials can be used inside the same clinic or can be transferred to and used in another clinic until doses' OVL ends or can be wasted. Constraint (7) shows the usage of doses inside vials opened at session s in clinic i if $|S| - ovl < s \leq |S| - lt$. Doses inside opened vials can be used inside the same clinic or can be transferred to and used in another clinic until the end of the day or can be wasted. Constraint (8) shows the usage of doses inside vials opened at session s in clinic i if $s > |S| - lt$. Doses inside opened vials can be used inside the same clinic until the end of the day or can be wasted.

The next two constraints ensure that demand is always fully satisfied. Constraints (9) and (10) state that demand at session s in clinic i is satisfied by vials opened at session s and before, and doses transshipped from other clinics.

Subsequently, we build the link among the vial opening, vial usage, and vial transshipment decisions. Constraint (11) limits the number of vials that can be opened at a specific session. The reason for this constraint is to be more realistic and prevent opening too many vials to cover further session demands. Constraint (12) indicates if there is no vial opened at session s, then no doses from that session can be used at session s'. Constraint (13) indicates if there is no vial is opened at session s in clinic i, then no doses from that session can be transshipped at s' and be used at session s'' in clinic i. Constraint (14), (15) links the decision variables $Y_{iss'k}$ and $B_{iss'k}$. Constraint (16) assures if vials are opened at sessions s and s' where $s' > s$, then doses inside the vials opened at session s cannot be used sessions after s'. Constraint (17) states if a vial is opened at session s' then doses inside a vial opened earlier then s' cannot be transshipped. Constraint (18) assures if vials are opened at session s, then doses inside the vials must be used at session s.

The following constraints indicate the transshipment basics. Constraint (19) makes sure that a clinic can transfer its doses to only one clinic. Constraint (20) specifies a clinic can either send or receive a vial at a specific transshipment point. Constraint (21) denotes that if $s > |S| - lt$, no transshipment decision cannot be made at session s, because the remaining time until the end of the day is less than the lead time. Constraint (22) ensures a clinic cannot transship its doses to itself.

The next two constraints enforce a condition to perform transshipment. Constraints (23) and (24) indicate a clinic cannot make transshipment if its remaining doses is smaller than demand during the remaining OVL. The rest of the constraints are integer, non-negativity, and binary constraints

We also provide some optional parameters and constraints that can be used by the decision maker if required. We provide them separately from the original formulation because they are not crucial for the problem and represent possible system restrictions which do not have to be compulsory for all system settings. They can directly be adjoined to the model.

q: minimum number of sessions between two sessions in which transshipment can be made
mrl: maximum limit for a receiving clinic in terms number of clinics it receives from

$$\sum_{s'=s-q}^{s-1} C_{s'} \leq q(1 - C_s) \qquad \forall s \in S, s > q \tag{31}$$

$$\sum_{s'=s+1}^{s+q} C_{s'} \leq q(1 - C_s) \qquad \forall s \in S, s \leq q \tag{32}$$

$$\sum_{i' \in I} Z_{i'isk} \leq mrl \qquad \forall i \in I, s \in S, k \in K \tag{33}$$

$$vO_{isk} - \sum_{s''=s}^{s'-1} Y_{iss''k} \leq \sum_{i' \in I} \sum_{s''=s'+ls}^{s+ovl-1} T_{ii'ss's''k} + M(1 - \sum_{i' \in I} Z_{ii'ss'k}) \tag{34}$$

$$\forall i, \in I, s, s' \in S, s \leq |S| - ovl, k \in K$$

$$vO_{isk} - \sum_{s''=s}^{s'-1} Y_{iss''k} \leq \sum_{i' \in I} \sum_{s''=s'+ls}^{|S|} T_{ii'ss's''k} + M(1 - \sum_{i' \in I} Z_{i,i',s,s',k}) \tag{35}$$

$$\forall i, i' \in I, s, s' \in S, s > |S| - ovl, k \in K$$

Constraints (31) and (32) ensure that there are at least q sessions between two sessions in which transshipment is permitted. Constraint (33) remarks a clinic can receive doses from at most mrl clinics. mrl is decided based on the lead time duration and travel times between clinics. This constraint functions as a presumptive coverage for courier movement. Constraints (34) and (35) assure if a clinic is making transshipment, it should send all its remaining doses inside the open vial.

In our problem, we do not integrate the courier movements that realize the transshipment decisions made, to prevent complexity. Instead, we assume that this part is out of the scope of our problem and present a presumptive coverage constraint for courier movements in Constraint 33. However, the movement of couriers among clinics to transport the vials according to the transshipment decisions must be studied and analyzed further to achieve the successful transportation of vials to centers on time. As a preliminary step for this study, we present a courier routing model that emphasizes and resolves several problem aspects in Appendix B.

To validate our model we conduct a preliminary experiment on a computer with an Intel(R) Core(TM) i9-10980XE CPU @ 3.00GHz processor and a 128 GB RAM by using Gurobi 9.5.1 as the optimization tool on Python 3.9. We create four instances based on two aspects and consider two options for each aspect. The first aspect is the number of clinics ($|I|$) for which we consider 2 and 4. Similar to the family health centers described in Chapter 2, these clinics consist of units and we assume that number of appointments made for a unit is UNIF(0,1) per session. In $|I| = 2$ instances, Clinic 1 and 2 have one and five units, respectively. Whereas, in $|I| = 4$ instances, Clinic 1, 2, 3, and 4 consist of one, five, seven, and two units, respectively. The second aspect is the number of scenarios ($|K|$) which has two options 5 and 10. While constructing the scenarios, we accept the no show rate as UNIF(0,0.3) which specifies the percentage of the total daily appointment of a clinic that does not show up. For all instances, we provide the solution obtained through the 2-stage SP model and the solution where no transshipment is performed to demonstrate the effect of 2-stage SP, in Table 3. In the table, the expected number of doses wasted over a day across all clinics is represented with KPI-1. Whereas KPI-2 provides the expected number of vials opened over a day across all clinics. In addition, KPI-3 shows the expected number of transshipments made over a day. In preliminary experiment, we set $v = 6$, $ovl = 6$, $lt = 1$, $c = 2$, and $|S| = 12$.

Table 3: Preliminary results

			2-stage SP					No transshipment		
Instance	$\vert I\vert$	$\vert K\vert$	**KPI-1**	**KPI-2**	**KPI-3**	**Solution time (sec.)**	**Gap**	**KPI-1**	**KPI-2**	**KPI-3**
1	2	5	5	6.2	1.2	0.8	0.0%	12.2	7.4	0
2	2	10	1.8	4.9	1.5	47.3	0.0%	7.8	5.9	0
3	4	5	2.8	12.8	2.2	3600.5	64.2%	12.4	14.4	0
4	4	10	3	13.6	2.3	3601.0	90.6%	15	15.6	0

As shown in Table 3, the 2-stage SP model achieves significant savings in terms of the expected number of doses wasted (KPI-1) and the expected number of vials opened (KPI-2) by performing transshipment (KPI-3). Thus, our preliminary experiment validates the model performance. Moreover, as the number of clinics and scenarios increases, the problem complexity increases. Especially, an increase in the number of clinics causes a leap in complexity. As instances 3 and 4 demonstrate, the problem with $|I| = 4$ cannot be solved with a time limit of one hour, and result in a significantly large optimality gap. As a result, we understand that we should develop a solution method to obtain solutions in a reasonable amount of time.

CHAPTER V

SOLUTION METHOD

According to our preliminary runs of the 2-stage stochastic programming model provided in Table 3, the problem becomes rapidly complex as the number of clinics and scenarios increases. Therefore, we create a solution method that provides quality solutions in a short time. In this method, first, we form alliances. An alliance is a cluster of clinics that is a smaller part of the network, such that two clinics can only perform transshipment if they are both in the same alliance. Alliances are formed only once and valid for each day because forming different alliances every day might increase disrupture and miscommunication during transshipments.

There are two reasons behind the alliance logic. Firstly, the problem will no longer be complex because instead of solving the problem once for one large network, it is solved as many as the number of alliances. These problems will contain a smaller number of clinics which helps avoiding the complexity. That is, if the number of alliances is $|A|$, the problem will be solved for $|A|$ times. The second reason is, in practice, transshipment among all clinics in a network can be challenging if some portion of the clinics has a remote location compared to other clinics operating in the network. Therefore, a reasonable decision would be not to place two distant clinics in the same alliance to ease the transshipment process.

