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Innovative Applications of O.R.

Recycled incomplete identification procedures for blood screening

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ABSTRACT

The operation of blood banks aims at the cost-efficient supply of uncontaminated human blood. Each unit of donated blood goes through multiple testing for the presence of various pathogens which are able to cause transfusion-transmitted diseases. The blood screening process is comprised of two phases. At the first phase, blood units are screened together in pooled groups of a certain size by the ELISA (Enzyme Linked Immuno-Sorbent Assay) test to detect various virus-specific antibodies. The second phase of the screening process is conducted by PCR (Polymerase Chain Reaction) testing of the individual blood units of the groups found clean by the initial ELISA phase.

Thousands of units of donated blood arrive daily at the central blood bank for screening. Each screening scheme has associated testing costs and testing times. In addition, each blood unit arrives with an expiration date. As a result, the shorter the testing time, the longer the residual lifetime that is left for the blood unit for future use. The controller faces a natural and well-motivated operations management problem. He will attempt to shorten the testing period and reduce the testing costs without compromising too much on the reliability. To achieve these goals, we propose a new testing procedure that we term Recycled Incomplete Identification Procedure (RIIP). In RIIP, groups of pooled blood units which are found contaminated in the ELISA test are divided into smaller subgroups and again group-tested by ELISA, and so forth, until eventually the PCR test is conducted for those subgroups which are found clean. We analyze and optimize the performance of RIIP by deriving explicit formulas for the cost components of interest and maximize the profit associated with the procedure. Our numerical results suggest that it can indeed be profitable to do several cycles at ELISA.

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1. Introduction

The operation of blood banks, worldwide, is aimed at the supply of uncontaminated human blood. In the laboratories of the Central Blood Services (CBS's), each donated blood unit goes through multiple tests. These are aimed at determining 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; see, e.g., Hourfar et al. (2008), Kantanen, Koskela, and Leinikki (1996), Kline, Brothers, Brookmeyer, Zeger and Quinn (1989), Monzon et al. (1992), Schottstedt, Tuma, Bünger, and Lefèvre (1998), Steiner et al. (2010), Stramer et al. (2004).

Until 20 years ago, the routine testing was done with the ELISA (Enzyme Linked Immuno-Sorbent Assay) test that detects virus-specific antibodies in the blood. This test serves as a marker for the number of antibodies detected after a person is infected. However, it is important to take into account the effect of the window period, defined as the period elapsing between the time a person is infected by the virus till a high concentration of antibodies is developed. The window period varies for different types of viruses. Examples of average window periods for some viruses are: 22 days for HIV, 70 days for HCV and 60 for HBV. This means that if a person has just recently been infected by a virus, the ELISA test fails to detect such an infection.

A few years ago, a new test called PCR (Polymerase Chain Reaction) has been developed. If a person was just recently infected, the PCR test immensely multiplies the number of antigens and thus makes it possible to detect the presence of pathogens in cases where the ELISA test fails to do so (for example due to the window period effect). Hence the PCR test has a much higher sensitivity (probability of a positive test result for an infected person)

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than the ELISA test. However, PCR is very expensive compared to ELISA.

Therefore, blood banks in the USA, Israel and some countries in Europe have established a screening protocol whereby all blood units are ELISA tested in groups and those which tested negative for ELISA are re-tested individually with PCR (see e.g. Hourfar et al., 2008; Schottstedt et al., 1998; Stramer et al., 2004).

The operation of blood bank systems is characterized by two crucial factors: (i) testing procedures and (ii) perishability. Testing is necessary, since only clean blood units are used for blood transfusion; groups found contaminated at ELISA, and units found contaminated at PCR, are discarded. Thousands of units of donated blood arrive daily at the central blood bank system for screening. Testing times and testing costs are associated with the screening process. In addition, each blood unit has an expiration date; after that it is perished. The controller faces a natural and well-motivated operations management problem. On the one hand, there is the need to make the testing period as short as possible; on the other hand, careful testing is required, which takes time and is costly. This raises the need to find more efficient group testing procedures, with the restriction of incomplete identification.

