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Review Articles

A Stochastic Approach to Blood Supply, Demand and Screening in Central Blood Banks - A Review

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Abstract: One of the major issues in securing blood supply to patients worldwide is to provide blood of the best achievable quality, in the needed quantities. Central Blood Services (CBS's) worldwide are daily faced with the problem how to satisfy demands for blood from various hospitals. These hospitals, in their turn, are faced with the problem how to satisfy demands for blood from their patients. To solve these problems in a cost-effective way is notoriously difficult, because (i) the amounts of available blood and of blood demand are random, (ii) blood can only be used during a limited amount of time, (iii) one must distinguish various blood components (red blood cells, plasma and platelets) with different associated costs and perishability and (iv) one must distinguish persons with different blood types (like AB^+ and O^-) with different capabilities to act as donor or as recipient. In this review paper we provide the subject background, describing the blood characteristics and the operation of CBS and hospital blood banks. In particular we describe blood demand, blood components and blood types. We depict blood screening procedures and their processing times and provide with some real data. Particularly we describe a stochastic approach to blood screening and inventory. An emphasis will be given to inventory management and blood allocation, stochastic imput-output of the inventory system and some cost functions involved.

Keywords: Blood Bank Service, Blood Demand and Supply, Blood Screening, Group Testing

Introduction

General Background

One of the major issues in securing blood supply to patients worldwide is to provide blood of the best achievable quality, in the needed quantities. In most countries blood, which is collected as whole blood units from human donors, is separated into different components which are subsequently stored in different storage conditions according to their biological characteristics, functions and respective expiration dates.

Blood units and components are ordered by hospital blood banks from the Central/regional Blood Services (CBS) according to their operational needs. The CBS has to run its inventory and supply according to these requests and to the need to keep sufficient stock for immediate release in emergency situations.

The *goal* of any CBS is to develop and analyze comprehensive models for the efficient, cost-effective operation of both CBS and hospital blood banks and their interplay, based on a survey of the real operation of such entities in various countries. These models are stochastic inventory models with the following special features: (I) perishable items (because the various blood components have finite expiration dates); (ii) several types of blood items with different capabilities to act as donor or as recipient (for example, AB^+ can be satisfied by all types and O^- can satisfy all types); (iii) the order in which blood units are issued may be important; a First In First Out (FIFO) policy is not always the natural order (this is related to features (i) and (ii)). Accordingly, one needs to extend existing stochastic inventory models for perishable items by also including features (ii) and (iii), with the goal to propose an optimal, or at least improved, cost-effective mode of operation. The relevant costs and revenues will be captured in a mathematical expression for a cost objective function which needs to be optimized.

Consequently, methods from operations management and probability theory (in particular stochastic inventory theory) are required to provide a detailed exact analysis and optimization of submodels which capture specific essential features of the blood issuing process. Such methods guide the quest for heuristic algorithms that provide a suboptimal solution to the general cost optimization problem. The related results lead to practical adjustments in CBS and hospital blood banks and in general will extend the range of inventory theory to important real-life storage systems with perishable items.

This review paper is organized as follows. In Section 2 we provide the subject background, describing the blood characteristics and the operation of CBS and hospital blood banks. In particular we describe blood demand, blood components and blood types. In Section 3 we depict blood screening procedures and their processing times. Section 4 is devoted to describing the notions of complete and incomplete identification group testing procedures. Some real data will also be presented in this section. In Section 5 we describe a stochastic approach to blood screening and inventory. An emphasis will be given to inventory management and blood allocation, stochastic imput-output of the inventory system and some cost functions involved. Section 6 outlines some research papers related to the stochastic approach. The paper is then concluded with some brief remarks.

The Operation of Blood Banks: Blood Components and Demand

In this section we successively discuss blood collection, blood testing, the various blood components (e.g., Red Blood Cells, plasma and platelets), the various blood types (ranging from O^+ to AB^-, see Section 2.3 for example), blood inventory management and blood issuing policies.

Blood Demand

In order for developed countries to maintain a sufficient inventory of blood units and components some 40; 000-50; 000 units of 'whole blood' (of 450 ± 50 ml) per one million inhabitants should be collected annually. Collections are performed in fixed donor sites or mobile blood drives. The bags containing the donated blood are then transferred under defined conditions to the CBS laboratories, for testing, processing, storage and supply.