Moreover, the alliances should be formed according to a certain logic that will somehow compensate for the loss of ability to perform transshipment among all clinics in the network. In other words, the possibility of performing transshipment will decrease because we only permit transshipment inside an alliance instead of permitting transshipment across the network. Therefore, characteristics of clinics that form alliances should follow a logic that increase the possibility of transshipment in each alliance. With our preliminary experiments shown in Table 3, we discover that the number of units of clinics plays a significant role in alliance logic because the greater number of units indicates a greater demand, and, similarly, a smaller number of units indicates a smaller demand for a clinic. According to these preliminary trials, we find that transshipments are, usually, performed from a clinic with smaller demand to a clinic with a larger demand. Because the clinics that have a lower demand rate are open to the risk of not being able to consume all doses inside an open vial before the expiration. These clinics usually send their remaining doses to the clinics with larger demand in which the transshipped doses will be almost certainly consumed due to the greatness of the demand. Figure 7 illustrates the transshipments in the solution obtained for the Instance 4 with $|I| = 4$ and $|K| = 10$ provided in Table 3. In the figure, we observe a network of four clinics with their number of units information, and the red arrows between clinics indicate the expected number of transshipments in the arrow's direction.

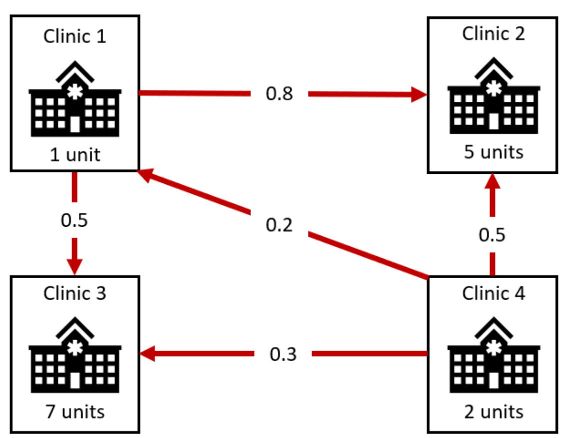

Figure 7: Transshipment behavior according to number of units

In conclusion, we should strike a balance in each alliance such that demand magnitudes of the clinics in each alliance create an environment that strengthens the transshipment possibility. Since the number of units of a clinic directly reflects the magnitude of the demand, we created an alliance model that uses the number of units of each clinic to find a balance in each alliance. In other words, we try to create equality in each alliance regarding the number of clinics with a smaller number of units and a larger number of units. In addition, we enforce a distance limit to prevent two distant clinics from being in the same alliance.

Sets:

I: set of clinics, $i \in I$

A: set of alliances, $a \in A$

Parameters:

u_i: number of units in clinic i

d_{ij}: distance between clinic i and j

$u^{average}$: average number of units in the network

u_i^{abs}: absolute value of the difference between u_i and $u^{average}$

l^{clinic}: maximum limit for the number of clinics in an alliance

$l^{distance}$: maximum limit for the distance between two clinics in an alliance

Decision Variables:

γ_{ia}: 1, if clinic i is in alliance a; 0, otherwise

G_1: an auxiliary variable that represents the maximum total $u_i - u^{average}$ rate in an alliance

G_2: an auxiliary variable that represents the minimum total u_i^{abs} rate in an alliance

$$\min \quad G_1 - \epsilon G_2 \tag{36}$$

s.t.

$$\sum_{a \in A} \gamma_{ia} = 1 \qquad \forall i \in I \tag{37}$$

$$\sum_{i \in I} \gamma_{ia} \leq l^{clinic} \qquad \forall i \in I \tag{38}$$

$$d_{ij} \leq l^{distance} + M(2 - \gamma_{ia} - \gamma_{ja}) \qquad \forall i, j \in I, a \in A \tag{39}$$

$$\sum_{i \in I} (u_i - u^{average})\gamma_{ia} \leq G_1 \qquad \forall a \in A \tag{40}$$

$$\sum_{i \in I} u_i^{abs} \gamma_{ia} \geq G_2 \qquad \forall a \in A \tag{41}$$

$$\gamma_{ia} \in \{0, 1\} \qquad \forall i \in I, a \in A \tag{42}$$

$$G_1, G_2 \geq 0 \tag{43}$$

Objective function (36) is formed by two parts. The first part is the primary objective and it minimizes the maximum total $u_i - u^{average}$ rate in an alliance. The second part is the secondary objective and it maximizes the minimum total u_i^{abs} rate in an alliance. Constraint (37) ensures each clinic only participates in one alliance. Constraint (38) limits the number of clinics in an alliance. Constraint (39) limits the distance between two clinics participating in the same alliance. Constraint (40) finds the maximum total $u_i - u^{average}$ rate among all alliances. Constraint (41) finds the minimum total u_i^{abs} rate among all alliances. The rest of the constraints are binary and non-negativity constraints.

After partitioning the clinics to form alliances, the problem should be solved for each alliance separately. However, even for an alliance with four clinics, the problem still would be a complex one, as shown in Table 3 and we are unable to obtain an optimal solution in a reasonable time. As a result, in the second step of the solution method, we reduce the complexity of the problem by fixing the only first stage decision C_s and solving the second stage of the problem for all specified transshipment sessions possibilities. For instance, if the number of sessions in a day is four and if we set the transshipment session limit c as two, then the possible transshipment sessions will be (1), (2), (3), (4), (1,2), (1,3), (1,4), (2,3), (2,4) (3,4). Solving the second stage problem for one transshipment possibility in an alliance approximately lasts for 15 seconds. After the second stage problem is solved for each transshipment possibility for each alliance, the possibility that performs the best is declared for each alliance according to the results. If an alliance has more than one transshipment possibility that perform the best, then we implement the following criteria. First, the transshipment possibility that forms the smallest union of transshipment sessions of all alliances is chosen. After this criteria, if we still have more than one possibility, we choose the possibility with the smallest expected number of transshipment performed. If this can also not leave us with one possibility, then we choose the possibility with the smallest expected number of doses transshipped. After these three criteria, if there is still more than one transshipment possibility for an alliance, we pick one randomly. Figure 14 provided in Appendix A shows the function of these criteria on an instance with two alliances. Figure 8 demonstrates our solution method with a flow chart.

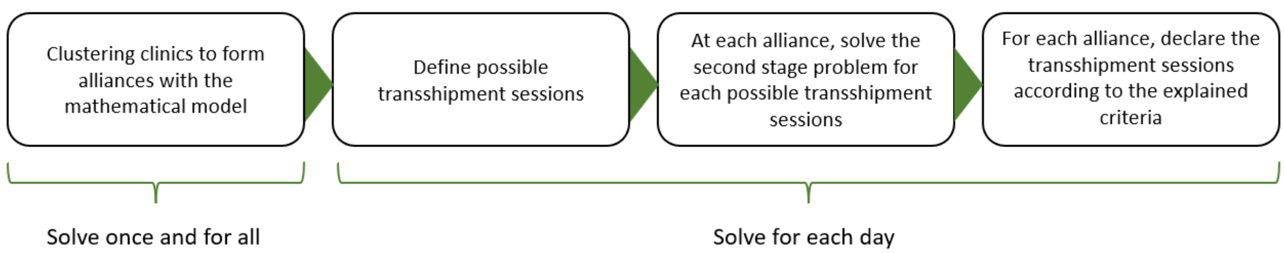

Figure 8: Steps of the solution method

CHAPTER VI

NUMERICAL STUDY

This section demonstrates how the case study data is generated based on the empirical study and interviews with experts. Also, a heuristic solution approach that provides quality solutions in a reasonable time for the case study instance is introduced.

6.1 Case Study

The case study is formed based on different data sources to create demand scenarios for each center as realistic as possible according to their size. The first data source is provided by a physician working at a family health center in the Tuzla district of Istanbul. This data contains coordinates and number of units information for all family health centers in the Tuzla district, and there are 24 family health centers in total. The number of units of a center is represented with n_i. Table 4 demonstrates the mentioned information for each center and Figure 9 illustrates their geographical position.

