European Journal of Operational Research 251 (2016) 107–123

Contents lists available at ScienceDirect

European Journal of Operational Research

journal homepage: www.elsevier.com/locate/ejor

Production, Manufacturing and Logistics

# Mitigating the impact of drug shortages for a healthcare facility: An inventory management approach

Samira Saedi [a], O. Erhun Kundakcioglu [b,*], Andrea C. Henry [c]

[a] Business Process Transformation, Texas Children's Hospital, Houston, TX United States
[b] Department of Industrial Engineering, Ozyegin University, Istanbul, Turkey
[c] Department of Pharmacy, Pharmacoeconomics & Formulary Management, Harris County Hospital District, Houston, TX United States

ARTICLE INFO

*Article history:*
Received 2 October 2013
Accepted 13 November 2015
Available online 22 November 2015

*Keywords:*
OR in health services
Heuristics
Inventory management
Markov chain
Drug shortages

ABSTRACT

Despite the importance and value of the pharmaceutical market, a significant portion of procurement spending including pharmaceuticals are lost. Coupling poor and reactive management practices with the inevitable national drug shortages, leads to lack of medicines causing patient suffering and direct life or death consequences. In this paper, we propose a stochastic model to find the optimal inventory policy for a healthcare facility to proactively minimize the effect of drug shortages in the presence of uncertain disruptions and demand.



## 1. Introduction

According to the World Health Organization (WHO), the United States has the highest healthcare expenditure in the world with $750 billion spent in the global pharmaceuticals market (Boerma, AbouZahr, & Ho, 2009). The United States pharmaceutical market itself is valued at around $306 billion (mar, 2010), with an annual growth of approximately 5 percent. However, a significant percentage of procurement spending (including pharmaceuticals) is known to be lost due to poor management practices around the world (Boerma et al., 2009). Inline with this report, Landry and Philippe (2004) estimate that 48 percent of the costs in the pharmaceutical supply chain can be avoided by better management.

Poor management practices in pharmaceutical supply chain also lead to significant shortages and inefficiencies in the delivery of critical healthcare supplies. A shortage occurs when a product is not commercially available in a sufficient quantity to meet the demand. Arbitrary selection of inventory policies, combined with national drug shortages, cause unavailability of drugs which pose a direct threat to the quality of care received by a patient. Unavailability of drugs also result in patient treatment times being prolonged or procedures (e.g., surgeries) being canceled. Specific examples of medical consequences for critical shortages can be found in Landis (2002).

The majority of the experienced shortages impact oncology drugs and inpatient pharmaceuticals. Recently, National Analysts Worldwide, a marketing research and consulting company, has conducted a survey on the impact of drug shortages on cancer care (Maas, 2012), that reveals 40 percent of oncologists had seen patients die sooner and 95% of physicians had a patient who was unable to receive timely treatment due to drug shortages.

Shortages of drugs can also have serious monetary implications. Medical professionals devote substantial time to find alternatives for drugs in shortage by investigating effects of substitute drugs. Meanwhile, medical staff spends additional time for finding drugs in shortage from other institutions or making new contracts with wholesale distributors for substitute drugs.

Considering the importance of the shortages both from quality of care and cost standpoint, our goal is to minimize the impact of national shortages for hospitals. A national drug shortage occurs as a result of raw material unavailability, manufacturing/regulatory issues, *inventory practices*, unexpected increases/shifts in demand, and natural disasters (Fox et al., 2009). As most of these causes are inevitable, we aim to better manage inventory in a hospital to minimize shortages and maximize quality of care. In this paper, we highlight the positive effect of minimizing the cost of shortage and substitution in conjunction with conventional costs (ordering, inventory holding) by adjusting the inventory related parameters for a hospital.

The remainder of the paper is organized as follows: Section 2 reviews relevant approaches in the supply chain management and inventory control literature. Section 3 presents our mathematical optimization framework that aims to minimize the expected total cost

* Corresponding author. Tel.: +902165649473.
*E-mail address:* erhunk@gmail.com, erhun.kundakcioglu@ozyegin.edu.tr, erhun@alumni.ufl.edu (O.E. Kundakcioglu).

http://dx.doi.org/10.1016/j.ejor.2015.11.017
0377-2217/

under the presence of uncertain national shortages on both mainstream drugs and substitutes. A heuristic solution algorithm for the model is presented in Section 4. Section 5 provides computational results and compares the proposed inventory policy with currently employed policies of two healthcare facilities. Concluding remarks are presented with directions for future research in Section 6.

## 2. Background

A pharmaceutical supply chain typically consists of four main levels: chemical plants, pharmaceutical plants, distribution affiliates, and healthcare facilities (Burns, 2002; Fox et al., 2009). The pharmaceutical shortage can be addressed through varying strategies introduced in each of these levels. Among the four pharmaceutical supply chain levels, the one that is most affected by shortages is the healthcare facility (e.g., hospital), which is in direct contact with patients. Despite the important role of the hospital in solving the problem of pharmaceutical shortages, formulating strategies for hospitals has been given little attention by researchers. This is likely a result of the complexity of the problem, involving the hospital size, geographic location, diversification, and various specializations (DeScioli, 2005). The study of pharmaceutical supply chains has typically been approached from either managerial analysis or quantitative modeling (Jaber, 2009). Managerial approaches include outsourcing (Li & Benton, 1996; Nicholson, Vakharia, & Erenguc, 2004), vendor managed inventory (VMI) (Kim, 2005), supply chain integration (Meijboom & Obel, 2007), and risk management in pharmaceutical supply chains (Breen, 2008).

Inventory investments in the healthcare industry are estimated to be between 10 percent and 18 percent of net revenues (Holmgren & Wentz, 1982; Nicholson et al., 2004). This percentage is even higher when considering hospitals only. Nathan and Trinkaus (1996) estimate the inventory management costs at anywhere between 17 percent and 35 percent of a hospital's total revenue.

It is noteworthy that general (non-healthcare) models have limitations for managing a pharmaceutical inventory. First and foremost, the primary goal of a healthcare facility is usually maximizing the *quality of service/care* rather than minimization of conventional costs (e.g., inventory holding, ordering). This does not imply that these services have no cost nor does it imply that inefficient management is acceptable. However, there are drastic differences in the perspectives of a production facility versus a healthcare facility. *Shortage* and *substitute* costs are expected to be more significant compared to *inventory holding* and *ordering* costs in a healthcare facility due to potential health consequences.

The second aspect that differentiates the pharmaceutical inventory is the cruciality of demand satisfaction. Shortages in pharmaceutical supply chains affect patients' lives directly, therefore must be avoided. In production or other service supply chains, shortages cause lost or backlogged customers (or might even attract some customers), which has a relatively low (or in some cases opposite) effect compared to the healthcare sector. Another aspect that sets pharmaceutical inventory management apart is that some of the items in shortage may be substituted with alternatives. Furthermore, in this study, zero fixed ordering cost and zero lead time are considered as a delivery vehicle visits our collaborating healthcare institution every day. To the best of our knowledge, a model that aims to minimize shortage and substitution costs where uncertain shortages are present in the form of *supply disruptions* has not been studied in the literature.

There exist several models in the inventory management literature that are somewhat relevant to the proposed work. First, Dellaert and van de Poel (1996) introduce an economic order quantity model for inventory control of an academic hospital in the Netherlands. Jayaraman, Burnett, and Frank (2000) focus on ideas to improve the flow of materials in a healthcare facility. Lapierre and Ruiz (2007) develop a model that optimizes the inventory control and logistics scheduling in a multi-echelon inventory problem to minimize inventory costs and balance the workload over the weekdays.

These models, however, do not take the uncertainties in the supply chain into account. Uncertainty can be short-term or long-term based on the time-frame over which the uncertainty affects the system (Subrahmanyam, Pekny, & Reklaitis, 1994). Long-term uncertainties such as demand uncertainty and changes in availability of a pharmaceutical item can be considered in inventory control models to find the optimal ordering policy to minimize shortages. There also exist short-term uncertainties such as recessions but this is outside our scope of work. We focus on long-term uncertainties in a hospital such as uncertainty in demand and uncertainty in supply in the form of disruptions due to material unavailability, manufacturers' production decisions, Food and Drug Administration (FDA) approval strategies etc.

Demand uncertainty is one of the major challenges in pharmaceutical inventory planning (Fox et al., 2009). Demand uncertainty is studied in forecasting studies (Syntetos, Boylan, and Disney, 2009; Syntetos, Nikolopoulos, and Boylan, 2010; Willemain, Smart, and Schwarz, 2004; Zhao and Lee, 1993) and in inventory control theory (Sani & Kingsman, 1997). Poisson process is widely-accepted for customer arrivals in the literature due to its appropriateness of assumptions (i.e., individual arrivals), except a few studies where compound Poisson distribution (e.g., negative binomial distribution) is more appropriate (Sani & Kingsman, 1997; Syntetos et al., 2009).

Supply uncertainty is presented in two forms in the literature: *yield uncertainty* and *disruption*. Yield uncertainty is considered when the quantity of supply delivered is a random variable and can deviate from the order quantity. Disruption is considered when the supply is subject to partial or complete failure. Disruptions are typically modeled as events which occur randomly and may have random length.

Table 1 shows some of the studies that have introduced inventory control problems with supply disruption. These studies consider disruptions of different forms (e.g., random disruptions from the supplier, natural disasters destroying the inventory etc.), different assumptions on lead time, and demand cancellation. Inventory planning can be modeled for a single or multiple period or more generally for an infinite-horizon. Demand on the other hand can be deterministic, random, or deterministic with dynamic numbers. Different inventory control policies in the studies are Economic Order quantity (EOQ), $(s, S)$, $(Q, r)$ and $(Q, r, T)$ (Nahmias, 2008). EOQ model finds an optimal order quantity to minimize the costs. In an $(s, S)$ policy, inventory is checked periodically and if the inventory level is below a certain level $(s)$, a replenishment will take place to restore the inventory level to maximum level $(S)$. $(Q, r)$ policy finds a fixed replenishment point $r$ and continuously tracks the inventory level. Whenever the inventory level falls below $r$, an order of quantity $Q$ will be placed. $(Q, r, T)$ is a $(Q, r)$ policy except for the time $T$ that the decision maker should wait before the order is placed if the previous order was placed during a supply disruption. We do not elucidate the contribution of each paper separately, but only present key differences.

Furthermore, there are studies that use integrated modeling for inventory and transportation decisions (Geunes & Zeng, 2001; 2003) investigating the effect of backlogging and expediting policies on inventory and transportation costs.

As mentioned above, another unique aspect of pharmaceutical supply chains is *substitution* (cde, 2006). When considering alternatives for therapies, some may be comparable, whereas others are not ideal considering side effect profiles. Numerous examples of mainstream/substitute drug pairs with varying levels of

**Table 1**
Inventory management under disruption literature.

| Article | No. of suppliers | Period | Demand | Policy |
|---|---|---|---|---|
| (Parlar & Berkin, 1991) | 1 | Multiple | Deterministic | EOQ |
| (Weiss & Rosenthal, 1992) | 1 | Finite-horizon | Deterministic | EOQ |
| (Parlar & Perry, 1995) | 1 | Multiple | Deterministic | $(Q, r, T)$ |
| (Berk & Arreola-Risa, 1994) | 1 | Multiple | Deterministic | EOQ |
| (Parlar, Wang, & Gerchak, 1995) | 1 | Finite-horizon | Random | $(s, S)$ |
| (Parlar & Perry, 1996) | 2 | Finite-horizon | Deterministic | $(Q, r)$ |
| (Gupta, 1996) | 1 | Mutiple | Random | $(Q, r)$ |
| (Parlar, 1997) | 1 | Single | Random | $(Q, r)$ |
| (Gurler & Parlar, 1997) | 2 | Multiple | Deterministic | $(Q, r)$ |
| (DeCroix & Arreola-Risa, 1998) | 1 | Multiple | Random | $(s, S)$ |
| (Arreola-Risa & DeCroix, 1998) | 1 | Infinite-horizon | Random | $(s, S)$ |
| (Gullu, Onol, & Erkip, 1999) | 1 | Multiple | Deterministic/dynamic | $(Q, r)$ |
| (Mohebbi, 2004) | 1 | Multiple | Random | $(Q, r)$ |
| (Tomlin, 2006) | 2 | Infinite-horizon | Random | EOQ |
| (Ross, Rong, & Snyder, 2008) | 1 | Finite-horizon | Random | EOQ |
| (Qi, Shen, & Snyder, 2009) | 1 | Multiple | Deterministic | EOQ |
| (Schmitt, Snyder, & Shen, 2010) | 1 | Single | Random | EOQ |
| (Schmitt & Snyder, 2010) | 3 | Infinite-horizon | Deterministic | $(Q, r)$ |
| (Yeo & Yuan, 2010) | 1 | Multiple | Random | $(Q, r)$ |

suitability[1] make pharmaceutical inventory management a unique problem. The majority of inventory control studies that consider substitution deal with *consumer-driven substitution*, where customers might accept or reject the substitutes (Dong, Kouvelis, & Tian, 2009; Hopp & Xu, 2008; Huang, Zhou, & Zhao, 2011; Khouja, Mehrez, & Rabinowitz, 1996; Kok & Fisher, 2007; Mahajan & Ryzin, 2001; McGillivray & Silver, 1978; Nagarajan & Rajagopalan, 2008; Parlar, 1988; Parlar & Goyal, 1984; Smith & Agrawal, 2000). Studies that consider *firm-driven substitution*, which may be more suitable in healthcare context, are single-period or finite-horizon models (Bassok, Anupindi, & Akella, 1999; Bayındır, Erkip, & Güllü, 2007; Dutta & Chakraborty, 2010; Hsu, Chung-Lun, & Wen-Qiang, 2005), thus fall short of providing a long-term inventory plan for hospitals. In sum, specific characteristics of pharmaceutical supply chain clearly mandates novel inventory control models. Next, we present our mathematical model and how aforementioned characteristics (substitution, random supply disruptions, demand uncertainty, unique cost structure) are addressed.