Blood Components

Blood consists of several components. We distinguish Red Blood Cells (RBC), plasma and platelets. Processing the Whole Blood (WB) units into the different components is done in parallel to the testing stage. WB units are separated into different components, which have different biological functions, storage conditions and expiration dates. They will be supplied to different patients according to their medical needs:

Packed Red Blood Cells (RBC)

This component, which is separated from the whole blood unit within 8-24 hours from collection (based on the storage conditions of the WB units), should be stored in the cold (average of 4°C) and can be used within 35 to 42 days, depending on whether additive solution is added. RBC can be supplied to hospitals as an unmodified component, leukodepleted-following filtration and removal of the White Blood Cells (WBC) from the RBC and /or as irradiated RBC unit - following Gamma irradiation with 2500 rad. In Israel the cost of an unmodified packed RBC unit for the hospitals is $40 and that of a leukodepleted unit is $70. Hospitals acquire all the RBC that the National CBS can produce.

Plasma

Plasma units are mandatorily made upon the production of an RBC unit. Plasma unit can be frozen and kept for about one year. From these plasma units a component called 'cryoprecipitate' can be made. These two components are kept frozen at –20°C and below and can be stored for one year after donation. The corresponding price for a plasma unit is around $40; hospitals acquire 28% of all the plasma units produced, in addition to cryoprecipitate units produced from 11% of all the plasma units prepared. The surplus plasma units made from 'whole blood' (recovered plasma) are used for fractionation and preparation of various pharmaceutical plasma derived products, such as Albumin, plasma derived Factor VIII and Immunoglobulin (IVIg).

Platelets

From each whole blood unit one random platelet unit is separated, which can be used for at most 5 days. The therapeutic dose to a bleeding patient is composed of 4-6 such random units. The CBS produces random platelet units from 60% of the WB units collected to provide the national needs, with corresponding cost of about $40/unit. In addition, single donor platelets are produced by Pheresis techniques for hemato-oncological patients. The cost of such an Apheresis unit to the hospitals is around 1000 US$ each.

Blood Types: The ABO and the Rh Blood Group Systems

The main features of this subsection is taken from Wikipedia under the search for 'blood types'. Relevant references are cited there and for brevity are not cited in this paper.

"There are several blood group systems. The two most important ones are *ABO* and the RhD (or just Rh) antigen; they determine someone's blood type (*A*, *B*, *AB* and *O*, with + or – denoting RhD status).

The *ABO* blood group system is the most important blood-group system in human-blood transfusion: In human blood there are two antigens and antibodies. The two antigens are antigen *A* and antigen *B*. The two antibodies are antibody *A* and antibody *B*. The antigens are present in the red blood cells and the antibodies in the serum. Regarding the antigen property of the blood all human beings can be classified into 4 groups, those with antigen *A* (group *A*), those with antigen *B* (group *B*), those with both antigen *A* and *B* (group *AB*) and those with neither antigen (group *O*). The antibodies present together with the antigens are found as follows: (1) Antigen A with antibody B; (2) Anti- gen B with antibody *A*;(3) Antigen *AB* has no antibodies; (4) Antigen nil (group *O*) with antibody *A* and *B*. There is an agglutination reaction between similar antigen and antibody (for example, antigen *A* agglutinates the antibody *A* and antigen *B* agglutinates the antibody *B*). Thus, transfusion can be considered safe as long as the serum of the recipient does not contain antibodies for the blood cell antigens of the donor.

The Rh blood group system (Rh meaning Rhesus) is the second most significant blood-group system in human-blood transfusion with currently 50 antigens. The most significant Rh antigen is the D antigen, because it is the most likely to provoke an immune system response of the five main Rh antigens. It is common for D-negative individuals not to have any anti-D IgG or IgM antibodies, because anti-D antibodies are not usually produced by sensitization against environmental substances".

