Optimal Allocation of Resources for Screening of Donated Blood

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(ABSTRACT)

Blood products, either whole blood or its components, are vital healthcare commodities for patients across all age groups, multiple diagnoses, and in a variety of settings. Meanwhile, blood shortages are common, and are projected to significantly increase in the near future in both developing and developed countries due to a limited supply of and increasing demand for blood, lack of resources, infrastructure. Unfortunately, today there remains a definable risk associated with the transfusion of blood and blood products. We explored, in depth, the resource allocation problem in reducing the risks of transfusion-transmitted infections (TTI). We developed models and algorithms to study the problem of selecting a set of blood screening tests for risk reduction, which we show to be very efficient in numerical studies with realistic-sized problems. This analysis also motivates the development of effective lower bounds with co-infection; our analysis indicates that these algorithms are very efficient and effective for the general problem. We also incorporate other objective functions and constraints (i.e., waste) into the analysis. Waste, defined as the fraction of disposed blood in the "infection-free" blood, is incorporated into the risk-based model as a constraint. As an important extension, we compared our results of the blood screening problem in risk model with that of weighted risk objectives, which allows for different weights for each TTI. We further explored efficient algorithms to study this extension of the model and analyze how the test composition changes with the different objectives. Finally, in the context of blood screening, the last extension we investigated is to include a "differential" testing policy, in which an optimal solution is allowed to contain multiple test sets, each applied to a fraction of the total blood units. In particular, the decision-maker faces the problem of selecting a collection of test sets as well as determining the proportion (or fraction) of blood units each test set will be administered to. We proposed the solution methodology and determined how the test sets under differential policy relate to those under the "same-for-all" policy; and how these changes impact the risk, and allow for better budget utilization.

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Chapter 1

Introduction

1.1 Motivation

In both rich and poor nations alike, public resources are inadequate to meet the increasing demand for healthcare. As a result, policy makers and healthcare providers are required to deliver healthcare in the most efficient and effective ways using the limited resources (Brandeau et al., 2004). The field of Operations Research (OR) offers a set of tools and methodologies that can be utilized to address operational and strategical decision-making in healthcare, with focus on an optimal allocation of the scarce resources to activities in the most beneficial way for the whole system. As such, OR methods have been used for various facets of healthcare planning and decision-making (Brandeau et al., 2004), and OR has already made, and further will make, considerable contributions for the effective and efficient delivery of healthcare services. Our research broadly falls within this area of using OR methods to improve the delivery of healthcare.

Healthcare is a high-risk, error-prone industry. This research focuses on an important aspect of healthcare delivery in a variety of clinical contexts, that of improving its safety, through the use of OR methodology. Specifically, we focus on two important procedures: blood transfusion and joint (hip and knee) replacement surgery. Both these procedures can greatly benefit the patients when properly delivered, but have adverse outcomes otherwise. These contexts have particularly been selected for several reasons. First, they represent procedures that have been associated with several adverse outcomes in the literature (e.g., mortality from joint surgery; transfusion-

transmitted human immunodeficiency virus infection); and more importantly, there are relevant and readily available data to study the healthcare safety within these clinical contexts.

Blood products, either whole blood or its components, are vital healthcare commodities for patients across all age groups, multiple diagnoses, and in a variety of settings. Most organ transplants, cancer therapies, heart and other surgeries, resuscitation of trauma victims, as well as care and survival of premature infants, children with severe anemia, and pregnant women with complications would not be possible without blood transfusion. As a result, there is high and increasing demand for blood worldwide, and a large number of people (e.g., 40 to 70% of the US population (Hay et al., 2006)) will need blood transfusion at some point in their lives.

Unfortunately, today there remains a definable risk associated with the transfusion of blood and blood products. These risks may occur in both the pre-clinical and clinical dimensions of the transfusion process, from blood collection from a donor through blood administration to a patient. Transfusion safety is concerned with identifying and mitigating the hazards associated with delivering transfusion care to patients. The potential hazards of blood transfusion can be grouped into several broad categories including infections, immune reactions, human and testing errors, and we incorporate each of these aspects through a Probabilistic Risk Assessment framework.

Next, we focus on one of these categories: the risk of transfusion-transmitted infections. These transfusion-transmitted infectious diseases (TTIs) include the human immunodeficiency virus (HIV), hepatitis viruses, human T-cell lymphotropic virus (HTLV), syphilis, West Nile Virus (WNV), Chagas' Disease, etc. Because blood products are an essential component of any health system, effective blood screening under limited budget is critical. However, this is compounded by the facts that (i) no blood screening test is perfectly reliable (each test has the possibility of providing false-positive or false-negative results); (ii) most screening tests are expensive and resources are limited; (iii) co-infections are likely for certain infections (e.g., HIV and hepatitis viruses B and C) and may impact the decision; (iv) the decision-maker needs to be also concerned of the "waste" in blood supply resulting from false positive testing errors, especially as blood shortages are on the rise worldwide. Our objective is to develop models and algorithms to study the problem of selecting a set of blood screening tests considering the important aspects outlined here. We also study an extension of the model by allowing "differential" testing, which provides flexibility by allowing different test sets to be administered to different portions of donated blood. These two problems constitute the basis of this dissertation for the

context of blood transfusion.

For the second clinical context, joint replacement surgeries are known as one of the most frequent elective procedures used to treat degenerative joint disease (DJD) in the United States (US). It is a cost-effective, therapeutic strategy for patients with hip and knee DJD because of its ability to increase mobility, reduce pain, and improve the quality and years of productive life (Dorr et al., 1990; Matsen, 1996; Ranawat et al., 1984; Rissanen et al., 1997; Segal et al., 2004; Chang et al., 1996; Liang et al., 1986). In 2003, approximately 200,000 total hip replacements, 100,000 partial hip replacements, 36,000 hip replacement revisions, and even more knee replacements were performed in the US (Zhan et al., 2007). The demand for joint replacement has remained high even for patients with advancing age. Approximately 60% of hip replacements were performed on those over 65 years of age. Our objective is to establish the relationship between mortality and surgeon volume, hospital volume, and hospital size so as to provide important insights into the factors that affect the quality of healthcare in this context.

1.2 Research Overview

For the research in blood safety, we first develop and analyze, in Chapter 3, a comprehensive risk model so as to quantify the overall risk from transfusion of red blood cells (RBC) in the United States. In particular, we use Probabilistic Risk Assessment (PRA), also known as fault tree analysis, which is a quantitative and deductive process analysis tool that can be used for risk assessment and management. While PRA has been commonly used in high-risk industries, such as nuclear power, aviation and aerospace, to investigate rare events that have potentially devastating outcomes, its use in healthcare has been limited. Utilizing PRA, we develop a comprehensive risk model of RBC transfusion by considering the relationship between the various risk points (events) and an adverse transfusion outcome. We determine the contribution of each event to an adverse transfusion outcome and identify the "critical points" that are the major contributors to the overall risk. This analysis then allows us to identify targeted interventions and evaluate their costs and benefits for risk reduction within a systematic framework.

In Chapters 4-6, we examine a more specific threat to the safety of blood transfusion: the risk of transfusion-transmitted infectious diseases (TTIs). New testing technologies are being developed, offering new options of price and efficacy so as to improve blood safety, but these technologies typically come at very high costs (Dzik, 2003;

Jackson et al., 2003). Thus, it is often the case that multiple tests, with varying degrees of efficacy and costs, are available for screening for the same infection. Then the questions faced by the decision-maker (Blood Bank or Blood Collection Center, such as the American Red Cross) include the following: (1) How should the limited resources be optimally allocated to the screening tests in order to minimize the risk of a TTI? and (2) How should the results of the selected battery of tests be interpreted, that is, what is the "decision rule" for concluding that the blood unit is infected by a certain infection when multiple tests are administered for it and their results are not in agreement? Furthermore, these questions are interrelated, in that, the risk of a TTI depends, in a complex way, on both the selected test battery and the decision rule adopted.

What complicates the problem further is the possibility of *co-infections* in blood donors, i.e., a donor being simultaneously infected with multiple TTIs, as some viruses, such as the HIV, may make the individual more susceptible to acquiring other viruses. Indeed, co-infections are likely for the HIV and the hepatitis viruses B and C (HBV, HCV). It is estimated that up to 10% of HCV-positive individuals test positive for the Hepatitis B surface antigen (HBsAg), and that up to 20% of HBV-positive individuals are co-infected with HCV (Gordona and Sherman, 2009). While 15% to 30% of HIV-infected individuals worldwide suffer from chronic HCV infection, among those HIV-positive individuals that are infected parenterally, such as haemophiliacs and intravenous drug users, chronic HCV infection can be as high as 75%. Chronic HBV infection, on the other hand, occurs in 10% of HIV-infected individuals (Carmo et al., 2000; Lincoln et al., 2003; Soriano et al., 2006). For the donor pool in the US, which undergoes systematic donor screening[1], these numbers will serve as upper bounds, as a portion of the individuals who are considered to be at risk for HIV or hepatitis viruses will be eliminated through donor screening. However, for some developing countries, these co-infectious donors, unfortunately, are *not* less likely to be in the donor pool, as donor screening is not rigorous and systematic (Lancet Editorial, 2005). Blood is collected exclusively from voluntary unpaid donors in only 39 of 178 countries, and "42% of blood collected from donors in medium and low Human Development Index countries comes from family replacement or paid donors, and this blood often contains a higher seroprevalance of TTIs than blood from voluntary non-remunerated donors" (American Red Cross, 2008). Therefore, it is important to explicitly model the co-infection possibility in the screening test

[1]Blood Centers in the US apply various donor screening procedures required by the Food and Drug Administration (FDA), such as donor questionnaires that are administered pre-donation, the deferral of men who have had sex with men within the past twelve months, and requiring the recruitment of voluntary, rather than paid, donors.

selection problem.

Moreover, in blood screening, there are multiple, often conflicting, measures, that are important for the decision-maker. For example, reducing the fraction of infection-free blood falsely discarded ("waste") is critical as the demand for safe blood is on a rise worldwide.

The most important metric, risk, is first introduced and investigated separately in Chapter 4 in the "risk-based" model. We show that for any set of tests, the decision rule known as the "Believe the Positive" rule is the one that minimizes the risk of a TTI. This result allows us to formulate the test selection problem as a $0-1$ polynomial programming problem, which selects a set of budget-feasible tests that minimizes the TTI risk. As stated above, the polynomial risk function arises due to the nonlinear contribution of each test to the overall risk. We then study a special case of the problem, which applies if the co-infection probabilities (i.e., the probability that the blood unit is simultaneously infected by a combination of TTIs) in donated blood are negligible. For this case, we develop optimal algorithms, which we show to be very efficient in numerical studies with realistic-sized problems. This analysis also motivates the development of a near-optimal algorithm and effective lower bounds for the general case with co-infection possibility; our analysis indicates that these algorithms are very efficient and effective for the general problem. Finally, we solve the test selection problem with realistic data from sub-Saharan Africa and discuss the test composition for various budget allocations.

We then expand our analysis to incorporate other objective functions and constraints (i.e., waste) into the analysis in Chapter 5. Waste, defined as the fraction of disposed blood in the "safe" blood, is incorporated into the risk-based model as a constraint. In addition, we further study the blood screening problem under a framework which allows for different weights for each TTI combination. Such a framework is more comprehensive and realistic than the basic risk model analyzed in Chapter 4, because the severity and social cost associated with the various TTIs could differ greatly, and this impacts the test composition selected. Our model in Chapter 5 is general enough to incorporate the metrics commonly used in the medical literature, such as the social cost, Quality-Adjusted Life Year (QALY), Disability-Adjusted Life Year (DALY), among others (Marshall et al., 2004; Van Hulst et al., 2010; Custer et al., 2005b; Zohrabian et al., 2004). Efficient optimal/near-optimal algorithm(s) for the "weight-based risk" model is explored. We further discuss the impact of introducing the weight-based model on the optimal test composition in Chapter 5.

Finally, for blood screening, a differential testing extension to **RMP** model is in-

vestigated in Chapter 6. By allowing a collection of test sets to be administered to various proportions of blood units, differential testing provides the decision-maker with flexibility and an opportunity for further risk reduction.

For the research in joint replacement, we determine the relationship between surgeon and hospital volume, hospital size and mortality after joint replacement surgery for elderly patients based on statistical analysis in Chapter 7. This retrospective study used the 2006 National Inpatient Sample (NIS) dataset from the Agency for Healthcare Research and Quality's (AHRQ) Health-care Cost and Utilization Project (HCUP). Patients over 65 years of age who received an inpatient hip or knee replacement were identified. Demographic, clinical, and utilization variables were identified and compared across surgical and hospital volume and hospitals of different sizes for the outcome of mortality. Bivariable comparisons were analyzed using a chi-square test. A logistic regression model was used to control for variables associated with mortality. Thresholds for both hip and knee replacement volumes by surgeon and hospital were empirically determined using linear regression.

Chapter 2

Literature Review

It is widely realized that the developing countries are facing a severe safe blood shortage for a long period(WHO, 2004). Experience in the developed countries shows that a pool of healthy, regular, voluntary donors without being rewarded financially is critical for countries or area to produce adequate safe blood supply. WHO's investigation has agreed with the claim that donors who give blood voluntarily are the safest donors. Only 39 of 178 countries, however, have completely voluntary, unpaid blood donation according to a survey conducted by WHO(WHO, 2004). The shortage of donors complicates the situation even more in the developing countries, where the blood is needed most. It is estimated in (WHO, 2004) that 81 million units of blood is donated globally every year, of which only 39% comes from developing countries, resulting a global blood shortfall of around 40 million units annually. Another issue arises during a blood shortage–possible ramifications during a major crisis (eg,hurricane, earthquake). Blood shortages normally occur in areas where disasters strike. All ARC blood service regions need to be fully operational to effectively supply blood during a major crisis, allowing blood to be moved from one part of the country to another. The current shortage is pushing the system to its limits. Furthermore, the study in Greinacher et al. (2007) of the effect of aging population on the blood supply and demand poses a challenge of providing adequate safe blood for both developing countries and developed countries in the near future. As the population structure in many industrialized countries currently changing with a shift from younger to older age groups, it is expected that the blood demand will grow resulted in the increase of blood transfusion in older population and that the blood supply will fall out of a decrease of blood donation in younger population(WHO, 2004). In the study of Greinacher et al. (2007), they found that the increased demand for

blood coincides with a significant reduction in blood donations because of the aging population. It is concluded from their model that "from 2008 the shortfalls will grow to 32 to 35 percent of the total demand in 2015 in the area" they studied. It can be inferred from this study that the blood shortage situation could be worsen because the demographic trends doubtlessly exist in many other industrialized countries.

Although it is widely claimed that 85 percent or90 percent or nearly all of the population in US will need blood sometime during their lifetime (New York State Department of Health, 2005),(American Red Cross, 2005),(American Red Cross, 2004), study conducted by Shauna N. Hay et al. concluded that the true rate of transfusion probably lies in the range of 40.9 to 71 percent(Hay et al., 2006). There are also some sources claimed that One in 20 Americans will require a blood transfusion at some point in their lives.). "A safe, plentiful supply of blood for transfusion is an essential component of any health system. But too many countries continue to use unsafe blood for transfusions and thousands of individuals die every year because supplies are short. In wealthy countries, demand is high and getting higher: one patient in every ten admitted to hospital needs some sort of blood product. Increasingly complex medical procedures and longer life expectancies are pushing up demand still further. For developing countries, the demand profile is different, but these nations are no less dependent on safe supplies. Women and children are the most in need. 70% of blood transfusions in Africa are given to children with malaria; the other major use for donated blood is to help treat women with post-partum haemorrhage. The 100 000 annual deaths attributed to this complication are evidence of the scale of the unmet need." (Lancet Editorial, 2005)

As of 2008, the World Health Organization (WHO) estimates that more than 85 million units of blood are collected annually (WHO, 2010a). In the US, this number in 2006 is about 16 million units of blood collected, with around 14.5 million units transfused to about five million patients (Whitaker et al., 2007). The demand for blood products is only increasing worldwide. For developed countries, this is due to the increasingly complex medical procedures, such as autologous bone marrow transplants (Orfinger, 2000), and longer life expectancies. While for developing countries demand profiles are different, these nations are no less dependent on blood, with women and children being the most in need. In particular, 70% of blood transfusions in Africa are given to children with Malaria, followed by women with post-partum haemorrhage (Lancet Editorial, 2005). Moreover, the need for blood can increase significantly because of mass casualty disasters (e.g., hurricane, earthquake), or armed conflict (Orfinger, 2000).

In addition, our study is highly applicable in most countries and areas, because

although screening tests with high efficacies do exist, and are used, to some extent, in developed countries, there still remains a definable risk of TTI in those countries. For example, in the US, the average risk of a TTI is estimated at 1 in 340,000 (BloodBook, 2010). More importantly, in other parts of the world, the current situation is far from ideal: "Less than 30% of the countries have a well-organized blood collection service in place" (American Red Cross, 2008). Limited resources dictate that only 88% of blood donations worldwide are screened for "the basic quality assurance procedures" (WHO, 2010b), which correspond to the minimal procedures that should be performed, including screening for HIV, Hepatitis B, Hepatitis C, and Syphilis: Of those, 89% are in developed countries, 87% are in transitional countries, and only 48% are in developing countries... For the blood donations collected in the remaining 41 countries, which account for 22% of the global donations reported to WHO, the use of these basic quality assurance procedures is still unknown" (WHO, 2010b). Today, there remains a drastic risk associated with TTIs in some developing countries. For example, a study of transfusion data in the 1990's indicate that "the highest TTI risk was realized in Bolivia (233 infections per 10,000 transfusions); followed by five other countries (Peru, Colombia, Chile, Venezuela, and Guatemala, with 68 to 103 infections per 10,000 transfusions); and with somewhat lower risks in Honduras (9 per 10,000), Ecuador (16 per 10,000), and Paraguay (19 per 10,000)" (Schmunis et al., 1998). In Africa, with blood safety challenged by the HIV/AIDS and Malaria epidemics, the situation is dire: The proportion of both existing and new HIV infections attributable to blood transfusion in the sub-Saharan Africa is estimated at 10%! With 11 million HIV infections having occurred on the continent to date, the cumulative total of transfusion-associated HIV infections in Africa may exceed 1 million. As many as 25% of HIV-infected women and children in some areas of Africa acquired their infection from a blood transfusion (McFarland et al., 2003); 42% of HIV-infected children over the age of 1 year in Kinshasa, Zaire, acquired infection from a transfusion (McFarland et al., 2003). Up to 150,000 pregnancy-related deaths worldwide could be avoided each year through access to safe blood (American Red Cross, 2008). These numbers illustrate the magnitude of the problem, of providing clean blood to humans.

Although measures of testing accuracy are extensively discussed and widely used in many applications, they are not well defined and investigated in the existing literature, especially when various diseases resulting different social costs are considered. As important metrics of screening testing, Pepe (2004) has presented various measures of accuracy for a single test, their applications in the testing literature, and how they related to each other. For example, true positive fraction, known as sensitivity in the single disease setting, represents the fraction of existing abnormalities that are

correctly identified as such. Sensitivity (TPF) is widely used in biomedical research (Beutel, 2000), epidemiology (Walter and Irwig, 1988), and engineering application (Ozekici and Pliska, 1991; Raz and Kaspi, 1991) and accepted as an important measures of tests. In this research, we extend the concept of TPF to the multiple test in the blood screening setting. To illustrate the impact of different objective, we also compare the optimal test composition with respect to the TPF with that with respect to the risk, a more meaningful measure in the multiple testing of blood screening by definition. Our objective in this research, however, is three-fold: firstly, we would like to investigate how the various objective functions, extended from the measures of accuracy in single test setting, can be used in the blood screening scheme impact the optimal test composition, and eventually affect the quality and efficient usage of blood. Secondly, we noticed that the accurate estimation of prevalence, test performance and even cost, in the realistic setting could be difficult and expensive to do. As an extension of study in (Bish et al., 2010), we would like to discuss the uncertainty in these estimations and their impact on the screening scheme. Thirdly, we will extend the (infection) risk study in (Bish et al., 2010) to a generalized risk study by introducing the social costs for each disease and illustrate how the test composition in screening scheme could differ.

Resource allocation problems have long been studied by Operations Researchers (see, for instance, Brandeau 2004, for a review and references). A commonly used formulation that is somewhat related to our problem is the traditional knapsack problem, which selects, from a set of candidates, each with a known benefit (reward or revenue) and cost, an optimal set that is budget-feasible and that maximizes the total benefit (see Brandeau, 2004). However, our problem has major differences with the traditional knapsack problem. In our setting, candidate tests do *not* have constant returns to scale in the objective function, which is the "risk" of a TTI for blood classified as safe (i.e., the conditional probability that the blood unit is infected with at least one TTI, when the selected test set and the adopted decision rule indicate otherwise). A test's contribution to this risk depends not only on the efficacy of the test itself, but on the efficacies of the *entire* set of tests selected and the decision rule adopted. As we shall see, this complicates the problem considerably. Nevertheless, we further explored the efficient and effective near-optimal algorithm developed in (Bish et al., 2010) and investigated the impact of different objectives with budget and waste constraints on the optimal test composition.

Other relevant work includes studies that examine the relationship between screening and mortality reduction (or similar performance measures) for a certain disease. Many such studies are cost-effectiveness analyses, through the use of either Markov

processes (e.g., Jackson et al., 2003), simulation models (e.g., Lefrere et al., 1998), or empirical studies (e.g., Lander et al., 2009). The cost-effectiveness analysis is for comparison of specific interventions with each other. As such, it does not provide an optimization methodology, and most of these studies focus on one (or a limited number of) disease(s) and test options (AuBuchon et al., 2003). Our problem is also broadly related to the optimal allocation of screening inspection effort in a production setting under false positive and negative possibilities (see, for instance, Lindsay and Bishop, 1964; Ozekici and Pliska, 1991; Raz, 1986; Raz and Kaspi, 1991; and the references therein). However, there are important differences due to the unique characteristics of blood screening. Most production-related papers consider the objective to be the minimization of the total inspection cost, subject to a constraint on the percent defectives, whereas in blood screening, the decision-maker is mainly concerned with the minimization of a TTI risk, subject to a budget constraint (A social cost-based model is also introduced in this research later, providing an even more comparative study.). In addition, inspection plans are mostly modeled as a sequential process in a multi-stage production system, whereas in blood screening, the tests are to be administered simultaneously, due to the very short life-time of blood products and the relatively longer durations of shipment of the blood units to a test laboratory and of test administration. Furthermore, in our setting, there is possibility of co-infections in donated blood (which are created, hence detected, sequentially in production).

Data uncertainty issues are also extensively studied in the literature, including the estimation errors of disease prevalence in donor population from different countries or regions, and the metrics of test performances in the absence of a gold standard. The differences between the prevalence in different populations are investigated in the literature, for example, voluntary donor population and the injection drug users (IDU) population (Arora et al., 2010). The 3.5-year retrospective study on seroprevalence of HIV, HBV, HCV, and syphilis conducted at the blood transfusion centre of Maharaja Agrasen Medical College concluded a significantly higher prevalence in replacement donors as compared to voluntary donors.

We also understand the great differences of prevalence in all infectious disease between different countries, or regions. For instance, the HIV/AIDS adult prevalence rate ranges from 26.10% in Swaziland(ranked #1), to 0.60% in United States(ranked #70), to 0.10% in Egypt(ranked #163) according to (Central Intelligence Agency, 2005). Another example would be the prevalence of HBV infection. The prevalence of chronic HBV infection is low (<2%) in the general population in Northern and Western Europe, North America, Australia, New Zealand, Mexico, and south-

ern South America; intermediate (2%-7%) in South, Central, and Southwest Asia, Israel, Japan, Eastern and Southern Europe, Russia, most areas surrounding the Amazon River basin, Honduras, and Guatemala; high ($\geq$8%) in all of Africa; Southeast Asia, including China, Korea, Indonesia, and the Philippines, the Middle East, except Israel, South and Western Pacific islands, the interior Amazon River basin, and certain parts of the Caribbean (Haiti and the Dominican Republic)(Center for Disease Control and Prevention, 2010).

Meanwhile, it is important to realize the uncertainty of the prevalence data for a country/region. Prevalences based on the the reported cases of surveys of large groups of people are easily underestimated because many infections are undiagnosed or unreported. Different levels of healthcare quality in different countries/regions, different methods of gathering prevalence data, different study methodology may aggravate the bias (Grassly et al., 2004; Joseph et al., 1995; Shin et al., 2001; Walter and Irwig, 1988).

Take HIV prevalence as an example. Two main methods of data collection are commonly used in HIV surveillance: repeated seroprevalence surveys in the general population or in particular high-risk groups, such as sex workers or injecting drug users (IDU), and sentinel surveillance. Sentinel surveillance uses blood samples that have been drawn for other purposes (eg. screening for syphilis among pregnant women attending antenatal-care services). WHO and UNAIDS proposed the HIV sentinel surveillance as the primary approach to monitoring the prevalence of HIV in 1998. Not only antenatal-care are well-attended in many countries; but they also are considered reliable indicators of trends in prevalence. It is commonly recognized that HIV prevalence among pregnant women attending antenatal clinics is generally very similar to prevalence in the adult population as a whole (The World Bank Group, 2010; United Nations Development Group, 2003). However, small adjustments are often needed according to the findings of separate surveys of the general population, for example to adjust for underreporting in the most rural areas, or for large differences between male and female rates of infection.(Walker et al., 2001; Rodriguez and Hayes, 2002) UNAIDS has recommended two prevalence indicators to monitor the HIV epidemic: HIV prevalence in pregnant women attending antenatal-care, the main indicator for generalized epidemics, and HIV prevalence in sub-populations at high-risk such as IDUs or patients with structured treatment interruptions(STIs), which is particularly important in concentrated epidemics. (Zaba and Slaymaker, 2002) Although other population groups such as family planning (FP) and voluntary HIV counseling and testing(VCT) attenders and blood donors (BD) can also be adopted for prevalence study, they are currently not widely used , therefore, are

less internationally comparable. In a paper by WHO (Rodriguez and Hayes, 2002), the advantages and limitations of HIV prevalence estimates obtained from each of the data sources mentioned above and the extent to which they can be generalized to broader populations were discussed in detail.

Although usually not considered the main source of national prevalence estimates, population based surveys are also useful because they tell us how prevalence varies according to gender, race or other characteristics. One of the major disadvantages of population based surveys is that such survey usually are much more complicated and expensive than antenatal surveys. Nevertheless, population based surveys are becoming more popular recently, and their influence on national HIV prevalence estimates is increasing as well. Thirty countries in sub-Saharan Africa, Asia and the Caribbean conducted national population based surveys between 2001 and 2007 and revised their HIV prevalence estimates based on the results of these surveys, for instance, India in 2007.

No matter which approach adopted, the uncertainty of these estimates are unavoidable. Because the groups looked at by surveys can never be entirely representative of the wider population, and because no computer model is perfect. Therefore, an estimate is often accompanied by a range or 'plausibility bound', and the wider the range, the greater the uncertainty. The size of a plausibility bound is affected by the quality of the data and the number of steps and assumptions used to arrive at the estimate.

In addition to many studies of estimation error of disease prevalence, there has been a lot of effort to better control the estimation errors of test specificity and sensitivity (Shin et al., 2001; Joseph et al., 1995; Walter and Irwig, 1988). To determine the performance of a new diagnostic test, it is the routine to compare the result of new test with a "perfect" reference test (i.e. a gold standard). Although claimed to be "perfect", a reference test is usually less than perfect in reality. Enoe et al. (2000) presented a series of methods for estimating the accuracy of a diagnostic test comparing to an imperfect reference test with known misclassifications. Available methods of estimation is also presented in (Enoe et al., 2000) when the sensitivity and specificity of both tests are unknown. Some available statistical methods, are also discussed in (Enoe et al., 2000) when no reference test is available, such as maximum likelihood estimation and Bayesian inference. Same setting is also discussed in (Joseph et al., 1995), where a Bayesian approach is proposed.

Chapter 3

Probabilistic Risk Assessment and Cost/ Benefits of Risk Reduction Strategies

3.1 Introduction

Modern blood transfusion therapy started in 1901, with the discovery of the major blood groups by Landsteiner; and for over 50 years, the United States (US) has had an organized blood collection system. Approximately 10-14 million red blood cell (RBC) units and 1.5 million platelet transfusions are administered in the US annually (Despotis et al., 2008). These transfusions are provided to patients across all age groups, multiple diagnoses, and in a variety of settings. Unfortunately, today there remains definable risk associated with the transfusion of blood and blood products. These risks may occur in both the pre-clinical and clinical dimensions of the transfusion process, from blood collection from a donor through blood administration to a patient.

Transfusion safety is concerned with identifying and mitigating the hazards associated with delivering transfusion care to patients. The potential hazards of blood transfusion can be grouped into several broad categories including infections, immune reactions, human and testing errors (Kleinman et al., 2003a). In the last several decades, tremendous concern about blood safety has arisen both from the lay public and among professionals. As a result, dramatic improvements in transfusion

safety and a reduction of transfusion related human immunodeficiency virus (HIV 1-2) and hepatitis C virus (HCV), the two most substantial transfusion-transmitted infections of the 20th century, have occurred (Dzik, 2003). However, progress in other areas of transfusion safety has lagged behind. In particular, the clinical processes of blood product transfusion continue with highly variable practices and human errors that may contribute, albeit rarely, to adverse outcomes. These event types occur infrequently and randomly. As a result, it is extremely difficult to identify these events and understand their individual impact on an adverse outcome in transfusion without a comprehensive quantitative model that draws upon data that encompasses multiple institutions. Previous research regarding transfusion risks has been limited by descriptive studies that investigate one or another type of risk, focusing on a small number of cases and without considering the interactions among these risks and their relationship, if any, to human errors [see Dodd (1994), Despotis et al. (2008), Goodnough (2003), Goodnough et al. (2003), Greenwaldt (1997), and Kleinman et al. (2003a) for reviews, as well as the references therein]. The result is what seems to be an endless array of mandated screening tests and procedures focused on the collection of blood to reduce what are already very low frequency risk events to even lower occurrence rates.

In this chapter, we develop and analyze a comprehensive logical model designed to quantify the risk from transfusion of RBC in the United States. In particular, we use an engineering methodology known as Probabilistic Risk Assessment (PRA) or fault tree analysis, which is a quantitative and deductive process analysis tool that can be used for risk assessment and management. While PRA has been commonly used in high-risk industries, such as nuclear power, aviation and aerospace, to investigate rare events that have potentially devastating outcomes [see, for instance, Kumamoto and Henley (2000)], its use in healthcare has been limited [see Stockwell and Slonim (2006) for related discussion].

Utilizing PRA, we develop a comprehensive risk model of RBC transfusion by considering the relationship between the various risk points (events) and an adverse transfusion outcome. We determine the contribution of each event to an adverse transfusion outcome and identify the "critical points" that are the major contributors to the overall risk. This analysis then allows us to identify targeted interventions and evaluate their costs and benefits for risk reduction within a systematic framework.

Our work brings to public attention unnecessary testing that does little to minimize overall transfusion risks, as we find that none of the viral infections for transfusion that the lay public fears, including HIV 1-2, and the hepatitis B and C viruses,

contribute significantly to transfusion risk. While most leading causes of transfusion risks (i.e., febrile non-hemolytic reactions, allergic reactions, and RBC alloimmunization) result in clinically mild outcomes, the severe transfusion risks are caused mostly by circulatory overload and bacterial infection. In addition, acute reactions, caused by errors in various stages of the blood transfusion process, also contribute significantly to transfusion risk. Our study shows that interventions targeted at reducing the erroneous administration of blood will have a higher impact on the adverse outcome risk from RBC transfusion than aggressive screening that can further reduce the prevalence of viral infections, including HIV 1-2, hepatitis B and hepatitis C, in donated blood. Furthermore, there are error reduction programs for administration of blood, such as training/process improvement programs, or technology investments, such as barcode identification systems for compatibility testing and administration, that have been shown to be quite effective in various pilot studies; and such programs will be more cost-effective than a more aggressive screening of donated blood. Consequently, attention and resources that are focused on the blood administration process, rather than the blood screening process, will provide the highest risk reduction in RBC transfusion in the US, especially when limited resources are an important factor in the selection of transfusion safety programs. Thus, our study provides guidelines to improve the safety of RBC transfusion in the United States, which, we hope, future transfusion safety researchers and practitioners will find valuable. These are the main contributions of this study.

The remainder of this Chapter is organized as follows. In Section 3.2, we provide the details of our PRA models. Then Section 3.3 discusses the quantitative results obtained from the PRA analysis, including estimates of an adverse outcome risk from RBC transfusion in the US, and identifies the critical risk points in the transfusion process. Motivated by these critical risk points, in Section 3.4, we compare various risk-reduction strategies that are aimed at various processes of transfusion, including blood screening and blood administration, and analyze their costs and effectiveness in reducing the transfusion risk. Finally, in Section 3.5 we provide our conclusions and suggestions for improving transfusion safety, and present ideas for future research in this area. To facilitate the exposition, some mathematical derivations, tables, and data related discussions are relegated to the Appendix.

3.2 The Blood Transfusion Risk Analysis Model

3.2.1 Study Scope

We focus on the RBC transfusion risk in the United States and consider all broad categories of transfusion risk, including infections, immune reactions, human and testing errors (Kleinman et al., 2003a), as detailed in Section 3.2.2. We utilize the probabilistic risk assessment (PRA) methodology, and construct two PRA models of transfusion risk: (i) the "overall risk" model, which includes both the mild outcomes and the severe outcomes, as transfusion risk; and (ii) the "severe risk" model, which only includes risks that result in a severe outcome (e.g., mortality, major injury or other serious long-term consequences, a life threatening incident). The findings from both models, taken together, can be valuable in reducing the risk of an adverse transfusion outcome and in improving the health outcome of transfusion in general.

Possible events that may lead to an adverse transfusion outcome, their causes, and relationships used in the PRA models are carefully derived from the medical literature by capitalizing on the various types of information available for blood transfusion practices. In addition, the data for the PRA models come from a synthesis of many peer reviewed studies published in the medical literature that provide estimates of RBC transfusion risks in the United States.

Our agenda in the remainder of this section is as follows. In Section 3.2.2, we detail the transfusion-transmitted infections and transfusion reactions that we include in our models; in Section 3.2.3, we present the PRA models; and in Section 3.2.5, we discuss the sources of the risk estimates for each transfusion infection and reaction considered.

3.2.2 Transfusion Risks

Our model considers all broad categories of RBC transfusion risks, as detailed below.

Transfusion Infections

As of 2007, infectious disease testing of donated blood in the US includes the routine use of conventional serologic tests for antigens or antibodies to human immunodeficiency virus (HIV), type 1 and type 2 (HIV-1 and HIV-2); hepatitis B virus (HBV);

hepatitis C Virus (HCV); human t-cell lymphotropic viruses (HTLV), type 1 and type 2 (HTLV-1 and HTLV-2); and syphilis. In addition, mini-pool nucleic acid amplification testing (MP-NAT) is used for HIV-1, HCV, and West Nile virus (WNV) (in pools of 16 samples obtained from multiple donors). Finally, Enzyme-linked immunoassay (ELISA) test is performed for trypanosoma cruzi (Chagas disease) (American Red Cross, 2008). Nevertheless, viral infection is still possible due to "window-period transmissions," which are the main contributors of transmission of these diseases in transfusion (Kleinman et al., 2003a), as well as a chronic carrier state, viral variants not detectable by screening assays, or laboratory error. When the only significant transfusion risk comes from window-period transmissions, mathematical models known as the incidence/window-period models (Glynn et al., 2002; Kleinman et al., 1997) become appropriate to estimate the viral infection risks. These mathematical models typically take into account the window period, and incidence rate in repeat donors and first-time donors, together with their estimated weights in the population[1]. Our data for viral infection risks in transfusion come mainly from incidence/window-period models published in the literature, see Appendix A.3 for details. The medical literature indicates that the following types of infections can be transmitted in transfusion (see Appendix A.3 for a detailed discussion of each of these infections), all of which we include in our PRA models.

(I) Viral Infections:

- Retroviruses: HIV 1-2 and HTLV 1-2,
- Hepatitis viruses: Hep-A (HAV), Hep-B (HBV), Hep-C (HCV), Non-A-E Hepatitis Virus (Non-A-E HV),
- West Nile virus (WNV),
- Cytomegalovirus (CMV).

(II) Bacterial Infections:

- Sepsis,
- Treponema pallidum (syphilis).

[1]As such, these mathematical models do not consider human errors occurring during the blood collection process (i.e., processing, labeling, and storage of blood). Nevertheless, given the new technology implemented at many blood collection centers (e.g., American Red Cross), such human errors can be considered to have a small influence on the risk of viral infections.

(III) Protozoal Infections:

- Plasmodium (malaria),
- Babesiosis,
- Chagas disease,
- Toxoplasmosis.

Transfusion Reactions

Transfusion-related reactions the medical literature indicates include the following (see Appendix A.3 for a detailed discussion of each reaction), all of which we include in our PRA models:

- Hemolytic reaction (acute or delayed),
- Febrile nonhemolytic reaction,
- Allergic reaction,
- Anaphylaxis,
- Transfusion-associated Graft-versus-host disease (TA-GvHD),
- RBC alloimmunization,
- Transfusion-related acute lung injury (TRALI),
- Circulatory (volume) overload.

3.2.3 The PRA Model

We next discuss the development of the PRA models, one for the overall risk (both minor and severe outcome) and the other for the severe risk of RBC transfusion. Each fault tree consists of a set of "basic events," each of which represents the lowest-level events and, as such, needs no further development (e.g., HIV risk); a "top event," which represents the primary undesired event of interest (e.g., a mild or

a severe transfusion outcome for the overall risk model; a major transfusion outcome for the severe risk model); and a set of "intermediate events," which are all connected through logical operators. The following logical operators are used in our fault trees:

- AND gate indicates that the output event occurs if and only if all the input events occur.
- OR Gate indicates that the output event occurs if and only if at least one of the input events occurs.
- Inhibit Gate indicates that the output event occurs if and only if all input events occur and an additional conditional event occurs, that is, it is equivalent to an AND gate with a conditional event.

In what follows, we detail the development of the overall risk PRA model; the severe risk PRA model is similar. In the PRA model, each transfusion-transmittable infection and each transfusion reaction discussed in Section 2.2 are connected to the top event by an "OR" gate, i.e., an adverse transfusion outcome will occur if the screening tests fail to detect at least one of the infections in donated RBC, or if one of these reactions occurs during or after transfusion, see Figure 1 for the PRA model. As such, our risk estimates of transfusion-transmitted infections are slightly conservative, because not every unit of infected blood will cause a transfusion-transmitted infection. For example, for HIV infected blood that is used in transfusion, the risk of a transfusion-transmitted infection is 80-90% (e.g., Dodd et al., 2002); in addition, not every unit of donated blood will be used in transfusion.

Of particular importance to our study, in terms of intervention design, are the acute hemolytic reactions, which are mainly caused by the erroneous administration of blood, i.e., by the transfusion of ABO-incompatible RBCs (e.g., transfusing a B+ blood group to an A+ blood group individual). This error remains the leading cause of fatal transfusion reactions. As such, we model this error and its consequences in detail in our PRA model, as we describe next.

Modeling of Acute Hemolytic Reactions in PRA

Acute hemolytic reactions are mainly caused by the transfusion of ABO-incompatible RBCs. There are also other, less common, causes that may cause acute hemolytic

reactions, which have not been well understood in the medical literature; for completeness in our analysis, we include those causes in our model, and refer to them as "other types of incompatibility."

Let events A, E, and I respectively denote the events of an acute hemolytic reaction, erroneous administration of blood, and ABO incompatibility. Throughout, we denote the complement of an event by the superscript c. We attribute all ABO incompatibility to the erroneous administration of RBCs, as is done in the relevant literature (e.g., Linden et al., 2000). Only a portion of these erroneous administration incidents will lead to ABO incompatibility, as a "wrong" blood group may still be compatible with the patient's blood group (see Table A.2 in Appendix A.1 for the relationship between blood groups in terms of compatibility), that is, $I \subseteq E$. Furthermore, only a portion of the ABO incompatibility incidences will lead to acute hemolytic reactions [2]; and only a portion of these acute hemolytic reactions will be symptomatic (asymptotic acute hemolytic reactions can only be detected through lab tests; and hence, in the absence of those tests, they will be missed). As discussed above, an acute hemolytic reaction remains possible even without ABO incompatibility (event I), due to unexplained causes, which we refer to as "other types of incompatibility" (event I^c); see Figure 3.3 for a depiction of these relationships, and the acute hemolytic reaction sub-tree in Figure 3.2 for the modeling of these events and relationships in the fault tree.

Erroneous administration of blood (event E) can occur due to either non-blood bank errors (e.g., identification error, phlebotomy error, incorrect order sent), blood bank errors (e.g., testing wrong sample, technical testing error, wrong unit issued, clerical/transcription testing error, wrong unit tagged, clerical error recorded on wrong slip), or compound errors that occur both at the blood bank and outside the blood bank (e.g., wrong unit issued & identification error, wrong unit tagged & not detected) (Linden et al., 2000). Hence, if we let events BE, NE, and CE respectively denote the blood bank error alone, non-blood bank error alone, and compound error (which are all mutually exclusive by definition), then $E = BE \cup NE \cup CE$, see the acute hemolytic reaction sub-tree in Figure 3.2.

[2] We assume that if ABO incompatibility incidences lead to adverse effects, then these hemolytic reactions will be acute. We did not find any study that relates ABO incompatibility to a delayed hemolytic reaction.

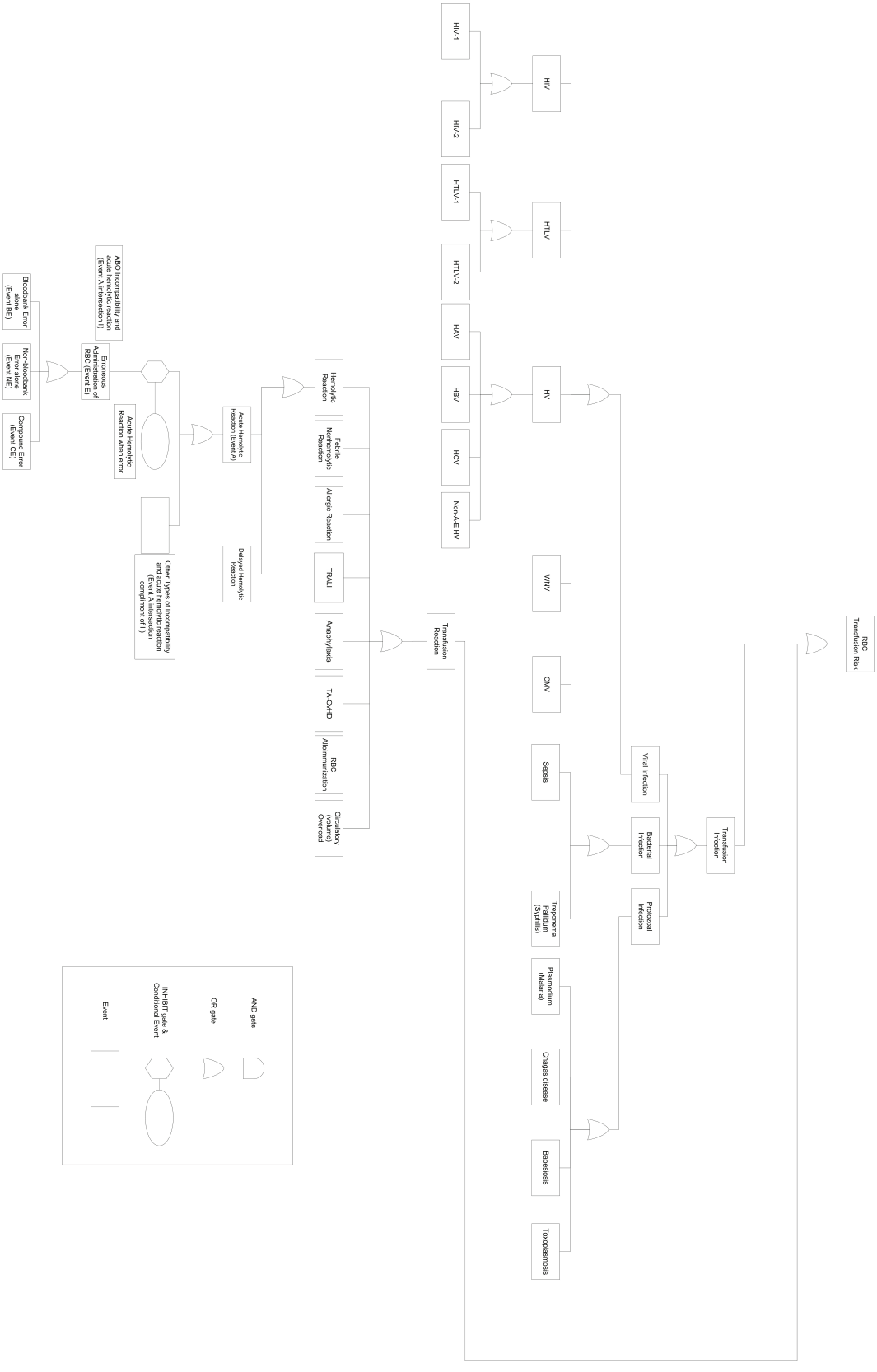

Figure 3.1: The PRA model of the overall RBC transfusion risk

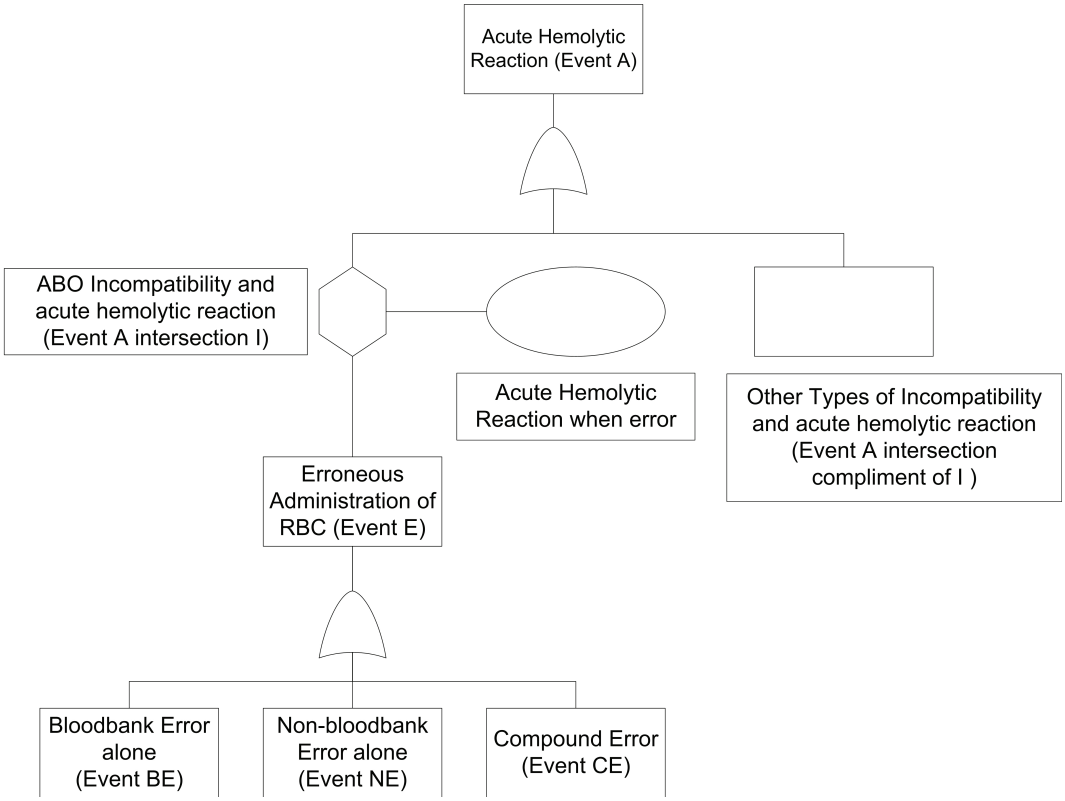

Figure 3.2: Acute Hemolytic Reaction Sub-tree

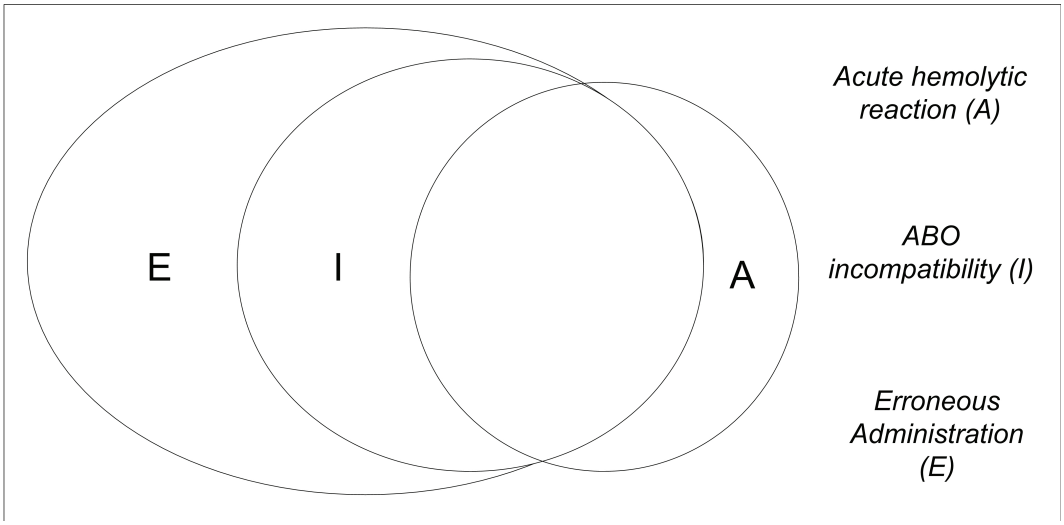

Figure 3.3: The relationship between events A, E, and I

3.2.4 Risk Estimates in the PRA Model

Risk estimates for transfusion infections and reactions are most often calculated based on transfusion of a single unit, rather than considering the total number of units transfused to a patient. While this is a reasonable assumption for some risks (e.g., infection risks), it is somewhat problematic for others (e.g., risks that are dependent entirely on recipient characteristics, such as volume overload). Nevertheless, in our study we use the risk per unit of RBC transfused, mainly due to data availability and also because these risks can then be compared with other risks that are to be expressed on a per unit basis. Similar approaches have been commonly used in the previous literature to study the risks associated with blood transfusion (e.g., Kleinman et al., 2003a) and the references therein). The analytic focus is on the RBC transfusion in the US. As such, the data estimates, detailed below, come from published literature that is associated with the RBC transfusion in the US.