## 3. Mathematical model

In this section, we present the real-life challenges in a healthcare facility with a set of assumptions and the data available. The proposed model in this paper is based on the following assumptions:

- There is a single supplier and orders are placed with zero fixed cost. The contract between a hospital and supplier typically allow orders to be placed in any frequency and quantity by charging variable cost only.
- Lead time is assumed zero because deliveries are made daily and overnight deliveries are possible as long as the item is available.
- There is an uncertainty in demand for each pharmaceutical item. We assume that demands are independent among items. The demand for item $i$ arrives according to a Poisson process with rate $\alpha_i$.
- Supply disruptions (e.g., national shortages) for pharmaceuticals occur randomly with uncertain durations. We assume the supply disruptions and their durations for item $i$ are independent and exponentially distributed with rates $\lambda_i$ and $\mu_i$, respectively. Each shortage of item $i$ costs $\pi_i$ independent from the duration of shortage.
- Each mainstream item $i$ might have one substitute which can be used instead of the main drug with a cost of $\pi_i'$. Substitute items can have supply disruptions independent from the main item. Supply disruptions and their durations for substitute of item $i$ are independent and exponentially distributed with rate $\lambda_i'$ and $\mu_i'$, respectively.
- There is no differentiation between mainstream and substitute drugs. When both are on hand, the total number of items is used rather than the exact number of mainstream and substitute items.
- For each item there is an associated shortage impact. The impact of a shortage on mainstream drugs is the same as that of its substitute. The pharmaceutical items under consideration are crucial such as chemotherapeutic drugs. Impacts are difficult to quantify but a subjective assessment is possible considering the effect of drug's absence on the maximum quality adjusted life years (QALYs), and how difficult it is to find the drug from other sources (if any) in an emergency.
- A continuous inventory review policy is employed for tractability purposes. An order will be placed for items under two conditions. First, when the inventory level of item $i$ is at *reorder level* $R_i$ and supply is available, an order of size $Q_i$ will be placed to bring it up to *order-up-to level*[2], $Q_i + R_i$. Second, when a supply disruption is over, an order is placed immediately to reach the $Q_i + R_i$ regardless of the current inventory level.
- In practice, items come in lots but lot sizes are not strict. Therefore, we assume items can be ordered in any quantity.
- A limited storage capacity of $V$ is under consideration. Note that due to the high cost/impact of a shortage compared to inventory holding, there will always be a tendency to carry as much as possible. The question is how to allocate the limited space for a set of critical items.
- Perishability of drugs has been considered by limiting the total inventory of each item proportional to its shelf life $l_i$.

In the light of these assumptions, the parameters to be used in the model are summarized in Table 2. The main goal of the healthcare

[1] For example, liothyronine injections have similar clinical efficacy when compared to levothyroxine injections for hypothyroidism, however, liothyronine injections may potentially cause more adverse effects (Refetoff, 1975; Surks, Schadlow, & Oppenheimer, 1972). Phenytoin and fosphenytoin both have efficacy in treating seizures, but the safety of fosphenytoin in pediatric patients has not yet been established. When comparing capecitabine with fluorouracil for colorectal cancer, the response rate is higher with capecitabine versus fluorouracil and leucovorin, but there are no significant differences between the two groups in overall survival, median duration of response, or median time to disease progression (Hoff et al., 2001).

[2] We use reorder level and safety stock level interchangeably because there is no lead time unless there is a shortage.

**Table 2**
Proposed model parameters.

| | |
|---|---|
| $\alpha_i$ | Demand rate for drug $i$ |
| $\lambda_i$ | Supply disruption rate for drug $i$ |
| $\mu_i$ | Rate of recovery from supply disruption for drug $i$ |
| $\lambda_i'$ | Supply disruption rate for substitute of drug $i$ |
| $\mu_i'$ | Rate of recovery from supply disruption for substitute of drug $i$ |
| $l_i$ | Shelf life of drug $i$ |
| $\pi_i$ | Shortage cost for drug $i$ |
| $\pi_i'$ | Substitution cost for drug $i$ (variable ordering cost for purchasing a substitute item) |
| $c_i$ | Variable ordering cost for mainstream drug $i$ |
| $h_i$ | Annual holding cost for drug $i$ |
| $v_i$ | Space occupied by drug $i$ |
| $V$ | Total warehouse capacity |

facility is to cope with national drug shortages. The idea is to allocate the available space for critical items' safety stocks so that the drawbacks of shortages are minimized. The decision for holding an item is affected by the shortage likeliness, probable duration of a shortage, demand rate, substitute availability, and volume of the drug as discussed in the sequel. Next, we present a novel mathematical model to manage the inventory of a healthcare facility in the most cost effective way where shortages and drug substitution are present.

### 3.1. A continuous time Markov chain model

In this section, we present a novel approach to manage the inventory of a healthcare facility that utilizes drug substitution. To the best of our knowledge, a setting where items are substitutable and there are random disruptions for all items is not considered in the pharmaceutical supply chain literature. In order to overcome this limitation of the previously proposed models, we propose a model that considers up to 2 drugs (one mainstream and one substitute/alternative) for each case. For computational simplicity, we evaluate a *reorder point model* (i.e., $(Q, r)$ policy). The model we propose considers random disruptions for substitutes as well as mainstream drugs using a continuous time Markov chain. Note that the objective function that should be minimized is the *expected total costs of the system*. In this model, states are denoted as triplets where the first entry denotes the inventory level, the second and third entry denote the availability of the mainstream and substitute item, respectively. The availability is denoted as A: *available* or U: *unavailable*. It is assumed that when item $i$ or the substitute becomes available after a supply disruption, an order will be placed to hit an inventory level of $Q_i + R_i$.

In order to find the expected costs associated with this system, we first find the limiting probabilities using balance equations on the transition-rate diagram in Fig. 1. It should be noted that corresponding Markov chains for each item are independent and we denote limiting probabilities for drug $i$ with $P^i$.

**Theorem 3.1.** *When one or both of the drugs (mainstream and substitute) is/are available, the limiting probabilities of hitting order-up-to level can be written as follows:*

$$P^i_{Q_i+R_i,A,A} = \frac{(\alpha_i+\lambda_i+\lambda_i')^{Q_i-1}(\lambda_i+\lambda_i')}{(\alpha_i+\lambda_i+\lambda_i')^{Q_i}-\alpha_i^{Q_i}} \sum_{k=R_i+1}^{Q_i+R_i} P^i_{k,A,A}, \quad i=1,\dots,m \tag{1}$$

$$P^i_{Q_i+R_i,U,A} = \frac{(\alpha_i+\mu_i+\lambda_i')^{Q_i-1}(\mu_i+\lambda_i')}{(\alpha_i+\mu_i+\lambda_i')^{Q_i}-\alpha_i^{Q_i}} \sum_{k=R_i+1}^{Q_i+R_i} P^i_{k,U,A}, \quad i=1,\dots,m \tag{2}$$

$$P^i_{Q_i+R_i,A,U} = \frac{(\alpha_i+\lambda_i+\mu_i')^{Q_i-1}(\lambda_i+\mu_i')}{(\alpha_i+\lambda_i+\mu_i')^{Q_i}-\alpha_i^{Q_i}} \sum_{k=R_i+1}^{Q_i+R_i} P^i_{k,A,U}, \quad i=1,\dots,m \tag{3}$$

**Proof.** See the Appendix. □

This helps us obtain closed form solutions for sum of limiting probabilities for four clusters of states.

**Theorem 3.2.** *Sum of limiting probabilities for each mainstream/substitute availability state can be obtained as follows:*

$$\sum_{k=R_i+1}^{Q_i+R_i} P^i_{k,A,A} = \frac{\mu_i\mu_i'}{(\mu_i+\lambda_i)(\mu_i'+\lambda_i')}, \quad i=1,\dots,m \tag{4}$$

$$\sum_{k=R_i+1}^{Q_i+R_i} P^i_{k,A,U} = \frac{\mu_i\lambda_i'}{(\mu_i+\lambda_i)(\mu_i'+\lambda_i')}, \quad i=1,\dots,m \tag{5}$$

$$\sum_{k=R_i+1}^{Q_i+R_i} P^i_{k,U,A} = \frac{\mu_i'\lambda}{(\mu_i+\lambda_i)(\mu_i'+\lambda_i')}, \quad i=1,\dots,m \tag{6}$$

$$\sum_{j=0}^{\infty} P^i_{Q_i+R_i-j,U,U} = \frac{\lambda_i\lambda_i'}{(\mu_i+\lambda_i)(\mu_i'+\lambda_i')}, \quad i=1,\dots,m \tag{7}$$

**Proof.** See the Appendix. □

Finally, we derive the limiting probability of a crucial state that helps us with the limiting probabilities when both mainstream and substitute are unavailable, $R_i+1, U, U$.

**Theorem 3.3.** *The limiting probability for state $R_i+1, U, U$ is*

$$\begin{aligned} P^i_{R_i+1,U,U} = {} & \frac{(\alpha_i+\mu_i+\lambda_i')^{Q_i-1}(\mu_i+\lambda_i')}{(\alpha_i+\mu_i+\lambda_i')^{Q_i}-\alpha_i^{Q_i}} \frac{\mu_i'\lambda_i}{(\mu_i+\lambda_i)(\mu_i'+\lambda_i')} \\ & \times \left( \frac{\lambda_i'\alpha_i^{Q_i-1}}{(\alpha_i+\mu_i+\mu_i')^{Q_i}} + \sum_{k=1}^{Q_i-1} \frac{\lambda_i'\alpha_i^{Q_i-k-1}(\frac{\alpha_i}{\alpha_i+\mu_i+\lambda_i'})^k}{(\alpha_i+\mu_i+\mu_i')^{Q_i-k}} \right) \\ & + \frac{(\alpha_i+\lambda_i+\mu_i')^{Q_i-1}(\lambda_i+\mu_i')}{(\alpha_i+\lambda_i+\mu_i')^{Q_i}-\alpha_i^{Q_i}} \frac{\mu_i\lambda_i'}{(\mu_i+\lambda_i)(\mu_i'+\lambda_i')} \\ & \times \left( \frac{\lambda_i\alpha_i^{Q_i-1}}{(\alpha_i+\mu_i+\mu_i')^{Q_i}} + \sum_{k=1}^{Q_i-1} \frac{\lambda_i\alpha_i^{Q_i-k-1}(\frac{\alpha_i}{\alpha_i+\mu_i'+\lambda_i})^k}{(\alpha_i+\mu_i+\mu_i')^{Q_i-k}} \right), \\ & i=1,\dots,m \end{aligned} \tag{8}$$

**Proof.** See the Appendix. □

Next, we use these limiting probabilities to obtain different costs and eventually build a mathematical programming formulation that would provide the best possible capacity allocation through inventory parameters.

### 3.2. Optimization problem

In this model, the objective function that should be minimized is the expected annual total costs (TC) of the system which is the summation of expected shortage cost (SC), expected mainstream item variable ordering cost (OC), expected substitution (or substitute ordering) cost (SubC), and expected holding cost (HC). Due to the specifics of healthcare sector described in the list of assumptions, there is no fixed ordering cost. In this formulation $\pi_i$ denotes shortage cost per item $i$, $\pi_i'$ denotes cost of ordering a substitute for each item $i$ and $h_i$ is holding cost per item $i$ per year and the objective is to minimize $\sum_{i=1}^m TC_i(Q_i, R_i)$, where

$$\begin{aligned} TC_i(Q_i,R_i) = {} & SC_i(Q_i,R_i) + OC_i(Q_i,R_i) + SubC_i(Q_i,R_i) + HC_i(Q_i,R_i), \\ & i=1,\dots,m \end{aligned} \tag{9}$$

Note that, shortage cost is charged when a state where both mainstream and substitute are unavailable is visited. Similarly ordering

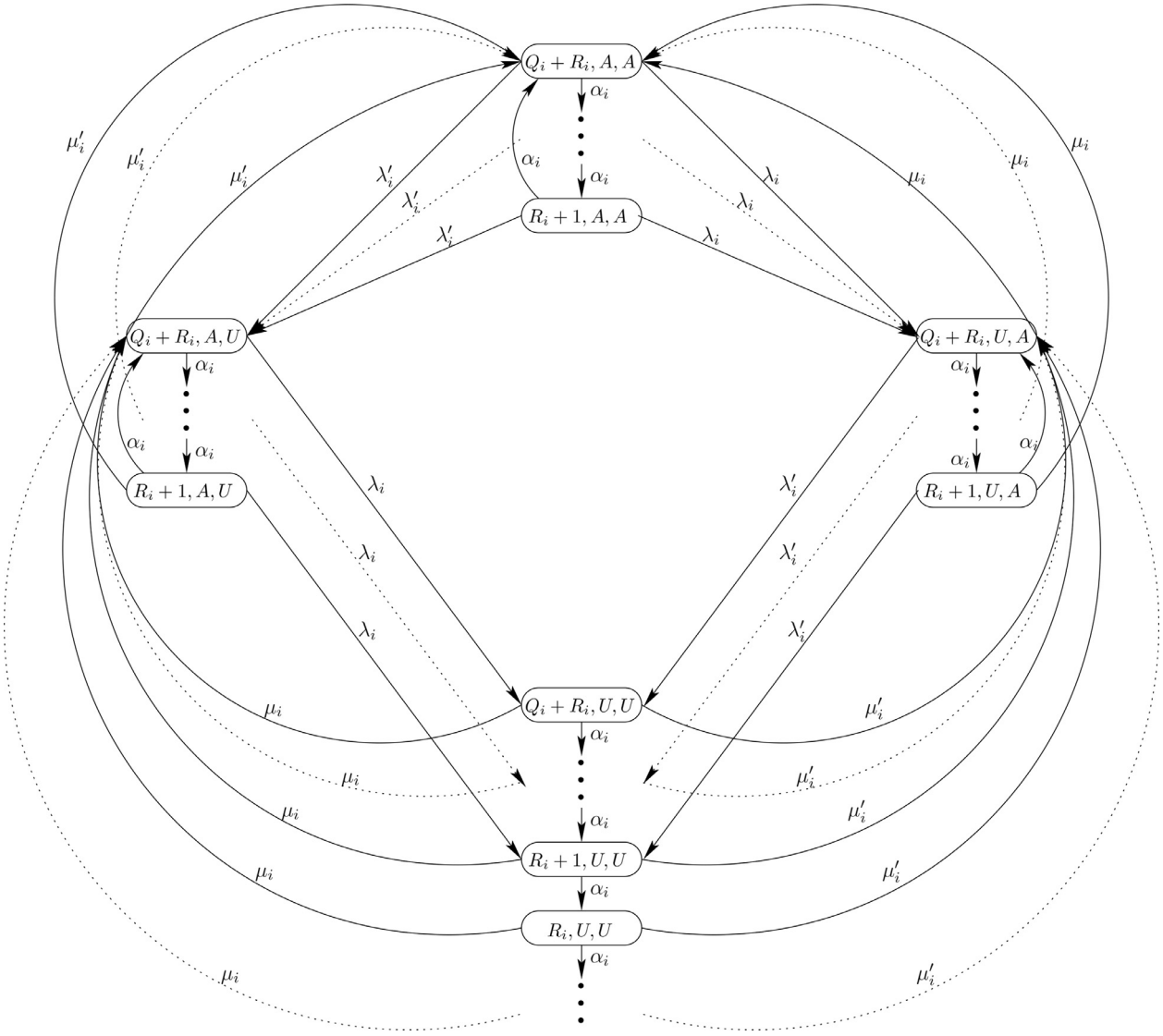


**Fig. 1.** Transition-rate diagram for item $i$ in the inventory system for the proposed model.

and substitution costs are charged when the transition is made indicating an order is placed. These rates are affected by the rate of the relevant transition rates independent from time spent in states. On the other hand, the holding cost is calculated considering the time spent in states using steady state probabilities directly. Thus, expected annual holding cost is

$$\begin{aligned} HC_i(Q_i, R_i) = h_i \Bigg[ & \sum_{j=0}^{Q_i-1} (Q_i + R_i - j) P^i_{Q_i+R_i-j,A,A} \\ & + \sum_{j=0}^{Q_i-1} (Q_i + R_i - j) P^i_{Q_i+R_i-j,A,U} \\ & + \sum_{j=0}^{Q_i-1} (Q_i + R_i - j) P^i_{Q_i+R_i-j,U,A} \\ & + \sum_{j=0}^{Q_i+R_i} (Q_i + R_i - j) P^i_{Q_i+R_i-j,U,U} \Bigg], \\ & i = 1, \ldots, m \end{aligned} \tag{10}$$