Consequently, in practice, there are 8 blood groups (types):

O^+, O^-, A^+, A^-, B^+, B^-, AB^+, AB^-, (O^+ stands for blood type *O* with Rh positive) where the interrelationship between the transfusion issuing policies among the 8 types is quite intricate as presented above. It turns out that each of the negative types can satisfy the corresponding positive type, but not vice versa. In addition, there are special interrelationships among the four positive types and also among the four negative types. For example, the type AB^+ can be satisfied by each of the 8 types, but not vice versa, whereas the O^- type can satisfy all the 8 types, but not vice versa. This special interrelationship among the 8 types is summarized in Table 1 (with $\sqrt{p}$ indicates that a recipient can get blood transfusion from an appropriate donor where *X* indicates the recipient cannot):

Table 1. The ABO system for donors and recipients

		Donors							
		O^+	A^+	B^+	AB^+	O^-	A^-	B^-	AB^-
Recipients	$O+$	√	X	X	X	√	X	X	X
	A^+	√	√	X	X	√	√	X	X
	B^+	√	X	√	X	√	X	√	X
	AB^+	√	√	√	√	√	√	√	√
	O^-	X	X	X	X	√	X	X	X
	A^-	X	X	X	X	√	√	X	X
	B^-	X	X	X	X	√	X	√	X
	AB^-	X	X	X	X	√	√	√	√

Nowadays, the percentages of the 8 blood types in the world population are roughly as follows: O^+ : 40%;O^- : 9%;A^+ : 31%;A^- : 7%;B+ : 8%;B^- : 2%;AB+ : 2%; AB^- : 1%

Blood Screening Procedures

Blood Screening (Testing)

In the laboratories of the Central Blood Services (CBS), each donated blood unit goes through multiple tests. These are aimed to determine the unit's blood type and the presence of various pathogens which are able to cause Transfusion- Transmitted Diseases, such as Hepatitis B (HBV), Hepatitis C (HCV), Human Immunodeficiency Virus (HIV) and Syphilis.

One remarkable fact is that about 35 years ago, before HBV and HCV testing of blood donations was mandatory, about 20% of the hepatitis cases were caused by blood transfusions. In the US, the FDA has progressively strengthened the overlapping safeguards that protect patients from unsuitable blood and blood products. Blood donors are asked specific questions about risk factors that could affect the safety of the donation and are deferred from donation if risk factors are acknowledged. FDA also requires blood centers to maintain lists of unsuitable donors to prevent further donations from these individuals. After donation, the blood is tested for several infectious agents. All tests must be negative before the blood is suitable for transfusion. In addition to these safeguards, FDA has significantly increased its oversight of the blood industry. The agency inspects all blood facilities at least every two years and 'problem' facilities are inspected more often. Blood establishments are now held to quality standards comparable to those expected of pharmaceutical manufacturers.

The cost of this screening is rising in developed countries and is a major economic burden in developing countries. The exact figures of costs to hospitals of acquiring and processing blood in the US and a survey of hospital-based blood banks and transfusion services are well detailed in (Toner *et al*., 2011); the annual costs of blood transfusion in the UK are presented in (Varney and Guest, 2003); the cost of blood transfusion in Western

Europe from five countries (UK, Sweden, Switzerland, Austria and France) is detailed in (Abraham and Sun, 2012; Schottstedt *et al*., 1998; Chiavetta *et al*., 2003; Jackson *et al*., 2003; AuBuchon, 2003; Stramer *et al*., 2004; Marshall *et al*., 2004; Hourfar *et al*., 2008; Ghandforoush and Sen, 2010; Stramer *et al*., 2011). Details are omitted for brevity.

The blood laboratories have developed two different test procedures. The older one is called Enzyme Linked Immuno-Sorbent Assay (ELISA). This procedure detects virus-specific antibodies in the blood. The benefit of this procedure is that it has high sensitivity and specificity, so the blood sample could be screened properly. There is one disadvantage though. There are viruses such as HIV, for which the immune system requires a lot of time to develop a high concentration of antibodies. As a result, the ELISA test cannot detect the virus during the first days (or weeks) after infection. Thus, the ELISA procedure has a lower analytic detection limit. Actually the period elapsing from the time a person is infected by some virus until antibodies can be detected, is called *window period*. Examples of average window periods for some viruses are: 22 days for HIV, 60 days for HBV and 70 days for HCV. During the window period, the ELISA method might provide wrong information about the blood sample. This problem was the motivation for the use of a new test procedure which is called Polymerase Chain Reaction (PCR). This test detects viral genetic material in the blood which is a distinct advantage because in this way the test has much higher sensitivity and specificity than ELISA during the window period. If a person just infected the PCR immensely multiplies the number of antigens and thus makes it possible to detect the presence of pathogens in cases where ELISA fails to do so (due to the window period effect). Thus, the PCR test increases the chances of early detection and decreases morbidity and mortality due to post transfusion infections (e.g. (Stramer *et al*., 2004; Hourfar *et al*., 2008). The PCR method can also be used during the window period. However, PCR is rather expensive relative to ELISA.