In summary, the rate of transfusion-transmitted infectious diseases are determined by incidence/window-period models commonly used in the literature; the rate of transfusion reactions come from mostly descriptive studies available in the medical literature (see Appendix A.3 for the specific data sources), with the exception of acute hemolytic reactions, which are mainly caused by the erroneous administration of blood. As such, the study of the risk of this particular transfusion reaction is especially important, because its rate can be significantly reduced by interventions

targeted at reducing system and/or human errors. In the following, we first discuss how we estimate this risk, and then provide a summary of the risks of all basic events in our fault tree.

Estimating the Acute Hemolytic Reaction Risk in PRA

Our objective is to estimate the relevant risks in the acute hemolytic reaction sub-tree in the PRA model. We have,

$$\Pr(A) = \Pr((A \cap I) \cup (A \cap I^c)) = \Pr(A \cap I) + \Pr(A \cap I^c), \tag{3.1}$$

where $\Pr(A \cap I) = \Pr(A)\Pr(A|I)$. As we want to link the event of an acute hemolytic reaction to the event of an erroneous administration of blood, and since $I \subseteq E$, we can rewrite this probability as follows:

$$\Pr(A \cap I) = \Pr(I)\Pr(A|I) = \Pr(E)\Pr(I|E)\Pr(A|I), \tag{3.2}$$

where $\Pr(E) = \Pr(BE) + \Pr(NE) + \Pr(CE)$ (since events BE, NE, and CE are mutually exclusive).

To estimate these probabilities, we use the dataset in Linden et al. (2000), which is the largest study on the erroneous administration of RBC in the US. In particular, Linden et al. (2000) collect data on RBC transfusions in the State of New York from 1990 through 1999, corresponding to a total of 9,000,000 transfusions, and report the number of erroneous administration of RBC, along with the underlying reasons for each case (i.e., in terms of events BE, NE, or CE) (see Table A.3 in Appendix A.2 for a summary of the Linden et al. (2000) data). In order to adjust for the underreporting of erroneous administration cases with no ABO-incompatibility, Linden et al. suggest using the compatible-to-incompatible ratio, $\frac{\Pr(I^c|E)}{\Pr(I|E)} (> 1)$, as an "adjustment factor," i.e., adjusting up the number of ABO-compatible cases with erroneous administration by multiplying it with the adjustment factor.

To determine the adjustment factor, we use the blood incident data in the US (see Table A.1 in Appendix A.1) to calculate the probability that the transfused unit will be compatible with the patient's blood group given erroneous administration, and find that $\Pr(I^c|E) = 0.5661$, leading to an adjustment factor of $\frac{0.5661}{0.4339} = 1.30$. (All details are included in Appendix A.2.) Our analysis leads to $\Pr(E) = \frac{1}{16{,}500}$ with $\Pr(BE|E)\Pr(E) = 0.29 \times \frac{1}{16{,}500} = 1.758 \times 10^{-5}$, $\Pr(NE) = 0.56 \times \frac{1}{16{,}500} = 3.394 \times 10^{-5}$, and $\Pr(CE) = 0.15 \times \frac{1}{16{,}500} = 9.091 \times 10^{-6}$.

Linden et al. (2000) further report that 117 (out of the 237 ABO-incompatible cases reported) have led to acute hemolytic reactions (either symptomatic or asymptomatic). The remaining 111 incidents have led to no adverse effect. Using this data, and noting again that $I \subseteq E$, we can calculate the required probabilities for our fault tree as follows:

$$\Pr(A|E) = \Pr(A|I \cap E)\Pr(I|E) = \frac{117}{237} \times \Pr(I|E) = 0.2142. \tag{3.3}$$

Substituting (3.3) in (3.2), we have

$$\begin{aligned} \Pr(A \cap I) &= \Pr(I)\Pr(A|I) \\ &= \Pr(E)\Pr(I|E)\Pr(A|I) \\ &= \frac{1}{16,500} \times 0.4339 \times \frac{117}{237} \\ &= 1.298 \times 10^{-5}. \end{aligned}$$

The overall risk of acute hemolytic reaction, $\Pr(A)$, is estimated at 1 in 18,000 in Klein et al. (2007). Then, from (3.1),

$$\begin{aligned} \Pr(A \cap I^c) &= \Pr(A) - \Pr(A \cap I) \\ &= \frac{1}{18,000} - 1.298 \times 10^{-5} \\ &= 4.258 \times 10^{-5}. \end{aligned}$$

3.2.5 Summary of Risk Estimates in the PRA Models

A summary of the risk estimates in the overall risk PRA model are provided in Table 3.1.

Serious/Life Threatening Risks Table 3.2 presents the serious outcome risk for transfusion-related infections and reactions (events that are reported in Table 3.1 as having extremely low to nonexistent risk are not included)[3]. Observe that we combine several

[3]Transfusion infections and reactions that are extremely unlikely to lead to a severe risk are not included.

Table 3.1: Summary of Risk Estimates in the PRA Models

Type of Infection/Reaction	Risk of Infection/Reaction	Data Source
Viral Infection		
HIV 1 & 2	1 in 2,000,000-3,000,000	(Klein et al., 2007)
HTLV 1 & 2	1 in 1,923,000	(Klein et al., 2007; Kleinman et al., 2003a)
Hepatitis Virus		
HAV	1 in 10,000,000	(Dodd, 1994)
HBV	1 in 100,000-200,000	(Klein et al., 2007)
	1 in 205,000-488,000	(Dodd et al., 2002)
	Hence an interval of 1 in 50,000 - 400,000 is considered	
HCV	1 in 1,000,000-2,000,000	(Klein et al., 2007)
Non-A-E HV†	Probably N/E	(Kleinman et al., 2003a)
WNV†	Extremely low to N/E	(Stramer, 2007)
CMV‡	Extremely low to N/E	(Kleinman et al., 2003a)
Bacterial Infection		
Sepsis	1 in 75,100	(Stramer, 2007)
Treponema pallidum (syphilis)†	Extremely low to N/E	(Kleinman et al., 2003a)
Protozoal Infection		
Plasmodium (malaria)	1 in 4,000,000	(Klein et al., 2007)
Chagas disease†	Extremely low to N/E	(Kleinman et al., 2003a)
Babesiosis	1 in 10,000,000	(Kleinman et al., 2003a)
Toxoplasmosis†	Extremely low to N/E	(Despotis et al., 2008)
Transfusion-related Reactions		
Hemolytic reaction		
Acute hemolytic reaction due to ABO incompatibility	1.298×10^{-5}	[see Section 3.2.4 and Appendix A.3]
Acute hemolytic reaction due to other types of incompatibility	4.258×10^{-5}	[see Section 3.2.4 and Appendix A.3]
Delayed hemolytic reaction	1 in 4,000 to 9,000	(Klein et al., 2007; Pineda et al., 1999)
Febrile non-hemolytic reaction	1 in 300	(Klein et al., 2007)
Allergic reaction	1 in 330 to 1,000	(Despotis et al., 2008)
Anaphylaxis	1 in 20,000 - 50,000	(Klein et al., 2007)
TA-GvHD	Extremely low to N/E	(Klein et al., 2007)
RBC alloimmunization	62.1 in 100,000	(Kleinman et al., 2003a)
TRALI	1.4 to 20 in 100,000	(Klein et al., 2007)
Circulatory overload	1 in 200 to 10,000	(Klein et al., 2007)

†The risks of these infections are estimated to be extremely low to nonexistent (N/E) in the United States. For completeness, we still keep them in our fault tree and assign them a negligible risk.
‡The true risk remains unknown depending on patient group and type of blood product, but it is reasonable to conclude that it is extremely low, as discussed in Appendix A.3.

events, including allergic reactions, anapylaxis, and TA-GvHD, into one event we refer to as "MISC": The combined mortality rate due to the events included in MISC is derived, via mathematical models, as 0.5 to 10 per million (Despotis et al., 2008).

Table 3.2: Summary of Serious Outcome Risks

	Serious Outcome Risk	Note	Source
Transfusion Infection			
Viral Infection			
HIV 1 & 2	1 in 2,000,000 - 3,000,000	all infected cases may suffer serious long-term complications	(Klein et al., 2007)
HBV	1 in 2,000,000 - 16,000,000	1 in 40 of transfusion-transmitted HBV infections lead to the serious outcome of a chronic carrier state	(Klein et al., 2007; Kleinman et al., 2003a)
HCV	1 in 5,000,000 -10,000,000	20% develop significant liver disease	(Alter and Seeff, 2000; Busch, 2001; Kleinman et al., 2003a)
Bacterial Infection	2-100 in 1,000,000		(Despotis et al., 2008)
Protozoal Infection			
Plasmodium (malaria)	1 in 36,363,636	fatality rate of 11%	(Kleinman et al., 2003a)
Transfusion Reaction			
TRALI	0.4 in 1,000,000		(Despotis et al., 2008)
Circulatory overload	1 in 200 to 10,000		(Klein et al., 2007)
Acute hemolytic reaction	0.8-1.2 in 1,000,000	results of published studies and FDA adverse-event reporting	(Despotis et al., 2008)
MISC (allergic reaction, anaphylaxis, TA-GvHD)	0.5-10 in 1,000,000		(Despotis et al., 2008)

3.3 Risk Assessment

Minimal cut sets and importance measures of events play an important role in the reliability analysis of fault trees. A *minimal cut set* is a minimal set of basic events whose failure ensures the failure of the system (i.e., causes the top event to occur) (e.g., Ross, 2007). Due to the special structure of our fault tree (i.e., with each basic event directly leading to the top event, with the exception of blood bank errors, non-blood bank errors, and compound errors), each basic event (with the exception of blood bank errors, non-blood bank errors, and compound errors) constitutes a minimal cut set on its own. Nevertheless, for completeness, we report the minimal cut sets and their risk.

At the basic event level, we determine the *importance* of each basic event, k K , which is the conditional probability that the top event (i.e., an adverse transfusion outcome) is a result of event k, given that the top event occurs, i.e., Pr (eventkoccurs|topeventoccurs). This measure is also known as the *criticality importance measure* of the event, and is commonly used in risk assessment of fault trees (e.g., Haimes, 1998).

3.3.1 Overall Transfusion Risk (Major and Minor Risks)

Part a of Tables A.5 and A.6 (in Appendix A.4) respectively report the importance measures and the minimal cut sets for the overall transfusion risk model in the "base case" (i.e., using the mid-point when the risk is of interval form). Using the lower and upper bounds of the risk intervals, we find that the overall risk of RBC transfusion lies in the interval [539.9, 1233.3] per 100,000 units of RBC transfused, with a point estimate of 600.8 for the base case.

Specifically, this risk is mainly due to febrile non-hemolytic reactions, with a point estimate of 333 in 100,000 units of RBC transfused, mild allergic reactions, with a point estimate of 150.38, and RBC alloimmunization, with a point estimate of 62.10, followed by circulatory overload, delayed hemolytic reaction, and TRALI, with a combined point estimate of 45.69 (Table A.6). Acute hemolytic reactions also contribute significantly, with a point estimate of 5.36 in 100,000 RBC units transfused. In other words, given that a transfusion hazard has occurred, 50% of the time it is in the form of a febrile non-hemolytic reaction, 25% of the time it is an allergic reaction, and 10% of the time RBC alloimmunization. The somewhat more serious risks, of TRALI, circulatory overload, and delayed or acute hemolytic reactions, represent around 9.9% of the cause of an adverse transfusion event. Interestingly, our analyses indicated that none of the viral infections that the lay public fears of transfusion (e.g., HIV and HCV) is a major source of transfusion risk.

3.3.2 The Severe Outcome Risk (Major Risk)

Part b of Tables A.5 and A.6 (in Appendix A.4) respectively report the importance measures and the minimal cut sets for the severe risk model in the "base case" (i.e., using the mid-point when the risk is of interval form). The range for severe transfusion risk in the US is [10.4327, 511.2] per 100,000 units of RBC transfused, with a point estimate of 25.4527 for the "base case."

Specifically, the critical factors leading to mortality or other severe outcome in RBC transfusion included circulatory overload, with a point estimate of 19.61 in 100,000 RBC units transfused, and bacterial infection, with a point estimate of 5.10. This is followed by MISC (allergic reaction, anapylaxis, TA-GvHD), with a point estimate of 0.53, and acute hemolytic reaction, with a point estimate of 0.10. Alternatively stated, given that a serious transfusion hazard has occurred, 77% of the time it is due to circulatory overload, 20% due to bacterial infection, and 2% due to MISC.

Acute hemolytic reactions, which are mainly caused by erroneous administration of blood, also contributed significantly to severe outcomes of transfusion. Given that a serious transfusion hazard has occurred, 0.39% of the time it is due to an acute hemolytic reaction. On the other hand, the two most dreaded transfusion-transmitted infections, HIV and HCV, do not contribute significantly to the severe outcome risk.

3.4 Risk Reduction Policies: Cost-benefit Analyses

Importance measures assist with identifying the basic level events that have the highest risks of occurrence for the outcome of interest so that improvement actions can be targeted at these events, provided there is room for improvement. To give an example, consider the overall risk model, where the main contributor to the overall risk is the febrile non-hemolytic reaction, with a point estimate of 333 per 100,000 units transfused. However, while this does help, from an analytic perspective in understanding what patients are suffering from, it is not particularly helpful from a clinical perspective because clinicians already recognize how common this adverse event is, what needs to be done to improve its occurrence, and how unlikely it is to cause the type of safety problems that leads to significant adverse occurrences. On the other hand, as discussed below in detail, much can be done to reduce the erroneous administration rate of blood, and there is also some room for further improving the safety of blood. In fact, there is huge public pressure on the decision-makers to allocate the majority of the available resources into the blood safety area; and so far this has been the case. "Enormous resources (financial, intellectual, technological, and governmental) have been invested in improving the purity, potency, and safety of blood that is collected, tested, packaged, and labeled as suitable for transfusion. [These include] increased scrutiny of donors, highly sensitive screening testing, NAT [technology], the wide spread application of good manufacturing practices However, overall transfusion safety, largely the province of hospitals, has received far less attention." (Dzik, 2003). Consequently, in what follows, we focus our discussion on these two particular areas that have potential for improvement: blood administration and donated blood screening processes.

We first quantify the improvement potential in each of these areas using our PRA models. Table 3.3 provides the resulting overall risk and severe outcome risk from transfusion if (i) hepatitis B virus were eliminated, (ii) HIV 1-2 and hepatitis C

virus were eliminated, (iii) HIV 1-2, hepatitis B virus, and hepatitis C virus were eliminated, and (iv) erroneous administrations (in terms of giving the wrong blood unit to the patient) were eliminated.

As Table 3.3 demonstrates, eliminating erroneous transmissions leads to a higher potential reduction, both in the overall risk and severe outcome risk of transfusion, than the combined effects of eliminating HIV 1-2, HBV, and HCV risks. These numbers demonstrate the "potential" for improvement if it were possible to totally eliminate these risks. While this may not be currently feasible, known solutions and FDA-approved technology already exist for reducing these risks, as we discuss below.

Table 3.3: The Effect of the Elimination of Various Risks on the Overall Risk and Severe Outcome Risk of Transfusion

Scenario	Overall risk per 100,000 units transfused	Severe outcome risk per 100,000 units transfused
Current	600.8000	25.4527
HBV risk eliminated	600.3550	25.4277
HIV 1-2 and HCV risks eliminated	600.6935	25.3994
HIV 1-2, HBV, and HCV risks eliminated	600.2498	25.3744
All erroneous transmissions eliminated	599.5380	25.3527

The current blood testing scheme utilizes the MP-NAT technology (in addition to antibodies) for HIV and HCV screening; the MP-NAT pools 16 blood samples together. While pooling reduces costs, it also slightly reduces the sensitivity of the test because of its diluting effect on virus-containing units. It is, however, possible to replace the MP-NAT for HIV and HCV with single-donation NAT (SD-NAT) (e.g., Jackson et al., 2003), increasing costs, but also increasing the sensitivity of the test. On the other hand, for the blood administration process, the decision-maker can invest in new technology and/or process improvement programs at blood collection centers or hospitals so as to bring down the rate of the erroneous administration of blood (some specific examples of such interventions are discussed below). Suppose the decision-maker is interested in comparing the following scenarios:

1. The current testing scheme: MP-NAT for HIV and HCV (in addition to antibodies for HIV and HCV).
2. A less aggressive testing scheme: Replace MP-NAT for HIV and HCV with

HIV p24 antigen (and continue to include the antibodies for HIV and HCV) - this was the FDA approved testing scheme before MP-NAT was licensed.

3. A more aggressive testing scheme: Replace MP-NAT for HIV and HCV with SD-NAT (and continue to include the antibodies for HIV and HCV).

4. A less aggressive error reduction strategy: Perform improvement actions so that a 10-fold reduction in the erroneous administration risk (over the current erroneous administration risk of 1 in 16,500 [Linden et al. (2000)]) can be achieved.

5. A more aggressive error reduction strategy: Perform improvement actions so that a 50-fold reduction in the erroneous administration risk (over the current erroneous administration risk of 1 in 16,500 [Linden et al. (2000)]) can be achieved.

Scenario 1 is the current scenario studied. For the other scenarios, we rerun the PRA models with modified risks[4], see Table 3.4 for results.

Recent studies indicate that drastic reductions in the erroneous administration risk are indeed possible through investments in technology, training, or process improvement programs (see Dzik, 2003, 2005) for detailed discussion]. For example, Davies et al. (2006) and Turner et al. (2003) study the benefits of a barcode patient identification system involving hand-held computers for blood sample collection, compatibility testing, and the administration of blood in cardiac surgery and hematology outpatient and inpatient clinics in the United Kingdom. After the new technology was introduced and staff was trained, significant improvements were realized in checking that the blood group and unit number on the blood pack matched the compatibility label (from 8% to 100%), and in the correct verbal identification of the patients (from 11.8% to 100%); similar improvements were found in other related measures. Saxena et al. (2004) describes how quality improvement efforts that involve nurse training and auditing in the Los Angeles County and University of Southern California Medical Center led to 100-percent compliance for all transfusion processes over a period of nine months; during this period no mistransfusions or blood administration near-misses have been reported.

Finally, we note that similar analysis is possible using other methods. For example, Jackson et al. (2003) analyzes the cost-effectiveness of NAT for HIV, HCV, and

[4]For Scenario 2, the HIV risk is estimated at 1 in 1.2 million and HCV risk at 1 in 230,000; for Scenario 3, the HIV risk is estimated at 1 in 2.8 million and HCV risk at 1 in 2.3 million (Jackson et al., 2003).

Table 3.4: A Cost-benefit Analyses of Different Interventions for Blood Screening and Administration

Scenario	Overall risk per 100,000 units transfused	Severe outcome risk per 100,000 units transfused	Estimated additional cost (over the current system)
Scenario 1-current	600.8	25.5	
Scenario 2 - less aggressive testing	601.2	26.3	$ 117.8 million†
Scenario 3 - more aggressive testing	600.5	25.5	$273 million‡
Scenario 4 - less aggressive error reduction program	599.6	25.4	e.g., training/process improvement programs - the cost of physician and nurse training, other educational efforts, and continued monitoring(Saxena et al., 2004)
Scenario 5 - more aggressive error reduction program	599.5	25.4	e.g., barcode patient identification system for blood sample collection, compatibility testing, and the administration of blood - the investment cost for a 1500-bed hospital is $0.75 million (Turner et al., 2003).

†We assume that (i) each unit of the HIV p24 antigen testing costs $4 (Jackson et al., 2003), (ii) a whole-blood donation yields, on average, 1.5 units transfused (Jackson et al., 2003), and (iii) the annual blood donation in the US is 14 million units (Despotis et al., 2008). Then the total HIV p24 antigen testing costs around $37.2 million. The total cost of MP-NAT for HIV and HCV is estimated as $155 million(Jackson et al., 2003).
‡Based on the assumption that the total cost of SD-NAT for HIV and HCV is $428 million (Jackson et al., 2003).

HBV (in terms of improvement to quality-adjusted life years (QALYs)[5]) using a Markov Decision Model (MDM), see Schaefer et al. (2004) for an in-depth treatment of MDMs for medical treatment problems. While MDMs allow for more details to the model, this comes at the expense of a huge increase in tractability. As the problem size increases, MDMs become increasingly more difficult to solve exactly. Therefore, it becomes computationally prohibitive to analyze all transfusion risks and their interactions or multiplicative effects on the patient's outcome, as we do here using PRA.

[5]We note that similar analysis using QALYs (instead of the probability of a transfusion hazard, as we do here) is also possible with fault trees, which form the basis of the PRA.

3.5 Conclusions

In this chapter, we develop a comprehensive risk model of RBC transfusion using the PRA methodology. Using our model, we quantify the current risk (both overall and severe transfusion risks), to the patient, coming from RBC transfusion in the United States, and identify the main "critical points" in the transfusion process. This analysis allows us to identify targeted interventions and evaluate their costs and benefits for risk reduction within a systematic framework.

Our work brings to public attention unnecessary testing that does little to minimize overall transfusion risks, as we find that none of the viral infections for transfusion that the lay public fears, including HIV 1-2, and the hepatitis B and C viruses, contribute significantly to transfusion risk. While most leading causes of transfusion risks (i.e., febrile non-hemolytic reactions, allergic reactions, and RBC alloimmunization) result in clinically mild outcomes, the severe transfusion risks are caused mostly by circulatory overload and bacterial infection. In addition, acute reactions, caused by errors in various stages of the blood transfusion process, also contribute significantly to transfusion risk. Our study indicates that attention and resources that are focused on the blood administration process, rather than the blood screening process, will provide the highest risk reduction in RBC transfusion in the US, especially when limited resources are an important factor in the selection of transfusion safety programs. Blood transfusion processes are already heavily regulated. Hence, the real "win" from a clinical perspective in improving blood transfusion safety may not be in further implementing health policy decisions that lead to more regulation, but be focused on the fundamentals of patient care like the elimination of adverse events (through the elimination of erroneous administration of blood), as our analysis suggests, as well as the elimination of other events like febrile reactions or circulatory overload, which have till now been considered an element of quality, but nonetheless affect the safe delivery of transfusions.

While we focus our attention for improvement actions to two main transfusion processes, of blood screening and administration, it is an important future research direction to use our model, risk estimates, and risk points for prioritizing interventions that focus on yet other transfusion processes. In particular, system level improvements can be classified into three separate operational areas. First, there is the guidance provided in law, which establishes minimal requirements for healthcare providers and institutions based upon licensure standards. Second, there are standards, regulations and certification, which provides the next level of oversight. Within transfusion care, there are standards from the College of American Patholo-

gists (CAP), the Centers for Medicare and Medicaid Services (CMS) and the Joint Commission. These standards provide the guiding principles to assure the safe and effective delivery of blood to patients. Certification of institutions and providers helps to demonstrate that expectations exceed the thresholds established in law. Finally, there are informal mechanisms for ensuring best practices and evidence based medicine. These approaches usually include comparative benchmarking. Taken together, these options provide a menu of interventions to improve transfusion care. The PRA performed in this body of work helps to inform interventions at each of these levels.

While the performance measures and concepts we use may be unfamiliar to the average clinician, they are important to consider since they can help provide an understanding of what needs to be done at various levels of the healthcare system to improve transfusion care, as we discuss above. In addition, it is important for clinicians to know the highest risk events so that providers are reminded on how to improve them in providing transfusion care.

This work is not without limitations. Modeling exercises like PRA only represent a view of reality through a particular lens. If the lens is incorrect or misaligned, the reality will be distorted. Second, while the risks identified here can assist in informing licensing, regulatory and certification standards, they represent only one piece of information that can assist in this arena and broader representation through other data sources and experts need to inform decision making.

While recognizing these important limitations, this work also has significant strengths. First, the PRA performed here represents the integration of the current estimates of blood transfusion risks. Second, the model provides an analysis of the current landscape of transfusion safety in the US based upon the prevailing evidence base in the peer reviewed literature. Third, the model can be easily updated as risks are eliminated and new risks are identified, thereby providing a methodology that produces a working document that can be regularly updated as the evidence base matures. Finally, the model provides an opportunity to apply a method used in other industries to an important category of low frequency, high risk events in healthcare and serves as the template for performing analyses on other healthcare problems like wrong site surgeries, patient falls, and healthcare associated infections.

Probabilistic risk assessment is an important tool with implications for transfusion safety as well as healthcare safety in general. It provides another method for visualizing and analyzing the risks related to the transfusion of blood and blood products, and can be integrated with other elements and tools to determine the best way to

advance transfusion care and safety in the US.

Chapter 4

Risk-based Optimization: Modeling, Algorithms, & Results

4.1 Introduction and Motivation

Blood products, either whole blood or its components, are vital healthcare commodities for patients across all age groups, with multiple diagnoses, and in a variety of settings. Major surgeries and cancer therapies require blood products. Furthermore, trauma victims, certain premature infants, children with severe anemia, and pregnant women with complications rely on blood products. As a result, there is high demand for blood worldwide, and a large number of people will need blood transfusion at some point in their lives (e.g., 40 to 70% of the US population, Hay et al., 2006). As of 2008, the World Health Organization (WHO) estimates that more than 85 million units of blood are collected annually (WHO, 2010a). In the US, this number in 2006 was about 16 million units of blood collected, with around 14.5 million units transfused to about five million patients (Whitaker et al., 2007). Furthermore, the demand for blood products is only increasing worldwide. For developed countries, this is due to the increasingly complex medical procedures, such as autologous bone marrow transplants, and longer life expectancies (Orfinger, 2000). While for developing countries demand profiles are different; these nations are no less dependent on blood, with women and children being the most in need. In particular, 70% of blood transfusions in Africa are given to children with Malaria, followed by women with post-partum haemorrhage (Lancet Editorial, 2005). Moreover, the need for blood can increase significantly because of mass casualty disasters (e.g., hurricane,

earthquake) or armed conflict (Orfinger, 2000).

There are many "transfusion-transmitted infections" (TTIs), i.e., diseases that can be transmitted through the use of blood products, including Human Immunodeficiency Virus (HIV), Hepatitis Viruses, with the major ones being B and C (HBV, HCV), Human T-cell Lymphotropic Virus (HTLV), Syphilis, West Nile Virus (WNV), and Chagas' Disease. Because blood products are an essential component of any health system, effective blood screening is required. However, no blood screening test is perfectly reliable (each test has the possibility of providing false-positive or false-negative results), most screening tests are expensive, and resources are limited. Furthermore, new testing technologies are always being developed, offering new options of price and efficacy (Dzik, 2003; Jackson et al., 2003). Thus, it is often the case that multiple tests, with varying degrees of efficacy and costs, are available for screening for the same infection. Then the questions are: **(1)** how should the limited resources be optimally allocated to the screening tests in order to minimize the risk of a TTI? and **(2)** how should the results of the selected battery of tests be interpreted, that is, what is the "decision rule" for concluding that the blood unit is infected by a certain infection when multiple tests are administered for it and their results are not in agreement? Furthermore, these questions are interrelated, in that, the risk of a TTI depends, in a complex way, on both the selected test battery and the decision rule adopted. These questions are the focus of this chapter.

What complicates the problem further is the possibility of *co-infections* in blood donors, i.e., a donor being simultaneously infected with multiple TTIs, as some viruses, such as the HIV, may make the individual more susceptible to acquiring other viruses. Indeed, co-infections are likely for the HIV, HBV, and HCV. 15% to 30% of HIV-infected individuals worldwide suffer from chronic HCV infection, and among those HIV-positive individuals that are infected parenterally, such as haemophiliacs and intravenous drug users, chronic HCV infection can be as high as 75%. Chronic HBV infection, on the other hand, occurs in 10% of HIV-infected individuals (Carmo et al., 2000; Lincoln et al., 2003; Soriano et al., 2006). Furthermore, it is estimated that up to 10% of HCV-positive individuals test positive for HBV (Gordona and Sherman, 2009). For the donor pool in the US, which undergoes systematic donor screening[1], these numbers will serve as upper bounds, as a portion of the individuals who are considered to be at risk for HIV, HBV, or HCV will be eliminated through donor screening. However, for some developing countries, these co-infectious donors,

[1]Blood Centers in the US apply various donor screening procedures, such as donor questionnaires that are administered pre-donation and requiring the recruitment of voluntary, rather than paid, donors.

unfortunately, are *not* less likely to be in the donor pool, as donor screening is not rigorous and systematic (Lancet Editorial, 2005). Blood is collected exclusively from voluntary unpaid donors in only 39 of 178 countries, and "42% of blood collected from donors in medium and low Human Development Index countries comes from family replacement or paid donors, and this blood often contains a higher seroprevalance of TTIs than blood from voluntary non-remunerated donors" (American Red Cross, 2008). Therefore, it is important to explicitly model the co-infection possibility in the screening test selection problem.

Resource allocation problems have long been studied by Operations Researchers (see, for instance, Brandeau, 2004, for a review and references). A commonly used formulation that is somewhat related to our problem is the traditional *knapsack* problem, which selects, from a set of candidates, each with a known reward and cost, the optimal set that is budget-feasible and that maximizes the total reward (see Brandeau, 2004). Our problem, due to its unique characteristics, exhibits major differences from the well-studied linear knapsack problem. In particular, in our setting, candidate tests do *not* have constant returns to scale in the objective function, which is the "risk" of a TTI for blood classified as infection-free (i.e., the conditional probability that the blood unit is infected with at least one TTI, when the selected test set and the adopted decision rule indicate otherwise). A test's contribution to this risk depends not only on the efficacy of the test itself, but on the efficacies of the *entire* set of tests selected and the decision rule adopted. Thus, our problem, even with the decision rule fixed *a priori*, falls into the general class of nonlinear knapsack problems with a nonseparable objective function, a problem considerably more difficult than other knapsack problems, and has received very limited attention in the literature (see Bretthauer and Shetty, 2002 for a review). These characteristics complicate the problem considerably. Nevertheless, our analysis provides efficient optimal algorithms for a special case of the problem, and efficient and effective near-optimal algorithms for the general problem.

Other relevant work includes studies that examine the relationship between screening and mortality reduction (or similar performance measures) for a certain disease. Many such studies are cost-effectiveness analyses (Busch et al., 2009; Leiby, 2001; Sendi et al., 2003), through Markov processes (e.g., Jackson et al., 2003; Schwartz et al., 1990; Van Hulst et al., 2009), simulation models (e.g., Custer et al., 2005a; Lefrere et al., 1998), decision trees (e.g., Marshall et al., 2004), or empirical studies (e.g., Lander et al., 2009). The cost-effectiveness analysis is for comparison of specific interventions with each other. As such, it does not provide an optimization methodology, and most of these studies focus on one (or a limited number of) dis-

ease(s) and test options (AuBuchon et al., 2003). Furthermore, cost-effectiveness analysis typically relies on quite restrictive assumptions, including that the interventions are perfectly divisible, have constant returns to scale, and are independent (Brandeau, 2004; Sendi et al., 2003; Van Hulst et al., 2010). Our work overcomes these limitations by providing an optimization methodology and by eliminating these assumptions.

In addition to medical and biomedical contexts (e.g., Beutel, 2000; Walter and Irwig, 1988), test efficacy parameters (i.e., false positive and false negative probabilities) are relevant in various engineering applications and statistical hypothesis testing (e.g., Ozekici and Pliska, 1991; Pepe, 2004; Raz and Kaspi, 1991), but are used within different models and frameworks. To give an example, false positives and false negatives are possible in screening and inspection in production, and as such, our problem can be seen as broadly related to the optimal allocation of screening and inspection effort in a production setting (e.g., Lindsay and Bishop, 1964; Ozekici and Pliska, 1991; Raz, 1986; Raz and Kaspi, 1991, and the references therein). Most production-based models minimize the total inspection cost, subject to a constraint on the percent defective, and inspection is typically modeled as a sequential process within a multi-stage production system. Another example broadly related to our problem is the Series-parallel Redundancy Allocation Problem (e.g., Chern, 1992; Hsieh, 2002; You and Chen, 2005), which will be discussed in some detail in Section 4.2.2. However, blood screening has unique characteristics, which imply different objectives, constraints, and operational characteristics, differentiating our setting from those. In particular, in blood screening, the most important objective is the minimization of a TTI risk, subject to a budget constraint. In addition, in blood screening, the tests are to be administered concurrently, due to the short life-time of blood products compared to the relatively longer durations required to ship blood units to a testing laboratory and for test administration; and there is possibility of co-infections in donated blood (which are created, hence detected, sequentially in production).

Our study is timely, because even in developed countries, where tests with high efficacies are used, there still remains a definable risk of TTI. For example, in the US, the average risk of a TTI is estimated at 1 in 340,000 (BloodBook). More importantly, in other parts of the world, the current situation is far from ideal. "Less than 30% of the countries have a well-organized blood collection service in place" (American Red Cross, 2008). Limited resources dictate that only 88% of blood donations worldwide are screened for "the basic quality assurance procedures" recommended by the WHO (WHO, 2010b), which correspond to the *minimal* procedures that should be

performed, including screening for HIV, HBV, HCV, and Syphilis; and this number is only 48% in developing countries. "For the blood donations collected in the remaining 41 countries, which account for 22% of the global donations reported to the WHO, the use of these basic quality assurance procedures is still unknown" (WHO, 2010b). Today, there remains a drastic risk associated with TTIs in some developing countries. For example, a study of transfusion data in the 1990's indicate that "the highest TTI risk was realized in Bolivia (233 infections per 10,000 transfusions); followed by five other countries (Peru, Colombia, Chile, Venezuela, and Guatemala, with 68 to 103 infections per 10,000 transfusions); and with somewhat lower risks in Honduras (9 per 10,000), Ecuador (16 per 10,000), and Paraguay (19 per 10,000)" (Schmunis et al., 1998). In Africa, with blood safety challenged by the HIV/AIDS and Malaria epidemics, the situation is dire: the proportion of both existing and new HIV infections attributable to blood transfusion in the sub-Saharan Africa is estimated at 10%. With 11 million HIV infections having occurred on the continent to date, the cumulative total of transfusion-associated HIV infections in Africa may exceed 1 million. As many as 25% of HIV-infected women and children in some areas of Africa acquired their infection from a blood transfusion; and 42% of HIV-infected children over the age of 1 year in Kinshasa, Zaire, acquired infection from a blood transfusion (McFarland et al., 2003). Up to 150,000 pregnancy-related deaths worldwide could be avoided each year through access to safe blood (American Red Cross, 2008). These numbers illustrate the importance of providing safe blood.

Our contributions, to this important problem in healthcare, include the following.

- Our modeling of the test selection problem does *not* rely on the restrictive assumptions made in cost-effectiveness analysis, which include that the interventions are perfectly divisible, have constant returns to scale, and are independent. Rather, we work with the actual risk function, which we express as a function of the test composition and the decision rule. This allows us to explicitly consider **(i)** the nonlinear contribution of each test to the overall TTI risk, and **(ii)** that this contribution depends not only on the efficacy of the test itself, but on the efficacies of the *entire* set of tests selected and the decision rule adopted. Furthermore, to our knowledge, our mathematical formulation is the first to integrate the decision rule with the test selection decision, and to model the co-infection possibility (which is likely for HIV, HBV, and HCV, as discussed above) in donors. Finally, these realistic and important aspects of the problem are modeled within an optimization framework, rather than rely on a cost-effectiveness analysis.

- From a theoretical perspective, we show that the "Believe the Positive" decision rule minimizes the risk of a TTI. This result allows us to formulate the test selection problem as a 0-1 polynomial programming problem, which selects a set of budget-feasible tests that minimizes the TTI risk. We then study a special case, the mono-infection setting, which applies if the co-infection probabilities in donated blood are negligible. For this case, we develop optimal algorithms. This analysis also motivates the development of an effective heuristic and lower bounds for the general case with co-infection possibility.

- Finally, we provide a case study on sub-Saharan Africa, Ghana, Thailand, and the United States, which represent regions with quite different TTI prevalence rates and blood screening policies. Our case study generates important policy insights. Specifically, we show that an optimization-based approach for the test selection that explicitly considers a region's particular prevalence rates can significantly reduce risk, especially for low budgets. Furthermore, for low testing budgets it might be better *not* to follow the WHO guidelines (which do not depend on prevalence rates), especially when there are high co-infection rates. Furthermore, we find that waste (i.e., blood discarded through false-positive test results) can be quite sensitive to the test set selected. Thus, waste should be a consideration in future research.

The remainder of the chapter is organized as follows. In Section 4.2, we introduce the notation and provide a mathematical formulation of the decision problem. In Section 4.3, we analyze the problem and provide equivalent mathematical programming formulations, lower bounds, and optimal algorithms (for the mono-infection setting) as well as a heuristic algorithm (for the general problem). Section 4.4 provides a summary of our extensive numerical study on the proposed heuristic, details the case studies of several regions, including the sub-Saharan Africa, Ghana, Thailand, and the US, and generates important policy insights. Finally, in Section 4.5, we provide our conclusions and suggest directions for future research.

4.2 The Notation and the Model

In the US, per FDA requirements, each blood donation must undergo screening tests for a set of transfusion-transmitted infections (TTIs). Depending on the outcomes of

the selected tests, the blood unit (i.e., all blood collected from the particular donor[2]) will be used or discarded. Consequently, the decision-maker (e.g., the American Red Cross) faces the problem of **(i)** selecting a set of tests, from a set of FDA-approved screening tests, to test each unit of blood for a set of FDA-recommended TTIs, and **(ii)** constructing a "decision rule" with which to classify each blood unit as "infection-free" (from all diseases considered) versus "infected" (by at least one disease) using the outcomes of the selected battery of tests.

Each screening test applies to a specific disease and provides binary results, with a "+" result indicating that the blood sample is reactive to the particular disease under the test (i.e., the test suggests that the blood unit is infected), and a "–" result indicating otherwise. Tests do not have perfect efficacy, and are characterized in terms of their "specificity" (probability of true negative) and "sensitivity" (probability of true positive). False positive and false negative test results are possible due to various reasons, including technical errors (e.g., lab errors due to misinterpretation, mislabeling), biological factors, such as the presence of antibodies, other diseases, or immunizations cross-reacting with test agents, "immunological window periods" (i.e., the period of early infectivity when an immunologic test is non-reactive, e.g., Bihl et al. (2007)), or simply due to imperfect level of knowledge (e.g., poorly-understood cross-reactions in healthy individuals); for a thorough discussion, see Dow (2000); Moore et al. (2007); Sayre et al. (1996). Sensitivity and specificity estimates are required for each FDA-approved test; we refer the interested reader to Pepe (2004) for a detailed discussion on how these parameters are typically estimated in practice.

If the decision-maker chooses to administer only one test for some disease i, then her decision rule for disease i is trivial: with a "+" test result, she classifies the blood unit as infected with disease i; and with a "–" result, she classifies it as free of disease i. If multiple tests are administered for the same disease, however, different decision rules are possible. For example, under the well-known "Believe the Positive" decision rule, the blood unit is classified as infected for disease i if at least one test in the selected battery for disease i returns a "+" result; equivalently, it is classified as free of disease i only if all tests in the battery come out "–" for disease i. On the other hand, under the "Believe the Negative" decision rule, the blood unit is classified as free of the disease if at least one test result in the battery is "–". Under the "Majority-based" decision rule, an odd number of tests are administered for each disease and the blood unit is classified according to the outcome provided by the majority of the tests (see

[2]While the amount of blood drawn per donor varies from 200 to 550 milliliters depending on the country, 450-500 milliliters is typical, which we refer to as a "blood unit." Blood samples for testing are collected from the donor at the time of donation.

Pepe, 2004, Chapter 9, for a detailed discussion and further references). Overall, the decision-maker will classify the blood unit as infection-free (hence keep it for possible transfusion) *only if* she concludes, based on the outcomes of all tests she administers and the decision rule she adopts, that the blood unit is free of each and every one of the diseases; otherwise, the blood unit will be discarded. Finally, all selected tests need to be administered *simultaneously* on the blood sample due to the long time requirements of the tests (including the transportation time to the testing laboratory) and the relatively short life-span of donated blood (Hillyer, 2001). As a result, the testing sequence is irrelevant in our setting.

In this setting, of a set of imperfectly reliable tests to select from to detect a set of diseases, the objective of the decision-maker is to minimize the risk of a transfusion-transmitted infection, i.e., the conditional probability that the blood unit classified as infection-free is in fact infected by some disease(s): this is the single most important objective for Blood Centers, which are very conservative about risk, and applies when the transfusion-transmission of any disease in the disease set is highly undesirable due to the major consequences to the patient. (This is the case for all TTIs that are in the WHO or FDA list of infections recommended for testing.) The decision-maker is resource-constrained, which we model in the form of a budget constraint on the total cost of test administration for a unit of blood.

Finally, another important consideration in blood screening is the fraction of blood units that are falsely rejected ("waste"). Reducing waste is essential, as blood shortages are common, and are projected to significantly increase in the near future in both developing and developed countries (Greinacher et al., 2007; WHO, 2004). Thus, one might also include a constraint in the optimization model to ensure that the fraction of wasted blood is below a certain threshold. We leave the consideration of waste for future research, and simply report the fraction of wasted blood in our numerical studies.

In what follows, we first present the notation, followed by the mathematical formulation of the decision problem.

4.2.1 Notation

Throughout, $\overrightarrow{X} = (X_i)$ denotes a vector, $\overline{X}$ denotes the complement of event X, and $|X|$ denotes the cardinality (size) of set X. Let $\overrightarrow{1_i}, i = 1, \cdots, n$, denote a $1 \times n$ unit row vector, with a "1" in the i^{th} place, and "0"'s elsewhere; and $\overrightarrow{0}$ and $\overrightarrow{1}$

respectively denote vectors of all "0"'s and all "1"'s. Let Ψ denote the set of diseases recommended for screening, Ω_i denote the set of tests available to the decision-maker for disease $i \in \Psi$, with $\Omega_i \bigcap \Omega_j = \emptyset$, for $\forall i, j \in \Psi, i \neq j$, and $\Omega \equiv \cup_{i \in \Psi} \Omega_i$, and $d(j)$ denote the disease test $j, j \in \Omega$, applies to. Let $n \equiv \mid \Psi \mid$, $m_i \equiv \mid \Omega_i \mid$, $i = 1, \cdots, n$, and $m \equiv \sum_{i=1}^{n} m_i$.