Detailed derivation of the annual holding cost with the necessary limiting probabilities is in the Appendix. Next, we calculate shortage and substitution costs using *annual rate* of visiting relevant states, which is either rate in or rate out. Expected shortage cost is obtained as:

$$\begin{aligned} SC_i(Q_i, R_i) &= \pi_i(\alpha_i + \mu'_i + \mu_i) \sum_{j=1}^{\infty} P^i_{-j,U,U} \\ &= \pi_i P^i_{R_i+1,U,U} \times \frac{{\alpha_i}^{R_i+1}}{(\alpha_i + \mu_i + \mu'_i)^{R_i}} \sum_{j=1}^{\infty} \left( \frac{\alpha_i}{\alpha_i + \mu_i + \mu'_i} \right)^j \end{aligned} \tag{11}$$

$$= \pi_i P^i_{R_i+1,U,U} \times \frac{{\alpha_i}^{R_i+1}}{(\alpha_i + \mu_i + \mu'_i)^{R_i}} \times \frac{\alpha_i}{\mu_i + \mu'_i}, \quad i = 1, \ldots, m \tag{12}$$

In order to find the cost of substitution, we focus on *the rate of ordering for substitute items* that can be computed and multiplied by per unit substitution cost as follows:

$$\begin{aligned} SubC_i(Q_i, R_i) = \pi'_i \Bigg( & \alpha_i Q_i P^i_{R_i+1,U,A} + \lambda_i \sum_{j=1}^{Q_i-1} (Q_i - j) P^i_{R_i+j,A,A} \\ & + \mu'_i \sum_{j=1}^{Q_i+R_i} j P^i_{Q_i+R_i-j,U,U} + \mu'_i (Q_i + R_i) \sum_{j=1}^{\infty} P^i_{-j,U,U} \Bigg), \\ & i = 1, \ldots, m \end{aligned}$$

**Table 3**
Heuristic algorithm parameters.

| | |
|---|---|
| $\gamma$ | Coefficient to construct the initial solution, e.g., initial order quantities are $\gamma$ times the daily demand where $\gamma \geq 1$ |
| $\theta$ | Number of critical items |
| $\beta$ | Fraction of warehouse that is initially allocated to critical items |

Details of derivation for substitution cost is in the Appendix. Finally, variable ordering cost for the mainstream items can be computer similar to the substitution cost as follows:

$$OC_i(Q_i, R_i) = c_i\left(\alpha_i Q_i (P^i_{R_i+1,A,U} + P^i_{R_i+1,A,A}) + \lambda'_i \sum_{j=1}^{Q_i-1}(Q_i - j)P^i_{R_i+j,A,A} + \mu_i \sum_{j=1}^{Q_i+R_i} jP^i_{Q_i+R_i-j,U,U} + \mu_i(Q_i + R_i)\sum_{j=1}^{\infty} P^i_{-j,U,U}\right), \quad i = 1, \ldots, m \tag{14}$$

Eqs. (3) and (5) are used together with balance equations to obtain

$$P^i_{R_i+1,A,U} = \frac{\alpha_i{}^{Q_i-1}(\mu'_i + \lambda_i)}{(\alpha_i + \mu'_i + \lambda_i)^{Q_i} - \alpha_i{}^{Q_i}} \times \frac{\mu_i \lambda'_i}{(\mu_i + \lambda_i)(\mu'_i + \lambda'_i)}, \quad i = 1, \ldots, m \tag{15}$$

Similarly, Eqs. (1) and (4) are used together with balance equations to obtain

$$P^i_{R_i+1,A,A} = \frac{\alpha_i{}^{Q_i-1}(\lambda'_i + \lambda_i)}{(\alpha_i + \lambda'_i + \lambda_i)^{Q_i} - \alpha_i{}^{Q_i}} \times \frac{\mu_i \mu'_i}{(\mu_i + \lambda_i)(\mu'_i + \lambda'_i)}, \quad i = 1, \ldots, m \tag{16}$$

The remaining terms can be found as explained in Eqs. (51), (58), and (59).

The optimal reorder points for all items that minimize the expected annual cost of the system can be obtained by solving

$$\min_{\mathbf{Q},\mathbf{R}} \quad \sum_{i=1}^{m} TC_i(Q_i, R_i) \tag{17a}$$

$$\text{subject to} \quad \sum_{i=1}^{m} v_i[Q_i + R_i] \leq V \tag{17b}$$

$$l_i \alpha_i \geq Q_i + R_i \tag{17c}$$

$$R_i \geq 0 \tag{17d}$$

$$Q_i \geq 0 \tag{17e}$$

The two constraints that have been considered in this model are capacitated warehouse (17b), and perishability constraints for drugs (17c). We ensure that the system never exceeds the available space even if all drugs are replenished at the same time, which is virtually impossible. Moreover, we guarantee that the hospital under consideration never carries more than the expected demand to appear during the average lifetime of a drug. It should be noted that a more rigorous model that integrates perishability can also be studied by keeping track of dates for each drug on hand in a stochastic framework. However, based on our discussions with healthcare professionals, we agreed that it is an overcomplicated model that is virtually impossible to implement considering varying and inconsistent expiration dates in different batches and some of the current inventory management tools that disregard expiration dates for simplicity. Despite the fact that there is significant spoilage in some hospitals, it is the way inventory is controlled and the technology employed that has to change before proposing through models.

It should be noted that the constraints are fairly easy to handle but the difficulty of the problem lies in the complicated objective function. In the next section we present our near-optimal solution approach for this computationally difficult problem.

## 4. Solution algorithm

When problem size increase, computation time for the formulation obtained in the previous section increases drastically because the objective of the proposed formulation is a nonconvex function. In this section, a practical heuristic algorithm is proposed to solve the problem and find the near-optimal solution. The parameters used in our algorithm are presented in Table 3.

Next, we explain the details of our Two-Phase Heuristic algorithm by referring to the corresponding line number in the pseudocode (see Algorithm 1 in the Appendix). In order to construct the initial solution for our algorithm, the order quantity of each item is fixed to $\gamma$ times the daily demand (Line 2). Assuming the orders are placed at least daily, $\gamma$ can be any number greater than or equal to one since we need to order at least one day's demand. After assigning a portion of the warehouse to the order quantities in Line 3, $\beta$ percent of the remaining capacity of warehouse is assigned to $\theta$ *critical* items (Line 8). Criticality of an item is quantified based on demand rate, shortage cost per item, and shortage rate for both the mainstream and its substitute. Note that the indices are assigned depending on criticality of items (i.e., first item has the highest demand, shortage cost, and shortage rate multiplication). Once the items are decided, warehouse capacity is distributed for safety stocks of these items based on their daily demand and volume. The idea is to allocate more space for larger items with higher daily demand. During this procedure, shelf lives of items are considered to make sure the assigned capacity is not expected to result in expired drugs. The remaining capacity of the warehouse is assigned to the rest of the items (noncritical) in a similar fashion considering their daily demand and volume (Line 9).

Next, we start with the initial solution and perform a neighborhood search. The neighborhood search includes two main steps, (1) removing the item that results in the minimum increase in the objective function per volume we free up (Lines 17–29), and (2) adding the item that results in the maximum decrease in the objective function per volume we occupy (Lines 31–42). The procedure continues until we observe no improvement in the objective function (17a).

To provide uniformity in the removing procedure, the volume we free up and occupy is initially approximately the size of the largest item, which gradually decreases (Line 13). Dividing the free space by each items volume, the decrement factor ($GR_i$) is calculated.

In the removal process, the initial order quantity and safety stock for each item is decreased by a decrement factor (Lines 18–21). The removal that results in minimum increase in the objective function per removal is chosen. We consider reducing the current order quantity or safety stock (Lines 22–28) and the total space is updated (Line 29). Adding process is similar to the removal process, where the increment factor ($GR_i$) is calculated by dividing the free space by the volume of the item considering the shelf life of the item and current quantity in stock (Line 31). The increment factor is added to both safety stock and order quantity (Lines 32–35). Increasing safety stock and order quantity are considered independently and the solution is

**Table 4**
Parameters for critical items to be stored. ▲ indicates a substitute for the mainstream drug presented in the previous row (shortage impact, demand rate, and volume are same with the mainstream drug).

| Item | Shortage impact | Demand rate (items/day) | Disruption rate $\left(\frac{\text{shortages}}{\text{year}}\right)$ | Expected disruption duration (months) | Volume ($ft^3$) |
|---|---|---|---|---|---|
| Acetazolamide | C | 1.39 | 1 | 6 | 0.033 |
| Acyclovir | C | 16.15 | 1 | 6 | 0.664 |
| Alfentanil | G | 2.22 | 1 | 2 | 0.125 |
| Alprostadil | C | 0.27 | 1 | 6 | 0.037 |
| Amino acid | E | 3.8 | 1 | 6 | 0.166 |
| Premixed TPN | ▲ | ▲ | 0 | – | ▲ |
| Asparaginase | F | 0.06 | 1 | 3 | 0.037 |
| Pegaspargase | ▲ | ▲ | 1 | 6 | ▲ |
| Bleomycin | A | 1 | 1 | 7 | 0.033 |
| Cisplatin | B | 2.38 | 1 | 6 | 0.125 |
| Cyclophosphamide | E | 4.39 | 1 | 2 | 0.166 |
| Cytarabine | A | 1.47 | 1 | 10 | 0.125 |
| Desmopressin | E | 4.27 | 1 | 3 | 0.166 |
| Dipyridamole | G | 8.7 | 2 | 3 | 0.008 |
| Regadenoson | ▲ | ▲ | 0 | – | ▲ |
| Doxorubicin | E | 4.22 | 1 | 7 | 0.125 |
| Epirubicin | ▲ | ▲ | 1 | 1 | ▲ |
| Etoposide | A | 3.77 | 1 | 7 | 0.008 |
| Etoposide Oral | ▲ | ▲ | 1 | 1 | ▲ |
| Fluorouracil | E | 22.11 | 1 | 1 | 0.664 |
| Capecitabine | ▲ | ▲ | 1 | 1 | ▲ |
| Folic Acid | F | 0.19 | 1 | 6 | 0.037 |
| Fosphenytoin | C | 28.25 | 2 | 4 | 0.664 |
| Phenytoin | ▲ | ▲ | 2 | 3 | ▲ |
| Furosemide | C | 98.11 | 1 | 6 | 0.001 |
| Bumetanide | ▲ | ▲ | 1 | 3 | ▲ |
| Intralipids | E | 0.62 | 1 | 8 | 0.166 |
| Leucovorin | A | 5.1 | 2 | 9 | 0.008 |
| Levothyroxine | F | 0.9 | 1 | 3 | 0.037 |
| Liothyronine | ▲ | ▲ | 0 | – | ▲ |
| Methotrexate | B | 3.63 | 2 | 3 | 0.166 |
| Mitomycin | C | 0.5 | 2 | 3 | 0.037 |
| Morphine | F | 248 | 1 | 3 | 0.001 |
| Hydromorphone | ▲ | ▲ | 1 | 1 | ▲ |
| Norepinephrine | B | 41 | 1 | 4 | 0.664 |
| Propofol | D | 152 | 1 | 6 | 0.664 |
| Succinylcholine | D | 46 | 1 | 6 | 0.001 |
| Rocuronium | ▲ | ▲ | 1 | 1 | ▲ |
| Sulfamethoxazole/TMP | F | 12.78 | 1 | 4 | 0.664 |
| Tromethamine | F | 0.22 | 1 | 4 | 0.125 |
| Sodium Bicarbonate | ▲ | ▲ | 0 | – | ▲ |
| Vinblastine | B | 1.04 | 1 | 3 | 0.033 |
| Vincristine | B | 2 | 1 | 6 | 0.033 |

updated based on the action that leads to the maximum decrease in the objective function (Lines 36–42).

## 5. Computational results

The healthcare facility we consider in this study is Harris County Hospital District (HCHD) in Houston, TX, which consists of a rehabilitation and specialty hospital, two full-service hospitals, 16 community health centers, seven school-based clinics, a dental and dialysis center, and mobile health units. HCHD participates in Disproportionate Share Hospital (DSH) programs, which is a special funding provided by the U.S. government for hospitals that treat significant populations of indigent patients. There are DSH programs for both Medicare and Medicaid, as well as for pharmacies, known as the 340B program. Inpatient pharmaceuticals are purchased through a wholesaler under an inpatient Group Purchasing Organization (GPO) account named Premier. Outpatient Pharmaceuticals are purchased through a wholesaler under Federal 340B Public Health Service (PHS) drug pricing program, which limits the cost of drugs to certain grantees of federal agencies. PHS pricing is subject to change quarterly. Participation in this program results in significant savings estimated to be 20–50 percent of the pharmaceuticals cost when compared with GPO pricing. The data provided by HCHD for critical items to be held in the warehouse is presented in Table 4. For privacy reasons, we do not present cost figures explicitly in this paper. Our results provide insights into the most efficient strategy for utilization of the 1200 $ft^3$ warehouse space reserved for these critical items.

In Table 4, the impact of shortages are estimated and categorized based on the QALYs of a patient without the drug and availability of alternative sources ("A" implies the highest impact, i.e., difficult to find from alternative sources, lower QALY during a shortage). Daily demand is obtained using the average over the last 3 years. Disruption information is organized by the status of drugs (i.e., FDA approval, raw material availability, national shortages in the past) and pharmaeconomic expertise. Holding costs are calculated based on ordering cost and an annual interest rate for all items except those that require special handling or refrigeration requirements. Items that are relatively costly to hold are doxorubicin, succinylcholine, amino acid, bleomycin, vincristine, vinblastine, asparaginase, and pegaspargase. Each row with ▲ sign corresponds to a substitute for the mainstream drug presented in the previous row. Thus shortage impact, demand rate, and volume are equal to that of the mainstream drug. For example, liothyronine is a substitute for levothyroxine.