The second source is based on two questions asked in our empirical study survey provided in Chapter 2. These questions are Q3: "How many units are there in your family health center?" and Q6: "How many doses, on average, are administered on a busy day in your family health center?" as provided in Table 1. We utilize these two questions because we only have the number of units information for each center as provided in Table 4. Therefore, we need a value to represent the demand for each center based on their number of units. Based on the division of the answers given by the participants, we derive the information of *the average number of people vaccinated on a busy day per unit for each participant*. Additionally, if we average each participant's information, we find *the average number of people vaccinated on a*

Table 4: Information on family health centers

ID	X coordinates	Y coordinates	n_i
1	29.4161	40.9264	1
2	29.3298	40.8706	1
3	29.3413	40.8649	3
4	29.3001	40.8553	5
5	29.2974	40.8559	1
6	29.3065	40.8390	2
7	29.2978	40.8456	2
8	29.3049	40.8476	3
9	29.3210	40.8293	4
10	29.3360	40.8848	2
11	29.3082	40.8211	5
12	29.3602	40.8405	4
13	29.3545	40.8945	3
14	29.3787	40.9033	2
15	29.3616	40.8339	3
16	29.3565	40.8272	5
17	29.3077	40.8215	2
18	29.3218	40.8653	7
19	29.3921	40.9084	1
20	29.3153	40.8249	2
21	29.3140	40.8181	2
22	29.3569	40.8311	6
23	29.3091	40.8298	3
24	29.3062	40.8317	5

busy day per unit. However, we need a session based information, so we divide *the average number of people vaccinated on a busy day per unit* by the number of sessions in a day which is $|S|$, and obtain *the average number of people vaccinated on a busy day per unit per session*. We set $|S| = 9$ because family health centers are working for 9 hours per day, and we accept session length as an hour. The value for *the average number of people vaccinated on a busy day per unit per session* is found as **3** and represented with μ. If we multiply μ with n_i for each center, we attain *the average number of people vaccinated on a busy day per session* which is denoted as r_i. Since r_i provides the demand rate of a center at each session for a busy day, we can estimate that this value represents the maximum demand rate at a session that a center can encounter.

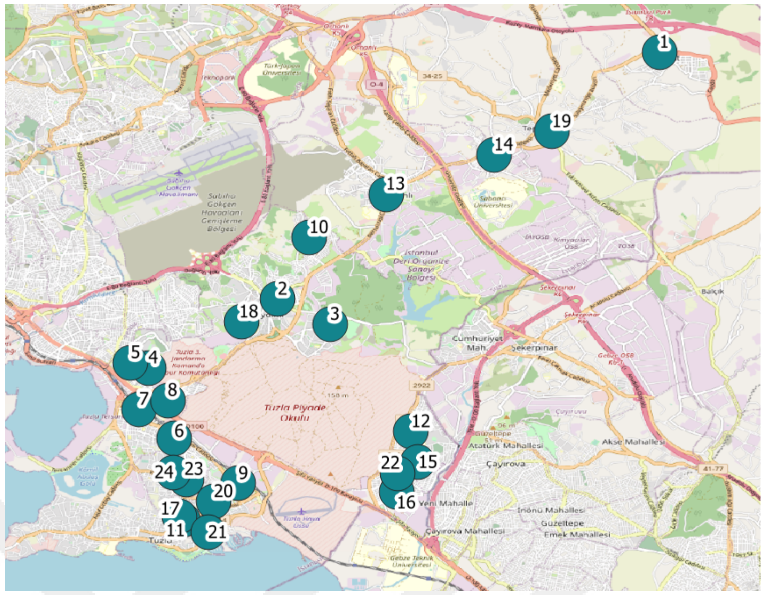

Figure 9: Family health centers on map

In the final step, We generate the appointment information, D_{is}, which is the number of appointments made for each session before the beginning of the day, and realized demand at each session and scenario, d_{isk}, which stands for the number of people who showed up for their appointment. To attain this information, we interviewed two family health practitioners in Istanbul to have approximate rates based on the expert knowledge for the appointment and no show percentages. In these interviews, we expressly ask them about the lowest, most likely, and highest observed percentages for occupancy and no show rates. Occupancy rates are used to create D_{is} because this rate indicates what percentage of the r_i is utilized through appointments made. No show rates are used to derive d_{isk} to specify what percentage of the D_is does not show up at each scenario. In addition, we want to examine the occupancy in terms of two different periods: high vaccination period and low vaccination period, because demand is not steady throughout the entire mass vaccination effort. It can be affected by the factors such as being at the beginning of the mass vaccination effort or a decrease in the number of positive cases and deaths. Based on these interviews, the values in Table 5 are obtained.

Table 5: Expert knowledge on occupancy and no show rates

Rate	Lowest	Most Likely	Highest
Occupancy rate during high vaccination	50%	70%	100%
Occupancy rate during low vaccination	0%	30%	100%
No show rate	0%	17%	30%

Using all information obtained, we apply the following algorithm to produce demand scenarios.

for each clinic i

for each session s

if high vaccination:

D_{is} = TRIA(0.5,0.7,1.0) r_i

else:

D_is = TRIA(0.0,0.3,1.0) r_i

for each scenario k:

$d_{isk} = D_{is}$ (1 - TRIA(0.0,0.17,0.3))

We perform a preliminary run on a computer with an Intel(R) Core(TM) i9-10980XE CPU @ 3.00GHz processor and a 128 GB RAM by using Gurobi 9.5.1 as the optimization tool on Python 3.9. According to this experiment, the 2-stage SP model cannot provide any solution, in four hours, for the network of 24 centers provided in the case study because considering all centers produces an extreme complexity. Since we need to have solutions delivered with the stochastic model, even with high a optimality gap, we obtain smaller case instances from the 24-center network. We name these smaller networks as north (**N**) and south (**S**) because we form them according to their geographical positions. This way, centers in the northern and southern part of the case study map will be separate networks of their own, and there will be two separate problems containing 12 centers. Figure 10 illustrates this separation on a map where the blue points represent the **N** network and the orange points represent the **S** network.

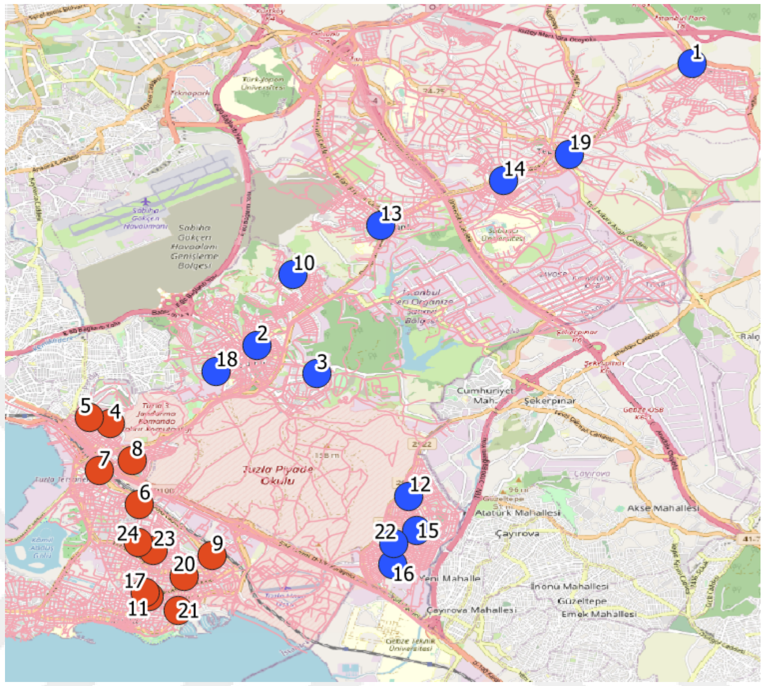

Figure 10: Two smaller networks: north (N) and south (S)

Furthermore, we created two demand instances containing 30 scenarios for each network: N-1, S-1, N-2, and S-2. Additionally, we expand the problem instances by considering two options for the distance threshold for alliances, transshipment policy, and lead time. For the distance threshold, which is the maximum allowed distance between two centers in an alliance, we consider ∞ km and 10 km, that is, in the first case, $l^{distance} = \infty$ km, and in the second case, $l^{distance} = 10$ km. For the transshipment policy, we investigate two different restrictions. The first restriction is the relaxed one in which the number of doses sent by a sender center can be less than or equal to the number of doses inside the open vial of the sender, meaning that optional constraints 24 and 25 are not added to the model. The second restriction is more strict, and the number of doses sent by a sender center must be equal to the number of doses inside the open vial of the sender, which means constraints 24 and 25 are added to the model. Finally, for the lead time, two options are taken into account as the lead time duration: one session and two sessions. Table 6 summarizes the options for each problem aspect to create instances considered. In total, we consider 32 instances.