Let $\overrightarrow{\Lambda} = (\Lambda_i)_{i=1,\cdots,n}$ denote the disease prevalence vector for a random unit of blood, consisting of binary elements, with a "1" in the i^{th} place indicating that the blood unit is *infected* with disease $i \in \Psi$, and a "0" indicating otherwise. Thus, the sample space of $\overrightarrow{\Lambda}$, which we denote by $\mathscr{S}(\overrightarrow{\Lambda})$, contains 2^n vectors, which collectively represent all prevalence possibilities for n diseases. We denote the joint probability mass function of the random vector $\overrightarrow{\Lambda}$ by $p_{\overrightarrow{\Lambda}}(\overrightarrow{\lambda}) \equiv Pr(\overrightarrow{\Lambda} = \overrightarrow{\lambda})$, for $\overrightarrow{\lambda} \in \mathscr{S}(\overrightarrow{\Lambda})$.

The decision-maker needs to make the following decisions:

Decision variables:

S	:	the set of tests to administer, where $S \subseteq \Omega$ and $S \equiv \cup_{i \in \Psi} S_i$, with $S_i \subseteq \Omega_i$ denoting the set of tests that apply to disease $i \in \Psi$.
$D(S)$	:	the decision rule (among all possible decision rules for test set S, given by the decision rule set $D(S) \in \mathscr{D}(S)$) adopted by the decision-maker for classifying the blood unit as free of all diseases when test set S is administered, $S \subseteq \Omega$.

Consider all blood units as post-screen blood that becomes available for transfusion in the special case where no test is selected (or selected test set is $\emptyset$). Consider a random unit of blood to be tested. We define the following events and parameters.

Events:

A^i+	:	the event that the random blood unit is infected by disease $i \in \Psi$.
$T_j^{d(j)}+$	:	the event that test j provides a positive result for disease $d(j), j \in \Omega$.
$T-(S, D(S))$	:	the event that the random blood unit is classified as free of all diseases based on decision rule $D(S) \in \mathscr{D}(S)$ and administered test set $S \in \Omega$.

Parameters:

$\Pr(T_j^{d(j)}- \mid A^{d(j)}-)$	:	specificity (true negative probability) of test $j \in \Omega$.
$\Pr(T_j^{d(j)}+ \mid A^{d(j)}+)$	:	sensitivity (true positive probability) of test $j \in \Omega$.
Q_j	=	$\Pr(T_j^{d(j)}- \mid A^{d(j)}+)/\Pr(T_j^{d(j)}- \mid A^{d(j)}-)$, $j \in \Omega$. (Denote $\overline{Q}_j = 1 - Q_j$.)
c_j	:	the unit cost of administering test $j \in \Omega$.
B	:	the total budget available per blood unit for administering the screening tests.
α	:	maximum allowable fraction on waste (the fraction of infection-free blood falsely discarded), also referred to as the waste tolerance limit.

$w(\overrightarrow{\lambda}),\ \overrightarrow{\lambda} \in \mathscr{S}(\overrightarrow{\Lambda})$: the weight corresponding to disease prevalence vector $\overrightarrow{\lambda}$ in the weighted risk model.

By definition, $Q_j, j \in \Omega$, represents the ratio of false negative probability to true negative probability. Therefore, tests with smaller Q_j values are desirable from a risk minimization perspective, as our mathematical programming formulation in Proposition 1 indicates. We assume, without loss of generality, that $Q_j \leq 1, j \in \Omega$, that is, each test has a higher true negative probability than false negative probability. This follows because any test not satisfying this assumption can be transformed into one that satisfies it by interpreting its result in the opposite way. Moreover, not surprisingly, this assumption already holds for all FDA-approved tests.

Because the number of blood units screened is *not* a decision variable (all donated blood needs to be screened), the test administration cost may be of any functional form (e.g., nonlinear in blood units). One needs to simply calculate the aggregate cost for each test $j \in \Omega$ (based on the estimated number of blood units to be screened during a period) and express it per unit, c_j.

Test sensitivity and specificity parameters, also known as classification probabilities, are commonly reported (by the medical literature, the FDA, and drug companies) by conditioning on the presence or absence of the corresponding disease only (Pepe, 2004), which we follow here. The implicit assumption being made is that test performance depends only on the specific disease it is being tested for, and *not* on other patient characteristics, such as other medical conditions the patient may have (which may cross-react with the test agents), demographics (e.g., age, gender), disease manifestation (e.g., severity, histology); see Pepe (2004), Chapter 3 for discussion and references. In the context of blood screening, with high co-infection rates among the HIV, HBV, and HCV, as discussed in Section 5.1, an important question that has received considerable attention is whether, among HIV, HBV, and HCV, the presence of one of them affects test outcomes for the others. However, the literature is mixed on the results. While most studies have not found any such correlation in various patient groups, a number of studies have indicated some correlation, e.g., Bonacini et al. (1999, 2001); Jafa et al. (2007); Richard et al. (1993); Zacharias et al. (2004). In summary, data on these effects are scarce, with conflicting findings, and hence, robust conclusions are difficult to make. Consequently, this assumption, which we formally state below, can be considered reasonable under the current medical knowledge.

Assumption **(A1)**: The outcome of test j for disease $d(j)$ depends only on the prevalence of disease $d(j)$ in the blood unit, and not on the prevalence of the other diseases,

that is, for $j \in \Omega$,

$$\Pr(T_j^{d(j)}+ \mid \overrightarrow{\Lambda}) = \Pr(T_j^{d(j)}+ \mid \Lambda_{d(j)}) \text{ and } \Pr(T_j^{d(j)}- \mid \overrightarrow{\Lambda}) = \Pr(T_j^{d(j)}- \mid \Lambda_{d(j)}).$$

Because a small number of trials have suggested higher false positive fractions for specific HIV tests for individuals co-infected with hepatitis viruses (e.g., Jafa et al., 2007, for the Oral HIV antibody test), we briefly discuss the impact of this possibility on our results. If this indeed were the case, then our model (detailed in the next section) would overestimate the TTI risk of a given test composition in donor populations with high co-infection rates by underestimating the benefits of the HIV tests, as they would have the added benefit of potentially removing some hepatitis-infected blood from the pool (of HIV "–" but hepatitis "+" donors). However, because HIV is the most prevalent disease in donor populations with high co-infection rates for HIV and the hepatitis viruses, HIV tests already get first priority in our optimization in such regions (e.g., sub-Saharan Africa, see Section 4.4). Consequently, we conjecture that the relaxation of **(A1)** would not have much impact on our optimal test composition.

Remark 1 *While we define test specificity and sensitivity for the case where each selected test is administered once to the blood unit, it is possible to generalize these parameters to settings where "repeat testing" (of the same test) is done for blood units with initial "+" results. [Some US Blood Centers routinely repeat any test with an initial "+" result twice; the final outcome of this test is considered "+" only if at least one of the repeat tests comes out "+" (Hillyer, 2001)]. The specificity and sensitivity of repeat tests need not be the same as those of the initial test (due to various reasons, including lab errors, such as misinterpretation of the test result). In this case, the sensitivity and specificity parameters of the test under repeat testing policy can be derived using the original sensitivity and specificity, along with sensitivity and specificity conditional on prior testing results, which are reported for several tests, e.g., Schwartz et al. (1990) and references.*

4.2.2 The Decision Problem

The decision problem can be formulated as follows.

Risk-based Minimization Problem **(RMP)**:

$$R^* \equiv \text{Minimize}_{S\in\Omega, D(S)\in\mathscr{D}(S)}\ R\left(S, D(S)\right) \equiv \Pr\left(\bigcup_{i\in\Psi} A^i+ \mid T-(S, D\left(S\right))\right) \quad (4.1)$$

$$\text{subject to } \sum_{j \in S} c_j \leq B. \tag{4.2}$$

Thus, among all test sets that satisfy the budget constraint in (4.2), the objective function in (4.1) selects an optimal test set and a decision rule, denoted respectively by S^* (with $S^* = \cup_{i \in \Psi} S_i^*$) and $D^*(S^*)$, that minimizes the conditional probability that the blood unit is infected by at least one disease, given that it is classified as "infection-free" under the selected test set and decision rule. We denote the corresponding optimal risk as R^*. Note that while **RMP** considers the disease set as *recommended* for screening, a constraint on FDA-*required* diseases can easily be incorporated into the formulation.

In addition to Assumption **(A1)**, we make the following assumption to analyze **RMP**.

Assumption **(A2)**: Test outcomes are conditionally and jointly independent given the prevalence vector, that is, for test $j \in \Omega$ and $S' \subseteq \Omega \setminus \{j\}$, for any two mutually exclusive sets $\{k_1, \ldots, k_f\}$ and $\{l_1, \ldots, l_g\}$ such that $\{k_1, \ldots, k_f\} \bigcup \{l_1, \ldots, l_g\} = S'$,

$$\begin{aligned}
\Pr\left(T_j^{d(j)} + | \overrightarrow{\Lambda}, T_{k_1}^{d(k_1)}+, \ldots, T_{k_f}^{d(k_f)}+, T_{l_1}^{d(l_1)}-, \ldots, T_{l_g}^{d(l_g)}-\right) &= \Pr\left(T_j^{d(j)} + | \overrightarrow{\Lambda}\right), \\
\Pr\left(T_j^{d(j)} - | \overrightarrow{\Lambda}, T_{k_1}^{d(k_1)}+, \ldots, T_{k_f}^{d(k_f)}+, T_{l_1}^{d(l_1)}-, \ldots, T_{l_g}^{d(l_g)}-\right) &= \Pr\left(T_j^{d(j)} - | \overrightarrow{\Lambda}\right).
\end{aligned}$$

Assumption **(A2)** is common in the medical literature, and holds reasonably well for tests that measure different markers in the blood (see Pepe (2004), Chapters 3 and 7). However, it may be violated for tests that measure similar disease markers (e.g., HIV antibodies), whose outcomes are likely to be *positively* correlated. Relaxing **(A2)** requires extensive data on joint sensitivity and specificity of related tests, which is not completely provided (and understood) in the medical literature. Furthermore, this assumption plays a critical role in our analysis, by allowing the reduction of the general problem to a polynomial programming problem, see Proposition 1 below. Consequently, we keep Assumption **(A2)** and briefly discuss its possible impact on our results. Under **(A2)**, our model overestimates the benefit of adding similar tests (e.g., HIV antibody tests of different brands) to the composition. While such a selection would likely not be optimal for low to moderate budgets, which is often the case in practice, it could be for high budgets under **(A2)**, which is where we expect the relaxation of **(A2)** to have an impact. [As a note, the current screening test composition policy of the American Red Cross includes multiple HIV tests that measure different markers (an antibody test and a nucleic acid test) (American Red Cross, 2008).]

Even under Assumptions **(A1)** and **(A2)**, and even when the decision rule is fixed *a priori*, **RMP** remains a difficult knapsack-type problem. In particular, it falls into the class of nonlinear knapsack problems with a nonseparable objective function, a problem considerably more difficult than other knapsack problems, and has received very limited attention in the literature (see Bretthauer and Shetty, 2002, for a review). Indeed, a special case of our problem, with the decision rule fixed as the BP rule and with each disease having one test available to choose from (i.e., $m_i = 1, i \in \Psi$), reduces to the Series-parallel Redundancy Allocation Problem, which is shown to be NP-hard (Chern, 1992), see Appendix B.2.

4.3 Equivalent Formulations, Lower Bounds, and Algorithms

We first show that for any set of tests, the Believe the Positive (BP) decision rule, which classifies the blood unit as infected if at least one test outcome in the battery is "+", is the one that minimizes the risk.

Property 1 *For any test set S and decision rule $D(S) \subseteq \mathscr{D}(S)$, we have*

$$\Pr\left\{\bigcup_{i\in\Psi} A^i+\left|\bigcap_{j\in S} T_j^{d(j)}-\right.\right\} \leq \Pr\left\{\bigcup_{i\in\Psi} A^i+|T-(S,D\,(S))\right\}.$$

Proof. See Appendix B.3. □

As noted in Pepe (2004), the BP rule is "useful if each test detects some subjects that are not detected with the others," which is typically the case in donated blood testing. Furthermore, this is the rule used in practice, where the decision-makers are highly concerned about risk.

Remark 2 *While the structure of the optimal decision rule (the BP rule) in our risk minimization setting is simple and independent of the test parameters, this need not be the case for other relevant metrics in blood screening. For example, we show in Xie et al. (2011) that for a weighted risk function, given by $\sum_{\overrightarrow{\lambda}\in\mathscr{S}\left(\overrightarrow{\Lambda}\right)\setminus\overrightarrow{0}} w(\overrightarrow{\lambda})\Pr\left(\overrightarrow{\Lambda}=\overrightarrow{\lambda}, T-(S,D(S))\right)$, with $w(\overrightarrow{\lambda})$ denoting the weight (e.g., social cost, burden on the individual) of prevalence vector $\overrightarrow{\lambda}$, the BP rule is no longer optimal, and the structure of the optimal decision rule remains an open question.*

With Property 1, we can, without loss of optimality, study **RMP** under the BP rule. Consequently, to simplify the exposition, we drop the decision rule variable from the notation. For $S_i \subseteq \Omega_i, i \in \Psi$, define $T^i-(S_i) \equiv \cap_{j \in S_i} T^i_j-$ and $T^i+(S_i) \equiv \cup_{j \in S_i} T^i_j+$. Then, noting that $S = \bigcup_{i \in \Psi} S_i$, we can express $T-(S)$ and $T+(S)$, which respectively correspond to the events that the blood unit is classified as infection-free versus infected (by at least one disease), as:

$$T-(S) = \cap_{i \in \Psi}\, T^i-(S_i) \quad \text{and} \quad T+(S) = \cup_{i \in \Psi}\, T^i+(S_i).$$

With Property 1, **RMP** can be reformulated as a 0-1 "polynomial programming problem," which refers to a family of nonlinear programming problems having a polynomial objective function and binary variables (e.g., Li and Sun (2006), Chapters 10 and 11). We do this by defining a binary decision variable, I_j, for each available test $j \in \Omega$, which equals 1 if test j is in the selected test composition (set S), and 0, otherwise. Also recall, from Section 4.2.1, that $\overrightarrow{\Lambda} = (\Lambda_i)_{i=1,\cdots,n}$ is the random disease prevalence vector for unit blood, expressed as a binary vector, with its joint pmf denoted by $p_{\overrightarrow{\Lambda}}(\overrightarrow{\lambda})$, $\overrightarrow{\lambda} \in \mathscr{S}(\overrightarrow{\Lambda})$.

Proposition 1 **RMP** *is equivalent to the following* 0-1 *polynomial programming problem:*

$$\underline{\textbf{RMP}}\textit{:} \qquad \textit{Minimize}_{I_j, j \in \Omega} \sum_{\overrightarrow{\lambda} \in \mathscr{S}\left(\overrightarrow{\Lambda}\right) \setminus \overrightarrow{0}} \left\{ p_{\overrightarrow{\Lambda}}\left(\overrightarrow{\lambda}\right) \prod_{i \in \Psi: \lambda_i = 1} \prod_{j \in \Omega_i} \left\{1 - \overline{Q}_j I_j\right\} \right\} \tag{4.3}$$

$$\textit{subject to} \quad \sum_{j \in \Omega} c_j I_j \;\leq\; B, \tag{4.4}$$

$$I_j \qquad \textit{binary},\ j \in \Omega. \tag{4.5}$$

Given the optimal solution to (4.3)-(4.5), denoted by $\{I^*_j, j \in \Omega\}$, *let* $S^* = \{j : I^*_j = 1, j \in \Omega\}$. *Then, the optimal risk is given by* $R^* = \Pr\left(\bigcup_{i \in \Psi} A_i \,|T-(S^*)\right)$.

Proof. See Appendix B.4. □

RMP is a difficult mathematical programming problem with a nonlinear objective function, which contains $\sum_{k=2}^{m} \binom{m}{k} = 2^m - (m+1)$ polynomial terms, ranging from

two-degree to m-degree polynomials, along with m one-degree terms. A standard approach for converting 0-1 polynomial programming problems into 0-1 linear (integer) programming problems, as described in Glover and Woolsey (1974), involves linearizing the objective function by introducing a *new* decision variable to represent each and every one of the polynomial terms.[3] As such, instead of the m binary variables, $I_j, j \in \Omega$, that the original formulation contains, the linearization procedure will lead to $2^m - 1$ binary variables, along with a large number, $\sum_{k=2}^{m} (k+1)\binom{m}{k}$, of additional constraints, producing a large-size integer programming problem, especially for practical problem sizes where the number of candidate tests, m, is typically in the order of 50-80 (FDA, 2010). (For a special case of **RMP**, however, the size of such a linearized formulation becomes manageable, and we discuss its efficiency in Section 4.3.1.) Furthermore, we show, in the next section, that exploiting the special structure and properties of **RMP** allows us to develop highly effective algorithms for it. Consequently, in the remainder of the chapter, we pursue this avenue and study structural properties of **RMP**.

Observe that **RMP** finds the optimal test composition, which is then applied to *all* donated blood. An interesting question, both from a theoretical and a public policy perspective, is whether allowing for "differential policies" (with multiple test compositions, each applied to a certain fraction of the total blood) (i) are easy to obtain through an LP-relaxation of the formulation given above, and (ii) provide benefits over the current "same-for-all" policy. The following remark answers the first question, and we suggest this interesting extension as a future research direction.

Remark 3 *An LP-relaxation of* **RMP** *in (4.3)-(4.5) (obtained by allowing fractional values in* $[0, 1]$ *for the binary test variables* $I_j, j \in \Omega$*) will not be valid, as the objective function in (4.3), with fractional* $I_j, j \in \Omega$ *variables, will no longer correspond to the risk. (This follows from the proof of Proposition 1, which shows that the objective function in (4.3) is valid only with binary decision variables.)*

[3]Specifically, the objective function of **RMP** can be linearized by replacing each polynomial term involving $\prod_{j \in S} I_j$, for $S \subseteq \Omega$, with a new decision variable, Y, and by adding a new set of constraints, $\{Y \leq I_j, j \in S,\ Y \geq \sum_{j \in S} I_j - (|S| - 1)\}$. This is to ensure that $Y = 1$ if and only if $\bigcap_{j \in S} \{I_j = 1\}$ (Glover and Woolsey, 1974).

4.3.1 RMP with Mono-infections Only

We first analyze a special case of **RMP**, which we refer to as **RMP**^{0}, where the possibility of co-infections in the blood unit is negligible. Mathematically speaking, we assume $Pr(\overrightarrow{\Lambda} = \overrightarrow{\lambda}) = 0$, for $\overrightarrow{\lambda} \in \mathscr{S}(\overrightarrow{\Lambda}) : \sum_{i\in\Psi} \lambda_i > 1$. While this mono-infection setting deserves analysis in its own right (as the donor selection procedures in developed countries make the co-infection possibility unlikely), this analysis also motivates the development of near-optimal algorithms for the general case with co-infections. We use the superscript ^{0} to denote the optimal solution and its risk in this setting.

Corollary 1 *For the mono-infection setting,* **RMP** *reduces to the following:*

$$\underline{\textbf{RMP}^0}\textit{: Minimize}_{I_j, j\in\Omega} \sum_{i\in\Psi} p_{\overrightarrow{\Lambda}}(\overrightarrow{\lambda} : \lambda_i = 1) \left(1 - \sum_{j\in\Omega_i} I_j\overline{Q}_j + \sum_{j\in\Omega_i}\sum_{k\in\Omega_i, k>j} I_jI_k\overline{Q}_j\overline{Q}_k \right.$$
$$\left. - \sum_{j\in\Omega_i}\sum_{k\in\Omega_i,k>j}\sum_{l\in\Omega_i,l>k} I_jI_kI_l\overline{Q}_j\overline{Q}_k\overline{Q}_l + \cdots + (-1)^{|\Omega_i|} \prod_{j\in\Omega_i} I_j\overline{Q}_j \right) \quad (4.6)$$
$$\textit{subject to} \quad (4.4), (4.5).$$

Given the optimal solution to **RMP**^{0}*, denoted by* $\{I_j^{*0}, j \in \Omega\}$*, let* $S^{*0} = \{j : I_j^{*0} = 1, j \in \Omega\}$*. Then, the optimal risk is given by* $R^{*0} = \Pr\left(\bigcup_{i\in\Psi} A_i + |T - (S^{*0})\right)$.

Proof. Follows directly from Proposition 1, when the no co-infection assumption is imposed, i.e., $\Pr\left(\overrightarrow{\Lambda} = \overrightarrow{\lambda}\right) = 0$, for $\overrightarrow{\lambda} \in \mathscr{S}(\overrightarrow{\Lambda}) : \sum_{i\in\Psi} \lambda_i > 1$. □

The objective function in (4.6) is now additively *separable* in the diseases. The objective function corresponding to each disease $i, i \in \Psi$, will now have a single one-degree term, along with $\sum_{k=2}^{m_i} \binom{m_i}{k} = 2^{m_i} - (m_i + 1)$ polynomials, ranging from two-degree to m_i-degree polynomials. Diseases will still be interacting, however, through the common budget constraint. Then, for each disease $i \in \Psi$, were we given its own budget allocation, B_i, then **RMP**^{0} would decompose into n separate optimization problems, and as we show below in Lemma 1, each disease i's problem, **RMP**^{0}-$i(B_i)$, could be transformed into the linear knapsack problem, for which efficient pseudo-polynomial algorithms are known (e.g., Martello and Toth, 1990).

Observe also that for a given budget allocation vector, this special case (of mono-infections only) now requires only $\sum_{i\in\Psi}(2^{m_i} - 1)$ binary variables, rather than the

$2^m - 1$ binary variables that the original problem, **RMP**, calls for (with co-infection possibility). This reduction in the number of binary variables can be huge for practical-sized problems. For example, if $n = 10, m = 50$, and with 5 tests available for each disease, we now have $10 \times (2^5 - 1) = 310$ binary variables instead of the $2^{50} - 1 = 1.12 \times 10^{15}$. We pursue this decomposition idea formally in the next section.

Optimal Algorithms for $\mathbf{RMP}^0$

In what follows, we discuss three optimal algorithms or reformulations for $\mathbf{RMP}^0$ (with mono-infections only) and show that a specific reformulation of $\mathbf{RMP}^0$, which we refer to as the Testset-based formulation (**TS-B**), provides superior performance over the other approaches (in terms of computational times). We further utilize the **TS-B** in the development of a near-optimal algorithm for the general co-infection problem in Section 4.3.2.

A Shortest Path-based Approach

We first show that, for a given budget allocation vector to $\mathbf{RMP}^0$, each disease's problem can be formulated as a linear knapsack problem. This result then motivates an optimal Shortest Path-based Algorithm, whose arc costs are derived by solving a series of linear knapsack problems.

Lemma 1 *The optimal solution to* $\mathbf{RMP}^0$*-*$i(B_i)$*,* $i \in \Psi$*, corresponding to a given budget allocation* B_i*, can be determined by solving the following integer programming problem:*

$$\underline{\mathbf{RMP}^0\text{-}i(B_i)}\text{: } R_i^{*0'}(B_i) \equiv \textit{Minimize}_{I_j, j \in \Omega_i} \sum_{j \in \Omega_i} \ln\{Q_j\}\ I_j$$

$$\begin{aligned} \textit{subject to} \quad & \sum_{j \in \Omega_i} c_j\ I_j \leq B_i, \\ I_j \quad & \textit{binary},\ j \in \Omega_i. \end{aligned}$$

Given the optimal solution to $\mathbf{RMP}^0$*-*$i(B_i)$*, denoted by* $\{I_j^{*0}, j \in \Omega_i\}$*, let* $S_i^{*0} = \{j : I_j^{*0} = 1, j \in \Omega_i\}$*. Then, the optimal risk is given by* $R_i^{*0}(B_i) \equiv \frac{1}{1 + \frac{\Pr(A^i-)}{\Pr(A^i+)} \exp\left\{R_i^{*0'}(B_i)\right\}}$.

Proof. See Appendix B.5. □

Now we are ready to formulate $\mathbf{RMP}^0$ as a Shortest Path Problem. For this, we first multiply all test costs and the budget by a common factor so that they are all integral. For simplicity in exposition, in what follows, we keep the notation the same. We have the following result.

Proposition 2 $\mathbf{RMP}^0$ *can be formulated as a Shortest Path (SP) Problem on a "disease-expanded" network, whose arc costs are determined by solving a series of knapsack problems. The SP network consists of a source node,* B*, a sink node,* 0*, and* $n-1$ *copies of nodes* $0, 1, 2, \cdots, B$*, with the* i^{th} *copy denoted as* $x(i)$*,* $x \in Z_B^+ \equiv \{0, 1, 2, \cdots, B\}$*. The arc set consists of* $\{(B, x(1)), x \in Z_B^+\} \cup \{(x(i), y(i+1)), x, y \in Z_B^+, x \geq y, i = 1, 2, \cdots, n-2\} \cup \{(x(n-1), 0), x \in Z_B^+\}$*, with arc costs given by*

$$\begin{aligned} a_{(B,x(1))} &= R_1^{*0}(B - x(1)), \quad x \in Z_B^+, \\ a_{(x(i),y(i+1))} &= R_{i+1}^{*0}(x - y), \quad x, y \in Z_B^+, x \geq y, i = 1, 2, \cdots, n-2, \\ a_{(x(n-1),0)} &= R_n^{*0}(x(n-1)), \quad x \in Z_B^+, \end{aligned}$$

where $R_i^{*0}(B_i)$ *is the optimal objective value to* $\mathbf{RMP}^0$*-*$i(B_i)$ *with budget* B_i*, as defined in Lemma 1, for* $i \in \Psi, B_i \in Z_B^+$*.*

Proof. Follows directly from Lemma 1. □

Proposition 2 allows the use of efficient algorithms developed for the SP problem (e.g., Dreyfus, 1969), in conjunction with algorithms developed for the linear knapsack problem (for calculating the arc costs), for solving $\mathbf{RMP}^0$ to optimality. Nevertheless, while the development of the SP-based Algorithm is interesting from a theoretical perspective, the size of the SP network becomes very large for practical-sized problems. Consequently, we next propose a reformulation of $\mathbf{RMP}^0$, which performs very well in our numerical studies.

The Testset-based (TS-B) Reformulation

We reformulate **RMP** by replacing the binary test variables, $I_j, j \in \Omega$, in the original formulation (in Corollary 1) with binary variables, $I^i_{q_1,q_2,\cdots,q_k}$, $\forall \{q_1, q_2, \cdots, q_k\} \subseteq \Omega_i, i \in \Psi$ (we let $I^i_\emptyset$ and $I^i_{\Omega_i}$ respectively denote the binary variables corresponding to the empty set and set Ω_i), and add a set of constraints that ensure that $I^i_{q_1,q_2,\cdots,q_k} = 1$ if and only if $\{I_{q_1} = 1, \cdots, I_{q_k} = 1, I_p = 0, \forall p \in \Omega_i \setminus \{q_1, q_2, \cdots, q_k\}\}$.

Proposition 3 $\mathbf{RMP}^0$ *is equivalent to the following integer programming problem:*

$$\underline{\textbf{TS-B}}\textit{: Minimize} \sum_{i\in\Psi} p_{\overrightarrow{\Lambda}}(\lambda:\lambda_i=1) \left(\begin{array}{l} \sum\limits_{j\in\Omega_i} Q_j I^i_j + \sum\limits_{j\in\Omega_i}\sum\limits_{k\in\Omega_i,k>j} Q_jQ_kI^i_{jk} + \\ \sum\limits_{j\in\Omega_i}\sum\limits_{k\in\Omega_i,k>i}\sum\limits_{l\in\Omega_i,l>k} Q_jQ_kQ_lI^i_{jkl} + \cdots + \prod\limits_{j\in\Omega_i} Q_jI^i_{\Omega_i} + I^i_{\emptyset} \end{array} \right)$$

$$\textit{subject to} \quad \sum_{i\in\Psi} \left\{ \begin{array}{l} \sum\limits_{j\in\Omega_i} c_jI^i_j + \sum\limits_{j\in\Omega_i}\sum\limits_{k\in\Omega_i,k>j} (c_j+c_k)\, I^i_{jk} + \\ \sum\limits_{j\in\Omega_i}\sum\limits_{k\in\Omega_i,k>j}\sum\limits_{l\in\Omega_i,l>k} (c_j+c_k+c_l)\, I^i_{jkl} + \cdots + \left(\sum\limits_{j\in\Omega_i} c_j\right) I^i_{\Omega_i} \end{array} \right\} \leq B$$

$$\sum_{j\in\Omega_i} I^i_j + \sum_{j\in\Omega_i}\sum_{k\in\Omega_i,k>j} I^i_{jk} + \sum_{j\in\Omega_i}\sum_{k\in\Omega_i,k>j}\sum_{l\in\Omega_i,l>k} I^i_{jkl} + \cdots + I^i_{\Omega_i} + I^i_{\emptyset} = 1, \forall i \in \Psi$$

$$I^i_{q_1,q_2,\cdots,q_k} \textit{ binary, } \forall\{q_1,q_2,\cdots,q_k\} \subseteq \Omega_i, i \in \Psi.$$

Proof. Follows by applying the definition of the **TS-B** decision variables to the formulation in Corollary 1. □

Finally, as the third approach, we use the standard linearization approach (**ST-LIN**) detailed in Glover and Woolsey (1974) (and discussed above), commonly used for linearizing the objective function of 0-1 polynomial programming problems. While both **ST-LIN** and **TS-B** reformulations yield a comparable number of decision variables for the mono-infection setting, **TS-B** yields a significantly smaller number of constraints for realistic problem sizes, involving $10-14$ $(=n)$ diseases and $50-82$ $(=m)$ tests. For example, for scenarios with 10 (14) diseases and 50 (82) tests, **ST-LIN** yielded 510 $(1,186)$ decision variables and $2,031$ $(5,127)$ constraints, while **TS-B** yielded 520 $(1,200)$ variables but only 11 (15) constraints. This resulted in a huge increase in the CPU times for **ST-LIN** in our numerical studies. In particular, while all these problem instances were easily solved within 0.06 seconds under **TS-B**, **ST-LIN** required significantly longer CPU times, over $1,000$ seconds in several cases. In this chapter, all computational runs are performed on Dell DM051 with Intel Pentium(R) D CPU 2.80GHz, and the mathematical programming problems are solved in IBM ILOG OPL IDE.

In summary, our extensive numerical study suggests the superior performance (in terms of computational times) of the **TS-B** reformulation in solving mono-infection problems over both the **ST-LIN** and **SP-based** approaches. Consequently, we do not explore other approaches proposed in the literature for converting polynomial

programming problems to linear problems (e.g., Adams and Sherali, 1990; Chang and Chang, 2000; Sherali and Tuncbilek, 1992), and consider the **TS-B** reformulation when we study the co-infection setting in the next section.

4.3.2 RMP with Co-infections: Lower Bounds and Near-Optimal Algorithms

We now turn our attention to the general case of **RMP** with possible co-infections in donated blood. As stated in Section 5.1, co-infection rates can be significant, especially in developing countries that have high prevalence rates for major TTIs, and that have not established rigorous and systematic screening procedures for blood donors. **RMP**, for the general case, is a difficult optimization problem, as discussed in Section 4.2.2. Thus, in what follows, we first develop two lower bounds on its optimal risk. We then develop a near-optimal algorithm for it, which is motivated by our analysis of the mono-infection case.

Proposition 4 *(i)* $R^* \geq LB1$*, where* $LB1$ *is the optimal solution to:*

$$\underline{\textit{Problem}\ \ \textbf{LB1}\textit{:}}\quad LB1 \equiv \Pr\left(\bigcup_{i\in\Psi} A^i+\right) \times \qquad \begin{array}{l} \textit{Minimize}_{\ S\subseteq\Omega}\left\{\prod_{j\in S} Q_j\right\} \\ \textit{subject to} \quad \sum_{j\in S} c_j \leq B. \end{array} \tag{4.7}$$

(ii) In **RMP**, *set* $\Pr\left(\overrightarrow{\Lambda} = \overrightarrow{\lambda}\right) = 0$, $\forall \overrightarrow{\lambda} \in \mathscr{S}(\overrightarrow{\Lambda}) : \sum_{i\in\Psi} \lambda_i > 1$, *and solve the resulting instance of the mono-infection problem optimally (by one of the algorithms prescribed in Section 4.3.1), whose optimal solution we denote by* R^{*0}*. Then,* $LB2 \equiv R^{*0} \leq R^*$.

Proof. See Appendix B.6. □

For **RMP**, we propose the Co-infection Reallocation (**CR**) Heuristic, which is based on the idea of approximating the co-infection problem as a mono-infection problem. This is done by *reallocating* the probability of each co-infection prevalence vector to the corresponding mono-infection prevalence vectors in proportion to their original mono-prevalence probabilities, see Figure 4.1 for an example. Different probability reallocation rules are possible. In our numerical study, this specific rule dominated

the other rules considered in all scenarios tested. Recall that $p_{\overrightarrow{\Lambda}}(\overrightarrow{\lambda})$, $\overrightarrow{\lambda} \in \mathscr{S}(\overrightarrow{\Lambda})$, is the joint pmf of the prevalence vector in the co-infection setting.

The **CR** Heuristic:

STEP 0: Set $p^H_{\overrightarrow{\Lambda}}\left(\overrightarrow{\lambda}\right) = p_{\overrightarrow{\Lambda}}(\overrightarrow{\lambda})$, for $\overrightarrow{\lambda} \in \mathscr{S}\left(\overrightarrow{\Lambda}\right)$.

STEP 1: REPEAT for each $\overrightarrow{\lambda}' \in \mathscr{S}\left(\overrightarrow{\Lambda}\right) : \sum_{j\in\Psi} \lambda'_j > 1$ and $p_{\overrightarrow{\Lambda}}\left(\overrightarrow{\lambda}\right) > 0$:

- For each $i \in \Psi : \lambda'_i = 1$:

$$p^H_{\overrightarrow{\Lambda}}\left(\overrightarrow{1}_i\right) \leftarrow p^H_{\overrightarrow{\Lambda}}\left(\overrightarrow{1}_i\right) + p_{\overrightarrow{\Lambda}}\left(\overrightarrow{\lambda}'\right) \times \left(\frac{p_{\overrightarrow{\Lambda}}(\overrightarrow{1_i})}{\sum_{j\in\Psi,\lambda'_j=1} p_{\overrightarrow{\Lambda}}(\overrightarrow{1_j})}\right),$$

- $p^H_{\overrightarrow{\Lambda}}(\overrightarrow{\lambda}') \leftarrow 0$.

STEP 2: Solve the resulting mono-infection problem (with $p^H_{\overrightarrow{\Lambda}}\left(\overrightarrow{\lambda}\right)$, $\overrightarrow{\lambda} \in \mathscr{S}\left(\overrightarrow{\Lambda}\right)$) to optimality using the **TS-B** formulation and obtain its optimal test set, S^H.

STEP 3: Determine the risk to the original co-infection problem for test set S^H (i.e., $R(S^H)$) under the original joint pmf, $p_{\overrightarrow{\Lambda}}\left(\overrightarrow{\lambda}\right)$, $\overrightarrow{\lambda} \in \mathscr{S}\left(\overrightarrow{\Lambda}\right)$.

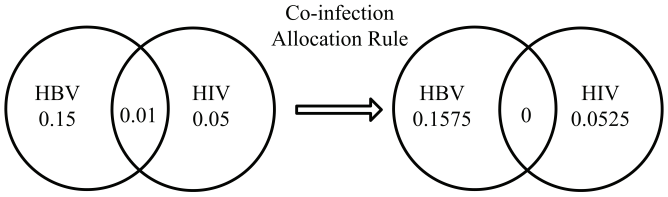

Figure 4.1: Example of the co-infection probability reallocation rule

4.4 A Numerical Study for the Co-infection Setting

Our objectives in this section are two-fold: **(i)** to study the effectiveness of the **CR** Heuristic for the test selection problem with co-infections, and **(ii)** to obtain insights

on the impact of problem parameters on the test composition. In what follows, we summarize the findings from our extensive numerical studies and provide details of a case study.

4.4.1 Effectiveness of the CR Heuristic and the Lower Bounds

Using small problem instances (n = 3-4 and m = 10-15), for which we could determine the optimal solution through enumeration, we studied the effectiveness of the **CR** Heuristic solution and the lower bounds. To extend the problem size over which enumeration is feasible, we use a simple, yet powerful, property of an optimal solution to Problem **RMP**, which leads to a significant reduction in the number of test sets that must be considered when using enumeration to find the optimal solution.

Property 2 *Set $S \subset \Omega$ is said to be a "dominant set" only if (i) $\sum_{j\in S} c_j \leq B$ and (ii) $\sum_{j\in S} c_j + c_k > B$ for any $k \in \Omega \setminus S$. The optimal solution to* **RMP** *must correspond to a dominant set.*

Proof. Since $Q_j \leq 1$ for all $j \in \Omega$ (see Section 4.2.1), selecting an additional test weakly lowers the risk. Hence, it trivially follows that for any test set $S \subset \Omega$ such that $\sum_{j\in S} c_j \leq B$, none of its proper subsets $S' \subset S, S' \neq S$ can have $R(S') < R(S)$, and the result follows. □

For these small problem instances, the **CR** Heuristic generated the optimal solution in 96% of the problem instances and the average percent deviation of the heuristic risk from the optimal risk was 0.16% (and no more than 0.52%). For developed countries with relatively larger testing budgets, the risk of a TTI is very low, and a deviation of 0.52% translates into a minuscule risk difference between the optimal solution and the heuristic solution. The lower bound, based on $LB1$ and $LB2$ of Proposition 4 ($LB \equiv \max\{LB1, LB2\}$)[4], had an average percent deviation from the optimal risk of 18.787% and a maximum deviation of 37.244%. We find that the performance of the LB was the worst at low budget levels. We then extended this study to large problem instances, representative of realistic problem sizes (n = 10 and m = 50), for which we compared the heuristic risk with the lower bounds. For these large problem instances, the average deviation of the heuristic risk from the lower bound was 2.27% for realistic co-infection rates. The heuristic run-times were less than 0.1 seconds for all scenarios.

[4]In our numerical study, $LB2$ outperformed $LB1$ in all but very small budget scenarios.

Next we present a case-study using realistic data from sub-Saharan Africa, and then compare some of these results against other regions, including Ghana, Thailand, and the United States.

4.4.2 A Case Study of the Sub-Saharan Africa Region

We first apply the **CR** Heuristic to a case study based on sub-Saharan Africa, where an estimated 22.4 million people have HIV infections (around two thirds of the global total). The HIV prevalence in sub-Saharan Africa varies, by country, from 2% to 26% (UNAIDS, 2008); we use 15% in this study. Besides HIV, the WHO recommends screening for HBV, HCV, and Syphilis (along with other diseases based on local conditions) (WHO, 2011), while the FDA adds HTLV, WNV, and Chagas' Disease (FDA, 2011) to the WHO recommendations. HBV, HCV, and HTLV prevalence rates for this region are estimated at 10%, 3%, and 3%, respectively (Kiire, 1996; Madhava et al., 2002; Proietti et al., 2005). Prevalence rates are difficult to estimate for the WNV, as most WNV infections occur in the form of outbreaks (Mostashari et al., 2001); we use 1% as an approximation for the prevalence rate, based on a study of WNV antibodies (Petersen, 2009). Syphilis and Chagas' Disease are omitted from the case study due to a lack of data. The HIV-infected population has a co-infection rate for HBV and HCV of 10% and 15%, respectively (Carmo et al., 2000; Lincoln et al., 2003), while the HCV-infected population has a co-infection rate for HBV of 10%, which is within the worldwide range of 9%-30% (see Adewole et al., 2009; Christian et al., 2010; Forbi et al., 2007; Gordona and Sherman, 2009; Otegbayo et al., 2008; Soriano et al., 2006). We ignore the triple co-infection rate of HIV-HBV-HCV. Table 4.1 displays the mono- and co-infection prevalence rates.

Table 4.1: Prevalence rates (%) in different regions

	Sub-Saharan Africa	Ghana	Thailand	US
Mono-HIV	11.250	3.000	0.601	0.008
Mono-HBV	8.200	14.351	2.196	0.067
Mono-HCV	0.450	1.641	0.243	0.291
Mono-HTLV	3.000	2.000	0.001	0.010
Mono-WNV	1.000	1.000	0.001	0.010
HIV-HBV	1.500	0.400	0.063	0.001
HIV-HCV	2.250	0.600	0.056	0.001
HCV-HBV	0.300	0.249	0.251	0.008

Table 4.1 also displays the prevalence rates for three other regions, which we use later

to study the impact of prevalence rates on test selection. For Ghana we use prevalence rates for HIV, HBV, HCV, and HTLV of 4%, 15%, 2.49%, and 2%, respectively (Van Hulst et al., 2009; Lal et al., 1994). To the best of our knowledge, there does not exist accurate and conclusive estimation on the prevalence of WNV in Ghana; we therefore use the same 1% estimate for sub-Saharan Africa in general. Likewise, we use the same co-infection rates as for sub-Saharan Africa. For Thailand we use prevalence rates for HIV, HBV, and HCV of 0.72%, 2.51%, and 0.39%, respectively (Van Hulst et al., 2009). There is little in the literature on the prevalence of HTLV or WNV in Thailand, but they are reported to be extremely low (Choudhury, 2010; Vrielinka and Reesink, 2004); thus we use a low prevalence rate of 0.001%. The HIV-infected population has estimated co-infection rates for HBV and HCV of 8.7%, and 7.8%, respectively (Sungkanuparph et al., 2004), and we use a co-infection rate for HCV with HBV of 10%. For the US, we use prevalence rates for HIV, HBV, HCV, and HTLV of 0.010%, 0.076%, 0.299%, and 0.0096%, respectively (Dodd et al., 2002; Eble et al., 1993). The prevalence of WNV is reported in the ranges of 0.001% to 0.02% (Biggerstaff and Petersen, 2002; Choudhury, 2010; ORD, 2011), and we use 0.01% as the estimate. For co-infection rates, among HIV-positive individuals studied from Western Europe and the US, HBV and HCV infections have been found in 6-14% and 9-27%, respectively (Alter, 2006). We use 6% and 9% as co-infection rates for HBV and HCV in the HIV-infected population, respectively, and a co-infection rate for HCV with HBV of 10%.

In this study, we allow test selection from all FDA-approved tests. We approximate the efficacy of each test using the data provided by the FDA (FDA, 2010). The administration cost data are approximated according to the study by Jackson et al., 2003 (actual costs are usually confidential). Consequently, the number of tests we consider for HBV, HIV, HCV, WNV, and HTLV are 6, 16, 7, 2, and 2, respectively. These tests represent a wide range of cost and efficacy (see Table 6.1). For example, the HIV test #10 costs \$13 and has a specificity of 1 and a sensitivity of only 0.805, compared to HIV test #16, which costs \$18 and has a specificity and sensitivity of 0.9967 and 0.9900, respectively, while HIV test #14 costs \$4 and has a specificity and sensitivity of 0.9880 and 0.9920, respectively.

Table 4.3 displays the test set selected by the **CR** Heuristic for budgets from \$2-60, along with the associated risk, the lower bound on the optimal risk ($LB = \max\{LB1, LB2\}$), and the waste, i.e., the percent of blood falsely rejected by screening, i.e., $\Pr\left\{\bigcup_{j\in S} T_j^{d(j)+} | \bigcap_{i\in\Psi} A^i-\right\}$. For brevity, Table 4.3 only shows the budget in \$5 increments after a budget of \$20. We note that every \$1 increment in the budget caused the selected test set to change until a budget of \$45. After this, the

Table 4.2: Efficacies and administration costs for FDA-approved blood screening tests

TTI	Test	Specificity	Sensitivity	Q_j	Cost($)	TTI	Test	Specificity	Sensitivity	Q_j	Cost($)
HBV	1	0.9839	0.9900	0.0102	3	HIV	17	0.9940	0.9970	0.0030	17
	2	0.9982	0.9600	0.0401	3		18	0.9983	0.9915	0.0085	5
	3	0.9980	0.9970	0.0030	4		19	0.9983	0.9984	0.0016	5
	4	0.9685	0.9882	0.0122	2		20	0.9977	0.9976	0.0024	5
	5	0.9380	0.8810	0.1269	5		21	0.9978	0.9972	0.0028	5
	6	0.9940	0.9810	0.0191	8		22	0.9960	0.9820	0.0181	4
HIV	7	0.9960	0.9970	0.0030	5	HCV	23	0.9979	0.6330	0.3678	4
	8	0.9790	0.9400	0.0613	15		24	0.9880	0.9640	0.0364	3
	9	0.9080	0.8560	0.1586	10		25	0.9984	0.9949	0.0051	5
	10	1.0000	0.8050	0.1950	13		26	1.0000	0.6330	0.3670	10
	11	0.9640	0.6530	0.3600	8		27	0.9380	0.8560	0.1535	15
	12	0.9930	0.9670	0.0332	18		28	0.9967	0.9900	0.0100	18
	13	0.9991	0.9975	0.0025	5		29	0.9730	0.9910	0.0092	16
	14	0.9880	0.9920	0.0081	4	WNV	30	0.9986	0.8690	0.1312	5
	15	0.9900	0.9950	0.0051	4		31	0.9890	0.9860	0.0142	4
	16	0.9967	0.9900	0.0100	18	HTLV	32	0.9963	0.9976	0.0024	4
							33	0.9989	0.9948	0.0052	5

largest budget increment without a change in the tests selected was \$3. Hence, the test selection problem is quite dynamic and budget sensitive. Without screening, the TTI risk is 27.950% in this region.[5] We observe that the heuristic risk is very close to the lower bound: the average deviation of the heuristic risk from the lower bound is 0.637%, with a maximum deviation of 11.496%, which occurred at the lowest budget level where the lower bound is not tight. We can see that the waste generated at each budget allocation is also quite dynamic; for instance, the waste jumps from 1.564% at a \$12 budget to 5.620% at a \$13 budget.

When the testing budgets are low, the cost of testing and the TTI prevalence rates are the dominant factors in the test selection. For instance, HBV test #4 is the only test affordable when the budget is \$2. A \$1 increase replaces this test with HBV test #1, which has better efficacy; this slightly decreases risk and halves the waste. At a budget of \$4, HIV test #15 is affordable, and as HIV is the most prevalent TTI in this region, this HIV test replaces the HBV test #1, even though these two tests have similar efficacies. Another \$1 increase in the budget replaces #15 with HIV test #19, which has better efficacy. Interestingly, when the budget increases to \$6, HIV test #15 regains its place in the solution, as test #19 is removed to accommodate

[5] "In 2007, the WHO's Global Database on Blood Safety indicated that "there were at least 400,000 blood donations in Africa (in 44 of 46 countries reporting) that were not tested for HIV, HBV and HCV"(Walkley, 2009).