**Table 5**
Safety stock and order quantities for 31 mainstream items under 3 different strategies.

| Item | Anonymous hospital's strategy | | HCHD's strategy | | Proposed policy | |
|---|---|---|---|---|---|---|
| | Safety | Order quantity | Safety | Order quantity | Safety | Order quantity |
| Acetazolamide | 1 | 2 | 8 | 12 | 624 | 2 |
| Acyclovir | 16 | 32 | 50 | 50 | 0 | 17 |
| Alfentanil | 2 | 4 | 10 | 10 | 0 | 3 |
| Alprostadil | 1 | 2 | 10 | 10 | 121 | 1 |
| Amino acid | 4 | 8 | 8 | 4 | 0 | 4 |
| Asparaginase | 1 | 2 | 5 | 5 | 0 | 1 |
| Bleomycin | 1 | 2 | 15 | 15 | 359 | 1 |
| Cisplatin | 2 | 4 | 15 | 15 | 425 | 3 |
| Cyclophosphamide | 4 | 8 | 15 | 15 | 151 | 5 |
| Cytarabine | 1 | 2 | 20 | 20 | 263 | 2 |
| Desmopressin | 4 | 8 | 10 | 10 | 203 | 5 |
| Dipyridamole | 9 | 18 | 20 | 30 | 0 | 9 |
| Doxorubicin | 4 | 8 | 20 | 30 | 0 | 5 |
| Etoposide | 4 | 8 | 40 | 40 | 429 | 4 |
| Fluorouracil | 22 | 44 | 10 | 10 | 0 | 23 |
| Folic Acid | 1 | 2 | 14 | 16 | 33 | 1 |
| Fosphenytoin | 28 | 56 | 100 | 100 | 0 | 29 |
| Furosemide | 98 | 196 | 125 | 125 | 33,813 | 99 |
| Intralipids | 1 | 2 | 20 | 20 | 36 | 1 |
| Leucovorin | 5 | 10 | 30 | 30 | 2748 | 6 |
| Levothyroxine | 1 | 2 | 12 | 12 | 0 | 1 |
| Methotrexate | 4 | 8 | 10 | 20 | 710 | 4 |
| Mitomycin | 1 | 2 | 20 | 20 | 149 | 1 |
| Morphine | 248 | 496 | 1700 | 2300 | 20,082 | 248 |
| Norepinephrine | 41 | 82 | 20 | 30 | 895 | 41 |
| Propofol | 152 | 304 | 100 | 100 | 0 | 152 |
| Succinylcholine | 46 | 92 | 25 | 25 | 4,709 | 46 |
| Sulfamethoxazole/TMP | 13 | 26 | 50 | 50 | 0 | 13 |
| Tromethamine | 1 | 2 | 5 | 5 | 0 | 1 |
| Vinblastine | 1 | 2 | 10 | 10 | 279 | 2 |
| Vincristine | 2 | 4 | 20 | 20 | 358 | 2 |

**Table 6**
Expected costs for 3 different strategies.

| | Anonymous hospital's strategy | HCHD's strategy | Proposed policy |
|---|---|---|---|
| Expected shortage cost | $ 158,702,574 | $ 157,044,031 | $ 121,416,360 |
| Expected substitution cost | $ 1,052,207 | $ 1,054,134 | $ 1,055,562 |
| Expected ordering cost | $ 563,736 | $ 565,713 | $ 594,273 |
| Expected holding cost | $ 2,663 | $ 3,352 | $ 146,373 |
| Expected total annual cost | $ 160,321,180 | $ 158,667,230 | $ 123,212,568 |

### 5.1. Results for the proposed algorithm

Current inventory control strategies in two healthcare facilities (an anonymous hospital in Houston, TX and HCHD) and the result of the heuristic model are presented in Table 5. As shown in the table, resulting order quantity levels of the heuristic algorithm, regardless of the initial solution, are always close to one day of demand. In general, order quantities are set to the smallest possible value based on how deliveries are made. It should also be noted that the maximum utilization levels[3] for Anonymous Hospital and HCHD are 46.4 percent and 41.6 percent, respectively. On the other hand the proposed policy has a maximum utilization level of 100 percent as expected.

The expected costs for each strategy have been summarized in Table 6. It is noteworthy from Table 6 that the expected savings using the proposed model is more than $35M per year compared to current strategies, when shortage impacts are matched with meaningful dollar costs. We do not present these shortage costs, purchase costs, and holding costs for HCHD explicitly for privacy purposes. The expected holding cost of the proposed model is higher than current strategies which do not utilize all available warehouse space.

[3] Maximum utilization level is an upper bound on the ratio of warehouse space that can be used if all items are replenished at the same time. Thus it is calculated by dividing the sum of safety stocks and order quantities into the total available warehouse space.

One clarification is needed at this point: *the overall decrease in the expected total annual cost is not solely based on the increased utilization of the warehouse.* That can be verified by the fact that objective function of the heuristic ranges between ~ $125M and ~ $155M for a set of feasible solutions, all of which have ~ 100 percent utilization. Next, we focus on the solution provided by the heuristic algorithm via Table 7.

In Table 7, items that have a substitute are presented bold. First column shows how many days of demand constitutes the safety stock. Drugs are listed in decreasing order of percentage of warehouse space allocated, which is presented in the second column. The last column in this table shows a soft measure for risk factor. It is the normalized value of multiplication of shortage impact, disruption rate and demand rate over the disruption recovery rate. The items that have a high shortage impact, high disruption rate, lengthy disruption duration (low recovery rate) and high demand rate have a higher risk factor value. In general, it is expected that (i) items with substitute occupy lower percentage of the warehouse, (ii) drugs with higher risk factor occupy higher percentage of the inventory space. This trend is generally observed in the table with a few exceptions:

- Although substitutes exist, some items occupy more space than expected because of the extremely high risk factors (e.g., Furosemide, Morphine).

**Table 7**
Ratio of the safety stock to the daily demand, percentage of the warehouse allocated to each item and shortage impact of each item.

| Item | # Of days safety stock would suffice ($R_i/\alpha_i$) | Percentage of total space | Risk factor |
|---|---|---|---|
| Norepinephrine | 22 | 51.792 | 0.00063 |
| Methotrexate | 196 | 9.877 | 0.00033 |
| Propofol | 0 | 8.411 | 0.00187 |
| Cisplatin | 179 | 4.463 | 0.00029 |
| Desmopressin | 48 | 2.877 | 0.00007 |
| **Furosemide** | 345 | 2.826 | 1.00000 |
| Cytarabine | 179 | 2.756 | 0.00040 |
| Cyclophosphamide | 34 | 2.158 | 0.00004 |
| Leucovorin | 539 | 1.836 | 0.03899 |
| Acetazolamide | 449 | 1.720 | 0.00043 |
| **Morphine** | 81 | 1.694 | 0.25278 |
| **Fosphenytoin** | 0 | 1.605 | 0.00058 |
| **Fluorouracil** | 0 | 1.273 | 0.00003 |
| Bleomycin | 359 | 0.990 | 0.00072 |
| Vincristine | 179 | 0.990 | 0.00093 |
| Acyclovir | 0 | 0.941 | 0.00025 |
| Vinblastine | 268 | 0.772 | 0.00024 |
| Sulfamethoxazole/TMP | 0 | 0.719 | 0.00003 |
| Intralipids | 58 | 0.512 | 0.00003 |
| Mitomycin | 298 | 0.463 | 0.00014 |
| **Succinylcholine** | 102 | 0.396 | 0.37509 |
| Alprostadil | 446 | 0.375 | 0.00007 |
| **Etoposide** | 114 | 0.289 | 0.01121 |
| Folic Acid | 174 | 0.105 | 0.00001 |
| **Amino acid** | 0 | 0.055 | 0.00014 |
| **Doxorubicin** | 0 | 0.052 | 0.00020 |
| Alfentanil | 0 | 0.031 | 0.00001 |
| **Tromethamine** | 0 | 0.010 | 0.00000 |
| **Dipyridamole** | 0 | 0.006 | 0.00111 |
| **Levothyroxine** | 0 | 0.003 | 0.00002 |
| **Asparaginase** | 0 | 0.003 | 0.00000 |

**Table 8**
Sensitivity analysis results for parameters of heuristic algorithm ($\theta$, $\gamma$, $\beta$).

| $\theta$ | $\beta\backslash$(percent)$\gamma$ | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|
| **0** | **0** | 123,271,739 | 123,245,312 | 123,246,508 | 123,256,405 | 123,252,420 | 123,261,898 |
| **5** | **20** | 123,213,575 | Infeasible | Infeasible | Infeasible | Infeasible | Infeasible |
| | **40** | 123,899,634 | 123,222,211 | 123,233,765 | Infeasible | Infeasible | Infeasible |
| | **60** | 124,755,834 | 123,222,584 | 125,231,165 | 123,255,107 | 123,252,781 | Infeasible |
| | **80** | **126,199,941** | 123,237,418 | 123,245,558 | 123,245,558 | 123,252,378 | Infeasible |
| **10** | **20** | **123,212,568** | Infeasible | Infeasible | Infeasible | Infeasible | Infeasible |
| | **40** | 123,222,211 | 123,222,053 | 123,233,843 | Infeasible | Infeasible | Infeasible |
| | **60** | 124,599,130 | 123,222,143 | 123,373,510 | 123,255,035 | Infeasible | Infeasible |
| | **80** | 126,145,371 | 123,265,171 | 123,344,149 | 126,100,488 | 123,259,413 | 123,261,838 |
| **15** | **20** | 123,261,838 | Infeasible | Infeasible | Infeasible | Infeasible | Infeasible |
| | **40** | 123,958020 | 123,283,118 | 123,256,781 | Infeasible | Infeasible | Infeasible |
| | **60** | 123,221,158 | 123,235,625 | 123,373,431 | 123,242,040 | Infeasible | Infeasible |
| | **80** | 123,277,472 | 123,222,572 | 123,263,466 | 123,260,669 | 123,260,073 | 123,262,075 |

- For some items, despite the relatively high risk factor, the percentage of the total space occupied is less than expected because they are relatively small items (e.g., Etoposide, Succinylcholine).
- Some items with substitutes and low risk factor occupy more space than expected because of their large volume (e.g., fosphenytoin, Fluorouracil).

Because there are a number of attributes for each item that affect the total expected cost, we do not expect a simple ordering of items based on one measure. However, a pairwise comparison reveals the reasoning behind the safety stock and order quantity levels. If the total space was assigned uniformly to all items, each should be allocated approximately 3 percent of the total warehouse space. However, for example, Norepinephrine occupies almost half of the warehouse space. This is because of the large volume — even though most of the warehouse is used, safety stock provides only 22 days of demand. Despite the capacity occupied by Norepinephrine, the number of days safety stock for Norepinephrine would suffice is the lowest among drugs with a shortage impact of B. Likewise, items that appear higher than expected on the list due to large volume such as fosphenytoin and Fluorouracil cannot even suffice for a day.

### 5.2. Sensitivity analysis

In this section, we present sensitivity analysis results to evaluate the effect of variations in input parameters such as disruption types and capacity on the expected total cost. Sensitivity analysis is performed for four group of input parameters: heuristic algorithm parameters, disruption related parameters, warehouse capacity, and shortage related parameters.

First group of the parameters are heuristic algorithm parameters used in constructing the initial solution. Table 8 shows the result of the heuristic algorithm under different values for $\theta$, $\gamma$, and $\beta$ with the best (123,212,568) and worst (126,199,941) solutions highlighted.

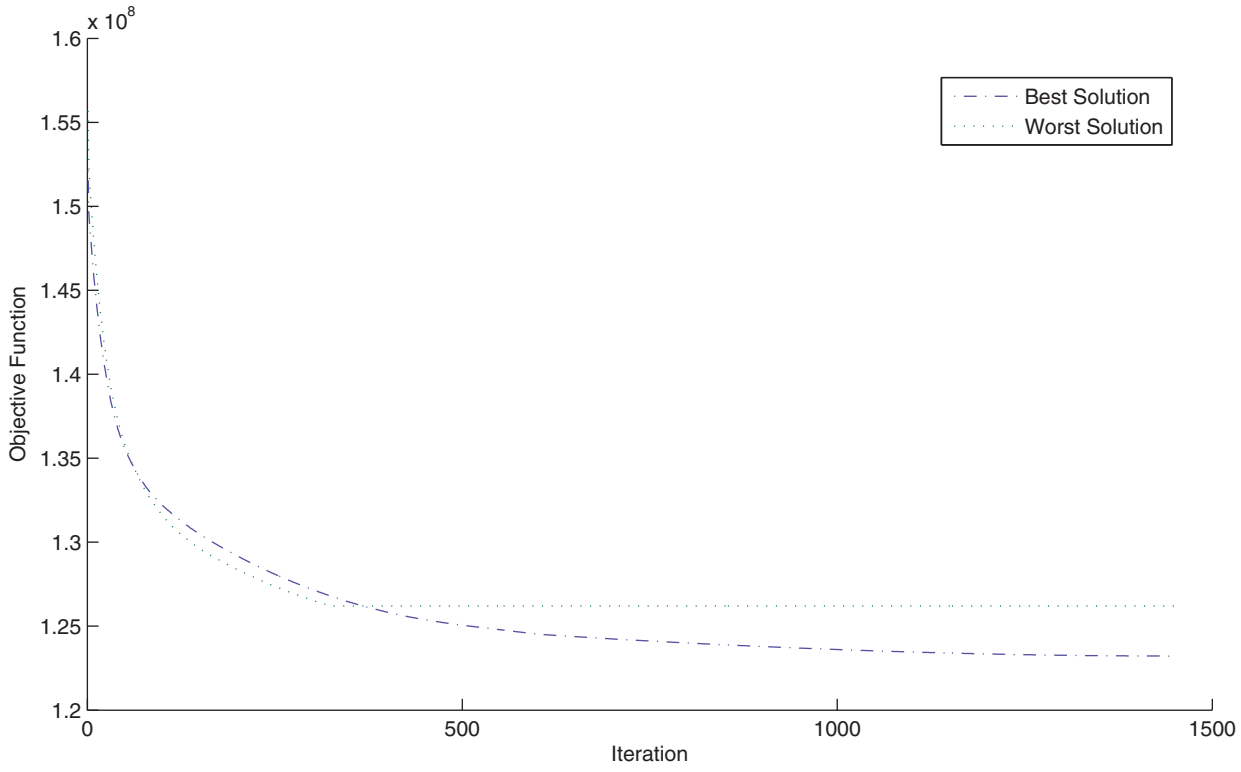


**Fig. 2.** Convergence of objective function for the best solution ($\theta = 10, \gamma = 1, \beta = 0.2$) and the worst solution ($\theta = 5, \gamma = 1, \beta = 0.8$).