Table 6: Aspects considered to create instances

Distance threshold	**Transshipment policy**	**Lead time**	**Network**
∞ km	Relaxed	1 session	N - 1
10 km	Strict	2 sessions	S - 1
			N - 2
			S - 2

In the following sections, we test these instances by using three solution methods. The first one is the 2-stage SP model. The second one is our heuristic solution approach described in Chapter 5, in which the network is first partitioned into alliances, with a mathematical model that balances the number of unit distribution in alliances and considers distance among centers, and the second stage of the 2-stage SP model is used to evaluate all transshipment session combinations. We name this heuristic approach as **H1**. The third method only differs from the H1 in forming the alliances, and the rest is the same. In the third method, alliances are formed randomly in contrast to the H1 where we use a mathematical model to form alliances. In the third method, distances among centers are also considered as in H1. We name the third method as **H2**. The reason behind testing the H2 is to analyze the performance of the H1's alliance forming approach. The methods are implemented on a computer with an Intel(R) Core(TM) i9-10980XE CPU @ 3.00GHz processor and a 128 GB RAM by using Gurobi 9.5.1 as the optimization tool on Python 3.9 and we impose a time limit of four hours.

6.2 Results

In this section, we demonstrate and evaluate the results produced with the case study. First, we present the results for solution methods under occupancy rate during low vaccination and compare their performances. Then, we provide the performances of the solution methods under occupancy rate during high vaccination. Finally, we observe the case study to produce valuable insights in terms of the effect of instances on the performance, session and transshipment relation, impact of the number of units on being the receiving and sending center, and performances of N and S networks.

6.2.1 Occupancy Rate During Low Vaccination

Before delving into the details of the results, we first introduce our performance metrics. As introduced earlier in Chapter 4, KPI-1 is the expected number of doses wasted over a day across all clinics, KPI-2 stands for the expected number of vials opened over a day across all clinics, and KPI-3 shows the expected number of transshipments made over a day.

Next, we analyze and discuss the results obtained through demand instances generated under occupancy rates during low vaccination provided in Table 5. These demand instances are for the networks N-1, S-1, N-2, and S-2, as indicated in Table 6. N-1 and N-2 are two different demand instances, both containing 30 scenarios and generated based on the network N. The same applies to S-1 and S-2 but for the network S. If these demand instances are realized in a system where transshipment is not practiced, and centers are isolated from each other, the results in Table 7 is obtained. In this table distance threshold, transshipment policy, and lead time aspects of Table 6 cannot be represented because these aspects are valid for a system that practices lateral transshipment.

Based on the performance of the no transshipment case, we introduce a new metric called **KPI-4** which is the expected number of doses saved from wastage relative to

Table 7: Performance of no transshipment

	No transshipment		
Network	KPI-1	KPI-2	KPI-3
N-1	34.5000	57.2000	0.0000
S-1	33.8333	56.1000	0.0000
N-2	32.1333	61.8000	0.0000
S-2	26.2667	54.9667	0.0000

Table 8: Performance metrics

Metric	**Definition**	**Formula**
KPI-1	Expected number of doses wasted over a day across all clinics	$\sum_{k\in K} p_k \sum_{i\in I} \sum_{s\in S} W_{isk}$
KPI-2	Expected number of vials opened over a day across all clinics	$\sum_{k\in K} p_k \sum_{i\in I} \sum_{s\in S} O_{isk}$
KPI-3	Expected number of transshipments made over a day	$\sum_{k\in K} p_k \sum_{i\in I} \sum_{i'\in I} \sum_{s\in S} Z_{ii'sk}$
KPI-4	Expected number of doses saved from wastage	(KPI-1 of no transshipment - KPI-1 of the method) + v (KPI-2 of no transshipment - KPI-2 of the method)

the performance of the no transshipment case. It is calculated based on the method's and no transshipment case's performance provided in Table 7. For KPI-4, we integrate both KPI-1 and KPI-2 because for each vial that is not opened, v doses are saved as, mentioned earlier. Thus, KPI-4 is the most significant indicator of the performance of a solution method due to its comprehensiveness, and methods should be compared based on this metric. Table 8 represents the performance metrics, and their definition and formulas.

Tables 9, 10, and 11 present the results obtained with methods 2-stage SP, H-1, and H-2 under 32 instances constructed based on the possibilities provided in Table 6. While obtaining results in Tables 9, 10 and 11 remaining parameters are set as c=2, v=6, ovl=6. That is, at most two sessions can be the transshipment sessions for a day, a vial contains six doses, and OVL lasts for six sessions.

As presented in Table 9, 2-stage SP cannot obtain solutions for more than half of the instances for a run time of four hours due to the complexity of the problem. In

Table 9: Performance of 2-stage SP

Distance threshold	Policy	Lead time	Network	2 - stage SP KPI-1	KPI-2	KPI-3	KPI-4	Solution time (sec.)	Gap
∞ km	Relaxed	1 session	N-1	6.9000	52.6000	4.7000	55.2000	14436.0142	90.82%
			S-1	9.2333	52.0000	5.3000	49.2000	14406.1116	82.72%
			N-2	-	-	-	-	-	-
			S-2	14.8667	53.0667	2.0667	22.8000	14401.4096	89.48%
		2 sessions	N-1	13.9000	53.7667	3.5333	41.2000	14405.9448	30.24%
			S-1	21.0333	53.9667	2.4000	25.6000	14408.9567	25.00%
			N-2	11.7333	58.4000	3.5333	40.8000	14414.3810	62.45%
			S-2	14.6667	53.0333	2.0667	23.2000	14408.6977	24.11%
	Strict	1 session	N-1	-	-	-	-	-	-
			S-1	-	-	-	-	-	-
			N-2	-	-	-	-	-	-
			S-2	-	-	-	-	-	-
		2 sessions	N-1	-	-	-	-	-	-
			S-1	-	-	-	-	-	-
			N-2	-	-	-	-	-	-
			S-2	-	-	-	-	-	-
10 km	Relaxed	1 session	N-1	6.9000	52.6000	4.7000	55.2000	14436.0142	90.82%
			S-1	9.2333	52.0000	5.3000	49.2000	14406.1116	82.72%
			N-2	-	-	-	-	-	-
			S-2	14.8667	53.0667	2.0667	22.8000	14401.4096	89.48%
		2 sessions	N-1	13.9000	53.7667	3.5333	41.2000	14405.9448	30.24%
			S-1	21.0333	53.9667	2.4000	25.6000	14408.9567	25.00%
			N-2	11.7333	58.4000	3.5333	40.8000	14414.3810	62.45%
			S-2	14.6667	53.0333	2.0667	23.2000	14408.6977	24.11%
	Strict	1 session	N-1	-	-	-	-	-	-
			S-1	-	-	-	-	-	-
			N-2	-	-	-	-	-	-
			S-2	-	-	-	-	-	-
		2 sessions	N-1	-	-	-	-	-	-
			S-1	-	-	-	-	-	-
			N-2	-	-	-	-	-	-
			S-2	-	-	-	-	-	-

Table 10: Performance of H1

Distance threshold	Policy	Lead time	Network	H1 KPI-1	H1 KPI-2	H1 KPI-3	H1 KPI-4	H1 Solution time (sec.)
∞ km	Relaxed	1 session	N-1	13.3000	53.6667	4.1333	42.4000	2298.9748
			S-1	15.6333	53.0667	4.0000	36.4000	1780.5125
			N-2	12.1333	58.4667	3.9000	40.0000	2235.3192
			S-2	18.2667	53.6333	1.4000	16.0000	1791.2717
		2 sessions	N-1	18.9000	54.6000	3.2000	31.2000	1339.5216
			S-1	22.6333	54.2333	2.5667	22.4000	1533.2993
			N-2	13.9333	58.7667	3.4667	36.4000	1341.8657
			S-2	18.2667	53.6333	1.4000	16.0000	1686.1814
	Strict	1 session	N-1	22.9000	55.2667	2.8333	23.2000	1844.8400
			S-1	27.2333	55.0000	1.4667	13.2000	1850.5634
			N-2	17.5333	59.3667	2.9667	29.2000	1854.4452
			S-2	20.0667	53.9333	1.3000	12.4000	1911.8231
		2 sessions	N-1	24.9000	55.6000	2.8000	19.2000	1372.9724
			S-1	29.6333	55.4000	0.8333	8.4000	1388.8004
			N-2	19.5333	59.7000	3.0667	25.2000	1380.4078
			S-2	20.6667	54.0333	1.9000	11.2000	1459.9217
10 km	Relaxed	1 session	N-1	16.7000	54.2333	3.1333	35.6000	1784.7295
			S-1	15.6333	53.0667	4.0000	36.4000	1780.5125
			N-2	16.9333	59.2667	3.2667	30.4000	1802.0792
			S-2	18.2667	53.6333	1.4000	16.0000	1791.2717
		2 sessions	N-1	22.1000	55.1333	2.3000	24.8000	1493.1911
			S-1	22.6333	54.2333	2.5667	22.4000	1533.2993
			N-2	18.9333	59.6000	2.7000	26.4000	1722.7045
			S-2	18.2667	53.6333	1.4000	16.0000	1686.1814
	Strict	1 session	N-1	27.9000	56.1000	1.5667	13.2000	1846.4739
			S-1	27.2333	55.0000	1.4667	13.2000	1850.5634
			N-2	22.3333	60.1667	2.1000	19.6000	1877.0108
			S-2	20.0667	53.9333	1.3000	12.4000	1911.8231
		2 sessions	N-1	30.5000	56.5333	1.0000	8.0000	1382.3706
			S-1	29.6333	55.4000	0.8333	8.4000	1388.8004
			N-2	24.1333	60.4667	1.6333	16.0000	1428.2043
			S-2	20.6667	54.0333	1.9000	11.2000	1459.9217