Table 4.3: The test composition generated by the **CR** Heuristic under varying budget allocations for the sub-Saharan Africa case study

Budget($)	HBV	HIV	HCV	WNV	HTLV	Risk(%)	Lower Bound (%)	Waste(%)
2	4					20.053	17.985	3.150
3	1					20.035	17.970	1.610
4		15				15.311	14.992	1.000
5		19				15.259	14.953	0.170
6	4	15				6.028	6.010	4.119
7	4	19				5.971	5.962	3.315
8	3	15				5.932	5.917	1.198
9	4	15	24			5.476	5.475	5.269
10	4	15			32	2.211	2.191	4.473
11	4	19			32	2.149	2.139	3.672
12	3	15			32	2.107	2.091	1.564
13	4	15	24		32	1.613	1.612	5.620
14	4	15		31	32	0.885	0.864	5.524
15	4	19		31	32	0.821	0.811	4.732
16	3	15		31	32	0.778	0.761	2.646
17	4	15	24	31	32	0.270	0.269	6.658
18	4	19	24	31	32	0.216	0.216	5.875
19	3	15	24	31	32	0.166	0.165	3.815
20	3	19	24	31	32	0.112	0.112	3.008
25	3,4	14,15	24	31	32	0.053	0.053	7.962
30	3,4	14,15	24,25	31	32	0.031	0.031	8.110
35	3,4	14,15	24,25	31	32	0.014	0.014	8.238
40	3,4	14,15	24,25	30,31	32,33	0.004	0.004	8.339
45	1,3,4	13,19	24,25	30,31	32,33	0.003	0.003	8.037
50	1,3,4	13,19	23,24,25	30,31	32,33	0.003	0.003	8.230
55	1,2,3,4	14,15,19	23,24,25	30,31	32,33	0.003	0.003	10.319
60	1,2,3,4	13,14,15,19	23,24,25	30,31	32,33	0.003	0.003	10.400

HBV test #4. The $6 budget is the first that allows testing for two TTIs, greatly reducing risk to around 6%. This switching to higher efficacy tests continues until the budget reaches $9, which allows, for the first time, a test for a third TTI (HCV in this case). At $10, the test for HCV is dropped, and one for HTLV is added; HCV and HTLV have the same prevalence rates in our case study data, but the HTLV test has better efficacy. In addition, HCV has a low mono-prevalence rate; therefore, many HCV infections are removed using HBV and HIV testing. Further improvement in risk is achieved as the budget increases to $17, which, for the first time, allows one test for each of the diseases considered, HIV, HBV, HCV, WNV, and HTLV. At $40, an additional $20 (to increase the budget to $60) decreases the overall risk by only 0.001% as more and more tests are administered.

Not surprisingly, we notice significant improvement in risk when increased budget levels allow **1)** a test for a previously untested disease to enter the set, or **2)** switching from a test for a less prevalent disease to one for a more prevalent disease. The

improvement from switching between tests for the same disease is relatively small, because of the existence of inexpensive tests with relatively high efficacies.[6] We again note the impact of co-infections; as another example, there are intervals (e.g., for budgets in \$14-16) for which a \$4 WNV test (#31) is used instead of a HCV test, despite the higher prevalence of HCV. This is partially because the WNV test has slightly better efficacy, but this selection is mainly driven by the low mono-infection rate for HCV (of 0.45%); many HCV infections are eliminated by the already-selected tests for HBV and HIV.

Finally, to obtain further insight, we study the impact of test sensitivity and specificity parameters on the test composition, and of the BP decision rule on risk and waste. Proposition 1 shows that optimal test sets are selected based on the test performance measure Q_j and cost $c_j, \forall j \in \Omega$. In Table 6.1, we report the characteristics of each test as a point estimate. However, test specificity and sensitivity are usually estimated in terms of a confidence interval.[7] For instance, HIV test #21 has an estimated specificity at 99.90% with a 95% confidence interval of [99.78%, 99.96%] and sensitivity at 100.00% with a 95% confidence interval of [99.72%, 100%]. Figure 4.2(a) plots each HIV test's Q-value, Q(UB) (with the test number displayed on top of each bar), clustered by cost. We see that for tests that cost \$4-5, the Q-values are quite similar. Figure 4.2(b) further details the Q-value intervals, obtained from the 95% confidence intervals for sensitivity and specificity, for those tests in the cost cluster of \$4-5. These results indicate that small changes in the estimated parameters could change the optimal test set (which we have also observed in our numerical analysis).

From Property 1, the BP rule is the risk minimizing rule and is also the one used by the US Blood Centers, which are rightly very conservative about risk. However, this primary focus on risk leads to increased levels of waste. Consequently, we now consider another decision rule, the Believe the Negative (BN) rule, which places the primary emphasis on waste reduction. This follows because under the BN rule, the blood unit is classified as free of a particular disease if at least one test result in the battery is "–". To understand the impact of the BP and BN rules on risk and waste, we consider the HIV with the 15% prevalence rate as in sub-Saharan Africa,

[6] To understand the impact of test selection for one disease, see the discussion on Table 5.7, where we observe a tremendous difference when different tests are selected when the same guidelines are enforced.

[7] Specifically, Table 6.1 reports the upper bounds on the Q_j measure (Q_j(UB)), derived from the lower bounds of the 95% confidence interval for test sensitivity and specificity. Recalling that tests with smaller Q_j values are desirable from a risk minimization perspective, this provides us with conservative estimates on test performances.

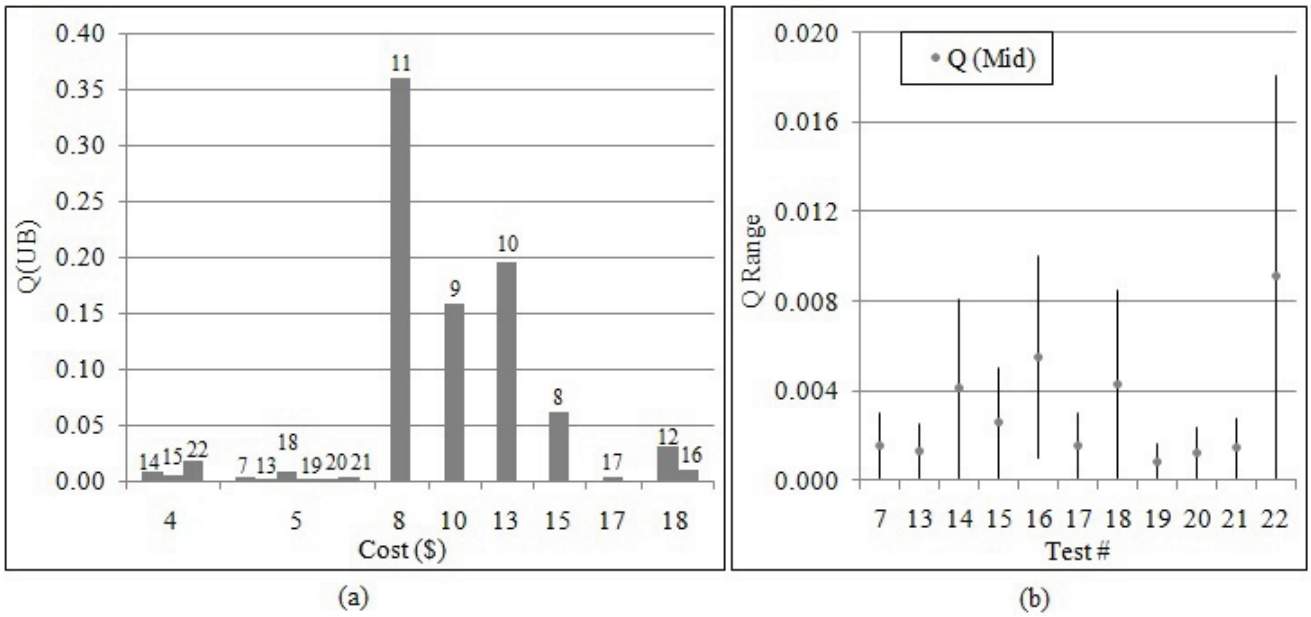

Figure 4.2: (a) The Q(UB) parameter for HIV tests grouped by cost (the test number is displayed on top of each bar), (b) the interval for the Q parameter, derived from the 95% confidence intervals for sensitivity and specificity, for tests in the \$4-5 cost range, with Q(Mid) denoting the mid-point of the interval

and the three HIV tests, # 14, 15, and 19, which were often part of the selected test composition for this region. Observe that when a single test is selected, the BP and BN rules will result in the same levels of risk and waste. Hence, in Table 4.4.2, we report the risk and waste levels under the BP and BN rules for two and three-test combinations in this set. We observe that the BP rule achieves significantly lower levels of risk than the BN rule for each possible test composition. In addition, the risk under the BN is increasing as more tests are selected. Thus, the use of the BN rule cannot be justified in blood screening, where safety is of utmost importance. On the other hand, the waste under the BP rule is relatively higher than that for the BN (as expected); to decrease waste we believe methodologies not based on the decision rule should be considered.

Table 4.4: Comparison of risk and waste levels under the BP and BN decision rules

Selected	BP		BN	
Test Set	Risk (per million)	Waste (%)	Risk (per million)	Waste (%)
$\{14, 15\}$	7.217	2.1880	2,282.1	0.01200
$\{14, 19\}$	2.290	1.3680	1,689.0	0.00204
$\{15, 19\}$	1.429	1.1683	1,162.0	0.00170
$\{14, 15, 19\}$	0.011	2.3543	2,559.2	0.00002

4.4.3 Extension of the Study to Ghana, Thailand, and the United States

To understand the impact of regional characteristics (prevalence and co-infection rates) on the test composition selected by the **CR** Heuristic, which we will refer to as the **RMP** model, we extend our case study to Ghana, Thailand, and the United States. Each of these countries face quite different TTI prevalence rates in their donor populations, see Table 4.1. In particular, prevalence rates for HIV, HBV, and HCV are high in Ghana (but lower than the sub-Saharan numbers in general), intermediate in Thailand, and relatively low in the United States (Van Hulst et al., 2009). We again restrict our study to HIV, HBV, HCV, HTLV, and WNV.

While selecting one test per each TTI recommended for screening in the WHO and FDA guidelines, we can find a test set that minimizes risk (Min-Risk), comprised of the test with the minimum Q-value for each TTI (Tests #3, 19, and 25 for the WHO, and 3, 19, 25, 31, and 32 for the FDA), and another that minimizes the required budget (Min-Cost) (Tests #4, 7, and 24 for the WHO, and 4, 7, 24, 31, and 32 for the FDA). These test sets are independent of prevalence and co-infection rates. The first part of Table 5.7 shows the required budget for each of these test sets, as well as their resultant risk and waste for sub-Saharan Africa, Ghana, Thailand, and the United States. In addition, in sub-Saharan Africa, blood is collected in two different ways (Busch et al., 2009). A majority (70-80%) of the blood is collected from "replacement donors," who are usually related to or a friend of the patient requiring transfusion, at the point of use in emergency situations (Lackritz et al., 1992). This method is inexpensive, as it does not involve donor recruitment expenses, the capital investment and infrastructure that the dedicated blood centers require (Owusu-Ofori et al., 2010), nor testing costs, as usually not even the basic HIV, HBV, and HCV tests are performed (Lara et al., 2007). Around 20-30% of the

blood is collected through a "voluntary donors" system utilizing dedicated collection centers that perform (to the extent possible) screening for HIV, HBV, and HCV (Van Hulst et al., 2010), following the WHO recommendations. These centers only exist in major cities, and their affordability and sustainability is a critical issue faced by most countries of sub-Saharan Africa (Busch et al., 2009; Field and Allain, 2007). Thus, per the existing practice, for sub-Saharan Africa and Ghana we also include the risk and waste generated from a 30% WHO testing scheme (*30% Testing*), where only 30% of the blood is tested using the given test set, and the remaining 70% is untested.

The second part of Table 5.7 reports the test set selected by the **RMP** model, given budget constraints that span the range of required budgets for the various testing schemes displayed in the first part of the table. For these solutions we do not enforce either the WHO or FDA guidelines, but we have identified the solutions that do conform with those guidelines in the table. While we do not display the tests selected for each region at each budget level, we note that only the test set selected, not the prevalence, determines the waste. Thus, by examining the waste values for a particular budget level, we can determine if different test sets are selected for the different regions; this happens often.

As Table 5.7 illustrates, the **RMP** model can achieve *significant risk improvements*. Consider the WHO Min-Risk test set, which requires a budget of \$14. At that budget level the **RMP** solution does better in every region. In sub-Saharan Africa this is done by selecting a test for HBV, HIV, HTLV, and WNV, while neglecting a test for the WHO-recommended disease HCV, see Table 4.3. For this region, at a \$13 budget, the **RMP** model does adhere to the WHO guidelines, and produces a lower risk than the WHO Min-Risk test set. It does this by selecting less expensive tests for the WHO-recommended diseases (tests #4, 15, and 24), which allows a fourth test for HTLV (test #32). A similar strategy is used in Ghana at the \$14 budget level, where the **RMP** selects tests #1, 15, 24, and 32. Thailand has similar results, but instead of adding a test for a disease not recommended by the WHO, it uses two tests for HBV (the tests selected for Thailand are #1, 4, 15, and 25) to reduce the overall risk. For the US, the **RMP** test set does not conform to the WHO guidelines (selecting tests #4, 24, 25, and 31). Similarly, for the \$22 budget required for the FDA Min-Risk test set, the **RMP** model does better, while still conforming to the FDA guidelines for every region except Thailand. It does this by choosing multiple, less expensive tests for particular TTIs, based on the prevalence and co-infection levels. It is also interesting to compare the existing scheme in sub-Saharan Africa and Ghana, in which only around 30% of the blood donations undergo regular

Table 4.5: Comparison of risk and waste for test sets that meet the WHO/FDA requirements and test sets that are generated by the **RMP** model (**CR** Heuristic) for different regions

		Sub-Saharan Africa		Ghana		Thailand		US	
Guideline	Budget($)	Risk(%)	Waste (%)	Risk(%)	Waste(%)	Risk(%)	Waste(%)	Risk(%)	Waste(%)
WHO Min-Risk	14	5.316	0.529	3.829	0.529	0.011	0.529	0.021	0.529
- *30% Testing*	4	21.160	0.159	17.417	0.159				
WHO Min-Cost	9	5.659	4.695	4.109	4.695	0.050	4.695	0.031	4.695
- *30% Testing*	3	21.263	1.409	17.501	1.409				
FDA Min-Risk	22	0.092	1.987	0.098	1.987	0.009	1.987	0.002	1.987
FDA Min-Cost	17	0.474	6.092	0.400	6.092	0.048	6.092	0.012	6.092
The **RMP** Model	3	20.035	1.610	9.857	1.610	0.952	1.610	0.107	1.200
	4	15.311	1.000	9.743	0.200	0.933	0.200	0.107	1.200
	5	15.259	0.170	7.542	4.312	0.660	4.312	0.039	4.312
	6	6.028	4.119	5.928	4.119	0.287	4.119	0.039	2.791
	7	5.971	3.315	5.894	2.594	0.282	2.594	0.030	3.305
	8	5.932	1.198	5.773	1.198	0.264	1.198	0.030	1.767
	9	5.476 *	5.269	4.062 *	5.269	0.042 *	5.269	0.030	5.365
	10	2.211	4.473	3.570	4.473	0.038 *	3.763	0.029	4.465
	11	2.149	3.672	3.534	2.954	0.021 *	2.384	0.020	4.369
	12	2.107	1.564	3.408	1.564	0.015 *	6.794	0.020	2.848
	13	1.613 *	5.620	1.609 *	5.620	0.013 *	6.013	0.020	1.456
	14	0.885	5.524	1.572 *	4.119	0.007 *	5.813	0.019	5.516
	15	0.821	4.732	1.442 *	2.745	0.005 *	5.023	0.011	4.722
	16	0.778	2.646	1.390	7.139	0.004 *	3.662	0.011	3.207
	17	0.270 †	6.658	0.349 †	6.658	0.004 *	2.131	0.010	1.820
	18	0.216 †	5.875	0.312 †	5.174	0.003 *	6.163	0.009	5.866
	19	0.166 †	3.815	0.178 †	3.815	0.003 *	4.818	0.003 †	5.675
	20	0.112 †	3.008	0.125 †	8.161	0.003 *	3.305	0.002 †	4.175
	21	0.079 †	7.391	0.111 †	7.391	0.002 *	8.060	0.002 †	2.802
	22	0.078 †	6.063	0.058 †	7.194	0.002 *	6.742	0.001 †	6.807

WHO/FDA Min-Risk: The lowest risk test set that meets the WHO/FDA requirements
WHO/FDA Min-Cost: The lowest cost test set that meets the WHO/FDA requirements
30% Testing: Partial (30%) fulfillment of the WHO requirements, 70% no testing
*: The **RMP** model generated test set that meets the WHO requirements
†: The **RMP** model generated test set that meets the WHO and FDA requirements

testing according to the WHO guidelines (see the 30% testing scheme for the WHO-compliant Min-Risk and Min-Cost test sets in Table 5.7) with a testing scheme that includes *all* blood donations, but at the same budget level. At the corresponding 30% testing budget levels, the all-unit testing scheme can afford to use only one test, but performs better than partial testing. We note that at the Min-Cost budget level we have often found alternative test sets that were compliant with guidelines and had slightly smaller risks.

In summary, *this case study highlights the importance of generating region-specific test composition for blood screening that explicitly takes into account the prevalence*

and co-infection rates of the TTIs. We also see that *following the WHO and FDA guidelines is no guarantee of an optimal testing regime - sometimes it is better to deviate from the recommendations. Test selection is complex, and always choosing the risk-minimizing test for each disease does not insure an overall risk-minimizing solution for a given budget level.* Furthermore, while the cheap, low-efficacy tests included in the test sets generated here (for relatively low budgets) may not be the ones currently used in developed countries with significantly lower TTI prevalence rates, our study shows that they can be very beneficial for high-prevalence countries with very limited budgets. *This underscores the need for developing a wide array of tests, with different costs and efficacies, for the same TTI.* These results also illustrate the sensitivity of the selected test set to the prevalence rates. While this is a complex relationship, our numerical study suggests certain relationships that were often satisfied. One important finding from our study was that for two TTIs with non-negligible co-infection rates, their mono-infection rates often determined which disease was tested for under a limited budget. In particular, we observed that prevalence rates could change without impacting the test set as long as the mono-infection prevalence ordering of the diseases was not altered. This, again, highlights the importance of splitting the disease prevalence rates into mono- and co-infection rates, as they impact the test composition differently.

4.5 Conclusions and Future Research Directions

The contributions in this work focus on a novel analytical modeling and algorithmic approach to the problem of selecting the optimal composition of blood screening tests, each with a different efficacy and administration cost, along with a decision rule with which to interpret the test results, so as to minimize the risk of TTI for blood deemed as infection-free under a resource constraint. We develop optimal algorithms for a special case of the problem where prevalence of co-infections are negligible, and a near-optimal algorithm and lower bounds for the general problem. Our numerical study indicates that the heuristic algorithm is very effective for realistic problem sizes. We use the heuristic algorithm to generate the test composition for realistic data from sub-Saharan Africa, Ghana, Thailand, and the United States. This case study highlights the importance of generating region-specific test compositions for blood screening, explicitly taking into account the regional mono and co-infection prevalence rates, rather than following static guidelines, especially when these guidelines allow for a wide range of possible selections. Indeed, the test compositions generated by our model depend critically on the TTI mono- and co-prevalence rates

in that region, outperforming the static WHO/FDA guidelines. This indicates that it is not always optimal to follow the WHO or FDA guidelines, even with budget levels that allow this. Our study also underscores the need for developing a wide array of tests, with different costs and efficacies, for the same TTI, as the tests selected for the various regions may vary significantly with the prevalence rates and budget availability. In addition, our study of sub-Saharan Africa shows that an all-unit testing scheme, even with fewer tests per blood unit, outperforms a partial testing scheme at the same budget level, and is certainly more equitable. With certain modifications, such modeling and algorithmic approaches can be applied in the context of other resource allocation problems in health care.

Several variations and extensions of this work are studied in the following chapters of this dissertation. An important direction is to incorporate the waste consideration (i.e., fraction of blood units that are falsely rejected) into the model, perhaps as a constraint. As discussed above, this is important, as the supply of blood products is not sufficient to satisfy the demand worldwide, and this gap is increasing. We considered that the transmission of each TTI in the FDA list of diseases is equally undesirable from the decision-maker's perspective. While all these TTIs have major consequences to the patient if transmitted, their costs to the society (including cost of treatment, cost of disability or deteriorating health condition of the patient) might be different. Therefore, it is important to understand how the algorithms and the resulting test compositions change when the social cost aspect is considered. This is further investigated in the next chapter. Another important direction that worth to study in the future is to relax Assumptions **(A1)** and **(A2)**, which, as discussed in this chapter, may be violated (especially **(A2)**) for certain tests and diseases.

We assume that the disease prevalence probabilities are known with certainty. This is rarely the case in practice, and additional resources need to be allocated to the collection of region-specific epidemiology data so as to obtain reliable prevalence estimates. Moreover, in blood collection, it is important that this prevalence data represents the donor population, rather than the general population. Similarly, test performance parameters (sensitivity and specificity) are not known with certainty, as we model here, and are typically estimated through resource-extensive clinical trials. Consequently, one faces the problem of how much of the limited resources to allocate to data collection and how much to blood screening, and this is a interesting, yet challenging, problem that we hope future research will address.

The relatively short life-time of blood products, compared to testing times, require blood to go through the various screening tests in parallel. One can also explore the benefits of a sequential testing scheme (in which whether or not the blood sample

needs to go through additional testing is determined dynamically by the current test outcomes), with the hope that if such benefits are found to be significant, then this will perhaps motivate biomedical researchers to investigate new technologies that would allow sequential testing of blood. Finally, differential screening, which allows different test compositions to be used for, perhaps in the different regions of the country, remains an interesting future research direction.

Chapter 5

Safety and Waste Considerations in Donated Blood Screening

5.1 Introduction and Motivation

In this chapter, we extend the problem of selecting an effective set of screening tests for donated blood in Chapter 4. The decision-maker (e.g., the American Red Cross, which supplies approximately 40% of the blood in the US) needs to allocate limited resources (e.g., budget) to screening tests so as to minimize the TTI risk, while ensuring that the fraction of blood wasted is below a certain threshold. Resource allocation problems, in general, have long been studied (see, for instance, Brandeau, 2004, for a review and references). A commonly used formulation that is somewhat related to our problem is the traditional knapsack problem, which selects, from a set of candidates, each with a known benefit (reward or revenue) and cost, an optimal set that is budget-feasible and that maximizes the total benefit (see Brandeau, 2004). This test selection problem has major differences with the traditional knapsack problem. Candidate tests do *not* exhibit constant returns to scale in the objective function, which is the "risk" (or "weighted risk") of a TTI for blood classified as infection-free (i.e., the conditional probability that the blood unit is infected with at least one TTI, when the administered test set indicates otherwise). A test's contribution to this risk depends not only on the efficacy of the test itself, but on the efficacies of the *entire* set of tests selected. This, along with the need to consider other, often conflicting, constraints, such as a constraint on the fraction of infection-free blood falsely discarded (waste), complicates the problem considerably. Nevertheless, we expand the

algorithm developed in Chapter 4 (for the test selection problem without the waste constraint) to this problem with the additional constraint and different objective functions, and show that it remains quite effective and efficient for this new formulation. More importantly, this solution approach allows us to study the relationship among the different metrics essential in blood screening: TTI risk, blood wasted, and weighted TTI risk; the latter allows us to consider the different costs/impacts of the various TTI's to the society or to the individual. The weighted risk model is general, and can incorporate various metrics that are commonly adopted in the medical literature to represent the impact of the various TTI's, such as their social costs, quality-adjusted life years, disability-adjusted life years, and so on. This analysis allows us to derive insights and guidelines on how these metrics impact the selected test set as well as the quality and efficiency of blood usage.

Our work generates important insights and findings that should be considered in decision-making. Specifically, our contributions, to this important problem of selecting a screening test set for donated blood, consist of the following.

- While the primary objective of the decision-maker in blood screening is to reduce the TTI risk, the waste metric, which has been ignored in many cost-effectiveness studies on blood screening (e.g., Jackson et al., 2003; Custer et al., 2005b; Van Hulst et al., 2010), needs to be explicitly considered in the model, as multiple budget-feasible test sets are often available, with comparable risks but quite different waste fractions.[1] This is driven by the fact that a wide range of blood screening tests (with varying levels of specificity, sensitivity, and cost) are typically available in the market; and as such, a number of test portfolios, consisting of tests with quite different characteristics, can often be constructed for a certain budget constraint. Interestingly, however, a reduction in risk does not necessarily come at the expense of an increase in waste, as there is no direct relationship between these metrics. This underscores the importance of incorporating the waste metric into the mathematical formulation.

- We study three objective functions that are relevant to the problem under study: minimization of the TTI risk (Problem **RMP**), minimization of the weighted TTI risk (Problem **W-RMP**), and minimization of the weighted total TTI risk (Problem **WT-RMP**), where the weights for each TTI represent the costs/burdens of the TTI to the society and/or the individual. We show that

[1] Schwartz et al. (1990) is a notable exception and considers both risk and waste for HIV through a Markov model, which allows for comparison of strategies for a single disease only, but not within an optimization framework.

W-RMP is more structurally difficult to solve than **RMP** and **WT-RMP**, but that **WT-RMP** can be used to approximate **W-RMP**. Our study generates insights on the relationship among these different metrics. We observe that the test sets generated by **WT-RMP** and **RMP** and their corresponding metrics differ significantly, especially when the prevalence and weight of the TTIs are not aligned (such as the Ghana example). This, once again, highlights the importance of generating region-specific test set for blood screening that explicitly takes into account the mono- and co-infection rates and weights of the TTIs. It also demonstrates the difficulty of making this important decision, as the objectives of reducing risk versus weighted risks sometimes conflicts, and a trade-off between risk, weighted risks, waste, and budget needs to be made by the decision-maker. Our optimization-based models provide tools to support and potentially improve this decision-making process.

The remainder of this chapter is organized as follows. In Section 5.2, we introduce the problem setting, the notation, and the assumptions used throughout the chapter. The relationship among the various measures of accuracy, commonly used for medical tests, and their implications for the screening test selection problem are discussed in Section 5.3. Mathematical formulations for the decision problem under various objectives, along with solution approaches and numerical studies, are detailed in Section 5.4. Finally, in Section 5.5, we conclude with a summary of our findings and suggest future research directions.

5.2 The Problem Setting, Notation, and Assumptions

Consider a Blood Center collecting blood from donors. In the US, per requirements by the Food and Drug Administration (FDA), each blood donation must undergo screening for a set of TTIs. Similarly, the World Health Organization (WHO) recommends screening for a set of TTIs. It is often the case that a number of screening tests, each with different performance characteristics and cost, are available for each TTI. Then, given these requirements/recommendations and the variety of the tests available, it is the Blood Center's responsibility to decide *which* particular screening test to administer for each TTI. Depending on the outcomes of the selected tests, the blood unit (i.e., all blood collected from the particular donor) will either be made available for transfusion or discarded. Consequently, the decision-maker faces

the problem of selecting a set of screening tests, from a set of commercially available tests, to administer to each unit of donated blood to test for a set of TTIs ("diseases") so as to minimize the overall TTI risk in blood transfusion.

Each screening test applies to a specific disease and provides binary results, with a "+" result indicating that the blood unit is infected, and a "–" result indicating otherwise. Tests do not have perfect efficacy, and are characterized in terms of their "specificity" (the conditional probability that the test provides a true "–" result, given that the blood unit is not infected by the disease) and "sensitivity" (the conditional probability that the test provides a true "+" result, given that the blood unit is infected by the disease), e.g., Pepe (2004). False positive and false negative test results are possible due to various reasons, as discussed in detail in Dow (2000); Johnson (1996); Moore et al. (2007); see also Chapter 4 for additional references. The sensitivity and specificity of each test are known by the decision-maker; these estimates are required for each FDA-approved test. Finally, all selected tests need to be administered concurrently on the blood sample due to the long time requirements of the tests (including the transportation time to a testing laboratory), compared to the relatively shorter life-span of donated blood (Hillyer, 2001).

In this setting, given a set of imperfectly reliable tests to select from to detect a set of diseases, the primary objective of the decision-maker is to minimize the "risk" (or weighted risks) of a transfusion-transmitted infection, i.e., the conditional probability that the blood unit classified as "infection-free" is, in fact, infected by some disease(s). The decision-maker is resource-constrained and also wants to limit the amount of infection-free blood falsely discarded ("*waste*"): We model these constraints in the form of a *budget constraint* on the total test administration cost per unit blood, and a maximum allowable *waste constraint* on the fraction of falsely discarded blood.

In practice the decision-maker also needs to adopt a "decision rule," which prescribes *when* to classify the blood unit as "infection-free" for a particular disease versus "infected," when the selected test set contains multiple tests for the same disease. The "Believe the Positive (BP)" rule is a commonly adopted decision rule in blood screening due to its conservative nature for classifying the blood unit as infection-free, which fits well with the objective of minimizing the TTI risk. Indeed, we show that the BP rule is the optimal decision rule for minimization of the TTI risk under a budget constraint in Chapter 4. In general, the BP rule is *not* necessarily optimal for general objective functions, such as the weighted risk objective functions studied in this chapter, as we elaborate in Section 5.2.2, where we also show that the form of the optimal decision rule may be quite complex in the weighted risk setting, as it is a function of problem parameters. Consequently, due to the primary emphasis, in

this setting, on risk reduction, we consider that the decision-maker adopts the BP rule in all the objective functions studied. In other words, we do not include it as a decision variable in the optimization problems.

Our notation and assumptions follow that of Chapter 4. We include important notations used in Chapter 4 along with the newly added notations as follows.

Decision variable:
$S \subseteq \Omega$: the set of tests to administer, where $S \equiv \cup_{i \in \Psi} S_i$, with $S_i \subseteq \Omega_i$ denoting the set of tests that apply to disease $i \in \Psi$. (Note that S_i is allowed to be $\emptyset$.)

Consider a random unit of blood to be tested. We define the following events and parameters:

Events:

- $A^i+ = \{\Lambda_i = 1\}$, $i \in \Psi$: the event that the blood unit is infected by disease i ($A^i- = \overline{A^i+}$).
- $T_j^{d(j)}+, j \in \Omega$: the event that test j provides a "+" result for disease $d(j)$ ($T_j^{d(j)}- = \overline{T_j^{d(j)}+}$).
- $T-(S)$, $S \subseteq \Omega$: the event that the blood unit is classified as free of all diseases based on the administered test set S and under the BP rule ($T+(S) = \overline{T-}(S)$). When $S = \emptyset$, $T-(\emptyset) = \Phi$; equivalently, $T+(\emptyset) = \emptyset$. We will also adopt the notation that when $S = \emptyset$, $\Pr\left(\bigcup_{j \in S} T_j^{d(j)}+\right) = 0$; equivalently, $\Pr\left(\bigcap_{j \in S} T_j^{d(j)}-\right) = 1$. These expressions will be used subsequently.

Parameters:

- "Specificity" of test $j = \Pr(T_j^{d(j)}- \mid A^{d(j)}-)$, $j \in \Omega$: the probability that test j provides a "–" result for disease $d(j)$ when the blood unit *is not* infected by disease $d(j)$, also known as the "true negative probability."
- "Sensitivity" of test $j = \Pr(T_j^{d(j)}+ \mid A^{d(j)}+)$, $j \in \Omega$: the probability that test j provides a "+" result for disease $d(j)$ when the blood unit *is* infected by disease $d(j)$, also known as the "true positive probability."

- $Q_j \equiv \frac{\Pr\left(T_j^{d(j)}-\middle|A^{d(j)}+\right)}{\Pr\left(T_j^{d(j)}-\middle|A^{d(j)}-\right)}$ (≤ 1) [2] $(\bar{Q}_j \equiv 1 - Q_j)$, $j \in \Omega$.
- c_j, $j \in \Omega$: unit cost of administering test j.
- B: total budget available per blood unit for administering the screening tests.
- α: maximum allowable fraction on waste (the fraction of infection-free blood falsely discarded), also referred to as the "waste tolerance limit."
- $w(\overrightarrow{\lambda})$, $\overrightarrow{\lambda} \in \mathscr{S}(\overrightarrow{\Lambda})$: the weight corresponding to disease prevalence vector $\overrightarrow{\lambda}$ in the weighted risk model.

By definition, $Q_j, j \in \Omega$, represents the ratio of false negative probability to true negative probability. Therefore, tests with smaller Q_j values are desirable from a risk minimization perspective (see (5.7) in Proposition 5).

Observe that we choose to express both the test administration cost $(c_j, j \in \Omega)$ and the total budget available (B) on a per unit basis. This is without loss of generality under the "same-for-all" policies, where the same set of screening tests is administered to *all* donated blood. Since the number of blood units screened is *not* a decision variable in our model (all donated blood needs to be screened), the test administration cost may be of any functional form (e.g., nonlinear in blood units). We simply need to calculate the aggregate testing cost for each test $j \in \Omega$ (based on the estimated number of blood units to be screened during a period) and express it on a per unit basis.

5.2.1 Model Formulations

With waste constraint introduced to the problem in Chapter 4, the mathematical formulation for the Risk Minimization Problem **(RMP)** under budget and waste constraints is redefined in this chapter as follows:

[2] This assumption, that $Q_j \leq 1, j \in \Omega$, is without loss of generality, because any test not satisfying this assumption can be transformed into one that satisfies it by interpreting its result in the opposite way. Moreover, not surprisingly, this assumption, which states that each test has a higher true negative probability than false negative probability, already holds for all the FDA-approved tests.

Risk Minimization Problem **(RMP)**:

$$Risk^* \equiv \text{Minimize}_{S\subseteq\Omega}\ Risk(S) = \Pr\left(\bigcup_{i\in\Psi} A^i+ \mid T-(S)\right) \tag{5.1}$$

$$\text{subject to } \sum_{j\in S} c_j \leq B \tag{5.2}$$

$$Waste = \Pr\left(T+(S)\mid \bigcap_{i\in\Psi} A^i-\right) \leq \alpha. \tag{5.3}$$

Thus, among all test sets that satisfy the budget and waste constraints in (5.2) and (5.3), the objective function in (5.1) selects the test set, denoted by S^* (with $S^* = \cup_{i\in\Psi} S_i^*$), that minimizes the conditional probability that the blood unit is infected by at least one disease, given that it is classified as infection-free under the given test set. We denote the corresponding optimal risk as $Risk^*$.

In **RMP**, we assume all infections (and their combinations) are equally undesirable. In reality, different infections have different impacts on society and individuals, in terms of costs of treatment, disability, loss of productivity, etc. These costs/burdens depend on the specific TTI as well as the characteristics of the transfusion recipients in the particular region. For example, in Ghana, transfusion recipients are mostly children (with malaria and anemia) and laboring women, whereas in the developed world, they are the elderly (Cobain et al., 2007; Van Hulst et al., 2009). Measures such as Quality-Adjusted Life Years (QALY), Disability-Adjusted Life Years (DALY) are commonly used in cost-effectiveness analysis to represent the overall burden of the disease (Marshall et al., 2004; Van Hulst et al., 2010). Therefore, from a public policy perspective, it is important to consider the different impacts of the TTIs in the test selection decision. Consequently, we introduce the Weighted Risk Minimization Problem (**W-RMP**).

Weighted Risk Minimization Problem **(W-RMP)**:

$$W\text{-}Risk^* \equiv \text{Minimize}_{S\subseteq\Omega}\ W\text{-}Risk(S) = \sum_{\vec{\lambda}\in\mathscr{P}(\vec{\Lambda})\setminus\vec{0}} w(\vec{\lambda})\ \Pr(\vec{\Lambda}=\vec{\lambda}|T-(S)) \tag{5.4}$$

$$\text{subject to (5.2) and (5.3).}$$

Observe that when the disease weights are equal for all disease combination vectors, objective function (5.4) in **W-RMP** reduces to that of **RMP**, (5.1). Also observe that the objective function of **RMP** represents the risk per randomly selected blood

unit, while the objective function of **W-RMP** represents the corresponding cost (or other related measure, such as QALY or DALY, as discussed above) per randomly selected blood unit. Thus, they both represent the risk or cost to a randomly selected transfusion recipient.

We also study another relevant objective function in the weighted risk setting, which represents the *total* cost (or other related measure) to the society of all the infectious blood units in the "safe" blood pool (i.e., all blood units that are classified as infection-free, hence, that are made available for transfusion). We refer to this last model as the Weighted Total Risk Minimization Problem **(WT-RMP)**.

Weighted Total Risk Minimization Problem **(WT-RMP)**:

$$WT\text{-}Risk^* \equiv \text{Minimize}_{S\subseteq\Omega}\ WT\text{-}Risk(S) = \sum_{\overrightarrow{\lambda}\in\mathscr{S}(\overrightarrow{\Lambda})\setminus\overrightarrow{0}} w(\overrightarrow{\lambda})\ \Pr(\overrightarrow{\Lambda}=\overrightarrow{\lambda}, T-(S)) \quad (5.5)$$

subject to (5.2) and (5.3).

Example 1 below demonstrates the differences among the three objective functions.

Example 1 *Suppose* $N = 120$ *units of blood, of which 10 units are infected with either Disease 1 or Disease 2, are undergoing screening (see Figure 5.1). Suppose that the societal costs for these two diseases are \$10,000 and \$1,000, respectively. Among the 110 units of the disease-free blood, suppose that 98 units have passed the screening tests; and among the 10 units of the infected blood, two have been falsely classified as disease-free blood: one unit infected by Disease 1, and the other infected by Disease 2. In this example, the objective function values for* **RMP**, **W-RMP**, *and* **WT-RMP** *can be respectively calculated as:*

$Risk = \frac{2}{98+2} = 2\%$, $W\text{-}Risk = \left(\frac{1}{100}\times 10{,}000\right)+\left(\frac{1}{100}\times 1{,}000\right) = \$110$, *and* $WT\text{-}Risk = (\frac{1}{120}\times 10{,}000)+(\frac{1}{120}\times 1{,}000) = \frac{\$11{,}000}{120} = \$91.67$. *Also,* $Waste = \frac{12}{110}$ *in this example.*

In the weighted risk setting, $W\text{-}Risk$ would serve as a more appropriate objective function than $WT\text{-}Risk$ due to three main reasons: (i) $W\text{-}Risk$ is a direct extension of $Risk$ in the weighted risk setting (see (5.1) and (5.4)); (ii) the $Waste$ level corresponding to the optimal solution obtained from **W-RMP** would be relatively lower

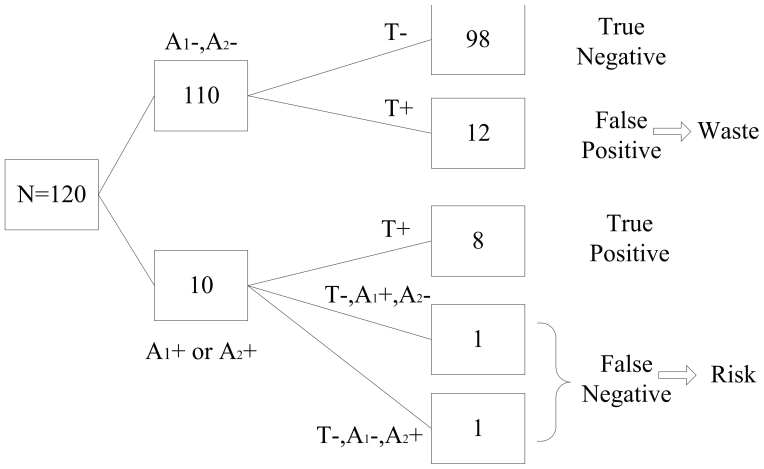

Figure 5.1: The Decision Tree Corresponding to Example 1 (with Numbers in Boxes)

than that of **WT-RMP**, where discarding more blood would always be preferred; and (iii) $W\text{-}Risk$ is more selective on the tests, as it takes into consideration not only the test's performance, but also the weight of its corresponding TTI. In other words, in order to reduce $W\text{-}Risk$, the test needs to perform well *and* its corresponding TTI needs to have a considerable weight, see the discussion on Example 5. However, although the test sets generated by **W-RMP** and **WT-RMP** could differ on occasions (see Example 5), we observe, in our numerical studies, that **W-RMP** and **WT-RMP** generate similar test sets in most cases; see Section 5.4.3. Consequently, $WT\text{-}Risk$ provides a good approximation for $W\text{-}Risk$, as we elaborate subsequently.

Assumptions: We make two assumptions to analyze **RMP**, **W-RMP**, and **WT-RMP**. Both assumptions are common in the medical literature (see, for instance, Pepe 2004)[3].

(A1) The outcome of test j for disease $d(j)$ depends only on the prevalence of disease $d(j)$ in the blood unit, and not on the prevalence of the other diseases in the disease set, that is, for $j \in \Omega$,

$$Pr(T_j^{d(j)}\ x \mid \overrightarrow{\Lambda}) = Pr(T_j^{d(j)}\ x \mid \Lambda_{d(j)}),\ \text{for } x \in \{+,-\}.$$

[3]For detailed discussions on the validity and impact of assumptions, see Section 4.2.1 in Chapter 4.

(A2) Test outcomes are conditionally and jointly independent given the prevalence vector, that is, for any test $j_1 \in \Omega$ and $S' \subseteq \Omega | \{j_1\}$,

$$Pr(T_{j_1}^{d(j_1)}\ x \mid \overrightarrow{\Lambda}, T_j^{d(j)}\ y, \forall j \in S') = Pr(T_{j1}^{d(j_1)}\ x \mid \overrightarrow{\Lambda}),\ \text{for } x, y \in \{+, -\}.$$

5.2.2 The Decision Rule

In this section, we consider the BP rule for the weighted risk objectives, and show, through counter-examples, that it need not be the optimal decision rule in the weighted risk setting. Throughout this section, we let $T-(D(S))$ denote event $T-(S)$ under decision rule D. We also represent the relevant metrics in terms of two parameters, D and S.

Example 2 *Consider two diseases, each with a corresponding test (Test i for Disease i, $i = 1, 2$) in the selected test set. Suppose that $Q_2 < 1$. (Recall that we assume, without loss of generality, that $Q_j \leq 1, j \in \Omega$. For all existing FDA-approved tests, this, in fact, is satisfied as an inequality, that is, $Q_j < 1, j \in \Omega$.)*

In the following, we show that when $p_{\overrightarrow{\Lambda}}(1,0) > 0$, that is, when the mono-prevalence rate of Disease 1 is nonzero in a particular population, and when the diseases have different weights, then a decision rule, D', which classifies the blood unit as infection-free only if Test 1 result is negative and Test 2 result is positive, dominates the BP rule. That is, under decision rule D', $T-(D'(\{1,2\})) = T_1^1 - \bigcap T_2^2+$, whereas under the BP, $T-(BP(\{1,2\})) = T_1^1 - \bigcap T_2^2-$.

For this purpose, we first consider the disease vector $\overrightarrow{\lambda} = (1,0)$ and show that

$$\Pr\left\{A^1+, A^2 - | T^1-, T^2-\right\} > \Pr\left\{A^1+, A^2 - | T^1-, T^2+\right\}. \tag{5.6}$$

This follows because, by Bayes' rule, the inequality in (5.6) can be equivalently written as:

$$\frac{\Pr\{A^1+, A^2-\}\Pr\{T^1-, T^2 - | A^1+, A^2-\}}{\Pr\{T^1-, T^2-\}} > \frac{\Pr\{A^1+, A^2-\}\Pr\{T^1-, T^2 + | A^1+, A^2-\}}{\Pr\{T^1-, T^2+\}}$$

$$\Leftrightarrow \frac{\Pr\{T^2 - | A^2-\}}{\Pr\{T^1-, T^2-\}} > \frac{\Pr\{T^2 + | A^2-\}}{\Pr\{T^1-, T^2+\}} \Leftrightarrow \frac{\Pr\{T^1-, T^2-\}}{\Pr\{T^2 - | A^2-\}} < \frac{\Pr\{T^1-, T^2+\}}{\Pr\{T^2 + | A^2-\}}$$

$$\Leftrightarrow \frac{\sum\limits_{\vec{\lambda} \in \mathscr{S}(\vec{\Lambda})} \Pr\left\{\vec{\Lambda} = \vec{\lambda}\right\} \Pr\left\{T^1-, T^2 - | \vec{\Lambda} = \vec{\lambda}\right\}}{\Pr\{T^2 - | A^2-\}} < \frac{\sum\limits_{\vec{\lambda} \in \mathscr{S}(\vec{\Lambda})} \Pr\left\{\vec{\Lambda} = \vec{\lambda}\right\} \Pr\left\{T^1-, T^2 + | \vec{\Lambda} = \vec{\lambda}\right\}}{\Pr\{T^2 + | A^2-\}}$$

$$\Leftrightarrow \sum_{\vec{\lambda}\in\mathscr{S}\left(\vec{\Lambda}\right)} \Pr\left\{\vec{\Lambda}=\vec{\lambda}\right\} \frac{\Pr\left\{T^1-|\vec{\Lambda}=\vec{\lambda}\right\}\Pr\left\{T^2-|\vec{\Lambda}=\vec{\lambda}\right\}}{\Pr\left\{T^2-|A^2-\right\}} < \sum_{\vec{\lambda}\in\mathscr{S}\left(\vec{\Lambda}\right)} \Pr\left\{\vec{\Lambda}=\vec{\lambda}\right\} \frac{\Pr\left\{T^1-|\vec{\Lambda}=\vec{\lambda}\right\}\Pr\left\{T^2+|\vec{\Lambda}=\vec{\lambda}\right\}}{\Pr\left\{T^2+|A^2-\right\}}$$

$$\Leftrightarrow \sum_{\left\{\vec{\lambda}:\lambda_2=0\right\}} \Pr\left\{\vec{\Lambda}=\vec{\lambda}\right\}\Pr\left\{T^1-|\vec{\Lambda}=\vec{\lambda}\right\} + \sum_{\left\{\vec{\lambda}:\lambda_2=1\right\}} \Pr\left\{\vec{\Lambda}=\vec{\lambda}\right\}\Pr\left\{T^1-|\vec{\Lambda}=\vec{\lambda}\right\}\frac{\Pr\left\{T^2-|A^2+\right\}}{\Pr\left\{T^2-|A^2-\right\}}$$

$$< \sum_{\left\{\vec{\lambda}:\lambda_2=0\right\}} \Pr\left\{\vec{\Lambda}=\vec{\lambda}\right\}\Pr\left\{T^1-|\vec{\Lambda}=\vec{\lambda}\right\} + \sum_{\left\{\vec{\lambda}:\lambda_2=1\right\}} \Pr\left\{\vec{\Lambda}=\vec{\lambda}\right\}\Pr\left\{T^1-|\vec{\Lambda}=\vec{\lambda}\right\}\frac{\Pr\left\{T^2+|A^2+\right\}}{\Pr\left\{T^2+|A^2-\right\}}.$$

This inequality holds if

$$\frac{\Pr\left\{T^2-|A^2+\right\}}{\Pr\left\{T^2-|A^2-\right\}} < 1 < \frac{\Pr\left\{T^2+|A^2+\right\}}{\Pr\left\{T^2+|A^2-\right\}} \Leftrightarrow \Pr\left\{T^2-|A^2+\right\} < \Pr\left\{T^2-|A^2-\right\} \Leftrightarrow Q_2 < 1.$$

Thus, decision rule D' dominates the BP rule for disease vector $\vec{\lambda}=(1,0)$. While the BP rule serves as a better decision rule for disease vectors $\vec{\lambda}=(0,1)$ and $\vec{\lambda}=(1,1)$, that is,

$$\Pr\left\{A^1-, A^2+|T^1-, T^2-\right\} < \Pr\left\{A^1-, A^2+|T^1-, T^2+\right\} \text{ and}$$

$$\Pr\left\{A^1+, A^2+|T^1-, T^2-\right\} < \Pr\left\{A^1+, A^2+|T^1-, T^2+\right\},$$

it follows that for a sufficiently large weight for the $\vec{\lambda}=(1,0)$ vector, decision rule D' dominates the BP rule for the W-Risk $(\{1,2\})$ measure.