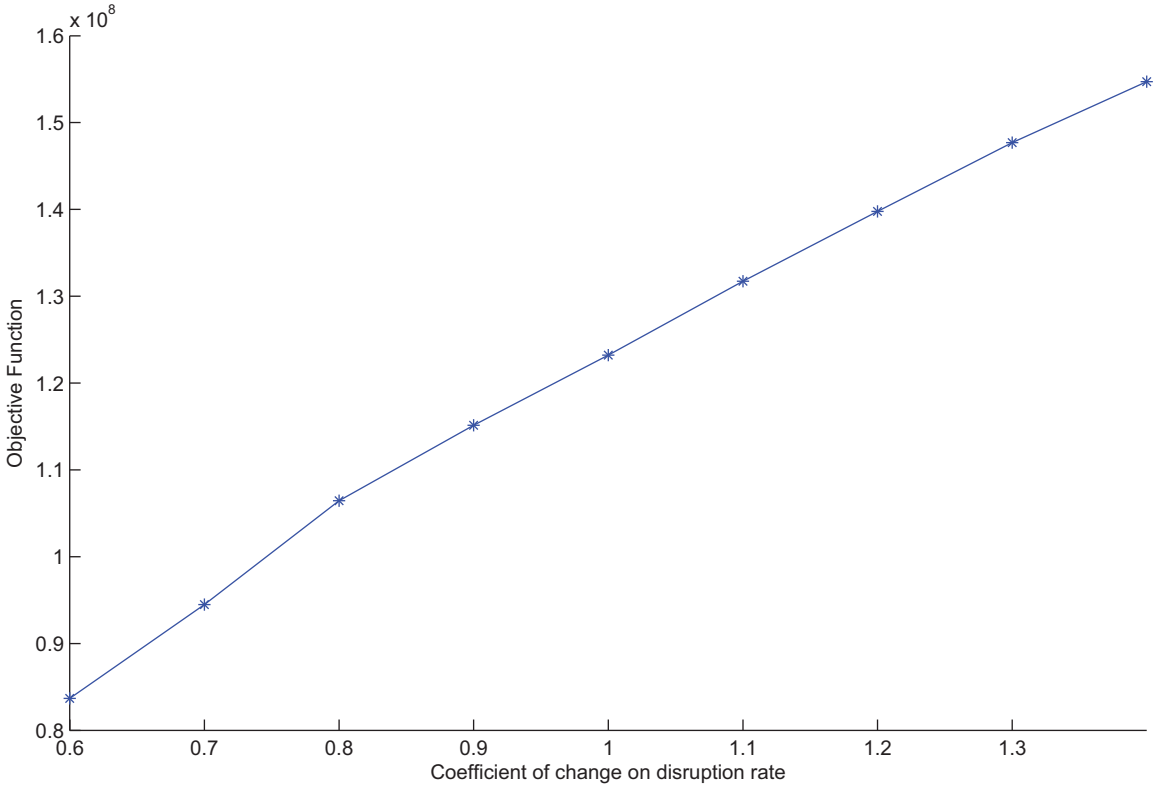


**Fig. 3.** Sensitivity analysis on supply disruption multiplier, $\zeta$ ($\theta = 10, \gamma = 1, \beta = 0.2$).

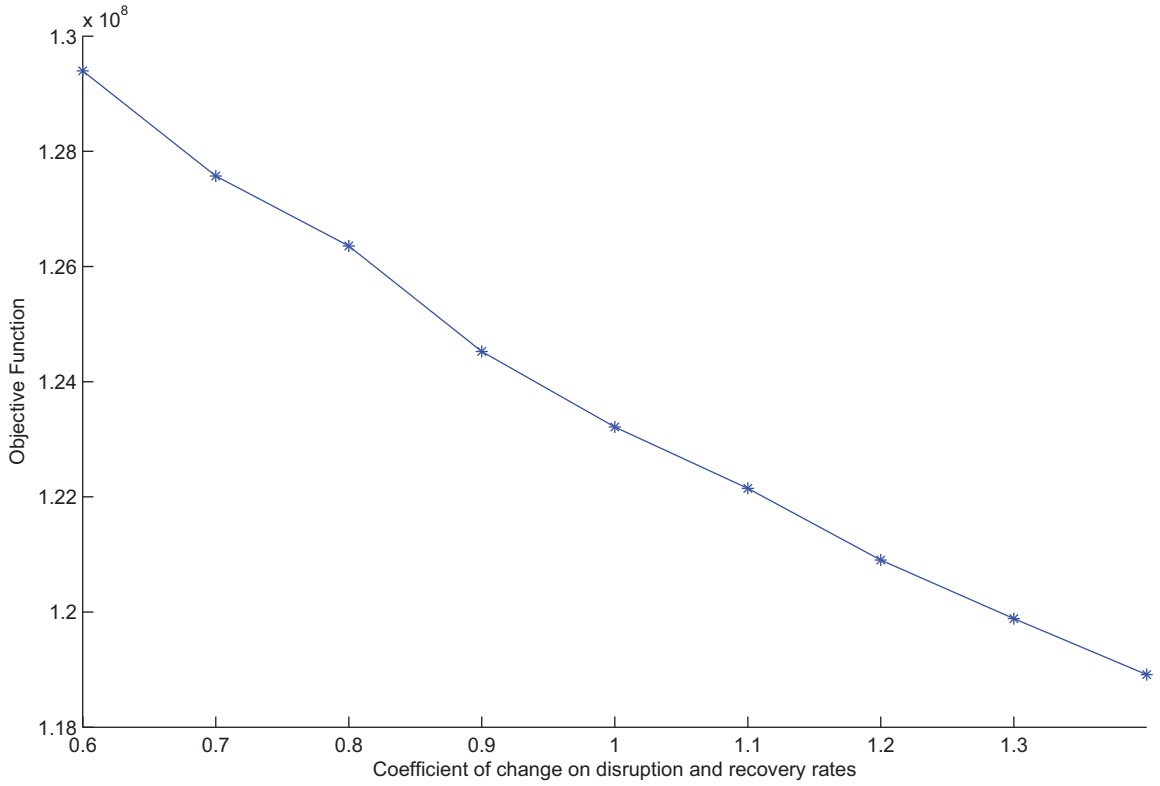


**Fig. 4.** Sensitivity analysis on supply disruption and recovery rate multiplier, $\zeta'$ ($\theta = 10$, $\gamma = 1$, $\beta = 0.2$).

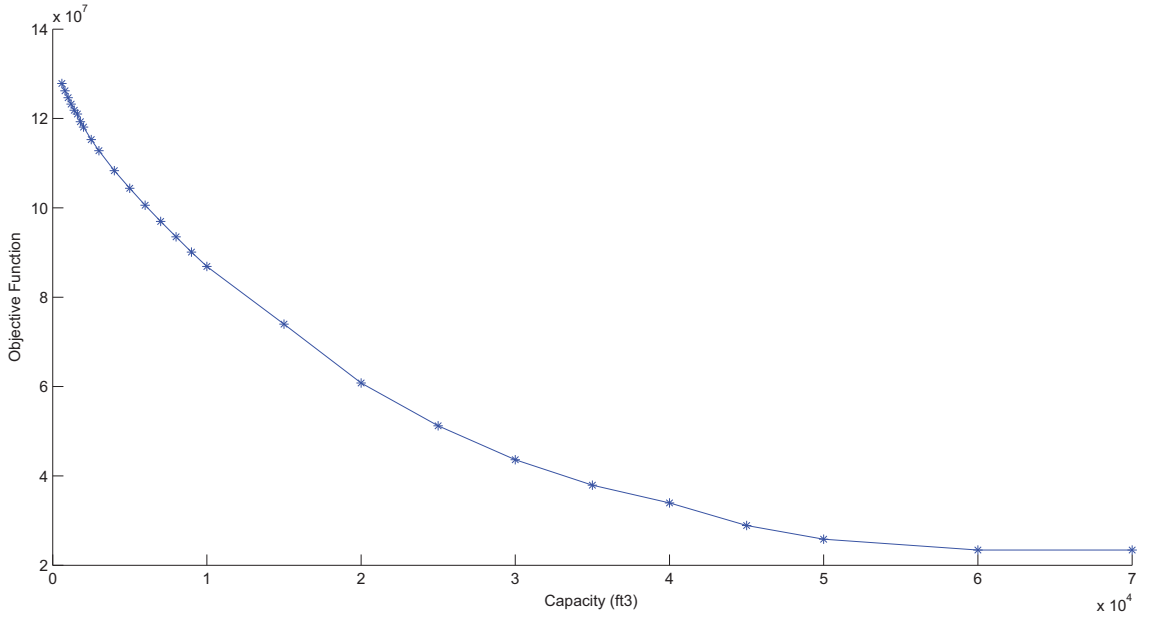


**Fig. 5.** The effect of total inventory space on expected cost ($\theta = 10$, $\gamma = 1$, $\beta = 0.2$).

The convergence of the objective function for the parameters that result in the best ($\theta = 10$, $\gamma = 1$, $\beta = 0.2$) and the worst ($\theta = 5$, $\gamma = 1$, $\beta = 0.8$) solutions are presented in Fig. 2.

The results show that (i) the second phase of the heuristic algorithm works pretty well improving the objective function value drastically, (ii) proposed neighborhood search is sensitive to the initial solution, and (iii) regardless of the values of input parameters, the objective function converges to a decent quality solution.

Second group of parameters are the rate of disruption and the rate of recovery from disruption. For this set of experiments we set $\theta$, $\gamma$, and $\beta$ to the values that provide the best solution above (i.e., $\theta = 10$, $\gamma = 1$, and $\beta = 0.2$). The input parameters are those in Table 4, where $\lambda$ is the disruption rate and $\mu$ is the reciprocal of the expected disruption duration.

In Fig. 3, we present the effect of rate of disruptions on the total cost. $\zeta$ is the coefficient of increase or decrease for disruption rates

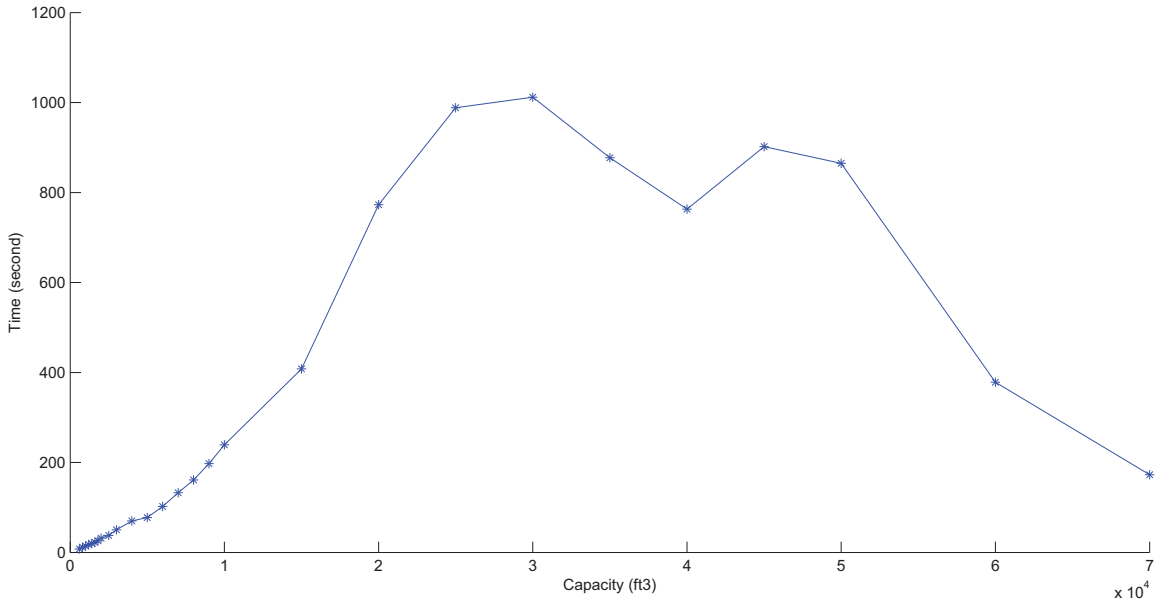


**Fig. 6.** The effect of total inventory space on solution time ($\theta = 10, \gamma = 1, \beta = 0.2$).

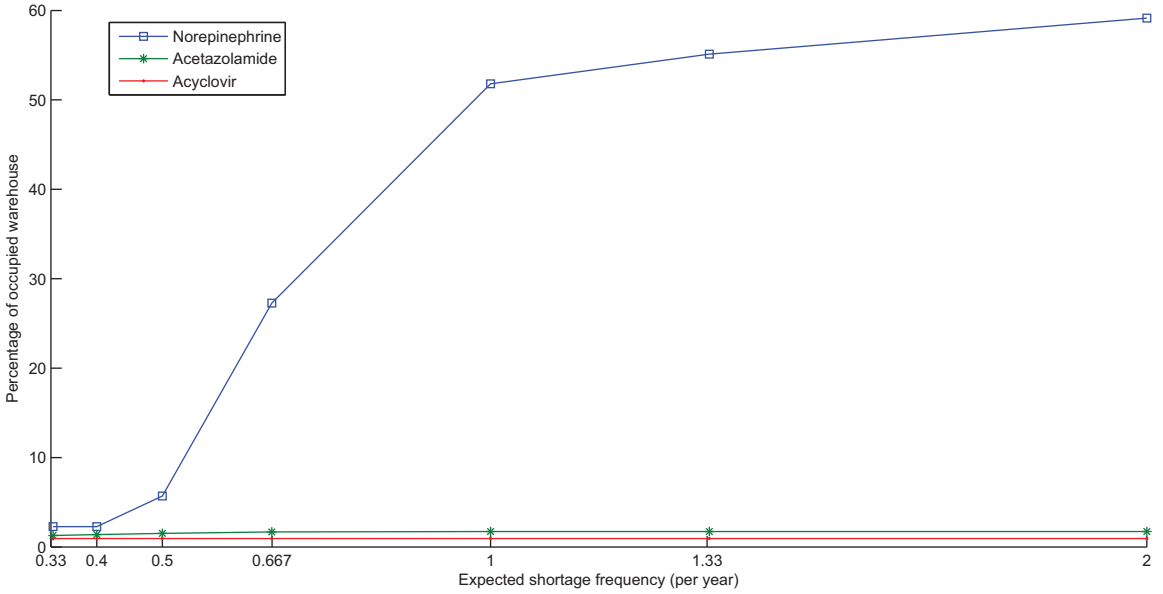


**Fig. 7.** Relationship between shortage frequency and space allocated by the heuristic for a subset of drugs.

($\lambda$). In other words, the disruption rate for each item, regardless of being mainstream or substitute, is multiplied by $\zeta$. As it is shown, increasing the rate of disruption will cause almost a linear increase in the expected total cost so objective function is highly sensitive to changes on the disruption rate.

Fig. 4 represents the changes in disruption and recovery rate simultaneously. In this figure, $\zeta'$ corresponds to the multiplier for both disruption and recovery rate (regardless of being mainstream or substitute), i.e., the new disruption rate for item $i$ is $\zeta' \times \lambda_i$ and its recovery rate from disruption is $\zeta' \times \mu_i$. As shown in the figure, if supplies are unavailable more frequently but the unavailability duration decreases, the expected total cost will decrease. This is because shorter and more frequent supply unavailability periods give the hospital a better opportunity for recovery, despite the fact that *long-run fraction of supply unavailability is the same*.

Next input parameter that we analyze is the total warehouse capacity. Fig. 5 shows, as it is expected, increasing the total capacity leads to a decrease in expected total cost. It should be noted that almost no cost improvement is observed beyond a certain value (for our data $\approx$ 60,000 ft$^3$). A further increase in capacity beyond this point provides only a marginal decrease in the expected shortage cost but increases the holding cost as well.