The main policy that the blood banks use in the USA and some countries in Europe is the following: All blood samples are tested in the ELISA station in batches (or groups) due to the lower cost. The batches found clean from this test are re-tested individually in the PCR station. If a blood sample is found clean from both of the stations, then it is stored and ready to be used. Batches found contaminated at ELISA and items found contaminated at PCR, are discarded and not used for blood transfusions (c.f., (Bish *et al*., 2011; Chick, 1996; Chiavetta *et al*., 2003; Gastwirth and Johnson, 1994; Hammick and Gastwirth, 1994; Hanson *et al*., 2006; Hourfar *et al*., 2008; Jackson *et al*., 2003; Kantanen *et al*., 1996; Litvak *et al*., 1994; Monzon *et al*., 1991; Schottstedt *et al*., 1998; Steiner *et al*., 2010; Stramer *et al*., 2004; 2011; Wein and Zenios, 1996; Zhu *et al*., 2001).

Processing (Or Service) Times

On the average it takes about 15 hours till blood samples arrive in the CBS from the times they have been donated. The average processing time of an ELISA test is around 1 hour and costs around $1: 5 per an average group (of blood units) of size 10; whereas that of the PCR is around 6 hours with an associated cost of about $60 per blood unit. Such time constraints are vital for platelets shelf-life, but less significant for RBC. However, such processing times should be taken into account in any blood screening procedure.

Group Testing Procedures for Blood Screening

Background

The issue of blood transfusion might be a question of life and death. This means that it is of paramount importance that all the blood units that enter the shelf are clean. Therefore, a necessary requirement is a meticulous inspection of all the blood units. However, since thousands of blood units (or blood samples) arrive at the central blood bank every day, a natural screening procedure must be based on the idea of group testing; otherwise, the screening process will take too long and the costs of this process will be too high.

Group testing deals with the classification of the items of some population into two categories: ‘Good’ and ‘defective’. It is assumed that the items are group testable, i.e., for any subset of the population it is possible to carry out a simultaneous test (group test) with two possible outcomes: ‘Success’ (also called ‘clean’, or ‘negative’), indicating that all items in the subset are good and ‘failure’ (also called ‘contaminated’, or ‘positive’), indicating that at least one of the items in the subset is defective without knowing which or how many are defective.

A contaminated group can be subject to further screening, or be scrapped. Employing suitably designed procedures of this kind leads to a significant reduction of the number of required tests and thus of screening costs, under controlled probabilities of misclassfication. A group testing procedure is therefore a cost-efficient technique. It has been applied in various areas, first and foremost, for blood screening to detect various viruses, for DNA screening, genetics as well as for agriculture (rice grain) and quality control for industrial production systems (e.g. (Bar-Lev *et al*., 1990; Macula, 1999; Xie *et al*., 2001; Uhl *et al*., 2001; Yamamura and Ishimoto, 2009). A key and comprehensive reference for various applications is the monograph by Du and Hwang (2000).

Complete Versus Incomplete Identification

One may currently distinguish two types of identification testing procedures: Complete and incomplete. The purpose of a complete identification group testing procedure is to classify each item in a given population as either clean or defective. This is done by testing groups of size m (a decision variable) in the ELISA station only. If a group is found clean it is aggregated for blood transfusion purposes, otherwise, if it is found contaminated it will be further re-tested by dividing it into subgroups. Such a procedure continues till each item in a given population is appropriately classified.

One could imagine two managerial reasons in which complete identification procedures are inefficient. The first one is that the tests are too expensive. Then a complete identification procedure leads to a high expected number of tests and, as a result, to high expected total testing costs. The second one is that the shelf-life is short (recall that the shelf-life of platelets is at most 5 days). Then the higher the number of tests, the shorter the residual shelf-life of clean items on the shelf. The idea of an Incomplete Identification group testing Procedure (IIP) was first introduced in (Bar-Lev *et al*., 1990) for some industrial problem and was subsequently further developed for blood screening (e.g. (Bar-Lev *et al*., 2017a; 2006). An IIP starts as above by first testing groups of size m in the ELISA station. However, as opposed to the previous case, a group found contaminated is scrapped; otherwise, it is aggregated and sent to the PCR station for individual testing. Such a procedure is cost-wise rather efficient as it significantly decreases the number of tests (whether grouped or individual). It is particularly efficient when the prevalence rate of the "deficiency" (like the prevalence rate of, say, HIV in the population) is rather small (c.f., (Johnson and Gastwirth, 2000; Tebbs *et al*., 2013; Tu *et al*., 1995; Wolf, 1985.).