Recall that the BP rule is optimal for **RMP**, which is a special case of **W-RMP**, when the weights for all disease combination vectors are equal. Observe that Example 2 does not contradict with this result, as it no longer serves as a counter-example when the disease weights are equal.

Thus, Example 2 demonstrates the sub-optimality of the BP rule for *W-Risk*, but only when the weight of one of the mono-prevalence vectors, $\vec{\lambda}=(1,0)$, is sufficiently large. While our analysis of **W-RMP** and **WT-RMP** does not require any restrictions on the weights, $w\left(\vec{\lambda}\right)$, $\vec{\lambda}\in\mathscr{S}\left(\vec{\Lambda}\right)$, in reality the disease vector weights will have certain relationships. In particular, the weight for any disease vector $\vec{\lambda}$ should be greater than the weight for any vector $\vec{\lambda}'$ that represents a subset of the

diseases in $\overrightarrow{\lambda}$. This implies, for the two-disease setting considered in Example 2, that $w(1,1) > max\{w(1,0), w(0,1)\}$; the weight corresponding to a co-infection vector is larger than the weights of each of the mono-infection vectors. Then, motivated by Example 2, the next question is whether one can construct a realistic numerical example in which the weight of $\overrightarrow{\lambda} = (1,0)$ is sufficiently large to make the BP rule sub-optimal, while still being in the acceptable range ($w(1,0) < w(1,1)$). Example 3 shows that this is indeed possible.

Example 3 *Suppose there are two diseases, Diseases 1 and 2, that are recommended for screening in a particular region. Diseases 1 and 2 have respective mono-prevalence rates of 1% and 14%, and a co-infection rate of 0.01%, see Figure 5.2. Disease 1 has a weight of* $\$10,000 (= w(1,0))$*, while Disease 2 has a weight of* $\$20 (= w(0,1))$*. Suppose that the weight corresponding to the co-infection vector* $\overrightarrow{\lambda} = (1,1)$ *is additive, that is,* $w(1,1) = w(1,0) + w(0,1) = \$10,020$*. Consider two tests, Test 1 [specificity* $=\Pr(T_1^1 - |A^1-)$ *=0.8, sensitivity=*$\Pr(T_1^1 + |A^1+)$*=0.8] for Disease 1, and Test 2 [specificity=*$\Pr(T_2^2 - |A^2-)$*=0.99, sensitivity=*$\Pr(T_2^2 + |A^2+)$*=0.99] for Disease 2.*

Consider two decision rules: BP and D', where the latter classifies the blood unit as infection-free only if T_1- and T_2+ (see Example 2). Then, $\Pr\left(\overrightarrow{\lambda}, T - (D(S))\right)$ *can be calculated for the four possible* $\overrightarrow{\lambda}$ *vectors under both the BP rule and D' rule. In what follows, we detail the calculations for the* $\overrightarrow{\lambda} = (0,0)$ *vector; other calculations are similar, see Table 5.1 for all results.*

$$
\begin{aligned}
&\Pr\left(A^1-, A^2-, T - (BP(\{1,2\}))\right) = \Pr\left(A^1-, A^2-, T_1^1-, T_2^2-\right)\\
&= \Pr\left(A^1-, A^2-\right)\Pr\left(T_1^1 - |A^1-\right)\Pr\left(T_2^2 - |A^2-\right) \ \text{(by (}\mathbf{A1}\text{))}\\
&= 0.8499 \times 0.8 \times 0.99 = 0.6731,\\
&\Pr\left(A^1-, A^2-, T - (D'(\{1,2\}))\right) = \Pr\left(A^1-, A^2-, T_1^1-, T_2^2+\right)\\
&= \Pr\left(A^1-, A^2-\right)\Pr\left(T_1^1 - |A^1-\right)\Pr\left(T_2^2 + |A^2-\right) \ \text{(by (}\mathbf{A1}\text{))}\\
&= 0.8499 \times 0.8 \times 0.01 = 0.0068.
\end{aligned}
$$

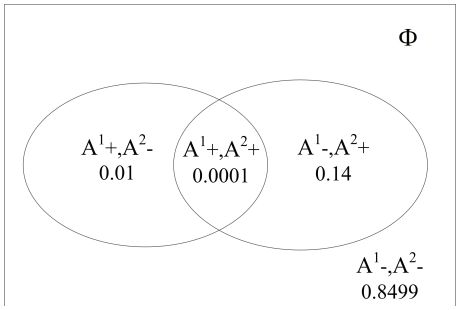

Figure 5.2: A Venn Diagram Representation of the Prevalence Rates in Example 3

Then, from Table 5.1,

$$\Pr\left(T-\left(BP\left(\{1,2\}\right)\right)\right)=\sum_{\overrightarrow{\lambda}\in\mathscr{S}\left(\overrightarrow{\Lambda}\right)}\Pr\left(\overrightarrow{\lambda},T_1^1-,T_2^2-\right)=0.6762,$$

$$Risk\left(BP\left(\{1,2\}\right)\right)=\sum_{\overrightarrow{\lambda}\in\mathscr{S}\left(\overrightarrow{\Lambda}\right)\setminus\overrightarrow{0}}\Pr\left(\overrightarrow{\lambda}|T_1^1-,T_2^2-\right)=\frac{0.0011+0.0020+2\times10^{-7}}{0.6762}=0.0046,$$

$$W\text{-}Risk\left(BP\left(\{1,2\}\right)\right)=\sum_{\overrightarrow{\lambda}\in\mathscr{S}\left(\overrightarrow{\Lambda}\right)\setminus\overrightarrow{0}}w(\overrightarrow{\lambda})\Pr\left(\overrightarrow{\Lambda}=\overrightarrow{\lambda}|T_1^1-,T_2^2-\right)$$

$$=\left(\$20\times\frac{0.0011}{0.6762}\right)+\left(\$10,000\times\frac{0.0020}{0.6762}\right)+\left(\$10,020\times\frac{2\times10^{-7}}{0.6762}\right)=\$29.3165.$$

$$\Pr\left(T-\left(D'\left(\{1,2\}\right)\right)\right)=\sum_{\overrightarrow{\lambda}\in\mathscr{S}\left(\overrightarrow{\Lambda}\right)}\Pr\left(\overrightarrow{\lambda},T_1^1-,T_2^2+\right)=0.1177,$$

$$Risk\left(D'\left(\{1,2\}\right)\right)=\sum_{\overrightarrow{\lambda}\in\mathscr{S}\left(\overrightarrow{\Lambda}\right)\setminus\overrightarrow{0}}\Pr\left(\overrightarrow{\lambda}|T_1^1-,T_2^2+\right)=\frac{0.1109+2\times10^{-5}+1.98\times10^{-5}}{0.1177}=0.9422,$$

$$W\text{-}Risk\left(D'\left(\{1,2\}\right)\right)=\sum_{\overrightarrow{\lambda}\in\mathscr{S}\left(\overrightarrow{\Lambda}\right)\setminus\overrightarrow{0}}w(\overrightarrow{\lambda})\Pr\left(\overrightarrow{\Lambda}=\overrightarrow{\lambda}|T_1^1-,T_2^2+\right)$$

$$=\left(\$20\times\frac{0.1109}{0.1177}\right)+\left(\$10,000\times\frac{2\times10^{-5}}{0.1177}\right)+\left(\$10,020\times\frac{1.98\times10^{-5}}{0.1177}\right)$$

$$=\$22.2224<\$29.3165.$$

Thus, the D' rule attains a lower W-Risk, but a significantly higher Risk and Waste, than the BP rule.

As discussed above, the sub-optimality of the BP rule for the *W-Risk* objective follows because switching from the BP rule to D' increases $\Pr\left(A^1-,A^2+,T-\left(D(S)\right)\right)$ from 0.0011 to 0.1109 (see Table 5.1). While this also reduces both $\Pr\left(A^1+,A^2-,T-\left(D(S)\right)\right)$ and $\Pr\left(A^1+,A^2+,T-\left(D(S)\right)\right)$, $w(1,0)$ is much higher than $w(0,1)$, and hence the

Table 5.1: *Risk* and *W-Risk* under the Different Decision Rules of Example 3

$\overrightarrow{\lambda}$	$w\left(\overrightarrow{\lambda}\right)$ (\$)	$\Pr\left(\overrightarrow{\lambda}, T-(D(S))\right)$	BP decision rule $(T-(BP(\{1,2\}))=T_1^1-,T_2^2-)$	D' decision rule $(T-(D'(\{1,2\}))=T_1^1-,T_2^2+)$
(0,0)	0	$\Pr\left(A^1-,A^2-,T-(D(S))\right)$	$0.8499\times0.8\times0.99=0.6731$	$0.8499\times0.8\times0.01=0.0068$
(0,1)	20	$\Pr\left(A^1-,A^2+,T-(D(S))\right)$	$0.14\times0.8\times0.01=0.0011$	$0.14\times0.8\times0.99=0.1109$
(1,0)	10,000	$\Pr\left(A^1+,A^2-,T-(D(S))\right)$	0.0020	2×10^{-5}
(1,1)	10,020	$\Pr\left(A^1+,A^2+,T-(D(S))\right)$	2×10^{-7}	1.98×10^{-5}
		$\Pr(T-(D(S)))$	0.6762	0.1177
		$Risk(D(S))$	0.0046	0.9422
		$W\text{-}Risk(D(S))$	29.3165	22.2224
		$Waste(D(S))$	$1-0.8\times0.99=0.208$	$1-0.8\times0.01=0.992$

result follows. However, observe that D' is quite a wasteful decision rule, with around 99% of infection-free blood incorrectly discarded, and produces a high level of *Risk* (94.22%) in this example.

Remark 4 *For* **W-RMP***:*

(i) The optimal decision rule depends on the weights, $w(\overrightarrow{\lambda})$. Consequently, there does not exist a "static" decision rule that is optimal for the W-Risk objective. Rather, the optimal decision rule depends on problem parameters (as illustrated in Examples 2 and 3).

(ii) Observe, from Example 3, that a necessary condition for the sub-optimality of the BP rule for W-Risk is a positive weight differential between the mono-prevalence disease vectors, that is, $w(1,0)\neq w(0,1)$. In fact, the BP rule is optimal for the W-Risk objective for the special case of the two-disease setting with $w(1,0)=w(0,1)$, i.e., the diseases have equal weights.

(iii) However, when the number of diseases is larger than 2 ($n>2$), the optimality of the BP rule for W-Risk in the equal-weight setting no longer holds.[4]

The following example illustrates that the BP decision rule need not be optimal for **WT-RMP** either.

[4]One can easily construct such a counter-example by assigning a sufficiently large weight to $\overrightarrow{\lambda}=\{1,0,0\}$, as a relationship similar to that in Example 2 follows in the three-disease setting, that is, $\Pr\left\{A^1+,A^2-,A^3-|T^1-,T^2-,T^3-\right\}>\Pr\left\{A^1+,A^2-,A^3-|T^1-,T^2+,T^3+\right\}$.

Example 4 *For any test set $S \subseteq \Omega$, consider the objective of minimizing the weighted total risk over all possible decision rules, $\mathscr{D}(S)$, with the waste constraint (5.12) relaxed. Then, for any decision rule $D(S) \in \mathscr{D}(S)$, it follows that*

$$\sum_{\overrightarrow{\lambda} \in \mathscr{S}(\overrightarrow{\Lambda}) \setminus \overrightarrow{0}} w(\overrightarrow{\lambda})\ \Pr(\overrightarrow{\Lambda} = \overrightarrow{\lambda}, \emptyset) \leq \sum_{\overrightarrow{\lambda} \in \mathscr{S}(\overrightarrow{\Lambda}) \setminus \overrightarrow{0}} w(\overrightarrow{\lambda})\ \Pr\left(\overrightarrow{\Lambda} = \overrightarrow{\lambda}, T - (D(S))\right).$$

Thus, the decision rule that minimizes the weighted total risk (in the absence of a waste constraint) is to classify all blood as infected.

While the inclusion of a waste constraint is likely to change this (unreasonable) decision rule, this example still demonstrates that the BP rule is not necessarily optimal for **WT-RMP**.

Nevertheless, the BP rule is the one used by the US Blood Centers due to their primary focus on safety; and incorporating the decision rule as a decision variable further complicates the optimization problem. Consequently, in this chapter, we adopt the BP decision rule throughout. Overall, the decision-maker will classify the blood unit as infection-free (hence make it available for use) *only if* the results of the tests and the BP rule indicate that the blood unit is free of all diseases tested for; otherwise, the blood unit will be discarded.

In the next section, we study how the different blood screening metrics relate to each other.

5.3 Some Properties of Risk, Waste, and Weighted Risks

Since the main focus in blood screening is on the three metrics, $Risk$, $Waste$, and the weighted risks, we first link the $Risk$ and $Waste$ metrics to the measures of accuracy used in the medical literature for diagnostic tests with binary outcomes. These are referred to as "classification probabilities" and "predictive values" in the medical literature, see Table 5.2.

Classification probabilities and predictive values are valuable in different contexts. Classification probabilities, namely the false positive fraction (FPF$\equiv \Pr\{T+|A-\}$) and true positive fraction (TPF$\equiv \Pr\{T+|A+\}$), are useful in evaluating the diagnostic accuracy of a test, and are commonly used in medical and biomedical research

(e.g., Beutel, 2000; Walter and Irwig, 1988) as well as in engineering applications and statistical hypothesis testing (e.g., Ozekici and Pliska, 1991; Raz and Kaspi, 1991).[5] On the other hand, predictive values are valuable in clinical contexts, where the main focus is on how well the test result predicts the true disease status. Observe that, unlike the classification probabilities, the predictive values depend not only on the test performance, but also on the prevalence of the disease. As such, they cannot be used to describe the inherent accuracy of the test (which is where the classification probabilities are helpful), but they reflect the confidence on the test results. Obviously, there is a direct relationship between the classification probabilities and the predictive values.

Since in blood screening there are *multiple* TTIs that need to be detected via a *set* of tests, we first extend the classification probabilities and predictive values to the multi-disease multi-test setting. Considering the BP decision rule and recalling that infection-free blood refers to blood that is free of all TTIs, while infected blood refers to blood that is infected by at least one TTI, the metrics in Table 5.2 follow. Thus, through focus on both $Risk$ and $Waste$, the decision-maker in the blood screening setting is concerned with both predictive metrics and classification metrics.

Table 5.2: Measures of Accuracy for Binary Diagnostic Tests

Metrics	Single-disease single-test setting (Pepe, 2004)	Multi-disease multi-test setting under the BP rule
(I) Classification Probabilities		
• False Positive Fraction (FPF)	$\Pr\{T+\|A-\}$	$\Pr\left\{\bigcup_{j\in S} T_j^{d(j)}+\,\middle\|\,\bigcap_{i\in\Psi} A^i-\right\}$ ≡ **Waste**
• True Positive Fraction (TPF)	$\Pr\{T+\|A+\}$	$\Pr\left\{\bigcup_{j\in S} T_j^{d(j)}+\,\middle\|\,\bigcup_{i\in\Psi} A^i+\right\}$
(II) Predictive Values		
• Positive Predictive Value (PPV)†	$\Pr\{A+\|T+\}$	$\Pr\left\{\bigcup_{i\in\Psi} A^i+\,\middle\|\,\bigcup_{j\in S} T_j^{d(j)}+\right\}$
• Negative Predictive Value (NPV)	$\Pr\{A-\|T-\}$	$\Pr\left\{\bigcap_{i\in\Psi} A^i-\,\middle\|\,\bigcap_{j\in S} T_j^{d(j)}-\right\}$ ≡ **1-Risk**

†For completeness, we define PPV as 0 when $S=\emptyset$.

[5]For example, in engineering applications, the terms TPF and FPF are referred to as the "hit rate" and "false alarm rate," respectively, while in the context of statistical hypothesis testing, they are referred to as "statistical power" and "significance level," respectively, see Pepe (2004), Chapter 2, for detailed discussion. While it is also common, especially in engineering and computer science applications, to consider only the overall probability of misclassification, given by $Pr(A+)(1-TPF)+Pr(A-)FPF$, this measure is not considered to be an adequate summary of the diagnostic accuracy of the test, as both TPF and FPF need to be known to assess its diagnostic accuracy.

In what follows, we first provide equivalent representations of these metrics in the multi-disease multi-test setting, in terms of test specificity and sensitivity parameters, which are known by the decision-maker. We will use these expressions subsequently when we reformulate and analyze the test selection problem.

Proposition 5 *For a given test set $S \subseteq \Omega$, the Risk, Weighted Total Risk, and Waste metrics in the multi-disease multi-test setting have the following equivalent representations under the Believe the Positive rule:*

$$Risk(S) = 1 - \frac{1}{1 + \frac{1}{\Pr\left(\bigcap_{i\in\Psi} A^i-\right)} \sum_{\vec{\lambda}\in\mathscr{S}\left(\vec{\Lambda}\right)\setminus\vec{0}} \left\{ \Pr\left(\vec{\Lambda}=\vec{\lambda}\right) \prod_{i\in\Psi:\lambda_i=1} \prod_{j\in S_i} Q_j \right\}}, \tag{5.7}$$

$$Waste(S) = 1 - \prod_{j\in S} \Pr\left(T_j^{d(j)} - | A^{d(j)}-\right), \tag{5.8}$$

$$WT\text{-}Risk\,(S) = \sum_{\vec{\lambda}\in\mathscr{S}\left(\vec{\Lambda}\right)\setminus\vec{0}} \left(w\left(\vec{\Lambda}\right) \Pr\left(\vec{\Lambda}=\vec{\lambda}\right) \prod_{j\in S} \Pr\left(T_j^{d(j)}- \mid \vec{\Lambda}=\vec{\lambda}\right) \right), \tag{5.9}$$

$$\textit{where } \Pr\left(T_j^{d(j)} - |\vec{\Lambda}=\vec{\lambda}\right) = \begin{cases} \Pr\left(T_j^{d(j)} - |A^{d(j)}-\right), & \textit{if } \Lambda_{d(j)}=0 \\ \Pr\left(T_j^{d(j)} - |A^{d(j)}+\right), & \textit{if } \Lambda_{d(j)}=1 \end{cases}.$$

Proof. For any $S \subseteq \Omega$, we have:

$$\begin{aligned} Risk(S) &= \Pr\left(\bigcup_{i\in\Psi} A^i + | \bigcap_{j\in S} T_j^{d(j)}-\right) \\ &= 1 - \frac{\Pr\left(\bigcap_{i\in\Psi} A^i-, \bigcap_{j\in S} T_j^{d(j)}-\right)}{\Pr\left(\bigcap_{i\in\Psi} A^i-, \bigcap_{j\in S} T_j^{d(j)}-\right) + \Pr\left(\bigcup_{i\in\Psi} A^i+, \bigcap_{j\in S} T_j^{d(j)}-\right)} \\ &= 1 - \frac{1}{1 + \frac{\sum_{\vec{\lambda}\in\mathscr{S}\left(\vec{\Lambda}\right)\setminus\vec{0}} \Pr\left(\vec{\Lambda}=\vec{\lambda}\right) \Pr\left(\bigcap_{j\in S} T_j^{d(j)} - | \vec{\Lambda}=\vec{\lambda}\right)}{\Pr\left(\bigcap_{i\in\Psi} A^i-\right) \Pr\left(\bigcap_{j\in S} T_j^{d(j)} - | \bigcap_{i\in\Psi} A^i-\right)}}. \end{aligned}$$

Then, it follows, by definition of Q_j and Assumption **(A1)**, that:

$$Risk(S) = 1 - \frac{1}{1 + \frac{1}{\Pr\left(\bigcap_{i\in\Psi} A^i-\right)} \sum_{\vec{\lambda}\in\mathscr{S}\left(\vec{\Lambda}\right)\setminus\vec{0}} \left\{ \Pr\left(\vec{\Lambda}=\vec{\lambda}\right) \prod_{i\in\Psi:\lambda_i=1} \prod_{j\in S_i} Q_j \right\}}.$$

For the second part, we have:

$$\begin{aligned} Waste(S) = \Pr\left(\bigcup_{j\in S} T_j^{d(j)} + | \bigcap_{i\in\Psi} A^i - \right) &= 1 - \Pr\left(\bigcap_{j\in S} T_j^{d(j)} - | \bigcap_{i\in\Psi} A^i - \right) \\ &= 1 - \prod_{j\in S} \Pr\left(T_j^{d(j)} - | A^{d(j)} - \right) \text{ (by } \textbf{(A1)}\text{)}. \end{aligned}$$

Finally, for the last part, from (5.5), we can write:

$$\begin{aligned} \textit{WT-Risk}\,(S) &= \sum_{\vec{\lambda}\in\mathscr{S}\left(\vec{\Lambda}\right)\setminus\vec{0}} w\left(\vec{\lambda}\right) \Pr\left(\vec{\Lambda} = \vec{\lambda}, \bigcap_{j\in S} T_j^{d(j)} - \right) \\ &= \sum_{\vec{\lambda}\in\mathscr{S}\left(\vec{\Lambda}\right)\setminus\vec{0}} w\left(\vec{\lambda}\right) \Pr\left(\vec{\Lambda} = \vec{\lambda}\right) \Pr\left(\bigcap_{j\in S} T_j^{d(j)} - \mid \vec{\Lambda} = \vec{\lambda}\right) \\ &= \sum_{\vec{\lambda}\in\mathscr{S}\left(\vec{\Lambda}\right)\setminus\vec{0}} w\left(\vec{\lambda}\right) \Pr\left(\vec{\Lambda} = \vec{\lambda}\right) \prod_{j\in S} \Pr\left(T_j^{d(j)} - \mid \vec{\Lambda} = \vec{\lambda}\right) \text{ (by } \textbf{(A2)}\text{)}. \end{aligned}$$

This completes the proof. □

We say that a metric, Γ, is monotone decreasing (increasing)[6] in the test set if for any $S \subseteq S' \subseteq \Omega$, we have $\Gamma(S) \geq \Gamma(S')$ ($\Gamma(S) \leq \Gamma(S')$).

Corollary 2 *Risk and WT-Risk are monotone decreasing, while Waste is monotone increasing in the test set.*

Proof. The results directly follow from the expressions in Proposition 5. □

On the other hand, the weighted risk, *W-Risk*, is not monotone in the test set, as the following counter-example demonstrates.

Example 5 *Consider again the problem instance in Example 3. Under the BP rule, we have that* $W\text{-}Risk(\{1\}) = \left(\$20 \times \frac{0.1120}{0.7939}\right) + \left(\$10,000 \times \frac{0.0020}{0.7939}\right) + \left(\$10,020 \times \frac{2\times10^{-5}}{0.7939}\right) = \$28.2646$ *(see Table 5.3), while* $W\text{-}Risk\,(\{1,2\}) = \$29.3165$ *from Example 3. Thus,* $W\text{-}Risk(\{1,2\}) > W\text{-}Risk(\{1\})$.

This example also serves as an instance where the test sets generated by **W-RMP** *and* **WT-RMP** *differ: WT-Risk is reduced by adding Test 2.*

[6]Throughout, we use the terms "decreasing" and "increasing" in the weak sense, to correspond to "nonincreasing" and "nondecreasing," respectively.

Table 5.3: *W-Risk* for the Two Test Sets under the BP rule in Example 3

$\overrightarrow{\lambda}$	$w(\overrightarrow{\lambda})(\$)$	$\Pr\left(\overrightarrow{\lambda}, T-(S)\right)$	Test Set = {1}	Test Set = {1, 2}
(0,0)	0	$\Pr\left(A^1-, A^2-, T-(S)\right)$	$0.8499 \times 0.8 = 0.6799$	$0.8499 \times 0.8 \times 0.99 = 0.6731$
(0,1)	20	$\Pr\left(A^1-, A^2+, T-(S)\right)$	$0.14 \times 0.8 = 0.1120$	$0.14 \times 0.8 \times 0.01 = 0.0011$
(1,0)	10,000	$\Pr\left(A^1+, A^2-, T-(S)\right)$	0.0020	0.0020
(1,1)	10,020	$\Pr\left(A^1+, A^2+, T-(S)\right)$	2×10^{-5}	2×10^{-7}
		$\Pr\left(T-(S)\right)$	0.7939	0.6762
		$Risk(S)$	0.1436	0.0046
		$WT\text{-}Risk(S)$	22.4404	19.8244
		$W\text{-}Risk(S)$	28.2646	29.3165
		$Waste(S)$	$1 - 0.8 = 0.200$	$1 - 0.8 \times 0.99 = 0.208$

This counter-intuitive result holds because expanding the current test set (with Test 1 only) to include a second good test (Test 2) for the highly prevalent Disease 2 will lower $\Pr(A_1-, A_2+, T-(S))$, while having little impact on $\Pr(A_1+, A_2-, T-(S))$, see Table 5.3. Thus, the proportion of blood units classified as infection-free, $\Pr(T-(S))$, significantly reduces with the inclusion of Test 2 in the test set (from 0.7939 to 0.6762). Hence, while the blood units having Disease 2 are largely eliminated by Test 2, the term $\Pr(A_1+, A_2 - |T-(S))$ still increases, because $\Pr(T-(S))$ is reduced from 0.7939 to 0.6732. Then, the counter-example follows because the term $\Pr(A_1+, A_2 - |T-(S))$ has a much higher weight than $\Pr(A_1-, A_2 + |T-(S))$ in the expression for *W-Risk*.

This example illustrates one of the major differences between the two objective functions, *WT-Risk* and *W-Risk*, in the weighted risk setting. Recall that *WT-Risk* is monotone decreasing in the test set (Corollary 2), that is, as long as a test's performance is good ($Q_j \leq 1$, $j \in \Omega$, which is without loss of generality in this setting), adding it to the test set reduces *WT-Risk* (but this decision is constrained by budget and waste constraints). As opposed to this, a test's good performance is not sufficient to reduce *W-Risk*. In addition to the test performance, one needs to consider the weight (or severity) of the TTI for which the test is administered. Thus, **W-RMP** is more selective than **WT-RMP**. We study the relationship between **W-RMP** and **WT-RMP** numerically in Section 5.4.3.

Next, we study the relationship between *Risk* and $Waste$, and expand this study to the weighted risks in Section 5.4.

Example 6 *Consider the single-disease single-test setting. In this setting,* $Waste$ $(= 1 - specificity)$ *depends only on the specificity of the test, while the Risk minimizing*

test set only depends on the ratio, $Q = \frac{\Pr(T-|A+)}{\Pr(T-|A-)} = \frac{1-sensitivity}{specificity}$*, see Proposition 5. Let* $\frac{\Pr\{A-\}}{\Pr\{A+\}} = 3$*, which does not impact the trend of change in this example. In the following four scenarios, we vary the test specificity and sensitivity parameters in steps of 0.05.*

Scenario 1. Specificity, $\Pr\{T-|A-\}$*, decreases from 0.95 to 0.50, while sensitivity,* $\Pr\{T+|A+\}$*, increases from 0.50 to 0.95.*

Scenario 2. Specificity, $\Pr\{T-|A-\}$*, decreases from 0.95 to 0.50, while sensitivity,* $\Pr\{T+|A+\}$*, remains constant at 0.50.*

Scenario 3. Specificity, $\Pr\{T-|A-\}$*, decreases from 0.95 to 0.50, while sensitivity,* $\Pr\{T+|A+\}$*, decreases from 0.95 to 0.50.*

Scenario 4. Specificity, $\Pr\{T-|A-\}$*, decreases from 0.95 to 0.50, while* $Q = \frac{\Pr(T-|A+)}{\Pr(T-|A-)}$ *remains constant at* $\frac{10}{19}$*.*

Figure 5.3 plots the values of Risk and Waste corresponding to each scenario. In the figure, the x-axis represents the different instances in each scenario obtained by varying the test sensitivity and specificity parameters, as indicated above. These results highlight the following:

(i) A reduction in risk does not necessarily come at the expense of an increase in waste (see Scenarios 2 and 3 in Figure 5.3).

(ii) The same level of risk may be attained by multiple test sets, each of which leading to quite different levels of waste (e.g., see Scenario 4 in Figure 5.3).

Thus, it is essential to consider both of these metrics in the formulation, as we do in this work, since both are important in the context of blood screening.

In the following section, we propose effective algorithms for the test selection problem. These algorithms allow us to study the relationship between $Risk$, weighted risks, and $Waste$ in the general setting.

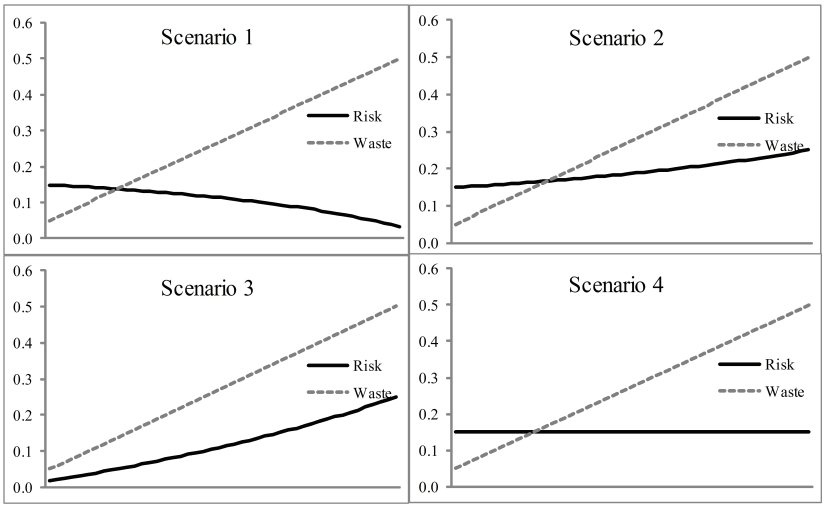

Figure 5.3: The *Risk* and *Waste* Metrics in Example 6 (Single-Disease Single-Test Setting)

5.4 Solution Methodologies, Lower Bounds, and Numerical Studies

This section is organized as follows. In Sections 5.4.1 and 5.4.2, we provide reformulations of **RMP** and **WT-RMP**, which lead to effective solution methodologies and lower bounds. Then, in Section 5.4.3, we present and discuss our numerical study.

5.4.1 Problem Reformulations

Proposition 5, together with Proposition 1 in Chapter 4, allows us to reformulate **RMP** as a 0-1 polynomial programming problem. In addition, we are able to transform **WT-RMP** into a 0-1 polynomial programming problem, as the following result indicates.

Proposition 6 *(a)* **RMP** *is equivalent to the following 0-1 polynomial programming problem:*

$$\underline{\textbf{RMP:}} \qquad \text{Minimize}_{x_j, j\in\Omega} \sum_{\overrightarrow{\lambda}\in\mathscr{S}\left(\overrightarrow{\Lambda}\right)\setminus\overrightarrow{0}} \left\{ p_{\overrightarrow{\Lambda}}\left(\overrightarrow{\lambda}\right) \prod_{i\in\Psi:\lambda_i=1} \prod_{j\in\Omega_i} \left\{1-\overline{Q}_j x_j\right\} \right\} \tag{5.10}$$

$$\text{subject to} \quad \sum_{j\in\Omega} c_j x_j \leq B \tag{5.11}$$

$$\sum_{j\in\Omega} \ln\left(\Pr\left(T_j^{d(j)} - |A^{d(j)}-\right)\right) x_j \geq \ln(1-\alpha) \tag{5.12}$$

$$x_j \quad \textit{binary},\ j\in\Omega. \tag{5.13}$$

Given an optimal solution to (5.10)-(5.13), denoted by $\{x_j^*, j\in\Omega\}$*, let* $S^* = \{j : x_j^* = 1, j\in\Omega\}$*. Then, the optimal risk is given by* $Risk^* = \Pr\left(\bigcup_{i\in\Psi} A_i + \left| \bigcap_{j\in S^*} T_j^{d(j)} - \right.\right)$.

(b) **WT-RMP** *is equivalent to the following 0-1 polynomial programming problem:*

$$\text{Minimize}_{x_j, j\in\Omega} \sum_{\vec{\lambda}\in\mathscr{S}\left(\vec{\Lambda}\right)\setminus\vec{0}} \left(w\left(\vec{\lambda}\right) \Pr\left(\vec{\Lambda} = \vec{\lambda}\right) \prod_{j\in\Omega} \left(1 - x_j \Pr\left(T_j^{d(j)} + |\vec{\Lambda} = \vec{\lambda}\right)\right)\right) \tag{5.14}$$

$$\text{subject to (5.11), (5.12), (5.13),}$$

where $\Pr\left(T_j^{d(j)} + |\vec{\Lambda} = \vec{\lambda}\right) = \begin{cases} \Pr\left(T_j^{d(j)} + |A^{d(j)}-\right), & \textit{if } \Lambda_{d(j)} = 0 \\ \Pr\left(T_j^{d(j)} + |A^{d(j)}+\right), & \textit{if } \Lambda_{d(j)} = 1 \end{cases}$.

Given an optimal solution to (5.14),(5.11)-(5.13), denoted by $\left\{x_j^{**}, j\in\Omega\right\}$*, let* $S^{**} = \left\{j : x_j^{**} = 1, j\in\Omega\right\}$*. Then, the optimal weighted total risk is given by* $WT\text{-}Risk^* = \Pr\left(\bigcup_{j\in S^{**}} T_j^{d(j)} + |\bigcup_{i\in\Psi} A^i + \right)$.

(c) In the single-disease multi-test setting, both **RMP** *and* **WT-RMP** *reduce to the two-dimensional linear knapsack problem, which is extensively studied in the literature (e.g., Lodi et al., 2002; Caprara and Monaci, 2004).*

Proof. The equivalence of the objective function in (5.10) to (5.1) is shown in Chapter 4, Proposition 1. Then it suffices to show that the waste constraint in (5.3) can be linearized as in (5.12). Using Eq. (5.8) in Proposition 5, we can write:

$$1 - \prod_{j\in S} \Pr\left(T_j^{d(j)} - |A^{d(j)}-\right) \leq \alpha$$

$$\Leftrightarrow \sum_{j\in S} \ln\Pr\left(T_j^{d(j)} - |A^{d(j)}-\right) \geq \ln(1-\alpha) \Leftrightarrow \sum_{j\in\Omega} \ln\left(\Pr\left(T_j^{d(j)} - |A^{d(j)}-\right)\right) x_j \geq \ln(1-\alpha).$$

Part (b) follows as (5.9) can be equivalently written as (5.14). Then, part (c) follows as a special case of parts (a) and (b). □

On the other hand, because the *W-Risk* objective function cannot be expressed in product form (which was the case for *Risk* and *WT-Risk*, see Proposition 5), **W-RMP** cannot be formulated as a 0-1 polynomial programming, and remains a difficult-to-solve problem. Consequently, in Section 5.4.3, we study the effectiveness of its approximation as **WT-RMP**.

An interesting question, both from a theoretical and a public policy perspective, is whether allowing for "fractional" policies (with multiple test sets, each applied to a certain fraction of the blood to be tested) (i) are easy to obtain through LP-relaxations of the formulations in Proposition 6, and (ii) provide benefits over the current "same-for-all" policy. Chapter 4 addresses the first question and shows that the LP-relaxation of **RMP** is not valid, as the objective function in (5.10), with fractional x_j values, no longer represents the *Risk* for a fractional policy. (A similar result applies to **WT-RMP**.) Hence, a study into fractional policies remains an important future research direction.

5.4.2 Solution Methodologies and Lower Bounds

In Chapter 4, we investigate the effectiveness of various approaches for linearizing **RMP** (with only the budget constraint included). For this purpose, we consider a special case of **RMP** under the mono-infection setting, which we refer to as $\mathbf{RMP}^0$, where the possibility of co-infections in the blood unit is negligible, that is, the probability of the random blood unit being infected by more than one disease in set Ψ is considered zero for all disease combinations. Mathematically speaking, we assume $Pr(\overrightarrow{\Lambda} = \overrightarrow{\lambda}) = 0$, for $\overrightarrow{\lambda} \in \mathscr{S}(\overrightarrow{\Lambda}) : \sum_{i \in \Psi} \lambda_i > 1$. While this mono-infection setting deserves analysis in its own right (as the donor selection procedures in developed countries make the co-infection possibility in the donor population unlikely), this analysis also motivates the development of near-optimal algorithms for the general case with co-infections. We use the superscript 0 to denote the mono-infection setting.

In the following, we first briefly outline the reformulation and solution approach proposed in Chapter 4 for **RMP** with the budget constraint only, because a variation of that approach proves to be quite effective for the models considered in this chapter, namely **RMP** and **WT-RMP**, under both budget and waste constraints. Specifically, the numerical studies in Chapter 4 indicate that for $\mathbf{RMP}^0$, a testset-based **(TS-based)** formulation consistently dominates, in terms of computational times, a

standard linearization approach, where the latter involves introducing a binary variable for each polynomial term (i.e., terms involving the product of binary variables, x_j, $j \in \Omega$) along with a set of constraints (Glover and Woolsey, 1974). In particular, in the **TS-based** reformulation approach, we reformulate $\mathbf{RMP}^0$ and $\mathbf{WT\text{-}RMP}^0$ by replacing the binary test variables, $x_j, j \in \Omega$, in the original formulation (in Proposition 6) with binary variables, $x^i_{q_1,q_2,\cdots,q_k}$, $\forall\{q_1, q_2, \cdots, q_k\} \subseteq \Omega_i, i \in \Psi$ (we let $x^i_\emptyset$ and $x^i_{\Omega_i}$ respectively denote the binary variables corresponding to the empty set and set Ω_i), and add a set of constraints that ensure that $x^i_{q_1,q_2,\cdots,q_k} = 1$ if and only if $\{x_{q_1} = 1, \cdots, x_{q_k} = 1, x_p = 0, \forall p \in \Omega_i \setminus \{q_1, q_2, \cdots, q_k\}\}$ (see the Appendix). Our extensive numerical study for $\mathbf{RMP}^0$ and $\mathbf{WT\text{-}RMP}^0$ indicates that the dominance of the **TS-based** formulation over the standard linearization approach continues to hold in our setting.

While the **TS-based** formulation provides an optimal solution for the mono-infection setting, namely for $\mathbf{RMP}^0$ and $\mathbf{WT\text{-}RMP}^0$, it is not necessarily optimal for the general case with co-infections. Therefore, we use the Co-infection Reallocation **(CR)** Heuristic, developed and shown to be very effective in Chapter 4 for **RMP** (with only the budget constraint), to solve both **RMP** and **WT-RMP** (with both budget and waste constraints). The **CR** Heuristic is based on approximating the co-infection setting as a mono-infection setting and solving it optimally as a mono-infection problem (see Chapter 4 for details). In particular, we use the **TS-based** reformulation to solve $\mathbf{RMP}^0$ and $\mathbf{WT\text{-}RMP}^0$ to optimality and embed the **TS-based** formulation into the **CR** Heuristic for **RMP** and **WT-RMP**.

In Chapter 4, we show that the optimal objective function value of $\mathbf{RMP}^0$ (in the mono-infection setting) provides an effective lower bound for the optimal objective function value of **RMP** (in the general co-infection setting), that is, $Risk^* \geq Risk^{*0}$. The following proposition gives a similar lower bound for **WT-RMP**.

Proposition 7 *In* **WT-RMP**, *set* $\Pr\left(\overrightarrow{\Lambda} = \overrightarrow{\lambda}\right) = 0, \forall \overrightarrow{\lambda} \in \mathscr{S}\left(\overrightarrow{\Lambda}\right) : \sum_{i\in\Psi} \lambda_i > 1$, *and solve the resulting instance of the mono-infection problem* $\mathbf{WT\text{-}RMP}^0$ *to optimality, and denote its optimal objective function value by* $WT\text{-}Risk^{*0}$. *Then,* $WT\text{-}Risk^{*0} \leq WT\text{-}Risk^*$.

Proof. Let $\mathscr{S}^1\left(\overrightarrow{\Lambda}\right)$ denote the subset of the sample space of the random vector $\overrightarrow{\Lambda}$ having only a single infection, that is, $\mathscr{S}^1\left(\overrightarrow{\Lambda}\right) = \left\{\overrightarrow{\Lambda} \in \mathscr{S}\left(\overrightarrow{\Lambda}\right) : \sum_{i\in\Psi} \lambda_i = 1\right\}$.

From Eq (5.14) in Proposition 6, the objective function of **WT-RMP** can be written as:

$$
\begin{aligned}
& \sum_{\overrightarrow{\lambda} \in \mathscr{S}\left(\overrightarrow{\Lambda}\right) \setminus \overrightarrow{0}} \left(w\left(\overrightarrow{\lambda}\right) \Pr\left(\overrightarrow{\Lambda} = \overrightarrow{\lambda}\right) \prod_{j \in \Omega} \left(1 - x_j \Pr\left(T_j^{d(j)} + | \overrightarrow{\Lambda} = \overrightarrow{\lambda}\right)\right)\right) \\
= & \sum_{\overrightarrow{\lambda} \in \mathscr{S}^1\left(\overrightarrow{\Lambda}\right)} \left(w\left(\overrightarrow{\lambda}\right) \Pr\left(\overrightarrow{\Lambda} = \overrightarrow{\lambda}\right) \prod_{j \in \Omega} \left(1 - x_j \Pr\left(T_j^{d(j)} + | \overrightarrow{\Lambda} = \overrightarrow{\lambda}\right)\right)\right) \\
& + \sum_{\overrightarrow{\lambda} \in \mathscr{S}\left(\overrightarrow{\Lambda}\right) \setminus \left\{\overrightarrow{0} \cup \mathscr{S}^1\left(\overrightarrow{\Lambda}\right)\right\}} \left(w\left(\overrightarrow{\lambda}\right) \Pr\left(\overrightarrow{\Lambda} = \overrightarrow{\lambda}\right) \prod_{j \in \Omega} \left(1 - x_j \Pr\left(T_j^{d(j)} + | \overrightarrow{\Lambda} = \overrightarrow{\lambda}\right)\right)\right) \\
\geq & \sum_{\overrightarrow{\lambda} \in \mathscr{S}^1\left(\overrightarrow{\Lambda}\right)} \left(w\left(\overrightarrow{\lambda}\right) \Pr\left(\overrightarrow{\Lambda} = \overrightarrow{\lambda}\right) \prod_{j \in \Omega} \left(1 - x_j \Pr\left(T_j^{d(j)} + | \overrightarrow{\Lambda} = \overrightarrow{\lambda}\right)\right)\right) \\
\geq & \text{Minimize}_{x_j, j \in \Omega} \sum_{\overrightarrow{\lambda} \in \mathscr{S}^1\left(\overrightarrow{\Lambda}\right)} \left(w\left(\overrightarrow{\lambda}\right) \Pr\left(\overrightarrow{\Lambda} = \overrightarrow{\lambda}\right) \prod_{j \in \Omega} \left(1 - x_j \Pr\left(T_j^{d(j)} + | \overrightarrow{\Lambda} = \overrightarrow{\lambda}\right)\right)\right), \qquad (5.15)
\end{aligned}
$$

where (5.15) is the objective function of $\mathbf{WT\text{-}RMP}^0$. Hence, the result follows. □

5.4.3 A Numerical Study - The Sub-Saharan Africa and Ghana Cases

Our objectives in this section are three-fold: (i) to investigate the impact of minimizing risk versus weighted risks (*W-Risk* and *WT-Risk*) on the test set, (ii) to study the impact of waste and budget on risk and weighted risk, and (iii) to study the potential benefits of our optimization-based approach over the existing FDA or WHO guidelines so as to provide insights to decision-makers. We study these research questions through an extensive numerical study, and discuss our findings through the sub-Saharan Africa and Ghana case studies, described in detail in Chapter 4. (Our other numerical studies provide similar findings.)

In sub-Saharan Africa, 32 (out of the 45) countries are among the world's poorest (Busch et al., 2009), and sub-Saharan Africa is more heavily affected by HIV and AIDS than any other region of the world. While the prevalence rate for HIV is also high in Ghana, it is lower than sub-Saharan Africa in general. In addition, HBV and HCV prevalence rates are both higher in Ghana than sub-Saharan Africa. Furthermore, due to a lack of budget and infrastructure in place for effective blood screening, the current blood screening practices are far from ideal in both regions, as further

discussed in Section 5.4.3. Thus, both regions face high TTI prevalence rates, but under quite a different infection structure. However, the WHO recommendations offer the same guidelines for blood screening, independent of the regional infection characteristics. Consequently, a blood screening program guided by the WHO recommendations would lead to similar blood testing composition in both regions (subject to their own budget constraints and infrastructure). Thus, a case study of these two regions provides us with an excellent vehicle to understand the impact of the various relevant objectives in blood screening (risk versus weighted risks), and the potential benefits of our optimization-based approach, which explicitly takes into consideration the regional infection characteristics, over static guidelines.