Table 11: Performance of H2

Distance threshold	Policy	Lead time	Network	H2 KPI-1	H2 KPI-2	H2 KPI-3	H2 KPI-4	H2 Solution time (sec.)
∞ km	Relaxed	1 session	N-1	21.9000	55.1000	3.5000	25.2000	1759.4151
			S-1	20.0333	53.8000	3.1333	27.6000	1773.4669
			N-2	20.7333	59.9000	2.5333	22.8000	1800.6257
			S-2	19.8667	53.9000	1.7000	12.8000	1767.9497
		2 sessions	N-1	26.5000	55.8667	2.2333	16.0000	1303.6594
			S-1	26.0333	54.8000	1.6667	15.6000	1514.3815
			N-2	22.7333	60.2333	2.4333	18.8000	1316.6414
			S-2	20.2667	53.9667	1.6000	12.0000	1557.6663
	Strict	1 session	N-1	32.9000	56.9333	0.3667	3.2000	1782.2470
			S-1	27.2333	55.0000	1.8000	13.2000	1845.9502
			N-2	25.9333	60.7667	1.1000	12.4000	1796.9714
			S-2	22.6667	54.3667	0.8667	7.2000	1852.8894
		2 sessions	N-1	33.3000	57.0000	0.2333	2.4000	1347.1623
			S-1	29.2333	55.3333	1.0667	9.2000	1388.0180
			N-2	26.7333	60.9000	0.9000	10.8000	1345.6170
			S-2	22.8667	54.4000	0.8000	6.8000	1409.1928
10 km	Relaxed	1 session	N-1	17.5000	54.3667	3.0000	34.0000	1794.0749
			S-1	20.0333	53.8000	3.1333	27.6000	1773.4669
			N-2	15.5333	59.0333	3.5000	33.2000	1814.5548
			S-2	19.8667	53.9000	1.7000	12.8000	1767.9497
		2 sessions	N-1	22.7000	55.2333	2.1667	23.6000	1333.2937
			S-1	26.0333	54.8000	1.6667	15.6000	1514.3815
			N-2	17.5333	59.3667	2.9333	29.2000	1348.9522
			S-2	20.2667	53.9667	1.6000	12.0000	1557.6663
	Strict	1 session	N-1	27.7000	56.0667	1.5000	13.6000	1821.9056
			S-1	27.2333	55.0000	1.8000	13.2000	1845.9502
			N-2	22.7333	60.2333	2.0333	18.8000	1839.1731
			S-2	22.6667	54.3667	0.8667	7.2000	1852.8894
		2 sessions	N-1	30.3000	56.5000	1.0333	8.4000	1357.6807
			S-1	29.2333	55.3333	1.0667	9.2000	1388.0180
			N-2	24.1333	60.4667	1.6333	16.0000	1372.4482
			S-2	22.8667	54.4000	0.8000	6.8000	1409.1928

instances for which 2-stage SP provides solutions, significantly large optimality gaps occurred. Additionally, for instances having ∞ km and 10 km distance threshold options, the results are the same because the distance threshold is only valid for heuristic approaches H1 and H2 which form alliances while considering the distance between the centers. Since 2-stage SP does not form alliances, variations in distance threshold are not valid for 2-stage SP. For the instances that produce results, 2-stage SP always performs better compared to our heuristic approaches, H1 and H2, in terms of the expected number of doses saved (KPI-4). On average, the expected doses saved is 36.8571 for 2-stage SP, and it provides, on average, 58.28% of less number of doses wasted (KPI-1) and 5.40% of less number of vials opened (KPI-2). At instances for which 2-stage SP produced results, the expected number of doses saved is 28.6857 for H1 and 18.2857 for H2. Moreover, on average, we have 42.74% and 31.94% of less number of doses wasted, and 3.96% and 2.96% of less number of vials opened when H1 and H2 methods are used, respectively. By looking at these generic results, we can claim that performance of the methods can be ordered as 2-stage SP > H1 > H2. However, due to the complexity of the problem, we cannot rely on 2-stage SP as it could not provide solutions for more than half of the instances even with a run time of four hours. As it is observed, 2-stage SP cannot produce solutions for the instances at which the transshipment policy is strict because we incorporate constraints 34 and 35, which makes the problem even more complex. Therefore, this gives the impression of validity of the 2-stage SP when a relaxed transshipment policy is implemented. Nevertheless, even with a relaxed transshipment policy, when the lead time is one session, and the demand instance is North-2, 2-stage SP cannot produce a solution in four hours. Therefore we need a solution method that we can rely on in terms of the quality of the solution and the solution time, such as H1 and H2. Although H1 outperforms H2 with the previously given generic results, we need to examine them in more detail.

Table 12: Comparing heuristic methods H1 and H2

Distance threshold	Policy	Lead time	Network	KPI-4 H1	KPI-4 H2	Solution time (sec.) H1	Solution time (sec.) H2
∞ km	Relaxed	1 session	N-1	42.4000	25.2000	2298.9748	1759.4151
			S-1	36.4000	27.6000	1780.5125	1773.4669
			N-2	40.0000	22.8000	2235.3192	1800.6257
			S-2	16.0000	12.8000	1791.2717	1767.9497
		2 sessions	N-1	31.2000	16.0000	1339.5216	1303.6594
			S-1	22.4000	15.6000	1533.2993	1514.3815
			N-2	36.4000	18.8000	1341.8657	1316.6414
			S-2	16.0000	12.0000	1686.1814	1557.6663
	Strict	1 session	N-1	23.2000	3.2000	1844.8400	1782.2470
			S-1	13.2000	13.2000	1850.5634	1845.9502
			N-2	29.2000	12.4000	1854.4452	1796.9714
			S-2	12.4000	7.2000	1911.8231	1852.8894
		2 sessions	N-1	19.2000	2.4000	1372.9724	1347.1623
			S-1	8.4000	9.2000	1388.8004	1388.0180
			N-2	25.2000	10.8000	1380.4078	1345.6170
			S-2	11.2000	6.8000	1459.9217	1409.1928
10 km	Relaxed	1 session	N-1	35.6000	34.0000	1784.7295	1794.0749
			S-1	36.4000	27.6000	1780.5125	1773.4669
			N-2	30.4000	33.2000	1802.0792	1814.5548
			S-2	16.0000	12.8000	1791.2717	1767.9497
		2 sessions	N-1	24.8000	23.6000	1493.1911	1333.2937
			S-1	22.4000	15.6000	1533.2993	1514.3815
			N-2	26.4000	29.2000	1722.7045	1348.9522
			S-2	16.0000	12.0000	1686.1814	1557.6663
	Strict	1 session	N-1	13.2000	13.6000	1846.4739	1821.9056
			S-1	13.2000	13.2000	1850.5634	1845.9502
			N-2	19.6000	18.8000	1877.0108	1839.1731
			S-2	12.4000	7.2000	1911.8231	1852.8894
		2 sessions	N-1	8.0000	8.4000	1382.3706	1357.6807
			S-1	8.4000	9.2000	1388.8004	1388.0180
			N-2	16.0000	16.0000	1428.2043	1372.4482
			S-2	11.2000	6.8000	1459.9217	1409.1928

Table 12 provides the expected number of doses saved from wastage results and run times for H1 and H2. Both methods have similar run times. H1 solutions take 1681.558 seconds, on average, which is approximately 28 minutes. Whereas H2 solutions last for 1604.7954 seconds, equivalent to approximately 27 minutes. As the run times are significantly close, we do not consider them as an indicator of choosing the best method. Moreover, among 32 instances, H1 performs better in 25 of them compared to H2. The success of H1 is the mathematical model used to partition the centers according to their number of units, which represents the demand rate. This approach creates a balanced environment in each alliance, increasing the possibility of transshipment. Since more transshipment means more doses saved according to the logic of the problem, H1 performs better in general. The reason behind the other 7 instances for which the H2 performs better is the distance threshold and the demand structure. In 6 out of 7 these instances, the distance threshold is 10 km. When the distance threshold is 10 km, H2 happens to have a similar number of units distribution among alliances as in H1. Besides, since H1 is formed solely on the number of units information, and the number of units alone is not sufficient for truly representing the demand structure, H2 outperformed the H1 in a small portion of the instances. Daily demand structures might be also utilized while forming the alliances if alliance forming is practiced every day, meaning, on each day, new alliances are formed. Since we choose the form alliances once and for all, independent from the daily demand, we can only consider the number of units information. Finally, due to the significant success of H1 in most of the instances and its acceptable run time, we can say that H1 can be relied upon for solving the problem and utilized as the main solution method.