In order to give some idea how real data are processed we mention the following. In Western European countries (as well as in the US, Israel and some other countries) about 40; 000 to 50; 000 blood donations are needed per 1 million persons per year. The following data for the years 2011-2012 have been provided to us by the Israeli Central Blood Bank. The data presented in Table 2 describe per year the number of blood donations (blood units), the number of blood units found contaminated at the ELISA station (including HIV, HBV and HCV) and the number of units found clean at the ELISA station but then found contaminated at the PCR station (for the two years 2011 and 2012 the population size of Israel was about 7; 800; 000 and 7; 900; 000, respectively).

Table 2. Data for the years 2011 and 2012 of the Israeli Central Blood Bank

		Cases confirmed positive by ELISA			
Donations	Year	HBV	HCV	HIV	Total
294,117	2011	126	62	13	201
298,470	2012	143	62	3	208

The table suggests that the estimated probability of finding a given unit to be contaminated at the ELISA station is approximately 0: 068%. Note that this estimated probability is smaller than the prevalence rate of the contaminating virus(es) in the population as those infected persons who are aware of their situation usually do not donate blood samples. This means that if the probability of contaminated blood units is not known, for some reason, then the prevalence rate in the population can be used as an upper bound for such a probability. All of the positive ELISA units were also judged positive by PCR, but, in addition, there were another 12 units in 2011 and 13 in 2012 that were only found positive by PCR (but not by ELISA). Hence, the estimated probability of those units found clean by ELISA but then found contaminated by PCR is 0: 004% for both years 2011 and 2012.

A Stochastic Approach to Blood Screening and Inventory

As can be readily seen the blood inventory and screening issues call for and can be handled by probabilistic and operation research (OR) tools. These tools embrace and incorporate various areas in probability and OR such as inventory management, chain supply, queueing theory, level crossing theory, perishable commodities and optimization of cost functions which take into account all related costs (c.f. (Bar-Lev and Perry, 1993; Bassok *et al*., 1999; Berk and Gürler, 2008; Claeys *et al*., 2010; Cohen, 1977; Doshi, 1992; Kaspi and Perry, 1983; 1984; Nahmias, 2011; Nahmias *et al*., 2004a; 2004b; Parlar *et al*., 2010; Perry, 1985; 1997; 1999; Perry and Posner, 1990; Perry and Stadje, 1999; 2000a; 2000b; Perry *et al*., 2000; Perry and Stadje, 2001; 2003; 2006; Zhang, 2013). The next subsections describe some features and ingredients of the stochastic approach. The section is concluded with outlining some research papers related to the stochastic approach.

Inventory Management and Blood Allocation

Both Central (national or regional) Blood Services and hospital blood banks face the major challenge to provide an efficient and cost-effective inventory management and blood issuing process. This process has to take into account health issues, (fluctuations in) actual demands, expiration dates of stored items, cost aspects, as well as requirements regarding safety stock.

According to the recommendation of Health Ministries in various countries, the CBS and the hospital blood banks have to maintain an inventory of at least 3 days work, while small and remote hospitals (over 2 hours drive from the CBS) are required to have a 5 days work inventory, in order to meet the routine needs of the medical system and to be able to respond to an immediate increase in demands during emergencies.

Based on a study of its inventory and knowledge of its patients, a hospital sends daily requests to the CBS for specific amounts of blood units and components, of the various types. For example, hospitals 1,...,*n* might ask, respectively, for $X_1,...,X_n$ units of blood type O^-. The CBS must decide how to meet the demands of blood units and components, by blood type and their age, using all available information regarding the quantity of ready-to-use units in the stock, those in preparation and the collection forecast. Furthermore, if inventory is too low, it might decide that specific actions are required – such as summoning donors according to specific blood types or conducting a general call in the media.