The current WHO guidelines call for screening blood for HIV, HBV, HCV, and syphilis, while the FDA adds HTLV, WNV, and Chagas' Disease to this list. Consequently, in our numerical study, we consider HIV, HBV, HCV, HTLV, and WNV. Syphilis and Chagas' Disease are omitted from the case study due to a lack of reliable data on test performance or disease prevalence. We explicitly model the co-infection possibility among HIV, HBV, and HCV, as these three infections have significant co-infection rates (Carmo et al., 2000; Lincoln et al., 2003; Gordona and Sherman, 2009; Soriano et al., 2006). In particular, it is estimated that the HIV-infected population has a co-infection rate for HBV and HCV of around 10% and 15%, respectively (Carmo et al., 2000; Lincoln et al., 2003), while the HCV-infected population has a co-infection rate for HBV of around 10% (Adewole et al., 2009; Christian et al., 2010). The co-infection rates in the case studies are calculated using these proportions. We ignore the triple co-infection rate of the HIV, HBV, and HCV due to a lack of data. Table 5.4 provides a summary of the mono- and co-infection prevalence rates for the TTIs considered for sub-Saharan Africa and Ghana. On the test side, we include the same 33 of the FDA-approved tests, whose efficacy and unit administration cost data are available (FDA, 2010; Jackson et al., 2003), see Table 6.1 in Chapter 4.

In addition to the above data, **WT-RMP** and **W-RMP** also require weights, $w(\overrightarrow{\lambda})$, $\overrightarrow{\lambda} \in \mathscr{S}(\overrightarrow{\lambda})$, for each possible disease prevalence vector. In this study, we consider the weight to be the social cost of an infection over the life-time of the infected individual, which is estimated in the literature for the HBV, HIV, HCV, HTLV, and WNV as \$15,079, \$274,437, \$11,161, \$10,000, and \$7,300, respectively (Custer et al., 2005b; Marshall et al., 2004; Stiguma et al., 2000; Zohrabian et al., 2004). We assume that the social costs of co-infections are additive, that is, $w(\overrightarrow{\lambda}) = \sum_{i \in \Psi : \lambda_i = 1} w(\lambda_i)$, $\overrightarrow{\lambda} \in \mathscr{S}(\overrightarrow{\Lambda})$.

Table 5.4: Prevalence Rates of the TTIs (%) in Sub-Saharan Africa and Ghana

	Sub-Saharan Africa	Ghana
Mono-HIV	11.250 (UNAIDS, 2008)	3.000 (Van Hulst et al., 2009)
Mono-HBV	8.200 (Kiire, 1996)	14.351 (Van Hulst et al., 2009)
Mono-HCV	0.450 (Madhava et al., 2002)	1.641 (Van Hulst et al., 2009)
Mono-HTLV	3.000 (Proietti et al., 2005)	2.000 (Lal et al., 1994)
Mono-WNV	1.000*	1.000*
HIV-HBV	1.500	0.400
HIV-HCV	2.250	0.600
HCV-HBV	0.300	0.249

*: Since most WNV cases occur in the form of outbreaks, there does not exist accurate and conclusive estimates on the prevalence of WNV in these regions. We therefore use 1% for sub-Saharan Africa in general, based on a study of WNV antibodies (Petersen, 2009).

In the following, we discuss the findings from this case study. The results of our other numerical studies are similar. All runs are performed in Dell DM051 with Intel Pentium(R) D CPU 2.80GHz using IBM ILOG Cplex Optimizer.

W-RMP versus WT-RMP (Small Problem Sizes)

Recall that **W-RMP** does not lend itself to linearization, as discussed in Section 5.4.1. Therefore, in our numerical studies, we solve **W-RMP** for small problem instances through complete enumeration, and compare its optimal solution with the optimal solution to **WT-RMP**. In particular, we consider only a subset of the tests[7] in Table 6.1 under a range of budgets ($5-30) and waste tolerance limits ($\alpha = 0.02 - 0.04$ and $\alpha = 1$, indicating no waste tolerance limit) for each of sub-Saharan Africa and Ghana. We find that the optimal test sets generated by **W-RMP** and **WT-RMP** are exactly the same in *all* 208 scenarios considered (in both the sub-Saharan Africa and Ghana case studies). This suggests that **WT-RMP** provides a very good approximation for **W-RMP**. Consequently, we drop **W-RMP** from further consideration in our realistic-sized problems in the remainder of this section, and focus on **RMP** and **WT-RMP** only.

Next, we study the effectiveness of the **CR** Heuristic for **RMP** and **WT-RMP** in sub-Saharan Africa considering all 33 tests in Table 6.1.

[7]The subset of the tests we consider are very cost-effective, and are often the ones selected by **RMP** and **WT-RMP**. Specifically, we consider ten tests, with two tests per disease: Tests 1,3 for HBV, 13,19 for HIV, 24,25 for HCV, 30,31 for WNV, and 32,33 for HTLV.

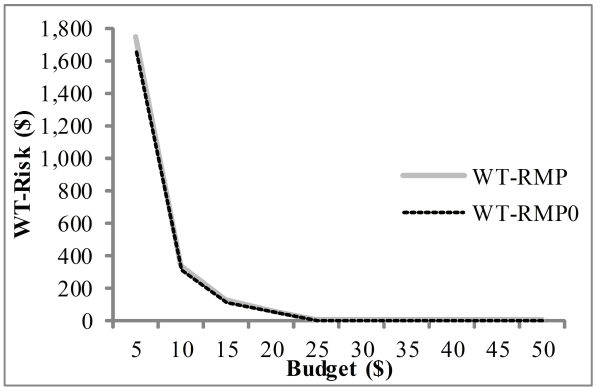

Figure 5.4: The Deviation of the **CR** Heuristic Solution from the Lower Bound for **WT-RMP** in the Sub-Saharan Africa Case Study - No *Waste* Tolerance Limit

Effectiveness of the CR Heuristic in the Co-infection Setting (Realistic Problem Sizes - Sub-Saharan Africa)

Recall that in the mono-infection setting $\mathbf{RMP}^0$ and $\mathbf{WT\text{-}RMP}^0$ can be solved to optimality quite efficiently using our **TS-based** reformulation. The **CR** Heuristic is shown to be very effective for **RMP** in the co-infection setting, see Chapter 4. In this section, we investigate the effectiveness of the **CR** Heuristic for **WT-RMP** by comparing its solution with the lower bound obtained by $\mathbf{WT\text{-}RMP}^0$ (see Proposition 7) for the sub-Saharan case study with all 33 tests in Table 6.1. We consider a range of budgets ($5-50) and relax the constraint on waste. In our numerical studies, the heuristic solution generated in the co-infection setting (by **WT-RMP**) is quite close to the lower bound (generated by $\mathbf{WT\text{-}RMP}^0$), with an average deviation of 11.31% and a maximum deviation of 22.63%. Consequently, we conclude that the **CR** Heuristic performs very well for **WT-RMP**.

Our analysis also indicates that both the optimal and heuristic test sets, respectively obtained for the mono-infection and co-infection settings, behave in a similar way for each parameter we study, namely the waste constraint, budget, and risk minimization versus weighted total risk minimization objectives.

The Optimization-based Approach versus the Current Practice

We first provide an overview of the current practice in sub-Saharan Africa, where 20-30% of blood is collected through Blood Centers that perform limited screening for HIV, HBV, and HCV (Van Hulst et al., 2010), following the WHO recommendations. This is done in city-based centers, whose affordability and sustainability remains a critical issue for most countries of sub-Saharan Africa (Busch et al., 2009; Field and Allain, 2007). The remaining 70-80% of blood is collected from "replacement donors," who donate blood for a specific patient at the point of use (Busch et al., 2009; Lackritz et al., 1992). This blood is often not tested (Lara et al., 2007). This method is much cheaper, as it does not involve donor recruitment expenses, capital investment and infrastructures for dedicated blood centers, nor testing costs (Owusu-Ofori et al., 2010). To model the current practice in sub-Saharan Africa, we consider, similar to Chapter 4, a testing scheme in which only 30% of the blood is tested following the WHO guidelines to the extent possible (i.e., constrained by budget availability), and the remaining 70% is untested. We refer to this as the 30% scheme.

There are multiple test sets that comply with the WHO (or FDA) guidelines by selecting one test per each TTI recommended for screening. From these, we can find a test set that minimizes *Risk* (Min-Risk) by selecting the test with the minimum Q-value for each TTI (Tests 3, 19, and 25 for the WHO, and 3, 19, 25, 31, and 32 for the FDA), and another that minimizes the required budget (Min-Cost) (Tests 4, 7, and 24 for the WHO, and 4, 7, 24, 31, and 32 for the FDA). As opposed to the selection criteria in an optimization-based model, such as **RMP** or **WT-RMP**, these test sets are derived directly from the guidelines, and therefore, are independent of regional mono- and co-infection prevalence rates.

The first part of Table 5.7 shows the required budget for each of these test sets under the different schemes, as well as their resultant risk, weighted risks, and waste for sub-Saharan Africa and Ghana. We also report the metrics for the 30% WHO testing scheme. The second and third parts of Table 5.7 report the test sets selected by **RMP** and **WT-RMP** model, given budget constraints that span the range of required budgets for the various testing schemes displayed in the first part of the table. To compare the optimization models with the current practice, for these solutions we do not enforce either the WHO or FDA guidelines, but we have identified the solutions that do conform with those guidelines in the table. We can make the following conclusions from our case study.

First, as Chapter 4 points out, **RMP** model can achieve *significant risk improvements*

over the current practice by choosing multiple, less expensive tests for particular TTIs, based on their prevalence and co-infection levels. In addition, we observe significant reduction in *W-Risk* and *WT-Risk* by using the optimization-based model, **WT-RMP**. This is achieved by selecting tests with higher efficacies for infections having higher prevalences and/or higher weights. Interestingly, even the test set generated by **RMP** provides significantly lower values of *W-Risk* and *WT-Risk*, despite the fact that it does not consider any disease weight data. This implies that tests with higher efficacies alone would provide significant improvement in *W-Risk* and *WT-Risk*.

In Chapter 4, we conclude that following the WHO and FDA guidelines is no guarantee of an optimal testing regime - sometimes it is better to deviate from the recommendations. This case study further extends this conclusion to **WT-RMP** and weighted risks. In the test sets generated by **WT-RMP** in sub-Saharan Africa, for example, the model chooses to fulfill the WHO guidelines only when the budget is as large as \$17. This deviation can be explained by the relatively lower mono-infection prevalence rate of HBV and its high co-infection rate with HIV: A portion of the HBV-infected individuals, who are also co-infected with the HIV, will be eliminated from the blood pool simply by HIV tests. In Ghana, however, the WHO guidelines are fulfilled at a budget level as low as \$9, because HBV is the most prevalent TTI in this region. This underscores the need to consider the regional infection characteristics while constructing risk minimizing test sets.

HBV is the most prevalent TTI in Ghana, while HIV, which has a much higher weight than HBV, is the most prevalent TTI in sub-Saharan Africa (see Table 5.4). The different infection structures in Ghana and sub-Saharan Africa lead to significantly different test sets and weighted risk values in these regions. First, we discuss this impact on the **RMP**-generated test sets and their corresponding metrics. For example, when budget increases from \$3 to \$4, *Risk*, *W-Risk*, and *WT-Risk* are all largely reduced in sub-Saharan Africa by administering a cheap test for HIV.[8] In Ghana, however, a similar improvement on weighted risk is not achieved until the budget reaches \$6, because **RMP** gives the first priority to HBV tests due to its high prevalence. Secondly, we observe this impact in **WT-RMP** as well. In sub-Saharan Africa, a test set that minimizes *WT-Risk* also reduces *Risk*, as HIV is not only the most prevalent infection, but also is the one having the highest weight. In Ghana, however, sometimes *Risk* is sacrificed for the purpose of *WT-Risk* minimization. For example, when the budget increases from \$3 to \$4, *WT-Risk* is reduced, but at a cost of increased *Risk*, by switching from Test 4 for HBV to Test 15 for HIV.

[8]The cheapest HIV test costs \$4, see Table 6.1.

We observe that the test sets generated by **WT-RMP** and **RMP** and their corresponding metrics differ significantly[9], especially when the prevalence and weight of the TTIs are not aligned (such as the Ghana example). This, once again, highlights the importance of generating region-specific test set for blood screening that explicitly takes into account the mono- and co-infection rates and weights of the TTIs. It also demonstrates the difficulty of making this important decision, as the objectives of reducing risk versus weighted risks sometimes conflicts, and a trade-off between risk, weighted risks, waste, and budget needs to be made by the decision-maker. Our optimization-based models provide tools to support and potentially improve this decision-making process.

It is also interesting to compare the existing schemes in sub-Saharan Africa and Ghana, in which only around 30% of the blood donations undergo regular testing according to the WHO guidelines (see the 30% testing scheme for the WHO-compliant Min-Risk and Min-Cost test sets in Table 5.7), with a testing scheme that includes *all* blood donations, but at the same budget level. At the corresponding 30% testing budget levels, the all-unit testing scheme can afford to use only one test, but performs better than partial testing in terms of risk. However, when the budget is extremely limited ($B \leq \$3$), we find that the 30% scheme performs slightly better than **WT-RMP** model. The reason is that fractional testing schemes provide additional flexibility, which leads to the improvement of the objectives. This motivates further future research on fractional testing schemes.

Impact of Waste and Budget on Risk and WT-Risk (Realistic Problem Sizes - sub-Saharan Africa)

Finally, to study the impact of waste and budget constraints on $Risk$ and $WT\text{-}Risk$, we restrict the focus to sub-Saharan Africa and vary both the maximum allowable waste fraction (α) and budget (B) in both mono-infection and co-infection settings, see Tables 5.5-5.6 for the generated test sets and their corresponding $Risk$, $Waste$, $WT\text{-}Risk$, and $W\text{-}Risk$ in the co-infection setting; the results for the mono-infection setting are similar.

First, for a given level of α, $Risk$ decreases in a *convex* manner as budget increases, see, for example, Figure 5.5 (a), which depicts the risk-budget curve for the co-

[9]While we do not display the tests selected for each region at each budget level, we note that only the test set selected, not the prevalence, determines the waste. Thus, by examining the waste values for a particular budget level, one can determine if different test sets are selected for the different regions; this happens often.

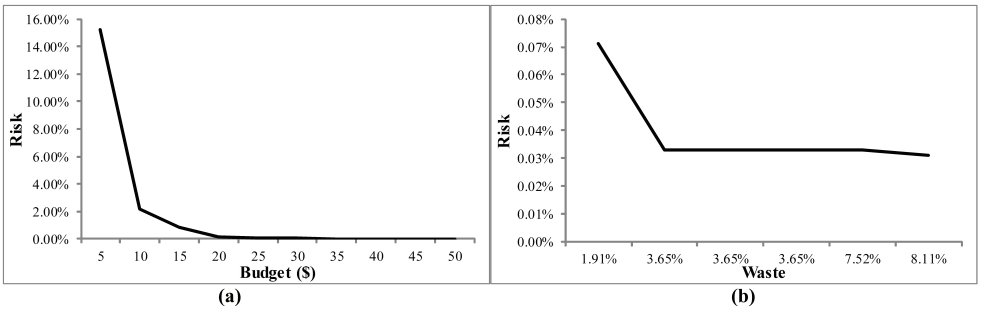

Figure 5.5: (a) *Risk* versus Budget (Co-infection Setting with $\alpha = 0.06$) (b) *Risk* versus $Waste$ (Co-infection Setting with $B = \$30$)

infection setting with $\alpha = 0.06$ (see also Tables 5.5-5.6). This is not surprising; the first \$5-\$10 spent on blood screening brings the highest risk reduction, after which the additional budget exhibits diminishing returns in *Risk*. On the other hand, for a given budget, reducing the waste tolerance limit, α, often leads to another test set with a comparable risk, but a much lower waste, see, for example, Figure 5.5 (b), which plots the risk-waste curve for $B = \$30$. Indeed, we find that it is often the case that there are multiple, budget-feasible test sets available, with comparable risks and quite different waste fractions, highlighting the importance of a risk-waste sensitivity analysis, as is done here. Only when the waste tolerance limit reduces to a very low level ($\alpha \leq 0.04$, see Tables 5.5-5.6), does the risk change considerably, as expected.

We observe that the weighted total risk exhibits a similar behavior to risk, in that it reduces drastically with budget at first, after which additional budget provides diminishing returns (see Figure 5.4). As stated in Proposition 2, waste is monotonically increasing in the test set. However, it is not necessarily monotonically increasing as more budget becomes available, as Figure 5.4 depicts.

5.5 Conclusions and Future Research Directions

In this chapter, we study an important problem faced by Blood Centers, of selecting screening tests for donated blood. This decision has a significant impact on health care quality in both developed and developing countries. We construct mathematical models of this decision problem, considering the various objective functions (minimization of the TTI risk and minimization of the weighted TTI risk) and constraints

(on budget and wasted blood) relevant in practice. Our work generates insights on the relationship among these different metrics, and on how they impact the test set. It also underscores the importance of considering these different metrics in decision-making through an optimization-based decision support system, as we find that the optimal test portfolio may have a complex structure, which we illustrate through examples.

There are numerous avenues that are worthy of future research effort. In this research, we adopt the Believe the Positive (BP) rule, which is a commonly adopted decision rule in blood screening (Pepe, 2004), in our models. While this decision rule has been shown to be the optimal rule for the risk minimization problem under a budget constraint [see Chapter 4], this is not necessarily so for the variations we consider in this chapter. Consequently, it is worthwhile to determine an optimal decision rule for each of the models we consider, and study how the test set generated by our models, considering the BP rule, and the corresponding risk, deviate from the "optimal" test set (under an optimal decision rule) and the corresponding risk. The focus on the BP rule is important, as it is the one that makes sense from a risk minimization point of view, but it is also important to understand its impact on the test set and the risk.

Our analysis relies on an assumption (Assumption **(A2)**), which states that test outcomes are conditionally and jointly independent given disease prevalence vector of the blood unit. However, as we discuss above, this assumption may be violated for tests that measure similar disease markers, as they will have similar immunological window periods, and hence, will have correlated outcomes. Consequently, it is important in future research to relax this assumption and study its impact on the test set.

Our treatment of the weighted risk minimization model relies on a heuristic algorithm. While our numerical studies indicate that this algorithm is very effective, as it generates solutions close to a lower bound, it is still an important future research direction to derive either exact algorithms that are also efficient, or heuristic algorithms with provable worst-case ratios for this important problem. This is a worthwhile research effort to pursue, as the weighted risk minimization problem is general enough to be able to incorporate a wide variety of metrics, including QALY, DALY, or social costs, commonly used in cost-effectiveness studies on blood screening.

Finally, on a broader, health policy, level, no data is perfectly accurate, and the decision-maker needs to allocate her limited resources among surveillance efforts (i.e., gathering more accurate data on disease prevalence rates and test performance) and

blood screening. While the former provides the decision-maker with better information, possibly leading to a test set that better represents reality, the latter actually reduces risk in blood. As a future direction, it is worthwhile to explore this trade-off to devise effective resource allocation schemes among these efforts. This is a problem we continue to study.

Table 5.5: The Test Sets Generated by **RMP** and **WT-RMP** under Varying Budget Allocations and Waste Tolerance Limits (α) for the Sub-Saharan Africa Case Study -1

Budget($)	Model	HBV	HIV	HCV	WNV	HTLV	Risk(%)	WT-Risk($)	W-Risk($)	Waste(%)
$\alpha = 1$*										
5	RMP		19				15.259	1748.2	2059.6	0.170
	WT-RMP		19				15.259	1748.2	2059.6	0.170
10	RMP	4	15			32	2.211	339.5	482.4	4.473
	WT-RMP	4	15			32	2.211	339.5	482.4	4.473
15	RMP	4	19		31	32	0.821	122.0	176.3	4.732
	WT-RMP	4	19		31	32	0.821	122.0	176.3	4.732
20	RMP	3	19	24	31	32	0.112	55.7	79.5	3.008
	WT-RMP	3	14,15		31	32	0.686	55.4	79.5	3.815
25	RMP	3,4	14,15	24	31	32	0.053	4.7	7.1	7.962
	WT-RMP	1,4	15,19	24	31	32	0.054	3.8	5.8	8.317
30	RMP	3,4	14,15	24,25	31	32	0.031	3.0	4.5	8.110
	WT-RMP	1,4	15,19	24,25	31	32	0.031	2.2	3.3	8.463
35	RMP	3,4	14,15	24,25	30,31	32	0.014	1.9	2.8	8.238
	WT-RMP	1,4	15,19	24,25	30,31	32	0.014	1.0	1.6	8.592
40	RMP	3,4	14,15	24,25	30,31	32,33	0.004	1.4	2.1	8.339
	WT-RMP	1,4	15,19	24,25	30,31	32,33	0.004	0.5	0.8	8.692
45	RMP	1,3,4	13,19	24,25	30,31	32,33	0.003	0.3	0.4	8.037
	WT-RMP	3,4	14,15,19	24,25	30,31	32,33	0.003	0.2	0.3	8.495
50	RMP	1,3,4	13,19	23,24,25	30,31	32,33	0.003	0.3	0.4	8.230
	WT-RMP	1,3,4	14,15,19	24,25	30,31	32,33	0.003	0.2	0.3	9.968
$\alpha = .08$										
5	RMP		19				15.259	1748.2	2059.6	0.170
	WT-RMP		19				15.259	1748.2	2059.6	0.170
10	RMP	4	15			32	2.211	339.5	482.4	4.473
	WT-RMP	4	15			32	2.211	339.5	482.4	4.473
15	RMP	4	19		31	32	0.821	122.0	176.3	4.732
	WT-RMP	4	19		31	32	0.821	122.0	176.3	4.732
20	RMP	3	19	24	31	32	0.112	55.7	79.5	3.008
	WT-RMP	3	14,15		31	32	0.686	55.4	79.5	3.815
25	RMP	3,4	14,15	24	31	32	0.053	4.7	7.1	7.962
	WT-RMP	2,4	15,19	24	31	32	0.064	4.3	6.4	6.984
30	RMP	1,2,4	15,19	25	31	32	0.033	2.3	3.4	7.518
	WT-RMP	3,4	13,19	25	31	32	0.034	2.2	3.3	5.160
35	RMP	1,2,4	15,19	25	30,31	32	0.016	1.1	1.7	7.648
	WT-RMP	3,4	13,19	25	30,31	32	0.017	1.1	1.6	5.293
40	RMP	1,2,4	15,19	25	30,31	32,33	0.006	0.6	1.0	7.749
	WT-RMP	3,4	13,19	25	30,31	32,33	0.007	0.6	0.9	5.397
45	RMP	2,3,4	13,19	24,25	30,31	32,33	0.003	0.3	0.4	6.701
	WT-RMP	2,3,4	13,19	24,25	30,31	32,33	0.003	0.3	0.4	6.701
50	RMP	1,2,3	13,19	23,24,25	30,31	32,33	0.003	0.3	0.4	5.416
	WT-RMP	2,3,4	7,15,19	24,25	30,31	32,33	0.003	0.2	0.3	7.920
$\alpha = .06$										
5	RMP		19				15.259	1748.2	2059.6	0.170
	WT-RMP		19				15.259	1748.2	2059.6	0.170
10	RMP	4	15			32	2.211	339.5	482.4	4.473
	WT-RMP	4	15			32	2.211	339.5	482.4	4.473
15	RMP	4	19		31	32	0.821	122.0	176.3	4.732
	WT-RMP	4	19		31	32	0.821	122.0	176.3	4.732
20	RMP	3	19	24	31	32	0.112	55.7	79.5	3.008
	WT-RMP	3	14,15		31	32	0.686	55.4	79.5	3.815
25	RMP	1,3	19	25	31	32	0.058	49.9	71.8	3.565
	WT-RMP	3	14,15	25	31	32	0.072	6.9	10.0	3.969
30	RMP	1,3	13,19	25	31	32	0.033	2.3	3.3	3.652
	WT-RMP	3,4	13,19	25	31	32	0.034	2.2	3.3	5.160
35	RMP	1,3	13,19	25	30,31	32	0.016	1.1	1.6	3.787
	WT-RMP	3,4	13,19	25	30,31	32	0.017	1.1	1.6	5.293
40	RMP	1,3	13,19	25	30,31	32,33	0.006	0.6	0.8	3.893
	WT-RMP	3,4	13,19	25	30,31	32,33	0.007	0.6	0.9	5.397
45	RMP	1,3	13,19	24,25	30,31	32,33	0.003	0.3	0.5	5.046
	WT-RMP	1,3	13,19	24,25	30,31	32,33	0.003	0.3	0.5	5.046
50	RMP	1,2,3	13,19	23,24,25	30,31	32,33	0.003	0.3	0.4	5.416
	WT-RMP	1,3	13,15,19	24,25	30,31	32,33	0.003	0.2	0.3	5.996

*: In all scenarios with $\alpha = 1$, **WT-RMP**^{0} (mono-infection setting) generated exactly the same test set as **WT-RMP**.

Table 5.6: The Test Sets Generated by **RMP** and **WT-RMP** under Varying Budget Allocations and Waste Tolerance Limits (α) for the Sub-Saharan Africa Case Study -2

Budget($)	Model	HBV	HIV	HCV	WNV	HTLV	Risk(%)	WT-Risk($)	W-Risk($)	Waste(%)
$\alpha = .05$										
5	RMP		19				15.259	1748.2	2059.6	0.170
	WT-RMP		19				15.259	1748.2	2059.6	0.170
10	RMP	4	15			32	2.211	339.5	482.4	4.473
	WT-RMP	4	15			32	2.211	339.5	482.4	4.473
15	RMP	4	19		31	32	0.821	122.0	176.3	4.732
	WT-RMP	4	19		31	32	0.821	122.0	176.3	4.732
20	RMP	3	19	24	31	32	0.112	55.7	79.5	3.008
	WT-RMP	3	14,15		31	32	0.686	55.4	79.5	3.815
25	RMP	1,3	19	25	31	32	0.058	49.9	71.8	3.565
	WT-RMP	3	14,15	25	31	32	0.072	6.9	10.0	3.969
30	RMP	1,3	13,19	25	31	32	0.033	2.3	3.3	3.652
	WT-RMP	1,3	13,19	25	31	32	0.034	2.3	3.3	3.652
35	RMP	1,3	13,19	25	30,31	32	0.016	1.1	1.6	3.787
	WT-RMP	1,3	13,19	25	30,31	32	0.017	1.1	1.6	3.787
40	RMP	1,3	13,19	25	30,31	32,33	0.006	0.6	0.8	3.893
	WT-RMP	1,3	13,19	25	30,31	32,33	0.007	0.6	0.8	3.893
45	RMP	2,3	13,19	24,25	30,31	32,33	0.004	0.5	0.7	3.666
	WT-RMP	1,3	13,19	23,25	30,31	32,33	0.005	0.4	0.6	4.095
50	RMP	3,6	13,19	24,25	30,31	32,33	0.003	0.4	0.5	4.071
	WT-RMP	1,3	7,13,19	23,25	30,31	32,33	0.004	0.3	0.4	4.478
$\alpha = .04$										
5	RMP		19				15.259	1748.2	2059.6	0.170
	WT-RMP		19				15.259	1748.2	2059.6	0.170
10	RMP	1	15	24			5.455	472.3	644.0	3.763
	WT-RMP	2,4	19				5.976	414.7	561.4	3.489
15	RMP	2	15		31	32	1.207	286.4	403.3	2.627
	WT-RMP	1	19	24		32	1.561	159.4	225.3	3.315
20	RMP	3	19	24	31	32	0.112	55.7	79.5	3.008
	WT-RMP	3	14,15		31	32	0.686	55.4	79.5	3.815
25	RMP	1,3	19	25	31	32	0.058	49.9	71.8	3.565
	WT-RMP	3	14,15	25	31	32	0.072	6.9	10.0	3.969
30	RMP	1,3	13,19	25	31	32	0.033	2.3	3.3	3.652
	WT-RMP	1,3	13,19	25	31	32	0.034	2.3	3.3	3.652
35	RMP	1,3	13,19	25	30,31	32	0.016	1.1	1.6	3.787
	WT-RMP	1,3	13,19	25	30,31	32	0.017	1.1	1.6	3.787
40	RMP	1,3	13,19	25	30,31	32,33	0.006	0.6	0.8	3.893
	WT-RMP	1,3	13,19	25	30,31	32,33	0.007	0.6	0.8	3.893
45	RMP	2,3	13,19	24,25	30,31	32,33	0.004	0.5	0.7	3.666
	WT-RMP	2,3	13,19	24,25	30,31	32,33	0.004	0.5	0.7	3.666
50	RMP	2,3	13,19	23,24,25	30,31	32,33	0.004	0.4	0.6	3.868
	WT-RMP	2,3	7,15,19	23,25	30,31	32,33	0.006	0.4	0.6	3.973
$\alpha = .02$										
5	RMP		19				15.259	1748.2	2059.6	0.170
	WT-RMP		19				15.259	1748.2	2059.6	0.170
10	RMP	3	19				5.875	431.4	565.6	0.370
	WT-RMP	3	19				6.004	431.4	565.6	0.370
15	RMP	2	19	24		32	1.867	198.3	275.3	1.910
	WT-RMP	2	19	24		32	1.927	198.3	275.3	1.910
20	RMP	2,3	13		31	32	0.698	142.9	200.8	1.928
	WT-RMP	3	19		31	32	0.858	113.8	159.7	1.830
25	RMP	3	19	25	31	32	0.092	54.4	76.9	1.987
	WT-RMP	3	13,19		31	32	0.827	55.2	77.6	1.919
30	RMP	2,3	19	25	31	33	0.071	51.5	72.8	1.908
	WT-RMP	3	13,19	25	31	33	0.083	6.5	9.2	1.820
35	RMP	2,3	13,19		31	33	0.046	52.1	73.2	1.997
	WT-RMP	2,3	13,19	25	31	33	0.047	3.0	4.3	1.997
40	RMP	2,3	13,19		31	33	0.046	52.1	73.2	1.997
	WT-RMP	2,3	13,19	25	31	33	0.047	3.0	4.3	1.997
45	RMP	2,3	13,19		31	33	0.046	52.1	73.2	1.997
	WT-RMP	2,3	13,19	25	31	33	0.047	3.0	4.3	1.997
50	RMP	2,3	13,19		31	33	0.046	52.1	73.2	1.997
	WT-RMP	2,3	13,19	25	31	33	0.047	3.0	4.3	1.997

Table 5.7: Comparison of *Risk* and *Waste* for Test Sets that Meet the WHO/FDA Requirements versus Test Sets Generated by **RMP** and **WT-RMP** for Sub-Saharan Africa and Ghana

		Sub-Saharan Africa				Ghana			
Guideline	B(\$)	Risk(%)	W-Risk (\$)	WT-Risk(\$)	Waste (%)	Risk(%)	W-Risk (\$)	WT-Risk(\$)	Waste(%)
Min-Risk[1]	14	5.316	489.6	370.6	0.529	3.829	334.1	265.2	0.529
- *30%*	4	21.160	30,476.0	30,440.3	0.159	17.417	9,734.5	9,713.8	0.159
Min-Cost[1]	9	5.659	1,177.3	856.9	4.695	4.109	536.2	409.1	4.695
- *30%*	3	21.263	30,682.3	30,586.2	1.409	17.501	9,795.1	9,757.0	1.409
Min-Risk[2]	22	0.092	76.9	54.4	1.987	0.098	29.2	22.0	1.987
Min-Cost[2]	17	0.474	804.0	546.6	6.092	0.400	240.1	173.7	6.092
RMP	3	20.035	41,871.4	37,119.4	1.610	9.857	12,225.5	10,242.7	1.610
	4	15.311	2,227.1	1,875.8	1.000	9.743	12,212.4	10,365.3	0.200
	5	15.259	2,059.6	1,748.2	0.170	7.542	10,345.3	8,218.4	4.312
	6	6.028	748.5	550.3	4.119	5.928	620.9	485.8	4.119
	7	5.971	580.9	430.4	3.315	5.894	615.6	489.1	2.594
	8	5.932	733.3	554.9	1.198	5.773	596.7	480.3	1.198
	9	5.476*	647.2	467.3	5.269	4.062*	401.2	304.1	5.269
	10	2.211	482.4	339.5	4.473	3.57	453.5	344.8	4.473
	11	2.149	307.8	218.3	3.672	3.534	448.0	345.9	2.954
	12	2.107	466.2	337.8	1.564	3.408	428.4	335.1	1.564
	13	1.613*	375.3	259.4	5.620	1.609*	224.8	165.5	5.620
	14	0.885	353.3	242.7	5.524	1.572*	219.3	164.0	4.119
	15	0.821	176.3	122.0	4.732	1.442*	199.6	151.2	2.745
	16	0.778	336.8	238.1	2.646	1.39	191.7	138.5	7.139
	17	0.270†	244.0	164.5	6.658	0.349†	99.7	71.7	6.658
	18	0.216†	95.3	64.8	5.875	0.312†	94.0	68.7	5.174
	19	0.166†	228.2	158.4	3.815	0.178†	74.0	54.7	3.815
	20	0.112†	79.5	55.7	3.008	0.125†	65.8	46.5	8.161
	21	0.079†	74.6	49.8	7.391	0.111†	28.6	20.4	7.391
	22	0.078†	74.4	50.4	6.063	0.058†	58.1	41.4	7.194
WT-RMP	3	20.053	41,874.7	36,549.5	3.150	9.857	12,225.5	10,242.7	1.610
	4	15.311	2,227.1	1,875.8	1.000	20.060	2,827.1	2,687.4	1.000
	5	15.259	2,059.6	1,748.2	0.170	20.048	2,787.6	2,671.7	0.170
	6	6.028	748.5	550.3	4.119	5.928	620.9	485.8	4.119
	7	5.971	580.9	430.4	3.315	5.914	578.9	456.6	3.315
	8	5.971	580.9	430.4	3.315	5.914	578.9	456.6	3.315
	9	5.971	580.9	430.4	3.315	4.062	401.2	304.1*	5.269
	10	2.211	482.4	339.5	4.473	4.050	365.5	279.3*	4.475
	11	2.149	307.8	218.3	3.672	4.050	365.5	279.3*	4.475
	12	2.149	307.8	218.3	3.672	3.891	341.2	268.2*	1.565
	13	2.045	291.6	212.9	0.738	1.609	224.8	165.5*	5.620
	14	2.121	228.6	158.8	5.620	1.595	188.1	139.7*	4.828
	15	0.821	176.3	122.0	4.732	1.559	182.6	137.6*	3.315
	16	0.798	172.6	121.4	3.217	1.429	162.9	124.4*	1.929
	17	1.536	162.3	110.7*	6.752	0.349	99.7	71.7†	6.658
	18	0.216	95.3	64.8†	5.875	0.336	62.5	45.3†	5.875
	19	0.193	91.8	63.4†	4.379	0.298	56.9	41.9†	4.379
	20	0.686	79.5	55.4	3.815	0.165	36.7	27.4†	3.008
	21	0.192	27.9	18.6†	7.778	0.111	28.6	20.4†	7.391
	22	0.169	24.4	16.5†	6.311	0.111	28.6	20.4†	7.391

Min-Risk[1], Min-Risk[2]: The lowest risk test set that meets the WHO and FDA requirements, respectively.
Min-Cost[1], Min-Cost[2]: The lowest cost test set that meets the WHO and FDA requirements, respectively.
- *30%*: Partial (30%) fulfillment of the WHO requirements, 70% no testing.
*: The **RMP** or **WT-RMP** model generated test set that meets the WHO requirements.
†: The **RMP** or **WT-RMP** model generated test set that meets the WHO and FDA requirements.

Chapter 6

Differential Blood Screening

6.1 Introduction and Motivation

In this chapter, we now consider a "differential" testing extension to the problem studied in the previous chapters, in which an optimal solution is allowed to contain multiple test sets, each applied to a fraction of the total blood units. Such fractional strategies provide important flexibility, and as such, has the potential to further reduce the TTI risk over the "same-for-all" class of policies currently in use in the US. In particular, the decision-maker faces the problem of selecting a collection of test sets as well as determining the proportion (or fraction) of blood units each test set will be administered to. From a theoretical as well as a public policy perspective, the research objectives are to understand how the test sets under differential policies differ from those under the same-for-all policies; and how this flexibility impacts the TTI risk.

The remainder of the chapter is organized as follows. In Section 6.2, we introduce the notation and provide a mathematical formulation of the decision problem. In Section 6.3, we provide an equivalent mathematical programming formulation, which allows us to characterize important structural properties of an optimal differential testing scheme. These properties further allow us, in Section 6.4, to devise a simple greedy algorithm, which generates the set of optimal solutions for a range of budgets. However, the number of parameters that need to be calculated a priori for the greedy algorithm increases exponentially in the number of tests available in the market. Consequently, in Section 6.5, we further refine the greedy algorithm by utilizing the

optimal solution for the non-differential testing problem **(RMP)**. This significantly reduces the number of test sets to be considered (hence, the number of parameters to be calculated a priori) for the differential testing problem. We illustrate this in Section 6.6 through a case study. Finally, in Section 6.7, we provide our conclusions and suggest directions for future research.

6.2 The Problem Setting, Notation, and Assumptions

In this chapter, we consider a Blood Center collecting blood from donors. In the US, per requirements by the Food and Drug Administration (FDA), each blood donation must undergo screening for a set of TTIs. Similarly, the World Health Organization (WHO) recommends screening for a set of TTIs. It is often the case that a number of screening tests are available for each TTI. Each screening test provides binary results, with a "+" result indicating that the blood unit is infected, and a "–" result indicating otherwise. Tests do not have perfect efficacy, and may provide false positive or false negative results (e.g., Dow (2000); Johnson (1996); Moore et al. (2007); see also Chapter 4 for additional references). All selected tests need to be administered concurrently on the blood sample due to the long time requirements of the tests (including the transportation time to a testing laboratory), compared to the relatively shorter life-span of donated blood (Hillyer, 2001).

Given these requirements/recommendations and the variety of the tests available, it is the Blood Center's responsibility to decide *which* particular screening test(s) to administer for each TTI. Depending on the outcomes of the selected tests, the blood unit (i.e., all blood collected from the particular donor) will either be made available for transfusion or discarded. Consequently, the decision-maker faces the problem of selecting a collection of test tests, from a set of commercially available tests, as well as determining the proportion of blood units each test will be administered to detect a set of TTIs ("diseases") so as to minimize the overall TTI risk in blood transfusion. The TTI risk is the conditional probability that the blood unit classified as "infection-free" is, in fact, infected by some disease(s). The decision-maker is resource-constrained: We model this in the form of a *budget constraint* on the total test administration cost per unit blood. Then, in order to minimize the risk, the decision-maker needs to decide (i) which test set(s) to administer; (ii) what fraction of blood units each selected test set is to be administered to.

Consider a random unit of blood to be tested. We define the following events and parameters.

Events:

S	:	the set of tests to administer, where $S \subseteq \Omega$.
A^i+	:	the event that the random blood unit is infected by disease $i \in \Psi$ ($A^i- \equiv \overline{A^i+}$).
$T+(S_k)$	:	the event that test set S_k provides a positive result ($T-(S_k) \equiv \overline{T+(S_k)}$).

For notational convenience, we label all subsets of set Ω as $S_0, S_1, \ldots, S_k, \ldots, S_f$, where $f = 2^{|\Omega|} - 1$, $S_0 = \emptyset$, and $S_f = \Omega$, with $T-(S_0) =$ universal event and $T+(S_0) = \emptyset$.

Parameters:

$\Pr\{T-(S_k)\}$	:	the probability that test set S_k provides a negative result for a random blood unit, $k = 0, 1, \ldots, f$.
$\Pr\left\{\bigcap_{i\in\Psi} A^i-, T-(S_k)\right\}$	:	the probability that the random blood unit is not infected with any disease and that test set S_k provides a negative result, $k = 0, 1, \ldots, f$.

The decision variables in the differential testing problem comprise of proportions associated with each possible test set, which can be interpreted as the proportion of the blood units that will be screened with the particular test set.

Decision variables:

p_k : proportion of blood tested with test set S_k, $k = 0, 1, \ldots, f$.
Let $\vec{p} = (p_i)_{i=0,1,\ldots,f} = (p_0, p_1, \ldots, p_k, \ldots, p_f)$ denote the vector of proportions.

Next, we provide a mathematical representation of the decision problem, which determines the vector $\vec{p}$ so as to minimize the TTI risk. The TTI risk refers to the conditional probability that a randomly selected blood unit is infected, given that it is classified as infection-free by the selected test set. Then, the problem of minimizing risk under differential testing (equivalently, maximizing 1-risk) can be formulated as follows:

Differential Testing Risk Minimization Problem (DF-RMP):

$$Maximize_{\vec{p}} \ (1 - Risk) \ = \ \frac{\sum_{k=0}^{f} p_k \Pr\left\{\bigcap_{i\in\Psi} A^i-, T-(S_k)\right\}}{\sum_{k=0}^{f} p_k \Pr\{T-(S_k)\}} \tag{6.1}$$

$$\text{subject to} \quad \sum_{k=0}^{f} p_k \left(\sum_{j\in S_k} c_j\right) \leq B \tag{6.2}$$

$$\sum_{k=0}^{f} p_k = 1 \tag{6.3}$$

$$p_k \geq 0, k = 0, 1, \ldots, f.$$

Let $\vec{p^*}$ denote the optimal solution to **DF-RMP**. If $p_k^* > 0$, we say that test set S_k belongs to the optimal solution.

From the objective function of **DF-RMP**, (6.1), we observe that for any two test sets, S_{k_1} and S_{k_2}, if $\frac{\Pr\left\{\bigcap_{i\in\Psi} A^i-, T-(S_{k_1})\right\}}{\Pr\{T-(S_{k_1})\}} = \frac{\Pr\left\{\bigcap_{i\in\Psi} A^i-, T-(S_{k_2})\right\}}{\Pr\{T-(S_{k_2})\}}$ and $\sum_{j\in S_{k_1}} c_j = \sum_{j\in S_{k_2}} c_j$, then these test sets are interchangeable in the optimal solution to **DF-RMP**. Therefore, if either of these test sets is part of an optimal solution, then there exist multiple optimal solutions, which correspond to various combinations of sets S_{k_1} and S_{k_2}, yielding the same total proportion, $p_{k_1}^* + p_{k_2}^*$. While, in case of multiple optima it is possible to generate all of these optimal solutions, in what follows we assume that there exist no such identical test sets, so the optimal solution is unique (Assumption **(A3)**). We also assume that *Risk* is decreasing in the test set. This assumption holds for all FDA-approved tests, and is also without loss of generality, as discussed in Chapter 4. These two assumptions mainly serve to simplify the subsequent presentation of the structural properties of the optimal solution to **DF-RMP**.

Note the use of the objective function in (6.1), rather than the expression,

$$\sum_{k=0}^{f} p_k \Pr\left\{\bigcup_{i\in\Omega} A^i + |T-(S_k)\right\}.$$

This is because the expression in (6.1) is the one that corresponds to the TTI risk under the differential testing scheme, and we demonstrate this idea in the following example.

Example 7 *Consider a single infection, with N units of blood to be tested for this infection. Consider a differential testing scheme, given by $\vec{p} = (p_1, p_2)$, and let $N_1 \equiv N \times p_1$ and $N_2 \equiv N \times p_2$ respectively denote the number of blood units tested with sets S_1 and S_2. Figure 6.1 depicts the decision tree and the outcomes corresponding to this testing scheme.*

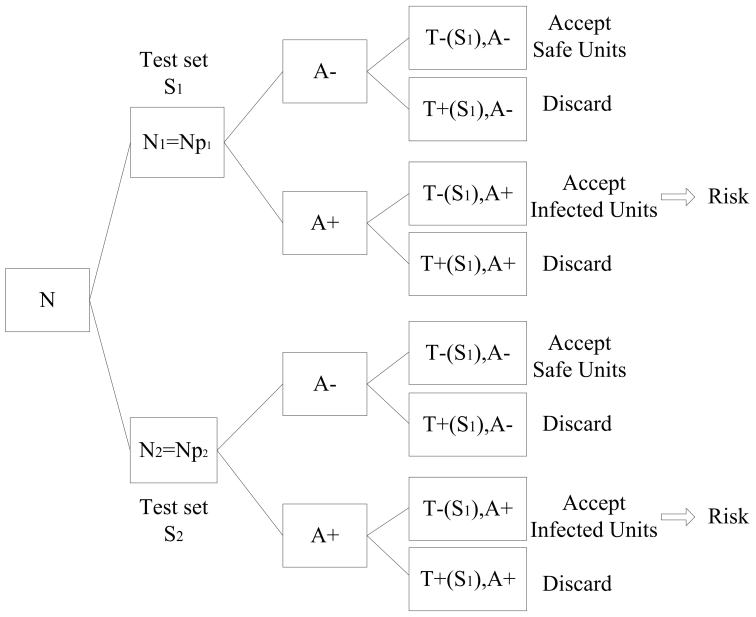

Figure 6.1: The Decision Tree Corresponding to the Differential Testing Scheme with Two Sets

Thus, the risk under this differential testing scheme is given by

$$\begin{aligned} Risk &= \frac{Np_1 \Pr(A+) \Pr(T-(S_1)|A+) + Np_2 \Pr(A+) \Pr(T-(S_2)|A+)}{\left\{ \begin{array}{l} Np_1 \Pr(A+) \Pr(T-(S_1)|A+) + Np_1 \Pr(A-) \Pr(T-(S_1)|A-) \\ +Np_2 \Pr(A+) \Pr(T-(S_2)|A+) + Np_2 \Pr(A-) \Pr(T-(S_2)|A-) \end{array} \right\}} \\ &= \frac{p_1 \Pr(T-(S_1), A+) + p_2 \Pr(T-(S_2), A+)}{p_1 \{\Pr(T-(S_1), A+) + \Pr(T-(S_1), A-)\} + p_2 \{\Pr(T-(S_2), A+) + \Pr(T-(S_2), A-)\}}. \end{aligned}$$

In general, for multiple diseases, the above expression can be written as:

$$Risk = \frac{\sum_{k=0}^{f} p_k \Pr\left\{\bigcup_{i\in\Psi} A^i+, T-(S_k)\right\}}{\sum_{k=0}^{f} p_k \Pr\{T-(S_k)\}},$$

which corresponds to the objective function in **DF-RMP**.

In the next section, we study an equivalent formulation of **DF-RMP**, which enables us to establish several important structural properties of an optimal solution to **DF-RMP**. These structural properties will allow us to construct an efficient algorithm that generates the optimal testing scheme under differential testing.