In the next section, we investigate the system behavior in detail to gain valuable insights by using the results obtained through H1 which provided better solutions in general.

6.2.2 System Behavior

In this section, we analyze the behavior of the system in terms of the effect of instance conditions on the system performance, the relation between sessions and transshipment, the impact of the number of units in a center on sending and receiving in transshipment, and performances of N and S networks by using the results obtained with H1 method.

First, we examine how the instance aspects, distance threshold, lead time, and transshipment policy affect the system performance. In Table 13, we show the averaged expected doses saved value of N-1, S-1, N-2, and S-2 demand instances under the examined instance aspects. According to the expected number of doses saved (KPI-4) on average values:

- When the distance threshold is set as ∞, it produces better performance compared to when the distance threshold is 10 km. That is, when there is no upper limit for the distance between two centers in an alliance, the system performs better. The reason for that is the mathematical model used to form alliances in H1 becomes more relaxed to construct a balanced environment in terms of the number of units because there is no upper limit distance restriction while forming the alliances.

- Moreover, instances in which the lead time is one session produced better results compared to the instances in which the lead time is two sessions because when the lead time is one session, there is one extra session for receiving center to consume the received doses compared to the two sessions as the lead time. Consequently, this extra session triggers the relatively more consumption of the transshipped doses and decreases the expected number of doses wasted and vials opened more when the lead time is one session. Thus, as the lead time decreases, the system performs better regarding the number of doses saved. So,

Table 13: Effect of instances on the system performance

Distance threshold	Policy	Lead time	KPI-4 (on average)
∞ km	Relaxed	1 session	33.7000
		2 sessions	26.5000
	Strict	1 session	19.5000
		2 sessions	16.0000
10 km	Relaxed	1 session	29.6000
		2 sessions	22.4000
	Strict	1 session	14.6000
		2 sessions	10.9000

transshipment decisions made under no distance upper limit for alliances and shorter lead time generate better solutions.

- However, after the transshipment decision is made, the transshipment process that motorcycle couriers perform will be challenging with a larger distance between centers and a smaller lead time for transporting vials on time. To prevent complexity, we assume that this part is out of the scope of our problem and present a presumptive coverage constraint for courier movements in constraint 33. However, the transshipment process should not be ignored and must be studied further to achieve the successful transportation of vials to centers on time. As a preliminary step for this study, we present a courier routing model that emphasizes and resolves several problem aspects in Appendix B.

- Furthermore, implementing a relaxed transshipment policy improves system performance with more expected doses saved compared to a strict transshipment policy. That is, when centers can send less number of doses than the quantity inside the open vial, instead of being forced to send all open vial content, we obtain better results.

Next, we discuss the impact of the number of units of a center on sending or receiving in a transshipment. Figure 11 presents the relation between the number of units of a center and the total expected number of times it becomes the sender in a transshipment. The same applies to Figure 12 but for becoming the receiver in a transshipment. The values are calculated by the summation of metrics across all instances. As we point out previously, Figure 11 shows that centers with a smaller number of units tend to send more in transshipment since their low demand rate becomes unable to consume all doses inside open vials more frequently. Additionally, when the number of units becomes more than two, the total expected number of times being a sender value decreases rapidly and does not differ significantly. Therefore, we can state that presence of centers having one or two units in an alliance is crucial for better results because there must be a sending clinic for transshipments to occur. Because transshipment occurs only when there is a chance of preventing the doses from being wasted and as the number of transshipments increases the wastage will decrease. Figure 12 demonstrates that there is no remarkable relation between the number of units and being the receiver center if the number of units is more than one. For centers with one unit, we observe that the total expected number of times being a receiver center is almost zero. Therefore, the presence of centers with more than one unit in alliances is also crucial for better transshipment performance. Additionally, in Figure 12, we observe two outlier values, one having two units and the other having three units. When we examine the centers that produce these outlier results by investigating the structure of the alliances they are in, we see that alliances of these centers contain more centers having one or two units compared to other alliances. Since having centers with one or two units is the indicator for sending more in transshipment, these outlier centers utilize this situation and receive more compared to other centers.

Finally, we compare the transshipment performance of the N and S networks. For the comparison, we sum the expected number of transshipments values across all instances in accordance with being in the N or S networks. Figure 13 displays the percentage of total expected transshipment performed in the N and S. As the pie

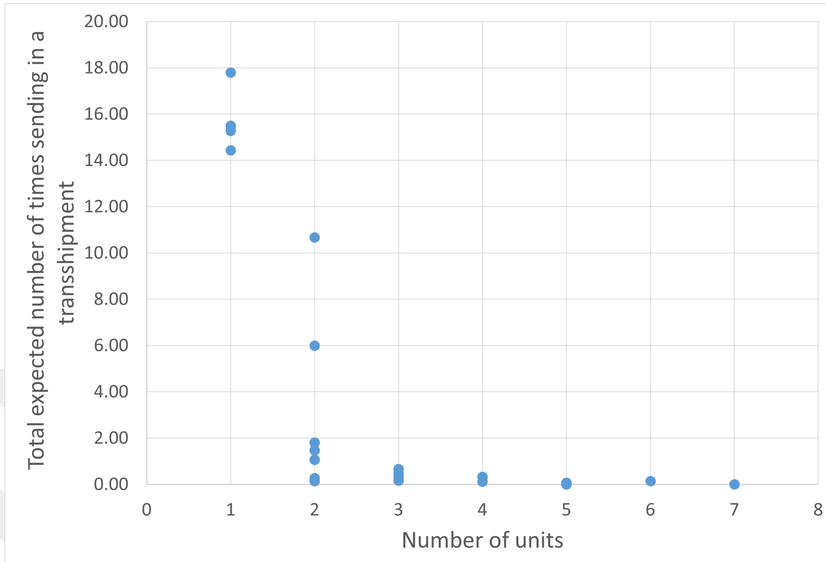

Figure 11: Impact of number of units on sending

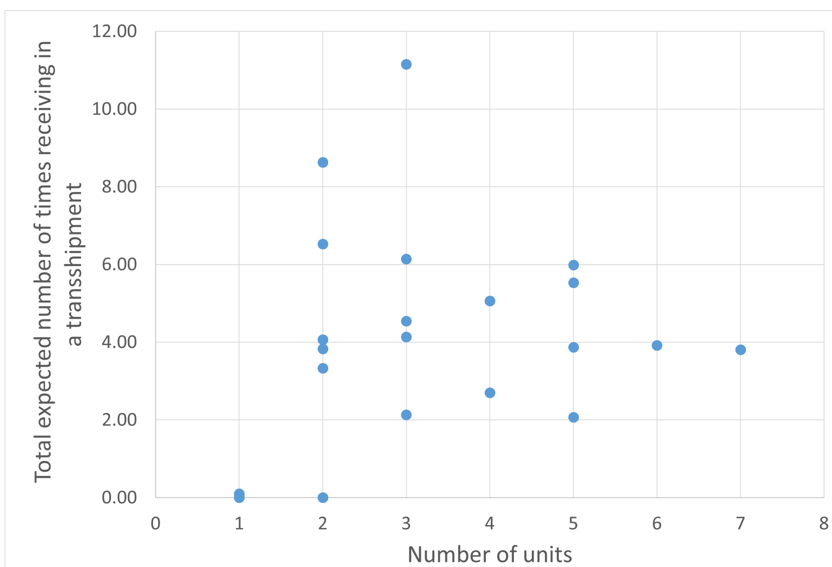

Figure 12: Impact of number of units on receiving

chart indicates, more transshipment is performed in the N than in the S. When we analyze the centers and alliances in these networks, we see that three centers having one unit and two centers having two units in the N, and one center having one unit and five centers having two units in the S. As shown in Figure 11, centers having less than or equal to two units play a crucial role in transshipment as the sending center, and the N network has five, whereas the S network has six of those clinics having less than or equal to two units. Looking at these numbers, we expect similar performance for the cases, but the N performs better. The reason for the superiority of the N in terms of the total expected number of transshipment is that the N has more centers having one unit, and centers having one unit explicitly sends more than centers having two units. Because of this situation, centers in the N network take the advantage of having more centers with one unit and perform more transshipment compared to the centers in the N network.