Another interesting observation is that runtime of our algorithm increases with increased warehouse space because of the number of feasible solutions (see Fig. 6). However, in the case of space abundance (more than 30,000 ft$^3$), the runtime might decrease because of the high quality initial solutions. As expected, increased space solves major drawbacks of national shortages to a certain extent. The practical implementation of this might be inventory pooling. A vast majority of the problems arising with national drug shortages can be alleviated via inventory pooling among hospitals. That available warehouse space, if managed well, will help reduce shortages as presented here and balance the variation in uncertain demand among different healthcare facilities as well.

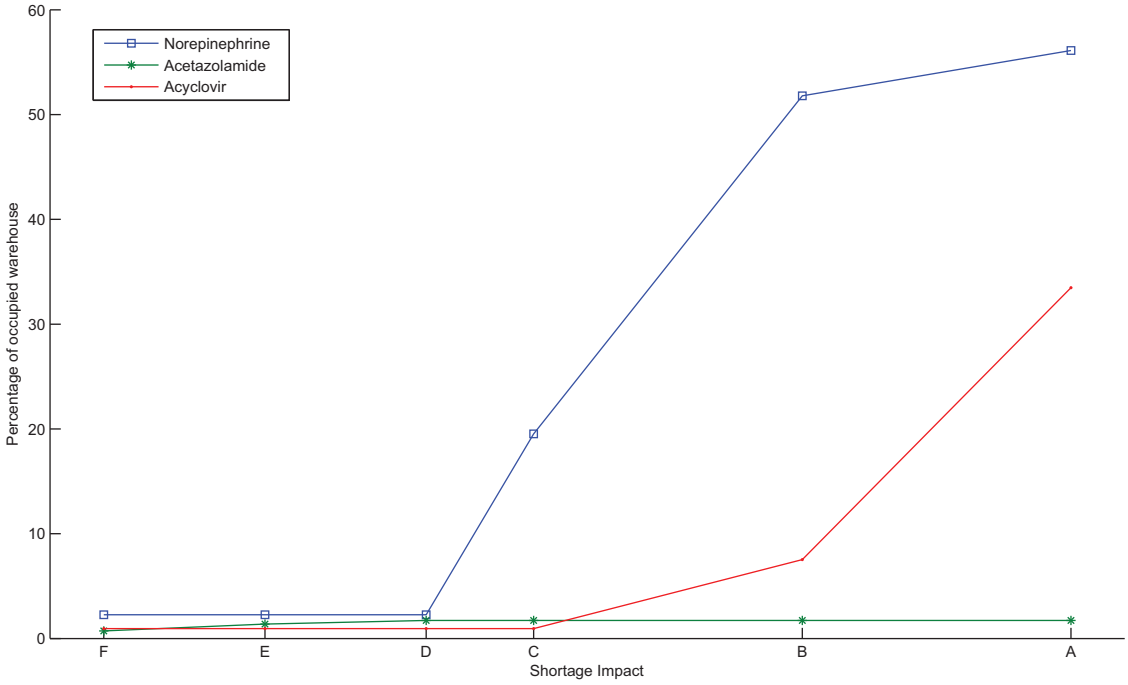


**Fig. 8.** Relationship between shortage impact and space allocated by the heuristic for a subset of drugs.

Finally, we investigate how sensitive our solutions are to shortage related parameters. In this set of experiments, we make adjustments on shortage rate and impacts for three drugs one by one, where we kept all other parameters the same. In each experiment, we report percentage of warehouse space occupied by the drug, whose parameter is changed. Fig. 7 shows the variation in occupied warehouse space by a drug when the expected shortage rate changes. We present results on three drugs (Norepinephrine, Acetazolamide, Acyclovir) that have no substitutes with an expectation of one shortage per year. Drugs selected have different demand rates (41/day, ∼ 1/day, ∼ 16/day) and occupy varying amounts of space in our original solution (∼ 52 percent, ∼ 2 percent, ∼ 1 percent). Fig. 7 shows more warehouse space is used by a drug when the expected shortage frequency increases, with no particular pattern. That trend is more apparent for Norepinephrine whose shortage impact is larger (B versus C for the other drugs).

Fig. 8 shows that increasing shortage impact has a stronger effect than increasing shortage frequency on occupied warehouse space. It should be noted that we were able to change the share of Acyclovir by increasing the shortage impact. The space allocated to Acetazolamide is not as sensitive as the other two drugs, which can be explained by its low demand rate. Note that the horizontal axis in Fig. 8 is drawn to scale to reveal the ratio of shortage costs for different impact categories.

## 6. Concluding remarks

The main goal of this paper is to present a framework for a healthcare facility to cope with inevitable supply disruptions. The more crucial an item is, the more safety stock is expected to be held. We present a stochastic optimization framework to find the optimal stock levels and order quantity levels that minimize the total cost, thus effect of supply disruptions. Conventional models consider the tradeoff among different costs of an item and achieving an optimal solution even in the case of unlimited capacity. What makes pharmaceutical supply chains unique is a set of attributes such as zero lead time, zero fixed-cost ordering, supply disruption, item substitution, and importance of service levels, implying a high warehouse utilization independent from the size. Therefore, we seek to find the balance point among items, considering the space occupied by an item, disruption rates, expected duration of a disruption (i.e., recovery rate), demand rate, as well as substitute item's disruption rate and duration. The results show that the proposed scheme is better compared to the current policies in all aspects of the inventory in a healthcare facility except for the holding cost, which is expected due to the currently low utilization of space.

Substitute items often cost more than mainstream drugs and may go short, however no model in the literature, to the best of our knowledge, utilizes that information. We assume that some of the drugs have substitutes and if they are available substitution can be performed with some cost. An interesting immediate extension of the model would be considering items with more than one substitute. From a computational perspective, the proposed heuristic can also be compared with metaheuristics in this domain. Furthermore, *quality of service* aspect related to substitutes can be emphasized in a future study. A substitute is typically not as effective as a mainstream drug for all patients. Some substitutes may not be preferred agents although they might be less expensive such as sodium bicarbonate (substituting tromethamine) or capecitabine (substituting fluorouracil). A multi-criteria framework can consider the total cost similar to a conventional inventory model on one dimension and the quality of service that assesses the impacts of shortage and substitution on another. Rather than one optimal solution, a set of solutions on the efficient frontier can be further evaluated under different conditions. Another interesting setting is the multi-facility extension of the model presented here. That would illustrate the benefits of inventory pooling among hospitals by shedding a light on the important performance measures under a similar stochastic framework.

## Acknowledgments

O. Erhun Kundakcioglu was partially supported by The Scientific and Technological Research Council of Turkey (TÜBİTAK) grant 115M564.

## Appendix

**Proof of Theorem 1.** Let $Q_i = Q$, $R_i = R$, $\alpha_i = \alpha$, $\lambda_i = \lambda$, $\mu_i = \mu$, $\lambda'_i = \lambda'$, $\mu'_i = \mu'$ for notational convenience.

First, we use the relationship among states that are grouped based on availability of a mainstream drug and its substitute. For example, when both the mainstream drug and its substitute are available (i.e., the set of states on top in Fig. 1), all limiting probabilities can be obtained in terms of $P_{Q+R,A,A}$ as follows:

$$P_{Q+R-j,A,A} = \left(\frac{\alpha}{\alpha+\lambda+\lambda'}\right)^j P_{Q+R,A,A} \quad j = 0,\ldots,Q-1 \tag{18}$$

Similarly, when the mainstream drug is unavailable and the substitute is available, we obtain

$$P_{Q+R-j,U,A} = \Omega^j P_{Q+R,U,A} \quad j = 0,\ldots,Q-1, \tag{19}$$

where $\Omega = \alpha/(\alpha+\mu+\lambda')$. When only the substitute drug is unavailable, the steady state probabilities are derived as

$$P_{Q+R-j,A,U} = \Omega'^j P_{Q+R,A,U} \quad j = 0,\ldots,Q-1, \tag{20}$$

where $\Omega' = \alpha/(\alpha+\lambda+\mu')$. Finally, when both the mainstream and substitute drugs are unavailable, we have

$$\begin{aligned} P_{Q+R-j,U,U} = {} & P_{Q+R,U,A}\left(\frac{\lambda'\alpha^j}{(\alpha+\mu+\mu')^{j+1}} + \sum_{k=1}^{j}\frac{\lambda'\alpha^{j-k}\Omega^k}{(\alpha+\mu+\mu')^{j-k+1}}\right) \\ & + P_{Q+R,A,U}\left(\frac{\lambda\alpha^j}{(\alpha+\mu+\mu')^{j+1}} + \sum_{k=1}^{j}\frac{\lambda\alpha^{j-k}\Omega'^k}{(\alpha+\mu+\mu')^{j-k+1}}\right) \\ & j = 1,\ldots,Q-1 \end{aligned} \tag{21}$$

and

$$P_{R-j,U,U} = P_{R+1,U,U}\left(\frac{\alpha}{\alpha+\mu+\mu'}\right)^{j+1} \quad j = 0,\ldots,\infty. \tag{22}$$

Using Eq. (18), we obtain

$$\sum_{k=R+1}^{Q+R} P_{k,A,A} = P^i_{Q_i+R_i,A,A}\left(\frac{1-(\frac{\alpha}{\alpha+\lambda+\lambda'})^Q}{1-\frac{\alpha}{\alpha+\lambda+\lambda'}}\right), \tag{23}$$

and thus

$$P^i_{Q_i+R_i,A,A} = \frac{(\alpha+\lambda+\lambda')^{Q-1}(\lambda+\lambda')}{(\alpha+\lambda+\lambda')^Q - \alpha^Q}\sum_{k=R+1}^{Q+R} P_{k,A,A}. \tag{24}$$

Similarly, Eqs. (19) and (20) can be used to obtain the following:

$$P^i_{Q_i+R_i,U,A} = \frac{(\alpha+\mu+\lambda')^{Q-1}(\mu+\lambda')}{(\alpha+\mu+\lambda')^Q - \alpha^Q}\sum_{k=R+1}^{Q+R} P_{k,U,A}, \tag{25}$$

$$P^i_{Q_i+R_i,A,U} = \frac{(\alpha+\lambda+\mu')^{Q-1}(\lambda+\mu')}{(\alpha+\lambda+\mu')^Q - \alpha^Q}\sum_{k=R+1}^{Q+R} P_{k,A,U}. \tag{26}$$

□

**Proof of Theorem 2.** Let $Q_i = Q$, $R_i = R$, $\alpha_i = \alpha$, $\lambda_i = \lambda$, $\mu_i = \mu$, $\lambda'_i = \lambda'$, $\mu'_i = \mu'$ for notational convenience.

The limiting probability for state $Q+R, A, A$ can be written equating the rate at which the process leaves and enters that state.

$$\begin{aligned} (\alpha+\lambda+\lambda')P_{Q+R,A,A} = {} & \mu'\sum_{k=R+1}^{Q+R} P_{k,A,U} \\ & + \mu\sum_{k=R+1}^{Q+R} P_{k,U,A} + \alpha P_{R+1,A,A}, \end{aligned} \tag{27}$$

We can rearrange terms and use Eq. (18) to obtain

$$\begin{aligned} P_{Q+R,A,A} = {} & \frac{\mu'}{\alpha+\lambda+\lambda'}\sum_{k=R+1}^{Q+R} P_{k,A,U} + \frac{\mu}{\alpha+\lambda+\lambda'}\sum_{k=R+1}^{Q+R} P_{k,U,A} \\ & + \left(\frac{\alpha}{\alpha+\lambda+\lambda'}\right)^Q P_{Q+R,A,A}. \end{aligned} \tag{28}$$

Adding $\sum_{k=R+1}^{Q+R-1} P_{k,A,A}$ on both sides, we have

$$\begin{aligned} \sum_{k=R+1}^{Q+R} P_{k,A,A} = {} & \frac{\mu'}{\alpha+\lambda+\lambda'}\sum_{k=R+1}^{Q+R} P_{k,A,U} + \frac{\mu}{\alpha+\lambda+\lambda'}\sum_{k=R+1}^{Q+R} P_{k,U,A} \\ & + \sum_{j=1}^{Q}\left(\frac{\alpha}{\alpha+\lambda+\lambda'}\right)^j P_{Q+R,A,A}, \end{aligned} \tag{29}$$

because Eq. (18) implies

$$\sum_{k=R+1}^{Q+R-1} P_{k,A,A} = \sum_{j=1}^{Q-1}\left(\frac{\alpha}{\alpha+\lambda+\lambda'}\right)^j P_{Q+R,A,A}.$$

Using properties of geometric series for the last term in Eqs. (29) and (23), we obtain

$$\sum_{k=R+1}^{Q+R} P_{k,A,A} = \frac{\mu'}{\lambda+\lambda'}\sum_{k=R+1}^{Q+R} P_{k,A,U} + \frac{\mu}{\lambda+\lambda'}\sum_{k=R+1}^{Q+R} P_{k,U,A}. \tag{30}$$

The limiting probability for state $Q+R, U, A$ can be obtained similar to $Q+R, A, A$. First, the limiting probability is written as

$$(\alpha+\mu+\lambda')P_{Q+R,U,A} = \lambda\sum_{k=R+1}^{Q+R} P_{k,A,A} + \mu'\sum_{j=0}^{\infty} P_{Q+R-j,U,U} + \alpha P_{R+1,U,A}. \tag{31}$$

Next, $\sum_{k=R+1}^{Q+R-1} P_{k,U,A}$ is added on both sides and we obtain

$$\sum_{k=R+1}^{Q+R} P_{k,U,A} = \frac{\lambda}{\mu+\lambda'}\sum_{k=R+1}^{Q+R} P_{k,A,A} + \frac{\mu'}{\mu+\lambda'}\sum_{j=0}^{\infty} P_{Q+R-j,U,U}. \tag{32}$$

Similarly, when the mainstream drug is available and the substitute is unavailable, we obtain

$$\sum_{k=R+1}^{Q+R} P_{k,A,U} = \frac{\lambda'}{\mu'+\lambda}\sum_{k=R+1}^{Q+R} P_{k,A,A} + \frac{\mu}{\mu'+\lambda}\sum_{j=0}^{\infty} P_{Q+R-j,U,U}. \tag{33}$$

Using the fact that the summation of limiting probabilities for all states is 1, i.e.,

$$\sum_{k=R+1}^{Q+R} P_{k,A,A} + \sum_{k=R+1}^{Q+R} P_{k,U,A} + \sum_{k=R+1}^{Q+R} P_{k,A,U} + \sum_{j=0}^{\infty} P_{Q+R-j,U,U} = 1 \tag{34}$$

and Eqs. (30), (32) and (33) we have

$$\sum_{k=R+1}^{Q+R} P_{k,A,A} = \frac{\mu\mu'}{(\mu+\lambda)(\mu'+\lambda')} \tag{35}$$

$$\sum_{k=R+1}^{Q+R} P_{k,A,U} = \frac{\mu\lambda'}{(\mu+\lambda)(\mu'+\lambda')} \tag{36}$$

$$\sum_{k=R+1}^{Q+R} P_{k,U,A} = \frac{\mu'\lambda}{(\mu+\lambda)(\mu'+\lambda')} \tag{37}$$

$$\sum_{j=0}^{\infty} P_{Q+R-j,U,U} = \frac{\lambda\lambda'}{(\mu+\lambda)(\mu'+\lambda')}. \tag{38}$$

It should be noted that plugging above equations in Eqs. (1), (2), and (3), steady state probabilities $P_{Q+R,A,A}$, $P_{Q+R,U,A}$ and $P_{Q+R,A,U}$ are found, which can be used to calculate all other steady state probabilities through Eqs. (18), (19), and (20). □

**Proof of Theorem 3.** Let $Q_i = Q$, $R_i = R$, $\alpha_i = \alpha$, $\lambda_i = \lambda$, $\mu_i = \mu$, $\lambda'_i = \lambda'$, $\mu'_i = \mu'$ for notational convenience.