Since ELISA testing is relatively cheap, we propose a new screening process that we term Recycled Incomplete Identification group testing Procedure (RIIP), by which groups of pooled blood units, which are found contaminated in the previous ELISA cycle, are divided into smaller subgroups and again group-tested by ELISA, and so forth, until finally the PCR test is conducted for those subgroups which are found clean.

The goal of this paper is to provide an analysis and optimization of the performance of RIIP, in particular minimizing the costs (or maximizing the profit) associated with the test procedure. Somewhat related papers are (Bish, Bish, Xie, & Slonim, 2011; Xie, Bish, Bish, Slonim, & Stramer, 2012). Those papers also study the problem of selecting an effective set of screening tests for donated blood. They focus on the problem of minimizing transfusion-transmitted infectious diseases, under certain budget constraints (Bish et al., 2011) and in addition also under waste constraints (Xie et al., 2012). Other optimization problems regarding blood management that have received much attention are supply chain management and inventory management. We refer to Beliën and Forcé (2012) for a very thorough literature review of inventory and supply chain management of blood products, and to the two recent studies (Blake & Hardy, 2014) and Civelek, Karaesmen, and Scheller-Wolf (2015) for interesting new results on inventory management policies.

In the next subsections we describe some features of a blood bank system. In Section 1.1 we describe the separation process of each blood unit into its three components along with their expiration dates and associated costs. The concept of group testing is reviewed in Section 1.2. In Section 1.3 we present the group testing procedures (complete and incomplete identification procedures) that are currently in use by blood banks. The further organization of the paper is outlined in Section 1.4.

1.1. Blood components

Blood consists of several components: Red blood cells (RBC), plasma and platelets. Processing the whole blood units into the different components is done in parallel to the testing stage. Whole blood 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:

1. *RBC* – This component, which is separated from the whole blood unit within 8–24 hours from collection, can be used within 35–42 days, depending on whether additive solution is added. Mostly, the cost of an unmodified packed RBC unit for the hospitals is $40 and that of a leukodepleted (solution added) unit is $70.
2. *Plasma* – Plasma units are automatically made upon the production of an RBC unit. The corresponding cost for a plasma unit is around $40; hospitals acquire 28% of all the plasma units produced.
3. *Platelets* – From each whole blood unit one random platelet unit is separated, which can be used for at most 5 days. The cost of producing random platelet units is about $40/unit (Bar-Lev, Stadje, & Van der Duyn Schouten, 2005).

With respect to the above expiration dates, the following should be taken into account. On average it takes about 15 hours till blood samples arrive in the CBS after the moment they have been donated. The average processing time of an ELISA test is around 1 hour and costs around $2.5 per average group (of blood units) of size 10, whereas that of the PCR is around 6 hours with an associated cost of about $85 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.

1.2. Group testing

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 (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 misclassification. 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, as well as for quality control for industrial production systems (see, e.g., Bar-Lev, Blanc, Boxma, Janssen, & Perry, 2013; Bar-Lev, Boneh, & Perry, 1990; Bar-Lev, Parlar, & Perry, 1995; Bar-Lev, Parlar, Perry, & Van der Duyn Schouten, 2007; Bar-Lev, Stadje, & Van der Duyn Schouten, 2003; 2004; 2005; 2006; Beliën & Forcé, 2012; Bish et al., 2011; Blake & Hardy, 2014; Chick, 1996; Civelek et al., 2015; Du & Hwang, 2000; Feller, 1968; Gastwirth & Johnson, 1994; Hammick & Gastwirth, 1994; Hanson, Johnson, & Gastwirth, 2006; Hourfar et al., 2008; Hughes-Oliver & Rosenberger, 2000; Johnson & Gastwirth, 2000; Litvak, Tu, & Pagano, 1994; Macula, 1999a; Macula, 1999b; Tu, Litvak, & Pagano, 1995; Uhl, Liu, Walther, Hess, & Naiman, 2001; Wein & Zenios, 1996; Wolf, 1985; Xie, Tatsuoka, Sacks, & Young, 2001; Xie et al., 2012; Yamamura & Ishimoto, 2009; Zhu, Hughes-Oliver, & Young, 2001).

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