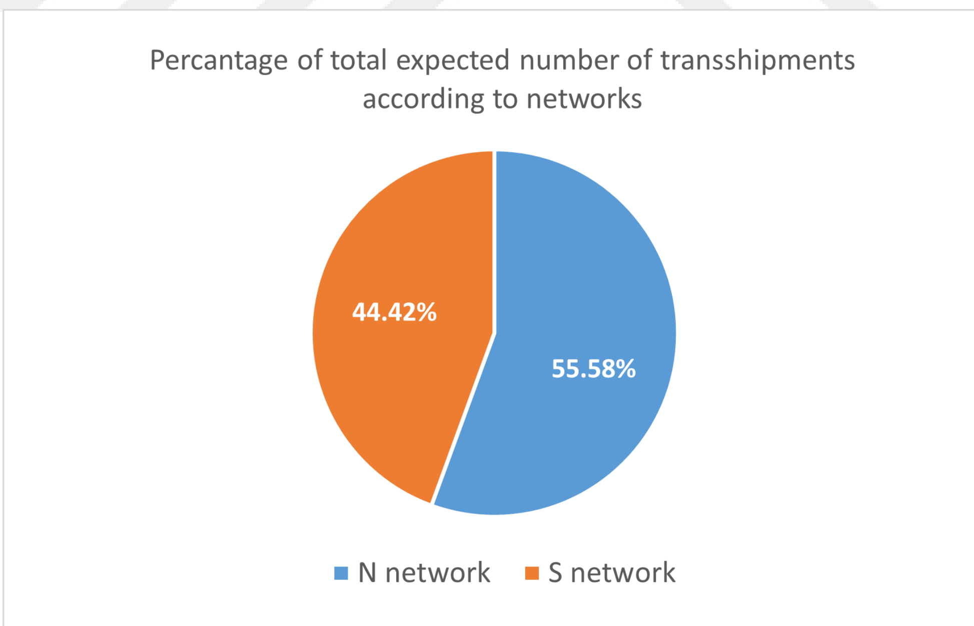

Figure 13: Transshipment performances of the networks

6.2.3 Occupancy Rate During Low Vaccination

When we implement our solution methods under the demand scenarios which are generated by occupancy rates during high vaccination as provided in Table 5, we notice that our solution methods do not produce fewer OVW and vial openings compared to a system where no transshipment occurs. That is, our solution methods become unnecessary. The reason behind this originates from the constraints 22 and 23, in which conditional transshipment is enforced. According to the condition, if a clinic cannot consume the doses inside the open vial with upcoming demand during the OVL of the doses, then the clinic becomes able to send its doses to another clinic. Otherwise, if the doses can be consumed with the upcoming demand, transshipment is prohibited. Since occupancy rates during high vaccination create higher demand rates, it causes dissatisfaction with the transshipment condition, and no transshipment occurs. If transshipment cannot be practiced, we cannot attain less wastage and vial openings compared to the no transshipment case. Thus, we can claim that our solution methods become useless for the periods in which high vaccination rates are observed.

CHAPTER VII

CONCLUSION AND FUTURE WORK

In this study, we address the problem of reducing OVW during the COVID-19 vaccine administration process. We focus on the mass vaccination efforts held in family health centers in Turkey and describe the vaccination operations in these centers in detail. We conduct an empirical study as a motivating force in which we collaborate with healthcare professionals working in family health centers. According to the survey, which is the main body of our empirical study, we discover that OVW and the current practices to prevent it are the most serious challenges faced in vaccine administration. Additionally, we find that performing lateral transshipment between clinics is the only reasonable practice to decrease OVW.

Consequently, we define a new problem in which lateral transshipment is implemented in a network of clinics to decrease OVW. Since we accept the possibility of appointment no shows, we formulate the problem as a 2-stage SP model. Due to the complexity of the problem, we provide two heuristic approaches. The main approach, H1, partition the network into smaller networks called alliances with a Mathematical model and then solves the problem for each alliance with the second stage of the 2-stage SP for each possible transshipment combination. The second approach, H2, is an extension of the first one in which the network is partitioned randomly.

Moreover, we present a case study based on the 24 family health centers in Tuzla, Istanbul. We obtain the number of units and location information for the centers. Then we synthesize these with our findings from the empirical study and interviews with health care practitioners the create demand instances. We generate 32 instances by considering two options for three problem aspects and demand instances. Due to the complexity of the problem, 2-stage SP is unable to provide solutions for more than half of the instances. Therefore we cannot rely on its observable success. Our heuristic approach H1 performs efficiently and provides quality solutions in an acceptable amount of time and performs better compared to H2. Thus, we use H1 as the primary solution method for further analysis of the proposed problem.

We conduct a detailed analysis to produce critical insights in respect of the system behavior. The system saves more doses from wastage by performing more transshipment if no distance restriction between clinics is enforced in alliances, centers can send fewer doses than the open vial content, and the lead time is short. In addition, small centers become the sender clinic for almost all transshipment, and larger centers act as a receiver center, in general. Therefore, the balance of units in alliances plays a key role to perform more transshipment and, relatedly, decrease OVW more. Our numerical analysis also reveals that our solution methods are suitable for using in periods with low vaccination rates but become unnecessary to use during periods with high vaccination rates.

The extensions of this work for further study are fourfold. Firstly, the out-of-scope concepts of our study, early shows, and late shows can be addressed for a more realistic representation of the demand. Secondly, a more elaborate heuristic approach can be developed using meta-heuristics and search methods to obtain better solutions. This study produces results and insights based on a specific case study of COVID-19 mass vaccination efforts held in family health centers. Future research can address the adaptation of the problem to other vaccine administration settings to verify its validity for several settings and cases. These settings can include different and/or multiple vaccine types, different causes such as childhood immunization, or combinations of varying vial presentations. Finally, future research can also focus on increasing the current practicality by delving into details of the transshipment process with courier movements that occurs after the transshipment decision. For the sake of simplicity, we did not incorporate this problem into our study and provide a preliminary courier routing model in Appendix B. This potential study can further develop this model by incorporating several more realistic aspects and evaluating its performance on real problem instances. In addition, the courier routing problem might be integrated into our problem, while preventing the increase in complexity, to give decisions from a broader perspective.

Appendix A. Selection of the best transshipment possibility for an alliance

Alliance	Possible transshipment sessions	Expected number of transshipment	Expected number of doses transshipped
1	2 and 5	3.5	4.2
2	2	2.4	3.6
	5	2.4	3.2
	2 and 5	2.8	3.5
	3 and 4	2.1	2.9

Eliminate 3 and 4 due to not forming the smallest union

Alliance	Possible transshipment sessions	Expected number of transshipment	Expected number of doses transshipped
1	2 and 5	3.5	4.2
2	2	2.4	3.6
	5	2.4	3.2
	2 and 5	2.8	3.5

Eliminate 2 and 5 due to greater expected number of transshipment

Alliance	Possible transshipment sessions	Expected number of transshipment	Expected number of doses transshipped
1	2 and 5	3.5	4.2
2	2	2.4	3.6
	5	2.4	3.2

Eliminate 2 due to greater expected number of doses transshipped

Alliance	Possible transshipment sessions	Expected number of transshipment	Expected number of doses transshipped
1	2 and 5	3.5	4.2
2	5	2.4	3.2

Figure 14: Selection of the best transshipment possibility for an alliance

Appendix B. Courier Routing Model

The problem addresses the routing of the couriers whose movements between clinics yield the successful transportation of the transshipped vials. The problem is solved at each transshipment session based on the solution provided by the VTP. According to these solutions, which clinic will make a transshipment to which clinic is known for the current session. Based on this information, the courier routing problem tries to realize as many transshipments as possible while minimizing the courier usage and total travel time. The main decisions of the problem include deciding on which transshipment decision to realize, which couriers to use, and visiting sequence of clinics on the routes of the used couriers.

In the problem, each courier has a starting clinic location at the beginning which is their final stop in the previous transshipment session. So there is no fixed location for couriers to start their routes. This factor plays a key role in the decision because total transshipment and courier usage should be minimized. Therefore, a courier who is located at a remote clinic at the beginning is less likely to be used if there is no transshipment decision regarding its surrounding clinic. Additionally, a courier can finalize its route at any clinic as long as it compromises with the objective and the constraints, and this final stop will be the starting clinic in the next transshipment session. This aspect is the first significant aspect of the problem and it resembles an open VRP. Open VRP is first introduced by Sariklis and Powell [33] as an extension of VRP in which vehicles do not have to start and end their routes at one fixed location such as a depot.