6.3 An Equivalent Formulation and Structural Properties

DF-RMP is a Linear Fractional Programming Problem (LFP). General Linear Fractional Programming Problems have been extensively studied in the literature, see Bajalinov (2003) for an overview. The most relevant result to our study is the Charnes & Cooper's Transformation (Charnes and Cooper, 1962), which allows any LFP with a bounded set of feasible solutions to be converted into a linear programming problem. Applying this transformation technique, **DF-RMP** can be equivalently formulated as follows (see Appendix D.1 for the derivation):

DF-RMP2 – Primal (DF-RMP2(P))

$$
\begin{aligned}
Maximize_{\vec{x}} \quad & \sum_{k=0}^{f} x_k \Pr\left\{\bigcap_{i\in\Psi} A^i-, T-(S_k)\right\} & \\
\text{subject to} \quad & \sum_{k=0}^{f} x_k \left(\sum_{j\in S_k} c_j - B\right) \le 0 & \leftarrow w_1 \\
& \sum_{k=0}^{f} x_k \Pr\{T-(S_k)\} = 1 & \leftarrow w_2 \\
& x_k \ge 0, k = 0, 1, \ldots, f, &
\end{aligned}
$$

where $x_k \equiv p_k t, k = 0, 1, \ldots, f$, and $t \equiv \frac{1}{\sum_{k=0}^{f} p_k \Pr\{T-(S_k)\}}$.

Observe that an optimal solution, $\overrightarrow{x}^*$, to **DF-RMP2(P)** uniquely determines an optimal solution, $\overrightarrow{p}^*$, to **DF-RMP**, where $p_k^* = \frac{x_k^*}{t}$, $k = 0, 1, \ldots, f$, and vice versa. That is, there is one-to-one correspondence between $\overrightarrow{x}^*$ and $\overrightarrow{p}^*$. Letting w_1 and w_2 denote the corresponding dual variables to **DF-RMP2(P)**, its dual problem can be formulated as follows:

DF-RMP2 – Dual (DF-RMP2(D))

$$
\begin{aligned}
& Minimize && w_2 & & \\
& \text{subject to} & & & & \\
w_2 \ge & \frac{\Pr\left\{\bigcap_{i\in\Psi} A^i-, T-(S_k)\right\}}{\Pr\{T-(S_k)\}} & + & \frac{\left(B - \sum_{j\in S_k} c_j\right)}{\Pr\{T-(S_k)\}} w_1, & \forall k \leftarrow x_k & \qquad (6.4) \\
& w_1 & \ge & 0 & & \\
& w_2 & & \text{unrestricted.} & &
\end{aligned}
$$

To simplify the notation, denote the intercept of Constraint (6.4) for k, $k = 0, 1, \ldots, f$, $\frac{\Pr\left\{\bigcap_{i\in\Psi} A^i-, T-(S_k)\right\}}{\Pr\{T-(S_k)\}}$, as $\overline{Risk}\,(S_k)$, which also equals to $1 - Risk(S_k)$ (see Chapter 4). From Problem **Dual**, we first make the following observations on the structure of

the optimal solution to the original Problem **DF-RMP** for some extreme cases of the problem. Although these observations are quite intuitive, we provide them for the sake of completeness.

Observations:

(i) If $B = 0$, then $p_0^*(0) = 1, p_k^*(0) = 0, \forall k \neq 0$ (from primal feasibility of **DF-RMP**).

(ii) If $B \geq \sum_{j \in \Omega} c_j$ ($\Leftrightarrow B \geq \sum_{j \in S_k} c_j, k = 0, 1, \ldots, f$), then the optimal solution to the dual problem is $w_1^* = 0$, $w_2^* = \max_{S_k, k=0,\ldots,f} \left\{ \overline{Risk}\left(S_k\right) \right\}$. Recall that $Q_j < 1, j \in \Omega$. Therefore, $p_f^* = 1$ (corresponding to set Ω) and $p_k^* = 0$, $\forall k \neq f$, similar to our results for the original **RMP** (see Chapter 4).

(iii) If $0 < B < \min_{j \in \Omega} c_j$ ($\Leftrightarrow 0 < B < \sum_{j \in S_k} c_j, k = 1, 2, \ldots, f$), then Constraint (6.4) for $k = 0$ becomes one of the binding constraints, as it is the only constraint having a positive coefficient of w_1. The other binding constraint is given by

$$\left\{ k : \arg\max_{S_k, k=1,\ldots,f} \frac{\overline{Risk}\left(S_k\right) - \overline{Risk}\left(S_0\right)}{B\left(\Pr\left\{T - \left(S_0\right)\right\}\right)^{-1} - \left(B - \sum_{j \in S_k} c_j\right)\left(\Pr\left\{T - \left(S_k\right)\right\}\right)^{-1}} \right\}.$$

For the general case, the following two propositions partially characterize the structure of the optimal solution to the original Problem **DF-RMP**.

Proposition 8 *If* $0 < B < \sum_{j \in \Omega} c_j$, *then Constraint (6.2) in* **DF-RMP** *is always binding in an optimal solution, that is,* $\sum_{k=0}^{f} p_k^* \left(\sum_{j \in S_k} c_j \right) = B$.

Proof. We prove the result by contradiction. Consider an optimal solution to **DF-RMP** given by $\vec{p^*}$, and suppose, to the contrary, that Constraint (6.2) is not

binding, that is, $\sum_{k=0}^{f} p_k^* \left(\sum_{j \in S_k} c_j \right) < B$. Multiplying each side of this inequality by t (> 0) and noting that $x_k^* = p_k^* t$, $k = 0, 1, \ldots, f$, by definition, we have that $\sum_{k=0}^{f} x_k^* \left(\sum_{j \in S_k} c_j - B \right) < 0$. Then, by complementary slackness conditions, $w_1^* = 0$. Since $\overline{Risk}\,(\Omega) > \overline{Risk}\,(S_k), \forall S_k \neq \Omega$ ($Q_j < 1, \forall j$), the feasible region of **DF-RMP2(D)** for w_2 becomes $w_2 \geq \overline{Risk}\,(\Omega)$. This, in turn, implies that $w_2^* = \overline{Risk}\,(\Omega) > \overline{Risk}\,(S_k), \forall S_k \neq \Omega$. Hence, complementary slackness conditions imply that $x_f^* \geq 0$ and $x_k^* = 0, \forall k \neq f$. Since $x_k^* = p_k^* t$ by definition and $t > 0$, the signs of p_k^* and x_k^* will be the same for $\forall k = 0, \ldots, f$. Therefore, the optimal solution to **DF-RMP** will be given by $p_f^* = 1$ and $p_k^* = 0, \forall k \neq f$ by (6.3). However, this implies that $\sum_{j \in \Omega} c_j < B$ from (6.2), which contradicts with the assumption that $0 < B < \sum_{j \in \Omega} c_j$. This completes the proof. □

Proposition 9 *Let $K^+ \equiv \{k : p_k^* > 0, k = 0, 1, \ldots, f\}$, that is, K^+ is the set of indices of all test sets for which $p_k^* > 0$ in an optimal solution. We have:*
(i) $|K^+| \leq 2$.
(ii) If $K^+ = \{k\}$, then $\sum_{j \in S_k} c_j = B$.
(iii) If $K^+ = \{k_1, k_2\}$, then it must be true that $B > \sum_{j \in S_{k_1}} c_j$ and $B < \sum_{j \in S_{k_2}} c_j$, or vice versa.

Proof. The proof of Part (i) follows because the number of basic variables in any basic feasible solution to Problem **DF-RMP2(P)** is two, and that the signs of p_k^* and x_k^* will be the same for $\forall k = 0, \ldots, f$. Therefore, the number of positive p_k^* in an optimal solution to **DF-RMP** is at most two. Part (ii) follows directly from Proposition 8. To prove Part (iii), by definition of set K^+ and from (6.3), we have $0 < p_{k_1}^* < 1$ and $p_{k_2}^* = 1 - p_{k_1}^* > 0$. By Proposition 8, we have $p_{k_1}^* \sum_{j \in S_{k_1}} c_j + p_{k_2}^* \sum_{j \in S_{k_2}} c_j = B$. Suppose that $\sum_{j \in S_{k_1}} c_j = \sum_{j \in S_{k_2}} c_j = B$. Then, by assumption, **(A3)**, we must have $\frac{\Pr\left\{ \bigcap_{i \in \Psi} A^i -, T - (S_{k_1}) \right\}}{\Pr\{T - (S_{k_1})\}} \neq \frac{\Pr\left\{ \bigcap_{i \in \Psi} A^i -, T - (S_{k_2}) \right\}}{\Pr\{T - (S_{k_2})\}}$. Without loss of generality, suppose $\frac{\Pr\left\{ \bigcap_{i \in \Psi} A^i -, T - (S_{k_1}) \right\}}{\Pr\{T - (S_{k_1})\}} < \frac{\Pr\left\{ \bigcap_{i \in \Psi} A^i -, T - (S_{k_2}) \right\}}{\Pr\{T - (S_{k_2})\}}$. Thus, from (6.1), the objective function value can be further increased by increasing p_{k_2} to 1 and decreasing p_{k_1} to 0, which contradicts with the fact that $K^+ = \{k_1, k_2\}$. Therefore, we must

have $B > \sum_{j \in S_{k_1}} c_j$ and $B < \sum_{j \in S_{k_2}} c_j$, or vice versa. This completes the proof. $\square$

Thus, the optimal solution to **DF-RMP** consists of at most two test sets, each with a fraction that sum to 1.

6.4 Optimal Algorithms to DF-RMP

We first note that **DF-RMP**, as an LFP, can be solved by a variation of the Simplex Method revised by Martos (1960, 1964). However, the Simplex Method provides an optimal solution at a given budget level, and the decision-maker needs to perform extensive sensitivity analysis to capture the optimal solutions and their corresponding risks for a range of budget levels, which is valuable information for public policy makers for allocating the blood screening budget. In addition, it is also important to provide the decision-maker with a "sense" of how the optimal testing scheme changes as the budget level varies. In this section, we study further structural properties of an optimal solution to **DF-RMP** to understand how the optimal solution changes with the budget. This analysis also provides us with a simple greedy algorithm that generates the optimal solution to **DF-RMP** for a range of budget levels, and that identifies all points of "switch" (in terms of budget levels) from a differential testing scheme (with two tests) to a single-testing scheme. Since differential testing scheme, even with two tests involved, might pose practical challenges as discussed in Section 6.1, such information is important for the decision-maker.

While we do not use Martos' Simplex Algorithm to solve the **DF-RMP**, we utilize the properties of LFPs derived in the literature to establish the optimality of our greedy algorithm. In particular, the following result, which extends the extreme point property of linear programming problems to LFPs, is critical for establishing the optimality of the greedy algorithm.

Lemma 2 *(Bajalinov (2003), Theorem 4.3) If the feasible set $\mathscr{S}$ in an LFP is bounded, then its objective function attains its maximal value over $\mathscr{S}$ in an extreme point of $\mathscr{S}$.*

Next we provide various properties that we use subsequently. The next result studies how the optimal solution to **DF-RMP** changes as the RHS of Constraint (6.2) (budget B) increases.

Corollary 3 *Consider an optimal solution to* **DF-RMP** *corresponding to a budget level B, with basic variables $p^*_{k_1}$ and $p^*_{k_2}$. If the budget increases from B to $B+\delta$, then the values of the current basic variables in the new optimal solution are given by $p^{*'}_{k_1} = p^*_{k_1} - \frac{1}{\sum_{j\in S_{k_2}} c_j - \sum_{j\in S_{k_1}} c_j}\delta$ and $p^{*'}_{k_2} = p^*_{k_2} + \frac{1}{\sum_{j\in S_{k_2}} c_j - \sum_{j\in S_{k_1}} c_j}\delta$.*

Proof. From the Simplex Method and Constraints (6.2)-(6.3), we have

$$\begin{pmatrix} p^*_{k_1} \\ p^*_{k_2} \end{pmatrix} = \begin{pmatrix} \sum_{j\in S_{k_1}} c_j & \sum_{j\in S_{k_2}} c_j \\ 1 & 1 \end{pmatrix}^{-1} \begin{pmatrix} B \\ 1 \end{pmatrix}.$$

When budget increases by δ, we have

$$\begin{aligned} \begin{pmatrix} p^{*'}_{k_1} \\ p^{*'}_{k_2} \end{pmatrix} &= \begin{pmatrix} \sum_{j\in S_{k_1}} c_j & \sum_{j\in S_{k_2}} c_j \\ 1 & 1 \end{pmatrix}^{-1} \begin{pmatrix} B+\delta \\ 1 \end{pmatrix} \\ &= \begin{pmatrix} \frac{1}{\sum_{j\in S_{k_1}} c_j - \sum_{j\in S_{k_2}} c_j} & -\frac{\sum_{j\in S_{k_2}} c_j}{\sum_{j\in S_{k_1}} c_j - \sum_{j\in S_{k_2}} c_j} \\ -\frac{1}{\sum_{j\in S_{k_1}} c_j - \sum_{j\in S_{k_2}} c_j} & \frac{\sum_{j\in S_{k_1}} c_j}{\sum_{j\in S_{k_1}} c_j - \sum_{j\in S_{k_2}} c_j} \end{pmatrix} \begin{pmatrix} B+\delta \\ 1 \end{pmatrix} \\ &= \begin{pmatrix} p^*_{k_1} - \frac{1}{\sum_{j\in S_{k_2}} c_j - \sum_{j\in S_{k_1}} c_j}\delta \\ p^*_{k_2} + \frac{1}{\sum_{j\in S_{k_2}} c_j - \sum_{j\in S_{k_1}} c_j}\delta \end{pmatrix}, \end{aligned}$$

and the result follows. □

Proposition 9 and Corollary 3 indicate important properties of an optimal solution to Problem **DF-RMP**, leading to the following results.

Corollary 4 *Suppose that an optimal solution to* **DF-RMP** *with budget B consists of two basic variables that are strictly positive, $p^*_{k_1} > 0$ and $p^*_{k_2} > 0$. Also suppose, without loss of generality, that $\sum_{j\in S_{k_2}} c_j > \sum_{j\in S_{k_1}} c_j$. Then, from Proposition 9, Corollary 3, and Constraint (6.3), we have that:*

(i) $p^*_{k_1} = \frac{\sum_{j\in S_{k_2}} c_j - B}{\sum_{j\in S_{k_2}} c_j - \sum_{j\in S_{k_1}} c_j}$ *and* $p^*_{k_2} = \frac{B - \sum_{j\in S_{k_1}} c_j}{\sum_{j\in S_{k_2}} c_j - \sum_{j\in S_{k_1}} c_j}$.

(ii) As the budget increases beyond B, $p^*_{k_1}$ will decrease, while $p^*_{k_2}$ will increase, up to a budget level $B' = \sum_{j \in S_{k_2}} c_j$, where $p^*_{k_1} = 0$ and $p^*_{k_2} = 1$.

(iii) As the budget further increases beyond B', the current basis $\{k_1, k_2\}$ will no longer be optimal. In particular, variable k_2 will leave the basis and a new variable will enter the optimal basis.

From Corollaries 3-4, we observe that there exist optimal solutions with $|K^+| = 1$, that is, $p^*_k = 1$ for some test set k at certain budget levels. We define these single-testing points as follows.

Definition 1 *A break point is the budget level, between 0 and $\sum_{j \in \Omega} c_j$, at which the optimal solution to* **DF-RMP** *is integral (that is, $|K^+| = 1$). We let $B_P(s), s \in Z^+$, denote the s^{th} break point and $k_P(s)$ denote the index of the optimal test set at $B_P(s)$. (By definition, at $B = B_P(s)$, $p^*_{k_P(s)} = 1$.)*

Observe that $B_P(1) = 0$, with $k_P(1) = 0$. That is, at budget level 0, the optimal solution is $p^*_0 = 1$, with no tests administered. We now provide a greedy algorithm that generates all break points for the range of budgets between 0 and $\sum_{j \in \Omega} c_j$.

THE GREEDY ALGORITHM FOR GENERATING BREAK POINTS

1: $s = 1$, $k_1(s) = 0$, $B(s) = 0$

2: **while** $B(s) < \sum_{j \in \Omega} c_j$ **do**

3: $$k_2 = \left\{ k : \arg\max_{S_k, k=1,\ldots,f: \sum_{j \in S_k} c_j > \sum_{j \in S_{k_1(s)}} c_j} \frac{\overline{Risk}(S_k) - \overline{Risk}\left(S_{k_1(s)}\right)}{\left(\sum_{j \in S_k} c_j - \sum_{j \in S_{k_1(s)}} c_j\right)(\Pr\{T - (S_k)\})^{-1}} \right\}$$

4: $s = s + 1$, $B(s) = \sum_{j \in S_{k_2}} c_j$, $k_1(s) = k_2$

5: **end while**

The following proposition guarantees that the greedy algorithm identifies every break point and its corresponding $k_1(s)$, which are critical for constructing the set of optimal solutions for **DF-RMP**.

Proposition 10 *$B(s)$ is a break point if and only if it is identified by the greedy algorithm.*

Proof. The proof follows by induction. The first break point trivially occurs at a budget level of 0, that is, $B(1) = B_P(1)$. Next, suppose that break point $B(s)$ is determined by the greedy algorithm, that is, $B_P(s) = B(s)$, with $k_P(s) = k_1(s)$. We need to prove that for the next break point, we have $B_P(s+1) = B(s+1)$ and $k_P(s+1) = k_1(s+1)$. By definition of a break point, which corresponds to an integral solution, and by Corollary 3, this is equivalent to proving that if $K^+ = \{k_1(s)\}$ when budget is $B(s)$, then, for any arbitrarily small $\delta > 0$, $K^+ = \{k_1(s), k_1(s+1)\}$ when budget is increased to $B(s) + \delta$.

Since $B(s)$ is a break point, $p^*_{k_1(s)}(B(s)) = 1, p^*_k(B(s)) = 0, \forall k \neq k_1(s)$. Suppose $K^+(B(s)+\delta) = \{k_1(s), k_2\}$ for some $k_2 \in \{0, 1, \ldots, f\} \mid \{k_1(s)\}$. From Corollary 3, if budget is increased to $B(s)+\delta$, then $p^*_{k_1(s)}(B(s)+\delta) = 1 - \frac{1}{\sum_{j\in S_{k_2}} c_j - \sum_{j\in S_{k_1(s)}} c_j}\delta$. Then, from Constraint (6.3), we must have $p^*_{k_2}(B(s)+\delta) = \frac{1}{\sum_{j\in S_{k_2}} c_j - \sum_{j\in S_{k_1(s)}} c_j}\delta$. Substituting this solution into (6.1), we obtain

$$\overline{R}(k_2,\delta) \equiv \frac{\Pr\left\{\bigcap_{i\in\Psi} A^i-, T-(S_{k_1(s)})\right\} - \frac{\Pr\left\{\bigcap_{i\in\Psi} A^i-, T-(S_{k_1(s)})\right\} - \Pr\left\{\bigcap_{i\in\Psi} A^i-, T-(S_{k_2})\right\}}{\sum_{j\in S_{k_2}} c_j - \sum_{j\in S_{k_1(s)}} c_j}\delta}{\Pr\left\{T-(S_{k_1(s)})\right\} - \frac{\Pr\left\{T-(S_{k_1(s)})\right\} - \Pr\left\{T-(S_{k_2})\right\}}{\sum_{j\in S_{k_2}} c_j - \sum_{j\in S_{k_1(s)}} c_j}\delta}.$$

From Corollary 4, test set $k \in \{0, 1, \ldots, f\}$ such that $\sum_{j\in S_k} c_j > \sum_{j\in S_{k_1(s)}} c_j$ that maximizes the first derivative of $\overline{R}(k,\delta)$ at $\delta = 0$ is the one that also maximizes the objective function in **DF-RMP**, (6.1), under budget $B + \delta$. Therefore, we have

$$k_2 = \left\{ k = 0, 1, \ldots, f \text{ and } \sum_{j\in S_k} c_j > \sum_{j\in S_{k_1(s)}} c_j : \arg\max \frac{\partial \overline{R}(k,\delta)}{\partial \delta}\Big|_{\delta=0} \right\}$$

$$\Leftrightarrow k_2 = k_1(s+1) = \left\{ k : \underset{S_k, k=1,\ldots,f: \sum_{j\in S_k} c_j > \sum_{j\in S_{k_1(s)}} c_j}{\arg\max} \frac{\overline{Risk}(S_k) - \overline{Risk}(S_{k_1(s)})}{\left(\sum_{j\in S_k} c_j - \sum_{j\in S_{k_1(s)}} c_j\right)\left(\Pr\left\{\bigcap_{j\in S_k} T_j^{d(j)}-\right\}\right)^{-1}} \right\}.$$

This completes the proof. □

The next result characterizes the optimal solution to **DF-RMP** at the non-break point budget levels. Denote the optimal solution to **DF-RMP** under budget B as $\overrightarrow{p}^*(B) = (p_i^*(B))_{i=0,1,\ldots,f}$.

Corollary 5 *The optimal solution to* **DF-RMP** *for a given budget level B, $B(s) < B < B(s+1)$, for some $s \in Z^+$, is given as follows.*

$$p^*_{k_1(s)}(B) = \frac{\sum\limits_{j \in S_{k_1(s+1)}} c_j - B}{\sum\limits_{j \in S_{k_1(s+1)}} c_j - \sum\limits_{j \in S_{k_1(s)}} c_j}, p^*_{k_1(s+1)}(B) = \frac{B - \sum\limits_{j \in S_{k_1(s)}} c_j}{\sum\limits_{j \in S_{k_1(s+1)}} c_j - \sum\limits_{j \in S_{k_1(s)}} c_j},$$

$$p^*_k(0) = 0, \forall k \neq k_1(s), k_1(s+1).$$

Proof. This result follows directly from Proposition 10 and Corollary 3. □

The following example illustrates how the duality theory can be used to interpret Proposition 10, providing an alternative explanation for it.

Example 8 *Consider four constraints in Problem* **DF-RMP2(D)** *when budget is $B(s)$, denoted as k_0, k_1, k_2, k_2', corresponding to primal variables $x_{k_0}, x_{k_1}, x_{k_2}, x_{k_2'}$, respectively, see Figure 6.3. Note that $\sum\limits_{j \in S_{k_0}} c_j < B(s) = \sum\limits_{j \in S_{k_1}} c_j$, $B(s) < \sum\limits_{j \in S_{k_2}} c_j$, and $B(s) < \sum\limits_{j \in S_{k_2'}} c_j$, following from the signs of slope $\frac{\left(B(s) - \sum\limits_{j \in S_k} c_j\right)}{\Pr\left\{\bigcap\limits_{j \in S_k} T_j^{d(j)} -\right\}}$ in (6.4). The arrows in Figure 6.3 indicate the feasible region. When budget is $B(s)$, we know that $K^+ = \{k_1\}$, and the (multiple) optimal solutions of Problem* **Dual** *lie on the line between points Y and Z, see Figure 6.3 (a).*

As the budget increases to $B(s) + \delta$, the slope of constraint k_1, $\frac{\left(B(s)+\delta - \sum\limits_{j \in S_{k_1}} c_j\right)}{\Pr\left\{\bigcap\limits_{j \in S_{k_1}} T_j^{d(j)} -\right\}}$, becomes positive. Hence, the new optimal solution to Problem **Dual** *becomes point Y', see Figure 6.3 (b), and the primal solution becomes $K^+ = \{k_1, k_2\}$, as the intersection of constraints k_2 and k_1 corresponds to the largest value of w_1 than the intersection*

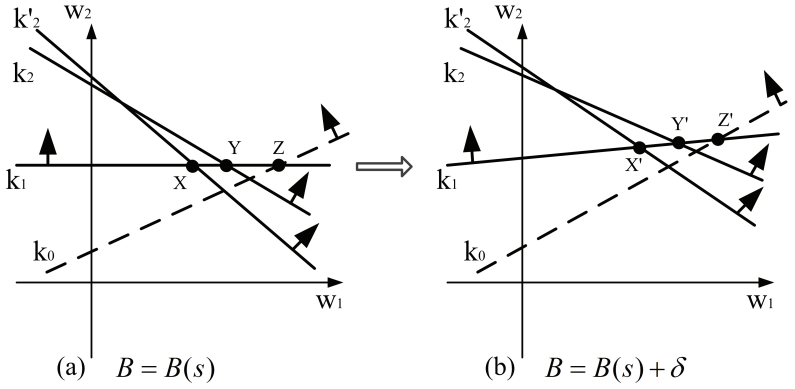

Figure 6.2: An Illustration of Proposition 10

of constraint k_1 *with any other constraint* k *satisfying* $\sum_{j \in S_k} c_j < \sum_{j \in S_{k_2}} c_j$. *Observe that the value of* w_1 *at the intersection of constraints* k *and* k_1 *is given by*

$$w_1(k) \equiv \frac{\overline{Risk}\,(S_k) - \overline{Risk}\,(S_{k_1})}{\left(\sum_{j \in S_k} c_j - \sum_{j \in S_{k_1}} c_j\right)\left(\Pr\left\{\bigcap_{j \in S_k} T_j^{d(j)} -\right\}\right)^{-1}}.$$

Therefore, $k_2 = \{k : \arg\max w_1(k)\}$, *which is in line with Proposition 10.*

The greedy algorithm provides a highly efficient way to generate a set of optimal solutions to **DF-RMP** for a range of budget levels. However, both Martos' Simplex Algorithm (for general LFPs) and the greedy algorithm proposed here for our specific LFP requires all parameters in the objective function, $\Pr\left\{\bigcap_{i \in \Psi} A^i -, T - (S_k)\right\}$ and $\Pr\{T - (S_k)\}$, to be calculated a priori, one for each potential test set. However, for n tests, there are 2^n test subsets, leading to an exponential increase in the number of parameters to be determined as the problem size increases. Since in reality there will be a large number of tests available in the market (e.g., currently there are around 40 FDA-approved blood screening tests in the US), such an approach may not be practical. Consequently, in the following section, we further refine the greedy algorithm by utilizing the solution to the non-differential testing problem **(RMP)**.

6.5 Relationship between Problems RMP and DF-RMP

Parameters in **DF-RMP**, $\Pr\left\{\bigcap_{i\in\Psi} A^i-, T-(S_k)\right\}$ and $\Pr\{T-(S_k)\}$, are often not readily available in the medical literature, which reports tests in terms of their specificity and sensitivity, defined as follows. Let $d(j)$ denote the disease test j applies to, $j \in \Omega$.

Test Efficacy Parameters:

$\Pr(T_j^{d(j)}- \mid A^{d(j)}-)$	:	specificity (true negative probability) of test $j \in \Omega$.
$\Pr(T_j^{d(j)}+ \mid A^{d(j)}+)$	:	sensitivity (true positive probability) of test $j \in \Omega$.
Q_j	=	$\Pr(T_j^{d(j)}- \mid A^{d(j)}+)/\Pr(T_j^{d(j)}- \mid A^{d(j)}-)$, $j \in \Omega$. In this chapter, we assume, without loss of generality, that all tests have $Q_j < 1, \forall j \in \Omega$.

Thus, the first step is to relate our parameters in **DF-RMP** to the test efficacy parameters readily available in the medical literature. For this, we utilize the following two assumptions, common in the medical literature (see, for instance, Pepe 2004)[1] and also used in Chapter 4 for the study of the non-differential testing problem **(RMP)**.
Let $\overrightarrow{\Lambda} = (\Lambda_i)_{i=1,\cdots,n}$ denote the disease prevalence vector for a random unit of blood, consisting of binary elements, with a "1" in the i^{th} place indicating that the blood unit is *infected* with disease $i \in \Psi$, and a "0" indicating otherwise. Thus, the sample space of $\overrightarrow{\Lambda}$, which we denote by $\mathscr{S}(\overrightarrow{\Lambda})$, contains 2^n vectors, which collectively represent all prevalence possibilities for n diseases. We denote the joint probability mass function of the random vector $\overrightarrow{\Lambda}$ by $p_{\overrightarrow{\Lambda}}(\overrightarrow{\lambda}) \equiv Pr(\overrightarrow{\Lambda} = \overrightarrow{\lambda})$, for $\overrightarrow{\lambda} \in \mathscr{S}(\overrightarrow{\Lambda})$.

Assumptions:

(A1) The outcome of test j for disease $d(j)$ depends only on the prevalence of disease $d(j)$ in the blood unit, and not on the prevalence of the other diseases in the

[1]For detailed discussions on the validity and impact of assumptions, see Section 4.2.1 in Chapter 4.

disease set, that is, for $j \in \Omega$,

$$Pr(T_j^{d(j)}\ x \mid \overrightarrow{\Lambda}) = Pr(T_j^{d(j)}\ x \mid \Lambda_{d(j)}),\ \text{for } x \in \{+,-\}.$$

(A2) Test outcomes are conditionally and jointly independent given the prevalence vector, that is, for any test $j_1 \in \Omega$ and $S' \subseteq \Omega \backslash \{j_1\}$,

$$Pr(T_{j_1}^{d(j_1)}\ x \mid \overrightarrow{\Lambda}, T_j^{d(j)}\ y, \forall j \in S') = Pr(T_{j1}^{d(j_1)}\ x \mid \overrightarrow{\Lambda}),\ \text{for } x, y \in \{+,-\}.$$

To reiterate, these assumptions are not needed for the main results in this chapter to hold. We mainly use them to calculate the parameters needed in the optimization model from data widely available in the medical literature. Further, the optimal solutions obtained for Problem **RMP** in Chapter 4 rely on these assumptions, which we use to generate the optimal solution under differential testing.

In practice, the decision-maker also needs to adopt a "decision rule," which prescribes *when* to classify the blood unit as "infection-free" for a particular disease versus "infected," when the selected test set contains multiple tests for the same disease. However, the decision rule was not discussed in this chapter, as it only impacts the parameter calculations in **DF-RMP**, and not the problem structure. The "Believe the Positive (BP)" rule, which classifies the blood unit as infected if at least one test outcome in the battery is "+", is a commonly adopted decision rule in blood screening due to its conservative nature for the non-differential testing problem. The BP rule is proven to be optimal (in Chapter 4) for minimizing the TTI risk, which is also the objective in the context of this chapter. Therefore, in this chapter, we adopt the BP rule to calculate the parameters needed for the optimization model. Recall, from Chapter 4, that **RMP** under BP rule is defined as follows.

Risk-based Minimization Problem **(RMP)**:

$$\text{Maximize}_{S\in\Omega} 1 - \Pr\left(\bigcap_{i\in\Psi} A^i- \mid \bigcap_{j\in S} T_j^{d(j)}-\right)$$

$$\text{subject to } \sum_{j\in S} c_j \leq B.$$

Observe that **RMP** is equivalent to **DF-RMP**, with p_k restricted to binary, $k = 0, 1, \ldots, f$. Hence, **RMP** provides an upper bound on the optimal risk (equivalently, a lower bound on the optimal objective function value) to **DF-RMP**.

Remark 5 *Under Assumptions* **(A2)** *and* **(A3)** *and the BP rule, we have the following expressions (see Chapter 4 for the derivations):*

- $T-(S) = \bigcap\limits_{j\in S} T_j^{d(j)}-$ *(by the BP rule).*
- $\Pr\left(\bigcap\limits_{i\in\Psi} A^i- \mid \bigcap\limits_{j\in S} T_j^{d(j)}-\right) = \dfrac{\Pr\left(\bigcap\limits_{i\in\Psi} A^i-, \bigcap\limits_{j\in S} T_j^{d(j)}-\right)}{\Pr\left(\bigcap\limits_{j\in S} T_j^{d(j)}-\right)}$ *(by Bayes' Theorem).*
- $\Pr\left(\bigcap\limits_{i\in\Psi} A^i-, \bigcap\limits_{j\in S} T_j^{d(j)}-\right) = \Pr\left(\bigcap\limits_{i\in\Psi} A^i-\right) \prod\limits_{j\in S} \Pr\left(T_j^{d(j)} - \mid A^{d(j)}-\right).$
- $\Pr\left(\bigcap\limits_{j\in S} T_j^{d(j)}-\right) = \sum\limits_{\overrightarrow{\lambda}\in\mathscr{S}\left(\overrightarrow{\Lambda}\right)} \left\{\Pr\left(\overrightarrow{\Lambda} = \overrightarrow{\lambda}\right) \prod\limits_{j\in S} \Pr\left(T_j^{d(j)} - \mid \overrightarrow{\Lambda} = \overrightarrow{\lambda}\right)\right\}$

Corollary 6 *Suppose the optimal test set for* **DF-RMP** *under budget B is $S_{k_1}^*$, that is, $K^+ = \{k_1\}$. Then, the optimal test set for* **RMP** *is also $S_{k_1}^*$.*

Proof. Follows directly from the fact that **RMP** is equivalent to **DF-RMP**, with binary restrictions on variables p_k, $k = 0, 1, \ldots, f$. □

Let $DF(B)$ and $NDF(B)$ respectively denote the indices of all test sets that are part of an optimal solution to **DF-RMP** and **RMP** for any budget level in $[0, B]$. Then, from Proposition 10, $DF(B) = \{k_P(s), s \in Z^+\}$.

Proposition 11 *For any budget range $[0, B]$, we have that $DF(B) \subseteq NDF(B)$.*

Proof. Follows directly from Corollary 6.

As discussed above, **DF-RMP** utilizes $2^{|\Omega|}$ decision variables, each of which requires two objective function coefficients to be calculated a priori. Proposition 11 indicates that a portion of these decision variables can be eliminated without loss of optimality. Our numerical study in the next section suggests that Proposition 11 can be very powerful, and leads to a significant reduction of decision variables in **DF-RMP**.

6.6 A Numerical Study - The Sub-Saharan Africa Case

Here we use sub-Saharan Africa case study first introduced in Chapter 4 to demonstrate our models and analysis. The TTIs included in this study are HIV, HBV, HCV, HTLV, and WNV. These include the major diseases recommended for screening by the WHO (WHO, 2011) and/or the FDA (FDA, 2011) except for Syphilis and Chagas' Disease, which are omitted from the case study due to a lack of data. The HIV prevalence in sub-Saharan Africa varies, by country, from 2% to 26% (UNAIDS, 2008); we use 15% in this study. HBV, HCV, and HTLV prevalence rates for this region are estimated at 10%, 3%, and 3%, respectively (Kiire, 1996; Madhava et al., 2002; Proietti et al., 2005). Prevalence rates are difficult to estimate for the WNV, as most WNV infections occur in the form of outbreaks (Mostashari et al., 2001); we use 1% as an approximation for the prevalence rate, based on a study of WNV antibodies (Petersen, 2009). The HIV-infected population has a co-infection rate for HBV and HCV of 10% and 15%, respectively (Carmo et al., 2000; Lincoln et al., 2003), while the HCV-infected population has a co-infection rate for HBV of 10%, which is within the worldwide range of 9%-30% (see Adewole et al., 2009; Christian et al., 2010; Forbi et al., 2007; Gordona and Sherman, 2009; Otegbayo et al., 2008; Soriano et al., 2006). We ignore the triple co-infection rate of HIV-HBV-HCV. To screen for these TTIs, we can select from 33 FDA-approved tests, whose efficacy and unit administration cost data are available (FDA, 2010; Jackson et al., 2003), see Table 6.1.

In the following, we discuss the findings from this case study. The results of our other numerical studies are similar.

6.6.1 Effectiveness of CR Heuristics for Problem RMP

By Proposition 11 and Corollary 6, we can find the optimal solutions under varying budget level B for **DF-RMP** by considering only the optimal test sets under budget level 0-B for **RMP**. However, **RMP**, first introduced in Chapter 4 remains to be a very difficult problem to solve to optimality. Chapter 4 proposed a highly effective heuristic, **CR** Heuristic, to give near-optimal test sets. The effectiveness of **CR** Heuristic in terms of deviation in objective function values are investigated in the numerical studies in Chapter 4.

Table 6.1: Efficacies and administration costs for FDA-approved blood screening tests

TTI	Test	Specificity	Sensitivity	Q_j	Cost($)	TTI	Test	Specificity	Sensitivity	Q_j	Cost($)
HBV	1	0.9839	0.9900	0.0102	3	HIV	17	0.9940	0.9970	0.0030	17
	2	0.9982	0.9600	0.0401	3		18	0.9983	0.9915	0.0085	5
	3	0.9980	0.9970	0.0030	4		19	0.9983	0.9984	0.0016	5
	4	0.9685	0.9882	0.0122	2		20	0.9977	0.9976	0.0024	5
	5	0.9380	0.8810	0.1269	5		21	0.9978	0.9972	0.0028	5
	6	0.9940	0.9810	0.0191	8		22	0.9960	0.9820	0.0181	4
HIV	7	0.9960	0.9970	0.0030	5	HCV	23	0.9979	0.6330	0.3678	4
	8	0.9790	0.9400	0.0613	15		24	0.9880	0.9640	0.0364	3
	9	0.9080	0.8560	0.1586	10		25	0.9984	0.9949	0.0051	5
	10	1.0000	0.8050	0.1950	13		26	1.0000	0.6330	0.3670	10
	11	0.9640	0.6530	0.3600	8		27	0.9380	0.8560	0.1535	15
	12	0.9930	0.9670	0.0332	18		28	0.9967	0.9900	0.0100	18
	13	0.9991	0.9975	0.0025	5		29	0.9730	0.9910	0.0092	16
	14	0.9880	0.9920	0.0081	4	WNV	30	0.9986	0.8690	0.1312	5
	15	0.9900	0.9950	0.0051	4		31	0.9890	0.9860	0.0142	4
	16	0.9967	0.9900	0.0100	18	HTLV	32	0.9963	0.9976	0.0024	4
							33	0.9989	0.9948	0.0052	5

Therefore, in this section of our numerical studies, we further study the difference in test sets by solving **RMP** for small problem instances through complete enumeration, and comparing its optimal solution with the solution given by **CR** Heuristic. In particular, we consider only a subset of the tests[2] in Table 6.1 under a range of budgets ($5-30) for each of sub-Saharan Africa and Ghana.

We find that the optimal test sets generated by **RMP** and test sets given by **CR** Heuristic are exactly the same in *all* 52 scenarios considered (in both the sub-Saharan Africa and Ghana case studies). This suggests that **CR** Heuristic provides a very good approximation for the optimal test sets in **RMP**. Consequently, we consider the test sets generated by **CR** Heuristic as the optimal test sets for **RMP** in our realistic-sized problems in the remainder of this section.

6.6.2 The Differential Testing Scheme versus Current Practice

In this section, we consider only the test sets generated by **CR** Heuristic for **RMP** (given as "Non-Differential Testing" in Table 6.3) to find the optimal solution under

[2]The subset of the tests we consider are very cost-effective, and are often the ones selected by **RMP** and **WT-RMP**. Specifically, we consider ten tests, with two tests per disease: Tests 1,3 for HBV, 13,19 for HIV, 24,25 for HCV, 30,31 for WNV, and 32,33 for HTLV.

differential testing scheme in **DF-RMP**. By greedy algorithm and Corollary 5, we can find the optimal solutions for "Differential Testing" scheme, given in Table 6.3. In addition, we provide the results of the current practice, including the test sets and corresponding risks, in Table 6.2.

Table 6.2: Results for WHO/FDA-compliant Test Sets and Partial Fulfilment of Guidelines

	Guidelines							*30% Testing*†	
	HBV	HIV	HCV	WNV	HTLV	Risk (%)	Cost ($)	Risk (%)	Cost ($)
Min-Risk[1]	3	19	25			5.316	14	22.406	4.2
Min-Cost[1]	4	15	24			5.476	9	22.639	2.7
Min-Risk[2]	3	19	25	31	32	0.092	22	21.473	6.6
Min-Cost[2]	4	15	24	30	32	0.474	17	21.897	5.1

Min-Risk[1], Min-Risk[2]: The lowest risk test set that meets the WHO and FDA requirements, respectively.
Min-Cost[1], Min-Cost[2]: The lowest cost test set that meets the WHO and FDA requirements, respectively.
†: Partial (30%) fulfillment of the WHO/FDA requirements, 70% no testing. The cost of *30% Testing* is 30% of the cost to follow its corresponding guidelines.

Table 6.2 shows the selected test sets when different guideline enforced and its resultant risk and cost. In 30% Testing column, we present the resultant risk of the partial fulfillment of WHO or FDA requirements, with fractional solutions denoted as $p_0 = 0.7, p_S = 0.3$, where S is the scenario of the guidelines enforced. Note that *30% Testing* scheme costs only 30% of the complete fulfillment of the guidelines. Table 6.3 report the test sets obtained by **CR** Heuristic in **RMP**, optimal solutions allowing differential testing by solving **DF-RMP**, and their resultant risks and costs. In Table 6.3, the costs of the test sets generated by non-differential testing scheme are the same as the budget level in this case study, except a few cases when $B = 1, 46, 50$. Meanwhile, the budget constraint is always binding in differential testing scheme, see Proposition 8.

From the greedy algorithm, we know that the optimal solution in **DF-RMP** is determined by the risk reduction per dollar, while $Q_j, j \in \Omega$ of a test and the prevalence of its corresponding infection determines risk reduction. Take $B = 2$ in Table 6.3 as an example in this case study. Although HIV is the most prevalent disease in this case study and #15 is a very cost-effective test for HIV that are often chosen in **RMP**, **DF-RMP** chooses an integral solution of implementing Test #4 for HBV as oppose to a partial fulfillment of Test #15. The reason is clear when we consider the risk reduction per dollar by each of these two tests. From Table 6.3, Test #4 yields $\frac{27.950\%-20.053\%}{2} = 3.95\%$ per dollar, while Test #15 yields only $\frac{27.950\%-15.311\%}{4} = 3.16\%$. This important relationship expands to the case of test set with multiple tests and is formulated in the greedy algorithm proposed in

Table 6.3: The Optimal Solutions Given by Differential and Non-differential Testing Scheme under Varying Budget Allocations

	RMP (Non-Differential)							**DF-RMP** (Differential)	
Budget($)	S^*	HBV	HIV	HCV	WNV	HTLV	Risk (%)	$\overrightarrow{p}^*$	Risk (%)
0	S_0						27.950	$p_0^* = 1$	27.950
1	S_0						27.950	$p_0^* = 0.50, p_1^* = 0.50$	24.269
2	S_1	4					20.053	$p_1^* = 1$	20.053
3	S_2	1					20.035	$p_1^* = 0.75, p_5^* = 0.25$	16.978
4	S_3		15				15.311	$p_1^* = 0.50, p_5^* = 0.50$	13.641
5	S_4		19				15.259	$p_1^* = 0.25, p_5^* = 0.75$	10.005
6	S_5	4	15				6.028	$p_5^* = 1$	6.028
7	S_6	4	19				5.971	$p_5^* = 0.75, p_9^* = 0.25$	5.105
8	S_7	3	15				5.932	$p_5^* = 0.50, p_9^* = 0.50$	4.161
9	S_8	4	15	24			5.476	$p_5^* = 0.25, p_9^* = 0.75$	3.197
10	S_9	4	15			32	2.211	$p_9^* = 1$	2.211
11	S_{10}	4	19			32	2.149	$p_9^* = 0.75, p_{13}^* = 0.25$	1.886
12	S_{11}	3	15			32	2.107	$p_9^* = 0.50, p_{13}^* = 0.50$	1.556
13	S_{12}	4	15	24		32	1.613	$p_9^* = 0.25, p_{13}^* = 0.75$	1.223
14	S_{13}	4	15		31	32	0.885	$p_{13}^* = 1$	0.885
15	S_{14}	4	19		31	32	0.821	$p_{13}^* = 0.67, p_{16}^* = 0.33$	0.682
16	S_{15}	3	15		31	32	0.778	$p_{13}^* = 0.33, p_{16}^* = 0.67$	0.478
17	S_{16}	4	15	24	31	32	0.270	$p_{16}^* = 1$	0.270
18	S_{17}	4	19	24	31	32	0.216	$p_{17}^* = 1$	0.216
19	S_{18}	3	15	24	31	32	0.166	$p_{17}^* = 0.50, p_{19}^* = 0.50$	0.163
20	S_{19}	3	19	24	31	32	0.112	$p_{19}^* = 1$	0.112
21	S_{20}	1,4	19	24	31	32	0.079	$p_{20}^* = 1$	0.079
22	S_{21}	3,4	19	24	31	32	0.078	$p_{20}^* = 0.50, p_{22}^* = 0.50$	0.069
23	S_{22}	1,4	19	25	31	32	0.059	$p_{22}^* = 1$	0.059
24	S_{23}	1,4	14,15	24	31	32	0.054	$p_{22}^* = 0.67, p_{25}^* = 0.33$	0.051
25	S_{24}	3,4	14,15	24	31	32	0.053	$p_{22}^* = 0.33, p_{25}^* = 0.67$	0.043
26	S_{25}	1,4	14,15	25	31	32	0.035	$p_{25}^* = 1$	0.035
27	S_{26}	3,4	14,15	25	31	32	0.034	$p_{25}^* = 0.80, p_{30}^* = 0.20$	0.031
28	S_{27}	3,4	15,19	25	31	32	0.033	$p_{25}^* = 0.60, p_{30}^* = 0.40$	0.028
29	S_{28}	1,4	14,15	24,25	31	32	0.032	$p_{25}^* = 0.40, p_{30}^* = 0.60$	0.025
30	S_{29}	3,4	14,15	24,25	31	32	0.031	$p_{25}^* = 0.20, p_{30}^* = 0.80$	0.021
31	S_{30}	1,4	14,15	25	30,31	32	0.018	$p_{30}^* = 1$	0.018
32	S_{31}	3,4	14,15	25	30,31	32	0.017	$p_{30}^* = 0.80, p_{35}^* = 0.20$	0.016
33	S_{32}	3,4	15,19	25	30,31	32	0.016	$p_{30}^* = 0.60, p_{35}^* = 0.40$	0.014
34	S_{33}	1,4	14,15	24,25	30,31	32	0.015	$p_{30}^* = 0.40, p_{35}^* = 0.60$	0.012
35	S_{34}	3,4	14,15	24,25	30,31	32	0.014	$p_{30}^* = 0.20, p_{35}^* = 0.80$	0.010
36	S_{35}	1,4	14,15	25	30,31	32,33	0.008	$p_{35}^* = 1$	0.008
37	S_{36}	3,4	14,15	25	30,31	32,33	0.007	$p_{35}^* = 0.67, p_{38}^* = 0.33$	0.007
38	S_{37}	3,4	15,19	25	30,31	32,33	0.006	$p_{35}^* = 0.33, p_{38}^* = 0.67$	0.006
39	S_{38}	1,4	14,15	24,25	30,31	32,33	0.005	$p_{38}^* = 1$	0.005
40	S_{39}	3,4	14,15	24,25	30,31	32,33	0.004	$p_{39}^* = 1$	0.004
41	S_{40}	3,4	15,19	24,25	30,31	32,33	0.003	$p_{40}^* = 1$	0.003
42	S_{41}	1,3	15,19	24,25	30,31	32,33	0.003	$p_{40}^* = 0.50, p_{42}^* = 0.50$	0.003
43	S_{42}	1,2,4	15,19	24,25	30,31	32,33	0.003	$p_{42}^* = 1$	0.003
44	S_{43}	1,2,4	13,19	24,25	30,31	32,33	0.003	$p_{43}^* = 1$	0.003
45	S_{44}	1,3,4	13,19	24,25	30,31	32,33	0.003	$p_{44}^* = 1$	0.003
46	S_{44}	1,3,4	13,19	24,25	30,31	32,33	0.003	$p_{44}^* = 0.67, p_{46}^* = 0.33$	0.003
47	S_{45}	1,2,4	14,15,19	24,25	30,31	32,33	0.003	$p_{44}^* = 0.33, p_{46}^* = 0.67$	0.003
48	S_{46}	1,3,4	14,15,19	24,25	30,31	32,33	0.003	$p_{46}^* = 1$	0.003
49	S_{47}	1,3,4	13,19	23,24,25	30,31	32,33	0.003	$p_{47}^* = 1$	0.003
50	S_{47}	1,3,4	13,19	23,24,25	30,31	32,33	0.003	$p_{47}^* = 0.50, p_{48}^* = 0.50$	0.003
51	S_{48}	1,2,4	14,15,19	23,24,25	30,31	32,33	0.003	$p_{48}^* = 1$	0.003

Section 6.3.