The CBS and the hospitals also have to decide about their blood issuing policy, viz., the order in which particular blood units are made available. In most countries blood is traditionally supplied to patients on a FIFO basis, with some exceptions (i.e., neonates, massive transfusion in trauma). The question of whether storage of RBC alters their capacity to deliver oxygen and affects patient outcome remains in a state of clinical equipoise. Studies of the changes during RBC storage have in some cases suggested that these changes impair RBC function and may be associated with worse clinical outcomes (Steiner *et al*., 2010), while others have found no effect.

The above-described decision processes of CBS and hospitals are highly complex, involving multiple health, logistic as well as cost-effectiveness criteria. There is a clear need for probabilistic models that are able to assist the CBS management and hospital managements, in developing effective inventory management and blood allocation processes. We believe that, to a considerable extent, this need can be satisfied by building upon and generalizing, recently developed models and methods for stochastic inventory systems with perishable items and for organ transplant systems.

Stochastic Input-Output of the Inventory System

The basic stochastic input-output inventory system for perishable items (as RBC, platelets and plasma have expiration dates) is the following. Items arrive randomly at an inventory system, henceforth also called 'shelf', in batches of units according to some stochastic arrival process. Each item is stored until it is either taken away by a demand or, after a certain amount of time on the shelf, is outdated (and then scrapped). The arrival times of these demands, which are all for single items, form another stochastic process, which is independent of the item arrival process. A demand remains unsatisfied if it arrives at an empty shelf. This basic model was studied in (Kaspi and Perry, 1983; 1984) (already with blood inventory management in mind), introducing the so-called virtual outdating process (see e.g. (Cohen, 1977; Doshi, 1992), under the assumption that the item and demand arrival processes are Poisson processes and that the shelf life time of items is constant (deterministic). Several extensions and ramifications have been studied; see for example (Bar-Lev and Perry, 1989; Berk and Gürler, 2008; Deniz *et al*., 2010; Doshi, 1992; Kaspi and Perry, 1983; 1984; Nahmias, 2011; Nahmias *et al*., 2004; 2004b; Parlar *et al*., 2010; Perry, 1985; 1997; Perry 1999; Perry and Posner, 1990; Perry and Stadje, 1999; 2000a; 2000b; Perry *et al*., 2000; Perry and Stadje, 2001; Perry, 2003; 2006; Boxma *et al*., 2001; Zhang, 2013). The main mathematical tools employed in those studies are level crossing theory for Markov processes, martingales and stopping times. A comprehensive survey of early results on perishable inventory systems is provided by (Nahmias, 2011).

The first goal of the stochastic approach is to develop models for a CBS incorporating the real requirements from practice as described previously. Regarding hospital blood banks, the following important issues have to be taken into account:

a) Combination of scheduled and random arrivals
b) Batch arrivals of blood units and demands
c) Demands with patience
d) Blood group handling: the ABO-Rh factor, which refers to the different capabilities of the various blood types (like AB^+ and O^-) to act as donor or as recipient
e) Issuing policies (deviating from FIFO)

Cost Functions Involved

The goal of a stochastic approach is to develop and analyze comprehensive models for the efficient, cost-effective operation of both CBS and hospital blood banks and their interplay. The relevant costs and revenues should be captured in a mathematical expression for a cost objective function which needs to be optimized. The most important revenues and costs involved in the operation of the CBS are:

- Revenues earned from satisfied demands (notice that this takes into ac-count lost revenues because of outdating);
- The purchase costs of the stored items
- The holding costs for the items on the shelf
- The penalties due to unsatisfied demand requirements

- Extra costs for performing additional blood drives (e.g., advertising)
- Payment to the CBS employees. This is very relevant, since extra-hours(beyond 7 working hours/day) and shifts during evenings, nights, week-ends and holidays lead to increased costs for the CBS
- The possible costs due to a change of the expiration dates for each of the component units

Adding the various costs, with appropriate weight factors, one can either try to evaluate the long-run average costs per time unit (this requires a steady-state analysis of the system) or try to determine the expected discounted costs over an infinite time horizon. For this purpose, one needs to determine various performance measures for each component and type, like the (mean) number of items 'on the shelf', the mean number of unsatisfied demands and of outdatings per day, as well as the frequency of additional blood drives.

The manager's objective is to minimize the expected cost of running the CBS in the above manner by suitably choosing the decision variables: This has to include (i) the dynamic control of the amounts of blood of each component and type which are sent to hospitals; (ii) an issuing policy specifying the order in which blood components of the different types are sent out in dependence of their current expiration dates; (iii) the decision on special actions increasing or decreasing the production of blood units.