The states during unavailability of both the mainstream drug and its substitute can be divided into two groups for convenience. Using Eq. (21) we have

$$P_{R+1,U,U} = P_{Q+R,U,A}\left(\frac{\lambda'\alpha^{Q-1}}{(\alpha+\mu+\mu')^Q} + \sum_{k=1}^{Q-1}\frac{\lambda'\alpha^{Q-k-1}\Omega^k}{(\alpha+\mu+\mu')^{Q-k}}\right) + P_{Q+R,A,U}\left(\frac{\lambda\alpha^{Q-1}}{(\alpha+\mu+\mu')^Q} + \sum_{k=1}^{Q-1}\frac{\lambda\alpha^{Q-1-k}\Omega'^k}{(\alpha+\mu+\mu')^{Q-k}}\right), \tag{39}$$

which can be simplified as

$$P_{R+1,U,U} = P_{Q+R,U,A}\left(\frac{\lambda'\alpha^{Q-1}}{(\alpha+\mu+\mu')^Q} + \frac{\lambda'\alpha^{Q-1}}{(\alpha+\mu+\mu')^Q}\sum_{k=1}^{Q-1}\times\left(\frac{\alpha+\mu+\mu'}{\alpha+\mu+\lambda'}\right)^k\right) + P_{Q+R,A,U}\left(\frac{\lambda\alpha^{Q-1}}{(\alpha+\mu+\mu')^Q} + \frac{\lambda\alpha^{Q-1}}{(\alpha+\mu+\mu')^Q}\sum_{k=1}^{Q-1}\times\left(\frac{\alpha+\mu+\mu'}{\alpha+\lambda+\mu'}\right)^k\right). \tag{40}$$

Using geometric series characteristics we obtain the following:

$$P_{R+1,U,U} = P_{Q+R,U,A}\left(\frac{\lambda'\alpha^{Q-1}}{(\alpha+\mu+\mu')^Q} + \frac{\lambda'\alpha^{Q-1}}{(\alpha+\mu+\mu')^Q}\times\left(\frac{(\alpha+\mu+\lambda')^Q-(\alpha+\mu+\mu')^Q}{(\lambda'-\mu')(\alpha+\mu+\lambda')^{Q-1}}-1\right)\right) + P_{Q+R,A,U}\left(\frac{\lambda\alpha^{Q-1}}{(\alpha+\mu+\mu')^Q} + \frac{\lambda\alpha^{Q-1}}{(\alpha+\mu+\mu')^Q}\times\left(\frac{(\alpha+\lambda+\mu')^Q-(\alpha+\mu+\mu')^Q}{(\lambda-\mu)(\alpha+\mu'+\lambda)^{Q-1}}-1\right)\right) \tag{41}$$

Note again that $P_{Q+R,U,A}$ and $P_{Q+R,A,U}$ are obtained using Eqs. (2), (6) and ([3,5]), respectively. □

*Derivation of holding cost*

Eq. (10) can be re-stated as

$$\begin{aligned} HC_i(Q_i,R_i) &= h_i(Q_i+R_i)\left[\sum_{j=0}^{Q_i-1}P^i_{Q_i+R_i-j,A,A}+\sum_{j=0}^{Q_i-1}P^i_{Q_i+R_i-j,A,U}+\sum_{j=0}^{Q_i-1}P^i_{Q_i+R_i-j,U,A}\right] \\ &\quad - h_i\left[\sum_{j=0}^{Q_i-1}jP^i_{Q_i+R_i-j,A,A}+\sum_{j=0}^{Q_i-1}jP^i_{Q_i+R_i-j,A,U} + \sum_{j=0}^{Q_i-1}jP^i_{Q_i+R_i-j,U,A}-\sum_{j=0}^{Q_i+R_i}(Q_i+R_i-j)P^i_{Q_i+R_i-j,U,U}\right], \end{aligned} \tag{42}$$

where

$$\sum_{j=1}^{Q_i-1}jP^i_{Q_i+R_i-j,A,A} = \frac{\alpha_i\left[(\alpha_i+\lambda_i+\lambda'_i)^{Q_i}-Q_i(\lambda_i+\lambda'_i)\alpha_i^{Q_i-1}-\alpha_i^{Q_i}\right]}{(\lambda_i+\lambda'_i)^2(\alpha_i+\lambda_i+\lambda'_i)^{Q_i-1}}P^i_{Q_i+R_i,A,A} \tag{43}$$

$$\sum_{j=1}^{Q_i-1}jP^i_{Q_i+R_i-j,A,U} = \frac{\alpha_i\left[(\alpha_i+\mu'_i+\lambda_i)^{Q_i}-Q_i(\mu'_i+\lambda_i)\alpha_i^{Q_i-1}-\alpha_i^{Q_i}\right]}{(\mu'_i+\lambda_i)^2(\alpha_i+\mu'_i+\lambda_i)^{Q_i-1}}P^i_{Q_i+R_i,A,U} \tag{44}$$

$$\sum_{j=1}^{Q_i-1}jP^i_{Q_i+R_i-j,U,A} = \frac{\alpha_i\left[(\alpha_i+\mu_i+\lambda'_i)^{Q_i}-Q_i(\mu_i+\lambda'_i)\alpha_i^{Q_i-1}-\alpha_i^{Q_i}\right]}{(\mu_i+\lambda'_i)^2(\alpha_i+\mu_i+\lambda'_i)^{Q_i-1}}P^i_{Q_i+R_i,U,A} \tag{45}$$

$$\sum_{j=0}^{Q_i+R_i}(Q_i+R_i-j)P^i_{Q_i+R_i-j,U,U} = \sum_{j=0}^{Q_i-1}(Q_i+R_i-j)P^i_{Q_i+R_i-j,U,U} + \sum_{j=Q_i}^{Q_i+R_i}(Q_i+R_i-j)P^i_{Q_i+R_i-j,U,U}. \tag{46}$$

The second term in (46) can be calculated as follows:

$$\sum_{j=Q_i}^{Q_i+R_i}(Q_i+R_i-j)P^i_{Q_i+R_i-j,U,U} = \sum_{j=0}^{R_i}(R_i-j)P^i_{R_i}\left(\frac{\alpha_i}{\alpha_i+\mu_i+\mu'_i}\right)^j = P^i_{R_i}\left(\sum_{j=0}^{R_i}R_i\left(\frac{\alpha_i}{\alpha_i+\mu_i+\mu'_i}\right)^j-\sum_{j=0}^{R_i}j\left(\frac{\alpha_i}{\alpha_i+\mu_i+\mu'_i}\right)^j\right) \tag{47}$$

$$= P^i_{R_i}\left(R_i\times\frac{(\alpha_i+\mu_i+\mu'_i)^{R_i+1}-\alpha_i^{R_i+1}}{(\mu_i+\mu'_i)(\alpha_i+\mu_i+\mu'_i)^{R_i}} - \frac{\alpha_i(\alpha_i+\mu_i+\mu'_i)\left[(\alpha_i+\mu_i+\mu'_i)^{R_i+1}-\alpha_i^{R_i}(R_i+1)(\alpha_i+\mu_i+\mu'_i)+R_i\alpha_i\right]}{(\alpha_i+\mu_i+\mu'_i)^{R_i+1}(\mu_i+\mu'_i)^2}\right) \tag{48}$$

We approximate the first term in (46) because the exact derivation is tedious.

$$\begin{aligned} \sum_{j=0}^{Q_i-1}(Q_i+R_i-j)P^i_{Q_i+R_i-j,U,U} &\approx \frac{Q_i+1+2R_i}{2}\sum_{j=0}^{Q_i-1}P^i_{Q_i+R_i-j,U,U} \\ &= \frac{Q_i+1+2R_i}{2}\left(\sum_{j=0}^{\infty}P^i_{Q_i+R_i-j,U,U}-\sum_{j=-\infty}^{R_i}P^i_{j,U,U}\right) \\ &= \frac{Q_i+1+2R_i}{2}\left(\sum_{j=0}^{\infty}P^i_{Q_i+R_i-j,U,U}-P^i_{R_i,U,U}\times\frac{\alpha_i+\mu_i+\mu'_i}{\mu_i+\mu'_i}\right) \end{aligned} \tag{49}$$

Eqs. (7) and (8) can be plugged in (49) to provide necessary term for holding cost.

*Derivation of substitution cost*

Eqs. (2) and (6) are used together with balance equations to obtain

$$P^i_{R_i+1,U,A} = \frac{\alpha_i^{Q_i-1}(\mu_i+\lambda'_i)}{(\alpha_i+\mu_i+\lambda'_i)^{Q_i}-\alpha_i^{Q_i}}\times\frac{\mu'_i\lambda_i}{(\mu_i+\lambda_i)(\mu'_i+\lambda'_i)} \tag{50}$$

For the second term, balance equations are used to provide

$$\sum_{j=1}^{Q_i-1}(Q_i-j)P^i_{R_i+j,A,A}=P^i_{Q_i+R_i,A,A}\sum_{k=1}^{Q_i-1}k\left(\frac{\alpha_i}{\alpha_i+\lambda_i+\lambda_i'}\right)^k \tag{51}$$

$$=P^i_{Q_i+R_i,A,A}\times\frac{\alpha_i\left[(\alpha_i+\lambda_i+\lambda_i')^{Q_i}-Q_i\alpha_i{}^{Q_i-1}(\alpha_i+\lambda_i+\lambda_i')+\alpha_i{}^{Q_i}(Q_i-1)\right]}{(\lambda_i+\lambda_i')^2(\alpha_i+\lambda_i+\lambda_i')^{Q_i-1}}, \tag{52}$$

where $P^i_{Q_i+R_i,A,A}$ can be obtained using (1) and (4).

The third term can be separated into two parts:

$$\sum_{j=1}^{Q_i+R_i}jP^i_{Q_i+R_i-j,U,U}=\sum_{j=1}^{Q_i-1}jP^i_{Q_i+R_i-j,U,U}+\sum_{j=Q_i}^{Q_i+R_i}jP^i_{Q_i+R_i-j,U,U}, \tag{53}$$

First part can be estimated as:

$$\sum_{j=1}^{Q_i-1}jP^i_{Q_i+R_i-j,U,U}\approx\frac{Q_i}{2}\sum_{j=1}^{Q_i-1}P^i_{Q_i+R_i-j,U,U}$$

$$=\frac{Q_i}{2}\left(\sum_{j=0}^{Q_i-1}P^i_{Q_i+R_i-j,U,U}-P^i_{Q_i+R_i,U,U}\right) \tag{54}$$

$$=\frac{Q_i}{2}\left(\sum_{j=0}^{\infty}P^i_{Q_i+R_i-j,U,U}-\sum_{j=Q_i}^{\infty}P^i_{Q_i+R_i-j,U,U}-P^i_{Q_i+R_i,U,U}\right) \tag{55}$$

Using sum of geometric series, $\sum_{j=Q_i}^{\infty}P^i_{Q_i+R_i-j,U,U}$ can be calculated as

$$\sum_{j=Q_i}^{\infty}P^i_{Q_i+R_i-j,U,U}=P^i_{R_i+1,U,U}\times\frac{\alpha_i}{\mu_i+\mu_i'} \tag{56}$$

and the steady state probability $P^i_{Q_i+R_i,U,U}$ can be calculated as:

$$P^i_{Q_i+R_i,U,U}=\frac{P^i_{Q_i+R_i,U,A}\lambda_i'}{\alpha_i+\mu_i+\mu_i'}+\frac{P^i_{Q_i+R_i,A,U}\lambda_i}{\alpha_i+\mu_i+\mu_i'} \tag{57}$$

Eq. (54) can be calculated plugging in Eqs. (56), (57) and (7).

Second part can be written as:

$$\sum_{j=Q_i}^{Q_i+R_i}jP^i_{Q_i+R_i-j,U,U}=Q_i\sum_{j=Q_i}^{Q_i+R_i}P^i_{Q_i+R_i-j,U,U}+\sum_{j=Q_i}^{Q_i+R_i}(j-Q_i)P^i_{Q_i+R_i-j,U,U}$$

$$=Q_iP^i_{R_i+1,U,U}\left(\frac{\alpha_i}{\mu_i+\mu_i'}\right)\left(1-\left(\frac{\alpha_i}{\alpha_i+\mu_i+\mu_i}\right)^{R_i+1}\right)$$

$$+P^i_{R_i+1,U,U}\left(\frac{\alpha_i}{\mu_i+\mu_i'}\right)^2$$

$$\times\left(1-\frac{\alpha_i{}^{R_i}(R_i+1)(\alpha_i+\mu_i+\mu_i')-R_i\alpha_i{}^{R_i+1}}{(\alpha_i+\mu_i+\mu_i')^{R_i+1}}\right) \tag{58}$$

Eq. (58) can be calculated using Eq. (8).

Last term to be calculated is $\sum_{j=1}^{\infty}P^i_{-j,U,U}$, using Eq. (8).

$$\sum_{j=1}^{\infty}P^i_{-j,U,U}=P^i_{R_i+1,U,U}\left(\frac{\alpha_i}{\mu_i+\mu_i'}\right)\left(\frac{\alpha_i}{\alpha_i+\mu_i+\mu_i'}\right)^{R_i+1} \tag{59}$$

Eqs. (50), (51), (53), (59) are plugged in (13) and derivation of substitution cost is complete.