Another significant aspect of the problem stems from the transshipment directions. Unlike classical VRPs, the courier routing problem should act according to the direction of the transshipment. That is, a courier cannot visit clinics along its route just by considering the travel time. Routes of the couriers must also be performed so that the sender clinic in a transshipment should be visited before the receiver clinic in that transshipment because the courier should first pick up the sender clinic's open vial. Lu and Dessouky [34] study a multiple vehicle pickup and delivery problem such that pickup locations must be visited before the delivery locations as in our problem.

The last significant aspect of the problem is the time limit issue and the trade-off that comes alongside it. As we specified in the VTP, there is a lead time for the transshipment to be performed and the receiving clinics can start to use received doses after this lead time. Therefore, each courier route performed must last shorter than the lead time. This time limit issue creates a trade-off between the number of transshipment realized and the number of couriers used. Since there is a time limitation for routes, either more couriers should be used for more transshipment to be realized or fewer couriers will be used which will fail some transshipment. The decision-makers should decide on the importance of these aspects so that they can modify the coefficients θ_1 and θ_2 which value them. Alp et al. [35] examine a similar trade-off between satisfying the demand on time and the number of vehicles used, and how it is affected by the lead time.

To the best of our knowledge, no other study in the literature focuses on open VRP, visiting sequence due to pickup and delivery, and the effect of the lead time on the trade-off between demand satisfaction and resource usage at the same time. Additionally, we are the first to consider these aspects in a vaccine transshipment setting. In the following, we provide the problem formulation.

Sets:

I: set of clinics, $i \in I$

V: set of motorcycle couriers, $v \in V$

Parameters:

B_{ij}: 1, if there is a transshipment request from clinic i to j; 0, otherwise

H_{vi}: 1, if courier v is at clinic i at the beginning; 0, otherwise

T_{ij}: travel time from clinic i to j; 0, otherwise

L_{time}: maximum route duration

Decision Variables:

w_v: 1, if courier v is used; 0, otherwise

x_{ij}: 1, if transshipment from clinic i to j is actualized; 0, otherwise

y_{ij}: 1, if transshipment from clinic i to j is failed; 0, otherwise

z^1_{vij}: 1, if transshipment from clinic i to j is performed by courier v; 0, otherwise

z^2_{vij}: 1, if courier v visits clinic i after clinic j; 0, otherwise

f_{vi}: 1, if clinic i is the final stop of courier v; 0, otherwise

s_{vi}: variable used for sub-tour elimination and visit sequences

$$\min \quad \theta_1 \sum_{i\in I}\sum_{j\in I} y_{ij} + \theta_2 \sum_{v\in V} w_v + \theta_3 \sum_{v\in V}\sum_{i\in I}\sum_{j\in I} T_{ij} z^2_{vij} \tag{44}$$

s.t.

$$x_{ij} + y_{ij} = B_{ij} \qquad \forall i,j \in I \tag{45}$$

$$\sum_{v\in V} z^1_{vij} = x_{ij} \qquad \forall i,j \in I \tag{46}$$

$$z^1_{vij} \le w_v \qquad \forall i,j \in I, v \in V \tag{47}$$

$$z^2_{vij} \le w_v \qquad \forall i,j \in I, v \in V \tag{48}$$

$$\sum_{i\in I} f_{vi} = 1 \qquad \forall v \in V \tag{49}$$

$$f_{vi} \le w_v + H_{vi} \qquad \forall i \in I, v \in V \tag{50}$$

$$\sum_{j\in I} z^2_{vij} \ge w_v H_{vi} \qquad \forall i \in I, v \in V \tag{51}$$

$$\sum_{j\in I} z^2_{vji} \le 1 - H_{vi} \qquad \forall i \in I, v \in V \tag{52}$$

$$\sum_{j\in I} z^2_{vji} \le \sum_{j\in I} z^2_{vij} + f_{vi} \qquad \forall i \in I, v \in V \tag{53}$$

$$2z^1_{vij} \leq H_{vi} + \sum_{p\in I}(z^2_{vip} + z^2_{vpi}) \qquad \forall i,j \in I, v \in V \tag{54}$$

$$2z^1_{vij} \leq f_{vi} + \sum_{p\in I}(z^2_{vjp} + z^2_{vpj}) \qquad \forall i,j \in I, v \in V \tag{55}$$

$$s_{vi} - s_{vj} \leq M(1 - z^1_{vij}) - 1 \qquad \forall i,j \in I, i \neq j, v \in V \tag{56}$$

$$s_{vi} - s_{vj} + |I|z^2_{vij} \leq |I| - 1 \qquad \forall i,j \in I, i \neq j, v \in V \tag{57}$$

$$s_{vj} \leq s_{vi} + M(1 - f_{vi}) \qquad \forall i,j \in I, i \neq j, v \in V \tag{58}$$

$$\sum_{i\in I}\sum_{J\in I} T_{ij} z^2_{vij} \leq L^{time} \qquad \forall v \in V \tag{59}$$

$$z^2_{vii} \leq 0 \qquad \forall i \in I, v \in V \tag{60}$$

$$w_v \in \{0,1\} \qquad \forall v \in V \tag{61}$$

$$x_{ij}, y_{ij} \in \{0,1\} \qquad \forall i,j \in I \tag{62}$$

$$f_{vi} \in \{0,1\} \qquad \forall v \in V, i \in I \tag{63}$$

$$z^1_{vij}, z^2_{vij} \in \{0,1\} \qquad \forall v \in V, i,j \in I \tag{64}$$

$$s_{vi} \geq 0 \qquad \forall v \in V, i \in I \tag{65}$$

The objective function (44) consists of two parts: primary and secondary. The primary part minimizes the total failed transshipment and its coefficient has a significantly higher value compared to the coefficients of the secondary part. The secondary part minimizes the number of couriers used and the total travel time and their coefficients have significantly low values. Constraint (45) states if there is a transshipment request from clinic i to j, it will either be actualized or failed. Constraint (46) ensures if transshipment i to j is actualized, it is performed by one courier. Constraint (47) assures if courier v is not used, it cannot be assigned to perform a transshipment. Constraint (48) provides if courier v is not used, it cannot make a route. Constraint (49) remarks that each courier should have one final stop. Constraint (50) states if courier v is not used, its final stop is its clinic at the beginning. Constraint (51) enforces that a courier that is used should travel to one clinic from its clinic at the beginning. Constraint (52) indicates that a courier's clinic location at the beginning must be the starting stop in its route. Constraint (53) ensures if courier v travels to clinic i from some other clinic, it should also travel to another clinic from clinic i unless clinic i is its final stop. Constraints (54), (55) state if vehicle v performs transshipment from i to j, then clinics i and j should be in its route. Constraint (56) provides if transshipment is from i to j, then j should be visited after visiting i. Constraint (57) is the sub-tour elimination constraint. Constraint (58) assures if clinic i is the final stop, then it should be visited the last. Constraint (59) limits the total route time of each courier. Constraint (60) implies that after visiting clinic i, clinic i cannot be the next visited stop. The rest of the constraints are binary and non-negativity constraints.

We conduct a preliminary experiment to validate our formulation. We create a synthetic instance with six clinics where the average travel time between clinics is 6.63 minutes, and three couriers are present. We assume three transshipment requests (from Clinic 3 to Clinic 1, from Clinic 4 to Clinic 3, and from Clinic 5 to Clinic 2) are made. Coefficient θ_3 is given a significantly small value compared to θ_1 and θ_2. The aim of the experiment is to demonstrate the effects of coefficients θ_1 and θ_2, and parameter L_{time} on the results obtained. We analyze different θ_1 and θ_2 values because we want to emphasize the previously mentioned trade-off between the number of transshipment requests realized and the number of couriers used. The reason for examining L_{time} parameter is to see the impact of the lead time on the system performance. In Table 14, we represent the number of transshipments actualized and failed with R_x and R_y, respectively. Additionally, the number of couriers used is notated by R_w.

According to Table 14, we observe that a decrease in lead time can cause an increase in courier usage. Also, an increase in θ_2 and a decrease in θ_1 may decrease the number of transshipment requests actualized. Thus, we obtain the anticipated

Table 14: Preliminary results for the courier routing problem

L_{time} (min.)	θ_1	θ_2	R_x	R_y	R_w
40	1	0.1	3	0	1
40	0.5	0.5	3	0	1
20	1	0.1	3	0	2
20	0.5	0.5	2	1	1

changes in results under varying parameters and validate our formulation with a synthetic instance created for the model validation.

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