In its full complexity, the cost optimization problem does not seem to be analytically tractable. However, a detailed exact analysis and optimization of submodels, which capture specific essential features of the blood issuing process, should be provided. Those results should guide in quest for heuristic algorithms that provide a suboptimal solution to the general cost objective optimization problem.

Some Research Works Related to the Stochastic Approach

The author along with other OR researchers and in consultation with blood bank practitioners have been engaged with some of the aforementioned stochastic approach to blood bank management. Their engagement has resulted in several papers, (c.f., (Bar-Lev *et al*., 2009; 2017; 2017a; 2017b; Bar-Lev and Perry, 1989; Bar-Lev *et al*., 2005; 1995; 2007; 2013; 2003; 2004a; 2004b; 2006). Other works can be found in (Abolnikov and Dukhovny, 2003; Kopach *et al*., 2008; Beliën and Forcé, 2012; Civelek *et al*., 2015; Ghandforoush and Sen, 2010; Karaesmen *et al*., 2011; Marshall *et al*., 2004; Sebastian *et al*., 2012; Shi and Zhao, 2010; Deniz *et al*., 2010; Blake and Hardy, 2014; Xie *et al*., 2012). The aim in those paper was to develop comprehensive inventory control and group testing models that incorporate the key features of a CBS and a hospital blood bank. CBS and hospitals face similar management problems, but there are some clear distinctions. For example, unlike a CBS, a hospital has continuous review (a continuous-time model) and demands arrive randomly instead of according to a daily pattern. In particular they have treated the following main ingredients.

The CBS should keep prespecified inventory levels of each of the above-mentioned blood components units, taking in consideration the eight specific blood types ($O^{\pm}$, $A^{\pm}$, $B^{\pm}$, $AB^{\pm}$) , sufficient for a certain number of working days, to enable its regular operation and to be prepared for any emergency increase in the demand for blood. For each of the component units one has to keep track of the number of units on the shelf of the, say m, different possible ages: For any $n \in \{0, 1, 2,...,m-1\}$ let $N_{ij}(n)$ be the m-vector whose k-th entry is the number of component units of age k and type ij at time n, where i = 1, 2, 3 stands for RBC, plasma and platelets, respectively and $j \in \{1,..., 8\}$ denotes the blood group. Then $N(n) = (N_{ij}(n))_{i = 1,2,3,\ j = 1,...,8}$ contains all relevant information about the contents (inventory levels) of the CBS. For a hospital blood bank, one needs to study a similar, but continuous-time, stochastic process.

Demands for the various components arrive at any time instant n (e.g., daily), either for single items or for batches. Inability to satisfy demand requirements results in penalties, which may differ for different kinds of demands (e.g., routine versus emergency demands).

Items also arrive at the CBS at any time n. There is a fixed set of scheduled blood donations and there are occasionally appearing donors, so that the exact number of donors is random, but the different components always occur in equal numbers. The CBS can control the underlying probability distribution, which means that one can choose from a set of possible distributions (where the cost of a stochastically larger distribution is of course higher than that of a smaller one).

The expiration dates of the components are fixed exogenously according to current medical standards. However, as mentioned above, some studies have shown a correlation between worse clinical outcomes and transfusion of RBC stored for a longer period of time (35 to 40 days, say). This may have an influence on the way RBC are managed. This means that the expiration date of RBC might be shorter, implying that it could also be taken as a decision variable.

Concluding Remarks

We would like to conclude this review paper with a quote of one of the CBS directors in one of the EU countries: "analysis of the current operation procedures, taking into account all the relevant needs, cost and revenue functions in probabilistic and statistical

terminology, may result in a base numerical approaches and provide the Transfusion Medicine field with recommendations to optimize blood inventory management, both in the level of the central/regional blood services and the hospital blood banks and the development of comprehensive probabilistic models for a more efficient, cost-effective operation for both the CBS and hospital blood banks and their interplay and will provide an optimal, or at least improved, operation. The collaboration among blood bank practitioners an Operation Research researchers sounds promising and will most beneficial for various blood bank aspects as optimization of blood inventory and screening as well as blood issuing policies".

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Ethics

This article is a review article and contains no new contributions. The author Professor Shaul K. Bar-Lev takes responsibility for any errors or typos in this article.

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