*Pseudocode for the two-phase heuristic algorithm*

**Algorithm 1** Two-Phase Heuristic.

**INPUT:** $(\alpha_1,\ldots,\alpha_m)$, $(\lambda_1,\ldots,\lambda_m)$, $(\lambda_1',\ldots,\lambda_m')$, $(\mu_1,\ldots,\mu_m)$, $(\mu_1',\ldots,\mu_m')$, $(h_1,\ldots,h_m)$, $(\pi_1,\ldots,\pi_m)$, $(\pi_1',\ldots,\pi_m')$, $(v_1,\ldots,v_m)$, $(l_1,\ldots,l_m)$, $\mathbf{V}$, $\gamma,\theta,\beta$

**OUTPUT:** $(R_1,\ldots,R_m)$, $(Q_1,\ldots,Q_m)$

{**Finding Initial Solution**}
$(Q_1,\ldots,Q_m)\leftarrow\gamma\times(\alpha_1,\ldots,\alpha_m)$
$V'\leftarrow V-\sum_{i=1}^{m}(v_i\times Q_i)$
**if** $V'<0$ **then**
  *Break*
  {**No feasible solution with provided parameters**}
**end if**
$R_k\leftarrow\min\{l_k\alpha_k-Q_k,\ \frac{\beta\times V'\alpha_kv_k}{\theta\sum_{i=1}^{\theta}\alpha_iv_i}\},\forall k\in1,\ldots,\theta$
$R_k\leftarrow\min\{l_k\alpha_k-Q_k,\ \frac{(1-\beta)\times V'\alpha_kv_k}{(m-\theta)\sum_{i=\theta}^{m}\alpha_iv_i}\},\forall k\in\theta+1,\ldots,m$
$t\leftarrow1$
{**Neighborhood Search**}
**while** $GR_{i\in1,\ldots,m}=1$ **do**
  $GR_i\leftarrow\frac{max(v_i)}{v_it},\forall i\in1,\ldots,m$
  $TC'(Q_i,R_i)\leftarrow\infty\ \forall i\in1,\ldots,m$
  **while** $\sum_{i=1}^{m}TC'(Q_i,R_i)-\sum_{i=1}^{m}TC_i(Q_i,R_i)>0$ **do**
    $TC'(Q_i,R_i)\leftarrow TC_i(Q_i,R_i)\ \forall i\in1,\ldots,m$
    {**Removal of items**}
    **for all** $i\in1,\ldots,m$ **do**
      $R_i'\leftarrow R_i-GR_i,\forall i\in1,\ldots,m$
      $Q_i'\leftarrow Q_i-GR_i,\forall i\in1,\ldots,m$
    **end for**
    $j\leftarrow argmin_{i\in1,\ldots,m}\frac{TC_i(Q_i,R_i')-TC_i(Q_i,R_i)}{v_iGR_i}$
    $k\leftarrow argmin_{i\in1,\ldots,m}\frac{TC_i(Q_i',R_i)-TC_i(Q_i,R_i)}{v_iGR_i}$
    **if** $\frac{TC_i(Q_k',R_k)-TC_i(Q_k,R_k)}{v_kGR_k}<\frac{TC_i(Q_j,R_j')-TC_i(Q_j,R_j)}{v_jGR_j}$ **then**
      $(Q_k,R_k)\leftarrow(Q_k',R_k)$
    **else**
      $(Q_j,R_j)\leftarrow(Q_j,R_j')$
    **end if**
    $V''\leftarrow V-\sum_{i=1}^{m}v_i(Q_i+R_i)$
    {**Adding new items**}
    $GR_i'\leftarrow min\{l_i\alpha_i-Q_i-R_i,\ \frac{V''}{v_i}\},\forall i\in1,\ldots,m$
    **for all** $i\in1,\ldots,m$ **do**
      $R_i''\leftarrow R_i+GR_i',\forall i\in1,\ldots,m$
      $Q_i''\leftarrow Q_i+GR_i',\forall i\in1,\ldots,m$
    **end for**
    $j'\leftarrow argmax_{i\in1,\ldots,m}\frac{TC_i(Q_i,R_i)-TC_i(Q_i,R_i'')}{v_iGR_i'}$
    $k'\leftarrow argmax_{i\in1,\ldots,m}\frac{TC_i(Q_i,R_i)-TC_i(Q_i'',R_i)}{v_iGR_i'}$
    **if** $\frac{TC_i(Q_{k'},R_{k'})-TC_i(Q_{k'}'',R_{k'})}{v_{k'}GR_{k'}'}>\frac{TC_i(Q_j,R_j')-TC_i(Q_j,R_j)}{v_{j'}GR_{j'}'}$ **then**
      $(Q_{k'},R_{k'})\leftarrow(Q_{k'}'',R_{k'})$
    **else**
      $(Q_{j'},R_{j'})\leftarrow(Q_{j'},R_{j'}'')$
    **end if**
  **end while**
  $t\leftarrow2t$
**end while**

## References

Arreola-Risa, A., & DeCroix, G. A. (1998). Inventory management under random supply disruptions and partial backorders. *Naval Research Logistics, 45*(7), 687–703.

Bassok, Y., Anupindi, R., & Akella, R. (1999). Single-period multiproduct inventory models with substitution. *Operations Research, 47*(4), 632–642.

Bayındır, Z. P., Erkip, N., & Güllü, R. (2007). Assessing the benefits of remanufacturing option under one-way substitution and capacity constraint. *Computers & Operations Research, 34*(2), 487–514.

Berk, E., & Arreola-Risa, A. (1994). Note on future supply uncertainty in EOQ models. *Naval Research Logistics, 41*(1), 129–132.

Boerma, T., AbouZahr, C., & Ho, J. (2009). World health statistics. *Technical report*. World Health Organization.

Breen, L. (2008). A preliminary examination of risk in the pharmaceutical supply chain (PSC) in the national health service (NHS)(UK). *Journal of Service Science and Management, 1*(2), 193–199.

Burns, L. R. (2002). *The Health Care Value Chain: Producers, Purchasers, and Providers*. San Francisco, CA, USA: Jossey-Bass.

DeCroix, G. A., & Arreola-Risa, A. (1998). On offering economic incentives to backorder. *IIE Transactions, 30*(8), 715–721.

Dellaert, N., & van de Poel, E. (1996). Global inventory control in an academic hospital. *International Journal of Production Economics, 46*, 277–284.

DeScioli, D. T. (2005). *Differentiating the hospital supply chain for enhanced performance*. Citeseer Phd thesis.

Dong, L., Kouvelis, P., & Tian, Z. (2009). Dynamic pricing and inventory control of substitute products. *Manufacturing & Service Operations Management, 11*(2), 317–339.

Dutta, P., & Chakraborty, D. (2010). Incorporating one-way substitution policy into the newsboy problem with imprecise customer demand. *European Journal of Operational Research, 200*(1), 99–110.

Fox, E. R., Birt, A., James, K. B., Kokko, H., Salverson, S., & Soflin, D. L. (2009). ASHP guidelines on managing drug product shortages in hospitals and health systems. *American Journal of Health-System Pharmacy, 66*, 1399–1406.

Geunes, J., & Zeng, A. Z. (2001). Impacts of inventory shortage policies on transportation requirements in two-stage distribution systems. *European Journal of Operational Research, 129*(2), 299–310.

Geunes, J., & Zeng, A. Z. (2003). Optimizing supply shortage decisions in base stock distribution operations. *Journal of Global Optimization, 26*(1), 25–42.

Gullu, R., Onol, E., & Erkip, N. (1999). Analysis of an inventory system under supply uncertainty. *International Journal of Production Economics, 59*(1-3), 377–385.

Gupta, D. (1996). The "(q; r)" inventory system with an unreliable supplier. *INFOR, 34*, 59–76.

Gurler, U., & Parlar, M. (1997). An inventory problem with two randomly available suppliers. *Operations Research, 45*(6), 904–918.

Hoff, P. M., Ansari, R., Batist, G., Cox, J., Kocha, W., Kuperminc, M., … Harrison, E. (2001). Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. *Journal of Clinical Oncology, 19*(8), 2282–2292.

Holmgren, J. H., & Wentz, W. J. (1982). *Material management and purchasing for the health care facility*. AUPHA Press.

Hopp, W. J., & Xu, X. (2008). A static approximation for dynamic demand substitution with applications in a competitive market. *Operations Research, 56*(3), 630–645.

Hsu, V. N., Chung-Lun, L., & Wen-Qiang, X. (2005). Dynamic lot size problems with one-way product substitution. *IIE Transactions, 37*(3), 201–215.

Huang, D., Zhou, H., & Zhao, Q. H. (2011). A competitive multiple-product newsboy problem with partial product substitution. *Omega, 39*(3), 302–312.

Jaber, M. Y. (2009). *Inventory management: non-classical views*. CRC.

Jayaraman, V., Burnett, C., & Frank, D. (2000). Separating inventory flows in the materials management department of hancock medical center. *Interfaces, 30*(4), 56–64.

Khouja, M., Mehrez, A., & Rabinowitz, G. (1996). A two-item newsboy problem with substitutability. *International Journal of Production Economics, 44*(3), 267–275.

Kim, D. (2005). An integrated supply chain management system: a case study in healthcare sector. *E-Commerce and Web Technologies*, 218–227.

Kok, A. G., & Fisher, M. L. (2007). Demand estimation and assortment optimization under substitution: methodology and application. *Operations Research, 55*(6), 1001–1021.

Landis, E. L. S. (2002). Provisional observations on drug product shortages: effects, causes, and potential solutions. *American Journal of Health-System Pharmacy, 59*, 2173–2182.

Landry, S., & Philippe, R. (2004). How logistics can service healthcare. *Supply Chain Forum, 5*, 24.

Lapierre, S. D., & Ruiz, A. B. (2007). Scheduling logistic activities to improve hospital supply systems. *Computers & Operations Research, 34*(3), 624–641.

Li, L. X., & Benton, W. C. (1996). Performance measurement criteria in health care organizations: Review and future research directions. *European Journal of Operational Research, 93*(3), 449–468.

Maas, A. (2012). *Oncology is Feeling Impact of Drug Shortages, High Costs*: 9 (editor). Specialty Pharmacy News, Atlantic Information Services.

Mahajan, S., & Ryzin, G. V. (2001). Inventory competition under dynamic consumer choice. *Operations Research, 49*(5), 646–657.

McGillivray, A. R., & Silver, E. A. (1978). Some concepts for inventory control under substitutable demand. *INFOR, 16*(1), 47–63.

Meijboom, B., & Obel, B. (2007). Tactical coordination in a multi-location and multi-stage operations structure: a model and a pharmaceutical company case. *Omega, 35*(3), 258–273.

Mohebbi, E. (2004). A replenishment model for the supply-uncertainty problem. *International Journal of Production Economics, 87*(1), 25–37.

Nagarajan, M., & Rajagopalan, S. (2008). Inventory models for substitutable products: optimal policies and heuristics. *Management Science, 54*(8), 1453–1466.

Nahmias, S. (2008). *Production and operations analysis*. McGraw-Hill.

Nathan, J., & Trinkaus, J. (1996). Improving health care means spending more time with patients and less time with inventory. *Hospital Materiel Management Quarterly, 18*(2), 66.

Nicholson, L., Vakharia, A. J., & Erenguc, S. (2004). Outsourcing inventory management decisions in healthcare: models and application. *European Journal of Operational Research, 154*(1), 271–290.

Parlar, M. (1988). Game theoretic analysis of the substitutable product inventory problem with random demands. *Naval Research Logistics, 35*(3), 397–409.

Parlar, M. (1997). Continuous-review inventory problem with random supply interruptions. *European Journal of Operational Research, 99*(2), 366–385.

Parlar, M., & Berkin, D. (1991). Future supply uncertainty in EOQ models. *Naval Research Logistics, 38*(1), 107–121.

Parlar, M., & Goyal, S. K. (1984). Optimal ordering decisions for two substitutable products with stochastic demands. *Opsearch, 21*(1), 1–15.

Parlar, M., & Perry, D. (1995). Analysis of a (q, r, t) inventory policy with deterministic and random yields when future supply is uncertain. *European Journal of Operational Research, 84*(2), 431–443.

Parlar, M., & Perry, D. (1996). Inventory models of future supply uncertainty with single and multiple suppliers. *Naval Research Logistics, 43*(2), 191–210.

Parlar, M., Wang, Y., & Gerchak, Y. (1995). A periodic review inventory model with markovian supply availability. *International Journal of Production Economics, 42*(2), 131–136.

Qi, L., Shen, Z. J. M., & Snyder, L. V. (2009). A continuous-review inventory model with disruptions at both supplier and retailer. *Production and Operations Management, 18*(5), 516–532.

Refetoff, S. (1975). Thyroid hormone therapy. *The Medical clinics of North America, 59*(5), 1147.

Ross, A. M., Rong, Y., & Snyder, L. V. (2008). Supply disruptions with time-dependent parameters. *Computers & Operations Research, 35*(11), 3504–3529.

Sani, B., & Kingsman, B. G. (1997). Selecting the best periodic inventory control and demand forecasting methods for low demand items. *Journal of the Operational Research Society, 48*(7), 700–713.

Schmitt, A. J., & Snyder, L. V. (2010). Infinite-horizon models for inventory control under yield uncertainty and disruptions. *Computers & Operations Research*.

Schmitt, A. J., Snyder, L. V., & Shen, Z. J. M. (2010). Inventory systems with stochastic demand and supply: Properties and approximations. *European Journal of Operational Research, 206*(2), 313–328.

Smith, S. A., & Agrawal, N. (2000). Management of multi-item retail inventory systems with demand substitution. *Operations Research*, 50–64.

Subrahmanyam, S., Pekny, J. F., & Reklaitis, G. V. (1994). Design of batch chemical plants under market uncertainty. *Industrial & Engineering Chemistry Research, 33*(11), 2688–2701.

Surks, M. I., Schadlow, A. R., & Oppenheimer, J. H. (1972). A new radioimmunoassay for plasma l-triiodothyronine: measurements in thyroid disease and in patients maintained on hormonal replacement. *Journal of Clinical Investigation, 51*(12), 3104.

Syntetos, A. A., Boylan, J. E., & Disney, S. M. (2009). Forecasting for inventory planning: a 50-year review. *Journal of the Operational Research Society, 60*, S149–S160.

Syntetos, A. A., Nikolopoulos, K., & Boylan, J. E. (2010). Judging the judges through accuracy-implication metrics: the case of inventory forecasting. *International Journal of Forecasting, 26*(1), 134–143.

Tomlin, B. (2006). On the value of mitigation and contingency strategies for managing supply chain disruption risks. *Management Science, 52*(5), 639.

U.S. department of health and human services, CDER manual of policies and procedures (MAPP) 6003.1: Drug shortage management. Food and Drug Administration, Rockville, MD. (2006).

U.S. (2010). – market summary. U.S. pharmaceuticals & healthcare report. *Technical report*. Business Monitor International Ltd..

Weiss, H. J., & Rosenthal, E. C. (1992). Optimal ordering policies when anticipating a disruption in supply or demand. *European Journal of Operational Research, 59*(3), 370–382.

Willemain, T. R., Smart, C. N., & Schwarz, H. F. (2004). A new approach to forecasting intermittent demand for service parts inventories. *International Journal of Forecasting, 20*(3), 375–387.

Yeo, W. M., & Yuan, X. M. (2010). Optimal inventory policy with supply uncertainty and demand cancellation. *European Journal of Operational Research*.

Zhao, X., & Lee, T. S. (1993). Freezing the master production schedule for material requirements planning systems under demand uncertainty. *Journal of Operations Management, 11*(2), 185–205.