We first observe that test sets obtained from **RMP** in Non-Differential Testing would

achieve significant reduction in risk by comparing the risk between Guidelines and **RMP** at the same budget level. The policy implication of this deviation is detailed in Chapter 5. In addition, by comparing the test sets and solutions of **RMP** and **DF-RMP**, we find that the solution given in these two models are the same at certain budget levels, $B = 0, 2, 6, 10, 14, \ldots$, which are highlighted in gray in Table 6.3. However, on the budget levels in between, $B = 1, 3, 4, 5, 7, 8, 9, \ldots$, **DF-RMP** adopts fractional solutions and thus achieves significant risk reduction at these budget levels, see also Figure 6.3. In most cases of this case study, where **DF-RMP** has a lower resultant risk, the budget constraint of **RMP** is binding in the optimal test set, e.g., $B = 3, 4, 5, 7, 8, \ldots$. For these cases, the risk reductions are achieved by allowing fractional solutions in **DF-RMP**. In a few cases where the budget constraint of **RMP** is not binding, that is, $B = 1, 46, 50$, the extra dollar per unit of the solutions obtained in **DF-RMP** also contributes the risk reduction. For example, there does not exist feasible solution in **RMP** when $B = 1$, while **DF-RMP** gives fractional results where budget constraint is still binding.

It is also interesting to compare the existing scheme in sub-Saharan Africa, in which only around 30% of the blood donations undergo regular testing (see the *30% Testing* scheme for the WHO-compliant Min-Risk and Min-Cost in Table 6.2). We approximate the cost of *30% Testing* to be 30% of the cost to follow the complete guidelines. For example, to follow the WHO guidelines of the Min-Risk scheme would cost \$14 with the resultant risk to be 5.316%. In this case, *30% Testing* would incur a cost of $0.3 \times \$14 = \$4.2$ and risk of 22.406%. At this budget level, **RMP** model is able to reduce the risk to 15.311%. Furthermore, **DF-RMP** model with differential testing, if implemented, is able to further reduce the risk to 12.939%[3]. Similar reduction in risk with different enforced guideline is observed by allowing differential testing, especially when the budget level is low, see Figure 6.3.

6.7 Conclusions and Future Directions

In this chapter, we continue the path of the constructed risk optimization model and consider a differential testing scheme to the problem of risk minimization, in which an optimal solution is allowed to contain multiple test sets, each applied to a fraction of the total blood units. We formulate the differential testing problem of risk minimization under budget constraint and propose the equivalent formulations of the problem. In addition, we discuss the structural properties of the formulated

[3]Optimal solution of **DF-RMP** is calculated to be $p_1^* = \frac{6-4.2}{6-2} = 0.45, p_5^* = \frac{4.2-2}{6-2} = 0.55$

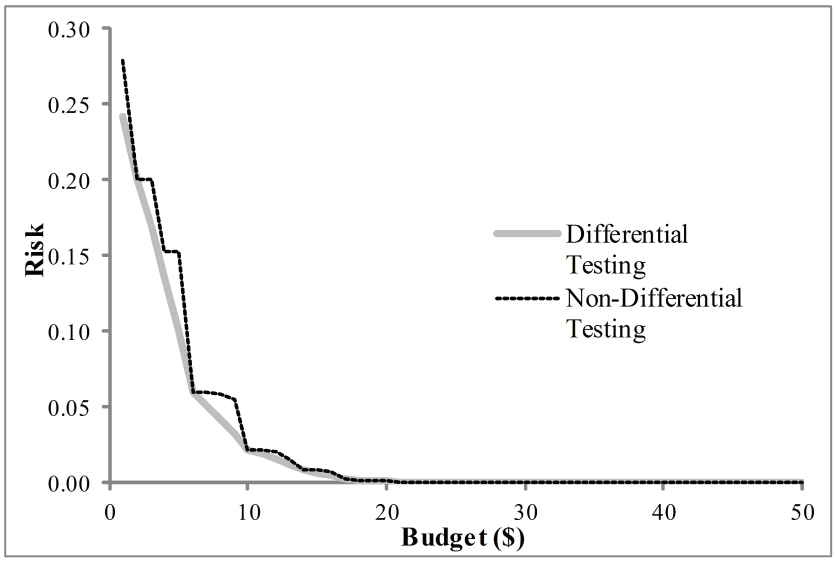

Figure 6.3: Differential Testing Scheme versus Non-Differential Testing Scheme (Budget B in $\$1 - 50$)

problem, based upon which we propose a simple greedy algorithm and prove that it is capable of finding the optimal solutions to the differential testing problem for a range of budget levels. We provide a numerical study on the effectiveness of the proposed algorithm and the results of both the optimization approach and current practice in sub-Saharan Africa. The numerical results show that flexibility in policy implementation by allowing a differential testing scheme further reduce risk over the "same-for-all" policy, which is currently in use in the US. The results also provide important policy implications on the implementation of blood screening schemes.

Several variations and extensions of this work are worthy of future research. An important direction is to incorporate the waste consideration (i.e., fraction of blood units that are falsely rejected) into the model for differential testing. Waste has been added to the non-differential testing as a constraint in Chapter 5. As another important measure for the performance of test set, waste will have a significant impact on both the solution methodology and the optimal solutions. Another important direction is to consider other important measures, such as weighted risk that considered in Chapter 5. It is important to understand how the algorithms and the resulting optimal solutions change when the social cost aspect is considered.

Chapter 7

Mortality Associated with Hip and Knee Replacement Volumes in Elderly Patients

7.1 Introduction

Both hospital and surgeon procedure volumes have been associated with lower rates of mortality and complications for several surgical procedures. (Dudley et al., 2000; Hannan et al., 1989, 1995, 1997, 1998; Jollis et al., 1997) This 'volume-outcome relationship' has also been investigated in joint replacement surgery. (Browne et al., 2009; Katz et al., 2001) The results for hospital volume and outcome in joint replacement appear to be inconsistent and inconclusive depending on the specified outcome and population. A direct relationship between surgeon volume and outcome does exist for these procedures. (Browne et al., 2009; Katz et al., 2001) However, empiric thresholds on procedure volume for a given outcome have not been determined. There is nothing in the literature to support or refute a hospital size-outcome relationship in joint replacement surgery. The outcomes of joint replacement patients, particularly for elderly patients with significant comorbid conditions, may depend as heavily on the healthcare team's performance as the surgeon's performance. Hence, smaller hospitals that are resource constrained may impact both the hospital personnel's and surgeon's ability to be successful in achieving optimal outcomes for elderly patients. Therefore, we examined the relationships between surgeon volume, hospital context (small, medium, large hospitals), hospital volume and mortality for elderly

patients undergoing joint replacement surgery in the US with the hope that it could inform effective practices for elderly patients.

7.2 Methods

7.2.1 Data Source

Data were obtained from the healthcare Cost and Utilization Project's (HCUP) Nationwide Inpatient Sample (NIS) of the Agency for Health-care Research and Quality (AHRQ). (Agency for Healthcare Research and Quality, 2010a) This dataset is the largest, all-payer, inpatient database in the US. During the study period of 2006, the NIS contains data from 5 to 8 million hospital discharges from approximately 1,000 hospitals sampled to approximate a 20-percent stratified sample of US community hospitals. These hospitals are heterogeneous with respect to geographic location, bed size, and the populations they serve. Participating hospitals provided discharge data including demographics, health status, co-morbidity, utilization, and hospital characteristics. Data were subjected to various reliability and validity checks before being incorporated into the database. In particular, the NIS dataset includes discharge-level variables such as age, gender, ethnicity, primary payer, disposition, diagnoses and procedures, utilization, and hospital characteristics. Coding for NIS is in accordance with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

7.2.2 Inclusion Criteria

Elderly patients ($>$ 65 years) who were surgically treated with hip or knee replacements were identified using the ICD-9 procedure codes for hip (00.70; 00.71; 00.72; 00.73; 00.74; 00.75; 00.76; 00.77; 00.85; 00.86; 00.87; 81.51; 81.52; 81.53; 81.69) and knee replacements (00.80; 00.81; 00.82; 00.83; 00.84; 81.54; 81.55).

7.2.3 Study Definitions and Outcomes

In-hospital mortality was the dependent variable of interest for this study. The primary predictor variables were hospital volume, surgeon volume and hospital bed

size. Individual hospitals and surgeons were identified by unique identifiers present as discrete variables within the dataset. Categorical groups were identified for both hospital and surgeon volume and defined as low, medium and high volume at significant changes in slope of the mortality curves.

- Hospital Volume: Hospital volume was defined as the annual number of joint replacement procedures performed in the hospital.
- Surgeon Volume: Surgeon volume was defined as the annual number of joint replacement procedures performed by the surgeon.
- Hospital Size: As determined by the NIS, hospital bed size was included in the analysis in the following manner depending on the location and teaching status of the hospital.(Agency for Healthcare Research and Quality, 2010b) Small rural hospitals are defined by having < 49 beds. Small urban hospitals have < 99 beds. If the urban hospital is a teaching hospital, it is considered 'small' if it has < 299 beds. Medium rural hospitals have 50-99 beds. Medium, urban, hospitals have 100-199 beds if non-teaching and 300-499 if a teaching hospital. Large, rural hospitals have >100 beds, large urban hospitals have > 200 beds if non-teaching, and >500 beds if teaching.

Potential confounders, including patient and hospital characteristics such as gender, age, race, hospital control and location were also identified and investigated for their associations with the outcomes of interest.

7.2.4 Analytic Sequence

After identifying the patients who underwent the specified procedures, bivariable analyses were performed using chi square tests to identify the patient and institutional level characteristics associated with mortality. A linear regression analysis was used to identify the empiric volume-mortality thresholds in each of the groups. To further adjust for the patient and hospital characteristics associated with mortality, a logistic regression model was performed. The odds ratios for mortality are reported. Data are reported as point estimates with their associated confidence intervals (CI). Reference groups were selected by identifying the category within a variable that had the lowest value. A p-value of < 0.05 was used as the significance level for all analyses and SAS was used to perform all of the analytics.

7.3 Results

7.3.1 Population and Institutional (Demographics) Results

We identified 49,609 and 65,161 elderly patients surgically treated with hip and knee replacements, respectively. Table 1 provides a comparison of the patient, hospital, utilization and volume characteristics for hip and knee replacements and their association with mortality. Males had higher mortality rates after joint replacement procedures than females (1.67% vs.1.15% for hip and 0.23% vs. 0.12% for knee, p<.001). Age was significantly associated with mortality for both hip and knee replacements (Table 7.1-7.3); and a linear trend existed between increasing age and mortality (Cochran Armitage Test for Trend <.001). Figure 7.1 further demonstrates the trend established by the Cochran Armitage Test by showing the mortality in different age groups. The LOS was also associated with mortality with a bimodal relationship characterized by significantly higher mortality rates for patients with LOS < 3 days and again at > 5 days. There were no statistically significant results observed between Payer, Region, Ownership, Location or Teaching status and mortality after joint replacement.

7.3.2 Volume-Outcome Results

Table 7.1-7.3 also describes the relationship between hospital size, hospital volume, surgeon volume and mortality for elderly patients hospitalized after joint replacement. Hospital bedsize was not an independent predictor for mortality for either hip or knee replacements (all p=NS). Hospital volume was independently associated with mortality after hip replacement (low-volume and medium-volume groups had mortality rates of 1.73% and 1.33%, respectively, compared to 0.94% for high-volume groups (p-value <.001). Hospital volume was not associated with mortality for knee replacements (Table 7.1-7.3). Surgeon volume was independently associated with mortality for both hip and knee replacements with the highest mortality rates being identified in the low (1.95%) and moderate (0.56%) surgeon volume for hip replacements and the lowest surgeon volume for knee replacements (0.12%). Table 7.2 describes the relationship when hospital volume and surgeon volume when considered together. For surgeons with low hip replacement procedure volumes there was a significant relationship with mortality in hospitals of all sizes (Table 7.2). However, there were no significant relationships for hip replacement mortality once the surgeons reached medium volumes, regardless of hospital size (Table 7.2). Mortality differences did

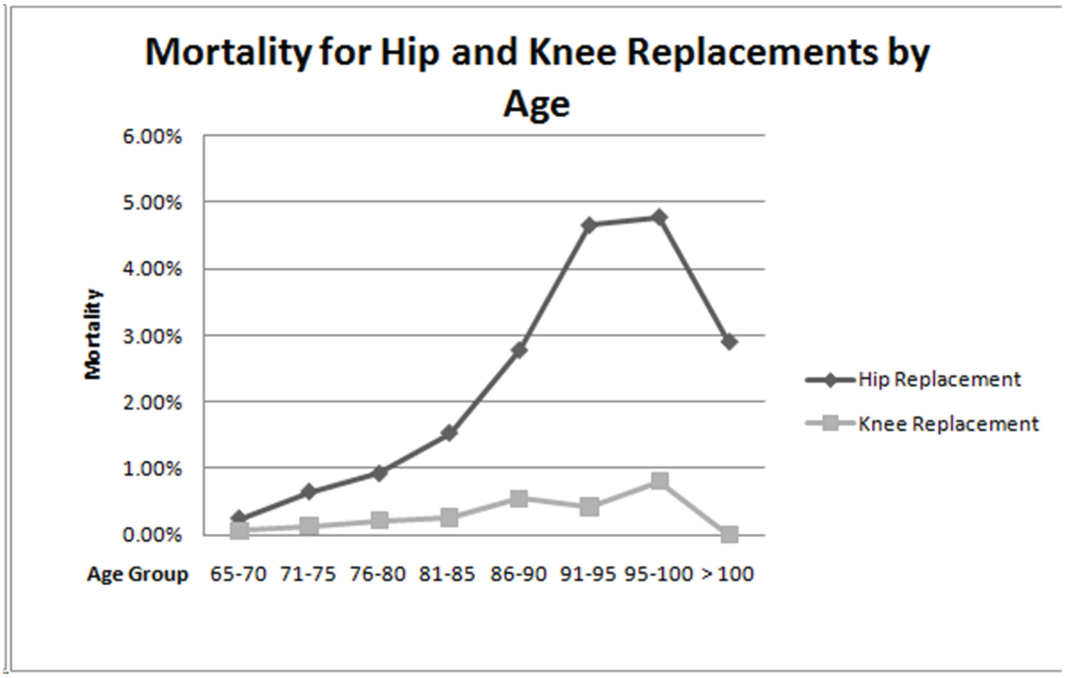

Figure 7.1: Mortality for Hip and Knee Replacements by Age Groups

Table 7.1: Population and Institutional Characteristics

Baseline Characteristics	Mortality after Hip Replacement N (%)	Odds Ratio (95% CI)	p-value	Mortality after Knee Replacement N (%)	Odds Ratio (95% CI)	p-value
Patient Characteristics						
Gender						
Male	271 (1.67)	1.45 (1.24,1.70)	<.001	55 (0.23)	1.93 (1.32,2.84)	<.001
Female	384 (1.15)	Reference		50 (0.12)	Reference	
Race/ethnicity						
White	412 (1.29)	Reference		73 (0.18)	Reference	
Black	27 (1.98)	1.55 (1.05,2.30)	0.03	2 (0.08)	0.46 (0.11,1.86)	0.26
Hispanic	28 (2.04)	1.60 (1.09,2.36)	0.02	5 (0.16)	0.91 (0.37 2.25)	0.84
Asian or Pacific Islander	7 (1.85)	1.45 (0.68,3.08)	0.33	0 (0.00)	N/A	N/A
Native American	2 (2.25)	1.76 (0.43, 7.19)	0.42	0 (0.00)	N/A	N/A
Other	16 (2.49)	1.96 (1.18,3.25)	0.008	0 (0.00)	N/A	N/A
Age						
65-70	25 (0.25)	Reference		15 (0.07)	Reference	
71-75	62 (0.65)	2.64 (1.66,4.20)	<.001	24 (0.13)	1.97 (1.03,3.76)	0.04
76-80	98 (0.92)	3.75 (2.42,5.83)	<.001	32 (0.22)	3.23 (1.75,5.98)	<.001
81-85	151 (1.53)	6.27 (4.10,9.58)	<.001	20 (0.26)	3.90 (1.99,7.61)	<.001
>86	319 (3.37)	14.19 (9.37,21.2)	<.001	14 (0.57)	8.57 (4.13,17.8)	<.001
Hospital Characteristics						
Hospital Ownership						
Government or private, collapsed category	368 (1.29)	1.10 (0.76,1.58)	0.62	58 (0.16)	1.09 (0.65,1.84)	0.73
Government, nonfederal, public	44 (1.23)	1.04 (0.66,1.65)	0.86	11 (0.22)	1.47 (0.70,3.10)	0.31
Private, non-profit voluntary	135 (1.32)	1.12 (0.76,1.65)	0.86	19 (0.15)	Reference	
Private, invest-own	76 (1.67)	1.43 (0.94,2.17)	0.09	11 (0.16)	1.11 (0.53,2.32)	0.79
Private, collapsed category	32 (1.17)	Reference		6 (0.15)	1.01 (0.40,2.54)	0.98
Location and teaching status						
Rural	86 (1.33)	1.02 (0.80,1.31)	0.85	17 (0.20)	1.31 (0.74,2.32)	0.35
Urban nonteaching	306 (1.33)	1.03 (0.87,1.21)	0.76	49 (0.16)	1.04 (0.68,1.58)	0.87
Urban teaching	263 (1.30)	Reference		39 (0.15)	Reference	

not exist for knee replacement procedures regardless of surgeon or hospital volumes Table 7.2).

7.3.3 Volume-Outcome Threshold Results

Figure 7.2 demonstrates the relationship of hospital (Panel A) and surgeon (Panel B) volume after hip replacements with mortality. Mortality for hip replacements decreases dramatically for the first 50 cases of hospital volume and continues to decrease up to 200 cases before reaching a plateau after 200 cases (Figure 7.2, Panel A). Linear regression for the low volume group had a coefficient of -1.29E-04 with an

Table 7.2: Mortality of Surgeon Procedure Volumes by Hospital Volume for Hip Replacement and Knee Replacement

		Hospital Annual Volume								
	Surgeon Annual Volume	*Mortality N (%)*	*Low Odds Ratio (95% CI)*	*p-value*	*Mortality N (%)*	*Medium Odds Ratio (95% CI)*	*p-value*	*Mortality N (%)*	*High Odds Ratio (95% CI)*	*p -value*
Hip Replacement	Low	186 (1.81)	2.97 (1.10, 8.03)	0.02	315 (1.53)	6.83 (2.19, 21.33)	<0.001	104 (1.44)	5.19 (2.62, 10.26)	<.001
	Medium	4 (0.61)	Reference		27 (0.68)	3.04 (0.92, 10.02)	0.06	7 (0.30)	1.10 (0.41, 2.95)	0.86
	High	N/A	N/A	N/A	3(0.22) (0.22)	Reference		9(0.28) (0.28)	Reference	
Knee Replacement	Low	17 (0.26)	N/A	N/A	17 (0.18)	1.47 (0.34, 6.39)	0.6	47 (0.15)	1.26 (0.65, 2.43)	0.49
	Medium	0 (0.00)	N/A	N/A	2 (0.12)	Reference		11 (0.14)	1.15 (0.50, 2.65)	0.75
	High	N/A	N/A	N/A	0(0.00) (0.00)	N/A	N/A	11(0.12) (0.12)	Reference	

Table 7.3: Population and Institutional Characteristics (Continued)

Baseline Characteristics	Mortality after Hip Replacement N (%)	Odds Ratio (95% CI)	p-value	Mortality after Knee Replacement N (%)	Odds Ratio (95% CI)	p-value
Utilization						
Length of Stay (Days)						
0	9 (40.91)	150.3 (62.1,364)	<.001	3 (8.82)	407 (101,1645)	<.001
1	34 (14.78)	37.7 (24.8,58.4)	<.001	7 (0.71)	30.1 (10.6,86.1)	<.001
2	50 (2.75)	6.13 (4.22,8.90)	<.001	15 (0.33)	14.0 (5.71,34.4)	<.001
3	64 (0.46)	Reference		7 (0.02)	Reference	
4	58 (0.49)	1.07 (0.75,1.52)	0.72	9 (0.05)	2.20 (0.82,5.92)	0.1078
5	63 (0.90)	1.96 (1.38,2.78)	<.001	7 (0.12)	4.87 (1.71,13.9)	<.001
6-10	165 (1.44)	3.17 (2.37,4.23)	<.001	23 (0.38)	16.1 (6.88,37.42)	<.001
11-50	207 (6.38)	14.8 (11.1,19.6)	<.001	32 (3.40)	148 (65,336)	<.001
>50	5 (13.89)	35.0 (13.2,92.9)	<.001	2 (18.18)	934 (170,5121)	<.001
Charges (Dollars)						
<=10000	1 (0.65)	0.96 (0.13,6.92)	0.97	0 (0.00)	N/A	N/A
10000-20000	49 (1.37)	2.05 (1.44,2.92)	<.001	4 (0.08)	1.89 (0.57,6.28)	0.29
20000-30000	107 (0.87)	1.29 (0.97,1.72)	0.08	9 (0.05)	1.12 (0.43,2.90)	0.82
30000-40000	84 (0.67)	Reference		8 (0.04)	Reference	
40000-50000	63 (0.83)	1.24 (0.89,1.72)	0.2	15 (0.15)	3.32 (1.41,7.84)	0.004
>50000	337 (2.67)	4.04 (3.18,5.14)	<.001	68 (0.51)	11.4 (5.49,23.78)	<.001
Payer						
Medicare	598 (1.33)	1.25 (0.90,1.74)	0.18	94 (0.16)	1.18 (0.57,2.43)	0.65
Medicaid	6 (2.16)	2.06 (0.86,4.91)	0.1	1 (0.17)	1.26 (0.16,10.08)	0.83
Private Insurance	38 (1.06)	Reference		8 (0.14)	Reference	
Self-pay	2 (1.35)	1.28 (0.31,5.34)	0.74	0 (0.00)	N/A	N/A
No Charge	1 (6.67)	6.66 (0.85,51.91)	0.04	0 (0.00)	N/A	N/A
Other	6 (1.52)	1.43 (0.60,3.41)	0.41	2 (0.36)	2.59 (0.55,12.22)	0.21
Region						
Northeast	128 (1.56)	1.45 (1.13,1.86)	0.004	13 (0.15)	1.11 (0.56,2.18)	0.77
Midwest	143 (1.15)	1.06 (0.83,1.36)	0.63	23 (0.13)	Reference	
South	267 (1.47)	1.36 (1.09,1.69)	0.006	47 (0.19)	1.44 (0.87,2.36)	0.15
West	117 (1.08)	Reference		22 (0.16)	1.19 (0.66,2.14)	0.55
Volumes/Bedsize						
Hospital Volume						
Low	190 (1.73)	1.86 (1.48,2.35)	<.001	17 (0.26)	1.78 (1.04,3.02)	0.03
Medium	345 (1.33)	1.43 (1.16,1.76)	<.001	19 (0.17)	1.14 (0.69,1.90)	0.61
High	120 (0.94)	Reference		69 (0.15)	Reference	
Surgeon Volume						
Low	358 (1.95)	8.02 (4.51,14.27)	<.001	47 (0.23)	1.91 (1.01,3.59)	0.04
Medium	42 (0.56)	2.29 (1.20,4.34)	0.01	12 (0.13)	1.05 (0.47,2.33)	0.91
High	12 (0.25)	Reference		12 (0.12)	Reference	
Hospital Bedsize						
Small	86 (1.23)	Reference		12(0.12)	Reference	
Medium	188 (1.47)	1.20 (0.93,1.55)	0.16	27 (0.16)	1.30 (0.66,2.57)	0.45
Large	381 (1.28)	1.04 (0.82,1.32)	0.73	66 (0.17)	1.37 (0.74,2.54)	0.31

R-Square 0.299, for the medium volume group the coefficient was 5.46E-05 with an R-Square 0.406, and for the high volume group the coefficient was 3.01E-06 with an R-Square 0.002. Mortality for hip replacements by surgeon volume demonstrated a similar relationship (Figure 7.2, Panel B). There was higher mortality for low volume surgeons with < 20 procedures annually. As surgical volume increased to medium volumes (21-50 annual procedures) and high volumes (>50), mortality continued to

decrease. Linear regression results for the low volume group had a coefficient -1.39E-03 with an R-Square 1, for the medium volume group the coefficient was -2.06E-03 with an R-Square 0.822, and for the high volume group the coefficient was 3.78E-05 with an R-Square 0.735. Figure 7.3 demonstrates the relationship of hospital (Panel A) and surgeon (Panel B) volume after knee replacements. Mortality for knee replacements decreased dramatically for the first 50 cases of hospital volume and continued to decrease up to 100 cases before reaching a plateau after 100 cases (Figure 7.3, Panel A). . Linear regression results for the low volume group had a coefficient of -7.27E-05 with an R-Square 0.954, for the medium volume group the coefficient was -3.00E-05 with an R-Square 0.825, and for the high volume group the coefficient was 1.36E-06 with an R-Square 0.006. Mortality for knee replacements by surgeon volume demonstrated a similar relationship (Figure 7.3, Panel B). There was higher mortality for low volume surgeons with < 40 procedures annually. As surgical volume increased to medium volumes (41-80 annual procedures) and high volume (> 80 annual procedures), the mortality rate continued to decrease. There were significant changes in the slopes of the line fit plots between low, medium and high volume groups. The linear regression results for the low volume knee replacement group had a coefficient -6.56E-05 with an R-Square 0.299, for the medium volume group a coefficient -6.70E-07 with an R-Square 0.00049, and for the high volume group a coefficient -1.77E-05 with an R-Square 0.793.

7.3.4 Logistic Regression Results

The logistic regression results for both hip and knee replacement mortality are presented in Table 7.4. After adjustment, the patient variables of age, race, and gender remained statistically significant for hip replacement mortality. In addition, charges, region and surgeon volume were independently associated with mortality after hip replacement. For knee replacements, only gender, age, and charges were found to be independently associated with mortality after adjustment and there was no statistical significance for either surgeon or hospital volume.

7.4 Discussion

Joint replacement is one of the most frequent elective procedures used to treat DJD in the US. Joint replacement research has focused largely on technological advances to optimize performance and minimize risk. There has been additional interest in

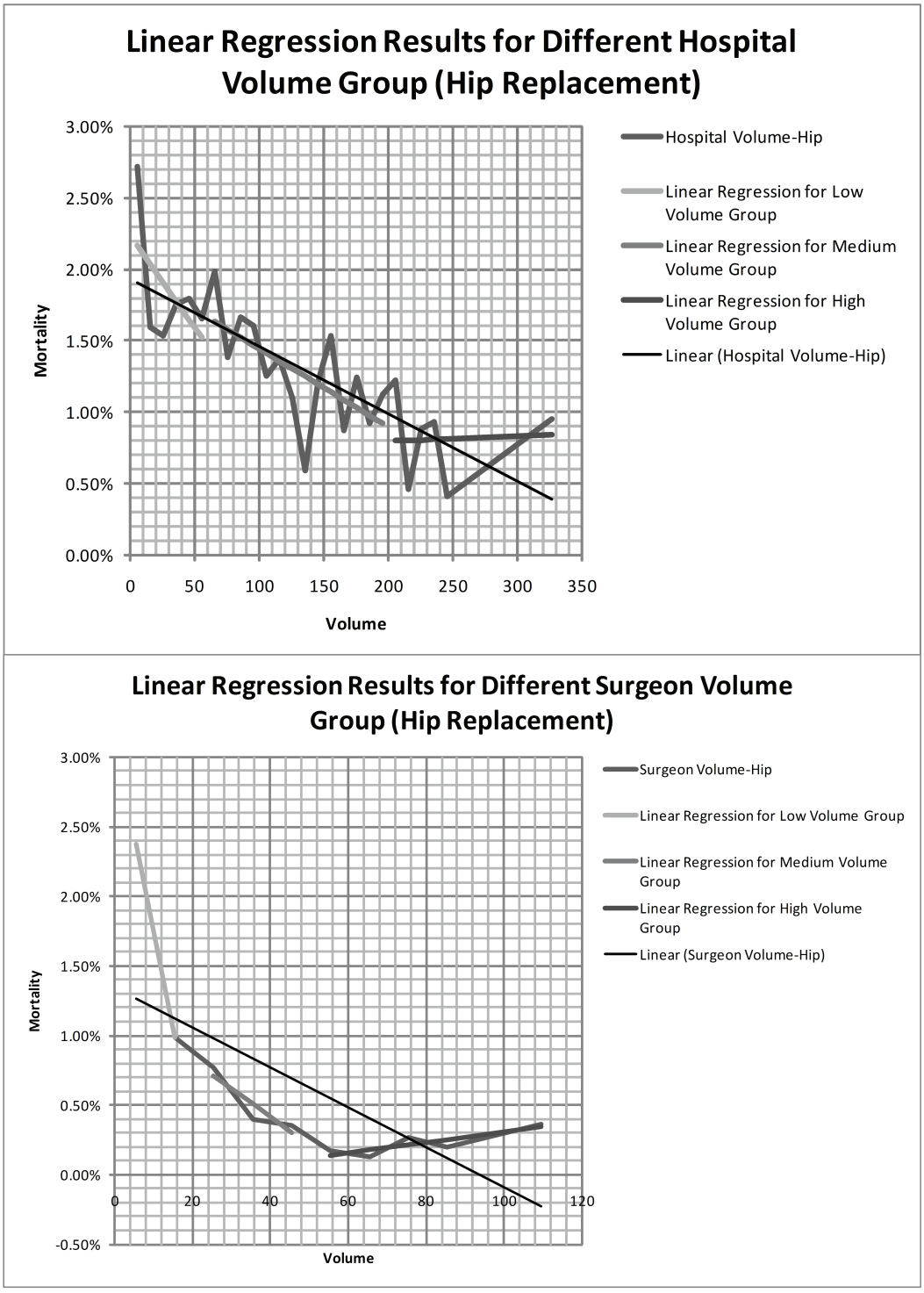

Figure 7.2: Linear Regression Results for Different Volume Groups for Hip Replacement by Hospital (Panel A) and Surgeon (Panel B)

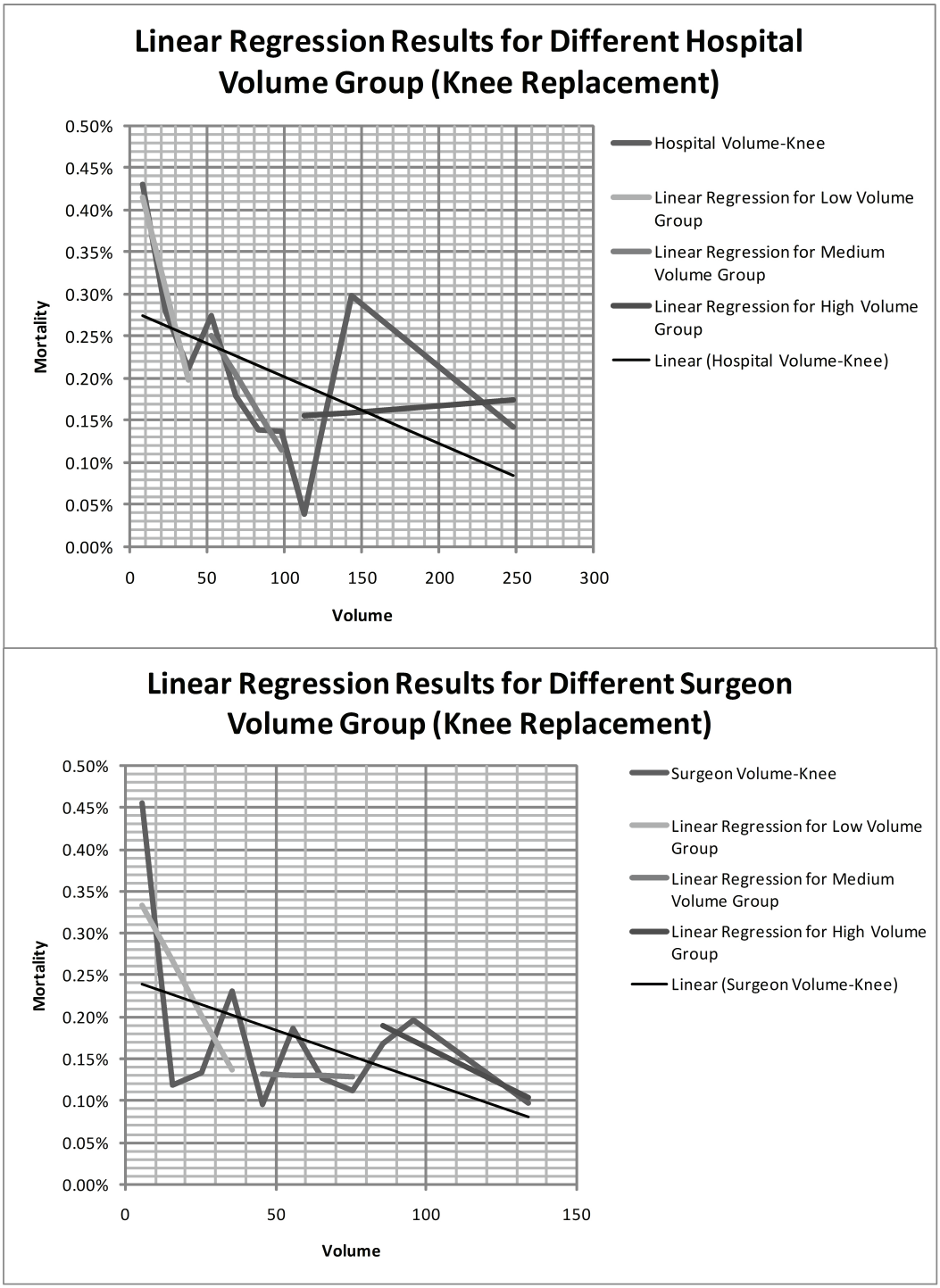

Figure 7.3: Linear Regression Results for Different Volume Groups for Knee Replacement by Hospital (Panel A) and Surgeon (Panel B)

Table 7.4: Results of Logistic Regression Analyses for Morality after Joint Replacement

Hip Replacement	Effects	Point Estimates (Odds Ratios)
Patient Characteristic	Gender	*1.663 (1.377, 2.008)
	Race/ethnicity	*0.868 (0.797, 0.946)
	Age	*0.904 (0.892, 0.915)
Hospital Characteristic	Control/Owners of hospital	0.910 (0.816, 1.015)
	Location and Teaching Status	0.884 (0.718, 1.087)
Utilization	Charge	*0.731 (0.677, 0.789)
	Payer	0.942 (0.820, 1.082)
	Region	*1.286 (1.158, 1.428)
Volume & Bedsize	Hospital Volume	1.000 (0.999, 1.001)
	Surgeon Volume	*1.020 (1.013, 1.028)
	Hospital Bedsize	0.988 (0.857, 1.139)
Knee Replacement	Effects	Point Estimates (Odds Ratios)
Patient Characteristic	Gender	*2.013 (1.288, 3.146)
	Race/ethnicity	1.453 (0.975, 2.164)
	Age	*0.917 (0.886, 0.949)
Hospital Characteristic	Control/Owners of hospital	1.258 (0.964, 1.643)
	Location and Teaching Status	1.502 (0.930, 2.425)
Utilization	Charge	*0.478 (0.383, 0.595)
	Payer	0.932 (0.691, 1.255)
	Region	0.973 (0.746, 1.268)
Volume & Bedsize	Hospital Volume	0.999 (0.998, 1.001)
	Surgeon Volume	1.004 (0.998, 1.009)
	Hospital Bedsize	1.049 (0.747, 1.475)

* denotes a statistical significance

improving care delivery to optimize patient outcomes. One delivery strategy is to direct patients toward hospitals and surgeons with particularly favorable results, which requires a quantitative study on the characteristics of such hospitals and surgeons. In particular, the association between surgical volumes and better patient outcomes has been investigated and verified for a wide range of surgeries and outcomes.

Despite the lack of a widely accepted definition on what constitutes a "high-quality" provider or hospital, significant efforts have attempted to associate procedure volume with various patient outcomes across a wide range of surgeries and specific conditions (Stone et al., 1992; Thiemann et al., 1999; Ward, 1999) including coronary artery bypass surgery, (Grumbach et al., 1995; Showstack et al., 1987) coronary angioplasty,(Hannan et al., 1997; Jollis et al., 1997, 1994; Kimmel et al., 1995) carotid endarterectomy,(Hannan et al., 1998) abdominal aortic resection,(Manheim et al., 1998) cancer surgery,(Begg et al., 1998) complex gastrointestinal surgery,(Gordon et al., 1998; Imperato et al., 1996) liver transplantation,(Edwards et al., 1999) cataract surgery(Ninn-Pedersen and Stenevi, 1996) and shoulder arthroplasty. (Hammond et al., 2003) Each of these studies consistently links better outcomes with a higher hospital or surgeon volume. A systematic review on orthopedics, Shervin et al. (2007) suggested the need for additional studies in the various subspecialties and popula-

tions of orthopedic surgery to establish a conclusive association between hospital or surgeon volume and specific patient outcomes (Shervin et al., 2007). Using the 2006 National Inpatient Sample (NIS), we determined the effectiveness of surgeon and hospital volume, and hospital size on mortality after joint replacement surgery for elderly patients. This research contributes to the literature by specifying the procedures (hip and knee replacements), the population (elderly patients >65 years), the outcome (mortality), and the volume characteristic (bedsize, hospital and surgeon volume). This level of specification is particularly important for evaluating effectiveness so that results can be compared across studies. While we were unable to demonstrate significant relationships for hospital size and mortality, we did find significant relationships for hip and knee replacements and hospital volumes and for the first time defined empiric threshold limits, based on the data, for these procedures where mortality rates changed significantly at different hospital and surgeon volumes.

Using Medicare claims data, Katz and colleagues investigated the volumes of primary and revision total hip replacements. (Katz et al., 2004, 2007) Their findings, especially for revision hip replacement, are limited because of small sample sizes, which are overcome by our use of the NIS. The authors observed that for revision hip replacements, surgeon, but not hospital volume was associated with mortality. The authors claimed a trend across all volume strata with higher volumes being associated with better outcomes. Their analyses failed to reveal volume thresholds that distinguished patient outcomes and also concluded that in high-volume centers with > 100 cases annually, surgeon volume was not associated with outcome. Unfortunately, mortality changes in different subgroups may be subtle and undetectable when the sample size is limited and the subgroups have insufficient volumes of procedures. Hence, we used nationally represented data to assure adequate power for detecting subgroup differences related to the context of care in small, medium and large volume hospitals. Browne investigated both surgeon and hospital volume in hip fracture patients using 14-years worth of data extracted from a nationwide database of US hospitals.(Browne et al., 2009) However, their subjective, threshold definitions for hospital and surgeon volumes as low, medium, and high limited the interpretation of their findings. They also failed to find statistical differences between medium volume providers and either high or low volume providers perhaps because of these nonspecific definitions.

In contrast to the robust literature examining outcomes after primary hip arthroplasty, the relationship between hospital and surgeon volume and outcomes following knee replacement has received little study. A few studies have suggested that low-

volume hospitals are associated with higher mortality and complications after total knee replacement.(Stone et al., 1992; Thiemann et al., 1999; Katz et al., 2004, 2007) However, the failure to adjust for relevant patient and hospital characteristics, (Stone et al., 1992) and to consider the surgeons' volumes Stone et al. (1992); Thiemann et al. (1999) have limited the conclusions of these studies. Katz et al. (2004) pointed out that the mortality in volume "appeared to be a threshold effect", which we captured in our analysis by introducing the empirical thresholds on both hospital volume and surgeon volume for both hip and knee replacements. Their analysis also suggested that the mortality was associated with hospital volume but not with surgeon volume and ascribed the observations in mortality to the fact that they "may reflect hospital factors such as the quality and intensity of anesthesia care, nursing, and other services." Our analysis focused on the elderly population demonstrates that neither hospital nor surgeon volume was found to be associated with patient outcome following knee replacement. We specifically attempted to capture the context of care, including anesthesia and nursing care, through the use of hospital bedsize and volume limits.

A few studies have attempted to address whether other factors are more important than volume for certain surgeries. (Ko et al., 2002) More than 30 different independent variables, including demographic factors (eg, age, gender, race, ethnicity, and socioeconomic status), burden of morbid and comorbid disease (prevalence and severity), and provider variables (eg, hospital size, location, teaching status, hospital and surgeon volume) were investigated for their association with mortality following colon cancer resection. The findings of Clifford and colleagues suggested that volume variables, although statistically significant, have a relatively smaller effect on outcome compared with other factors.(Ko et al., 2002) In our analysis, we introduced a number of patient and hospital level factors as potential confounders. We found some important relationships among independent variables including gender, race, age, region and charges for hip replacements and gender, age, and charges for knee replacements remained important.

While this study has significant strengths, namely the use of a nationwide database to identify the relationships between mortality, surgeon and hospital volume, there are also some important limitations. First, as in most administrative datasets, outcome definitions depend upon the available data or what can be derived from existing data elements. We attempted to use an important and well-defined outcome (hospital mortality) and previously described methods for our analyses; nonetheless, one must recognize the inherent imprecision of variables that arises from a misinterpretation bias at the level of data entry. Second, the surgeon-volume relationship is

just one of many variables that determine overall quality of care. Many other factors such as emergent surgery, surgeon accessibility, patient location and preferences may contribute to the overall quality of care. Finally, there has been controversy on the method of volume classification leading to contradictory conclusions on the relationships between volume and outcome. Our method resolves this problem by determining the empiric thresholds based on the trend in the data for the volume-mortality relationship. Although inpatient mortality is widely accepted as an important outcome measure, we recognize that there are other important outcomes that may be important for patients undergoing these procedures including quality of life that need to be taken into consideration when evaluating these procedures in the future.

7.5 Conclusion

Total joint replacement is frequently used to improve the mobility and quality of life for many patients. Elderly patients, in particular, may be at increased risk because of their comorbid conditions and potential for complications. By defining empiric surgeon and hospital volume thresholds for mortality, these patients may be able to be served in a way that best meets their needs.

Chapter 8

Conclusion

This dissertation focuses on improving the safety of healthcare delivery through the use of OR methodology in two clinical contexts: blood transfusion and joint (hip and knee) replacement surgery. Various OR methodologies, including the probabilistic risk assessment, optimization, and statistical analysis, are involved in different contexts of this research as the decision support tools to better serve the purpose of improving the safety and efficiency of healthcare delivery.

The first part of this dissertation consists of the development and analysis of a comprehensive risk model for RBC transfusion using the probabilistic risk assessment methodology. Using this model, one can quantify the current risk (both overall and severe transfusion risks), to the patient, coming from RBC transfusion in the United States, and identify the main "critical points" in the transfusion process. This analysis also has the potential to identify targeted interventions and evaluate their costs and benefits for risk reduction within a systematic framework. We have successfully identified the leading causes of transfusion risks, such as febrile non-hemolytic reactions, allergic reactions, and RBC alloimmunization, which usually result in clinically mild outcomes. We also find that the severe transfusion risks are caused mostly by circulatory overload and bacterial infection. This finding suggests that blood transfusion processes are already heavily regulated, therefore, attention and resources that are focused on the blood administration process instead will provide the highest risk reduction in RBC transfusion in the US, especially when limited resources are an important factor in the selection of transfusion safety programs. The result of this study implies that the improvement of health policy decisions should be focused on the fundamentals of patient care like the elimination of adverse events (through the

elimination of erroneous administration of blood) as well as other events like febrile reactions or circulatory overload, which have till now been realized to significantly affect the safety of transfusions. The contributions of this PRA analysis are four-folded. First, the PRA framework provides the integration of the current estimates of blood transfusion risks. Second, the model provides an overview analysis of the current landscape of transfusion safety in the US based upon the prevailing evidence base in the literature. Third, the model is readily available for what-if analysis or update as risks are eliminated and new risks are identified as new threats discovered, thereby providing a methodology that produces a working document that can be regularly updated as the evidence base matures. Finally, the model provides an opportunity to apply a method used in other areas or industries to an important category of low frequency, high risk events and serves as the template for performing analyses on other healthcare problems like wrong site surgeries, patient falls, and healthcare associated infections. Therefore, we conclude that probabilistic risk assessment is an important and useful tool with implications for transfusion safety as well as healthcare safety in general.

The contributions of this research in the context of resource allocation in blood screening, detailed in Chapters 4-6, focus on presenting a novel analytical modeling and algorithmic approach to a series of resource allocation problem in the design of blood screening schemes: selecting the optimal composition of blood screening tests; determining the appropriate performance metrics and their implications in the effectiveness of screening schemes; discussing the impact of decision rules for different objective functions; determining the optimal solution with respect to the differential testing scheme.

In Chapter 4, we first propose a model for selecting the optimal composition of blood screening tests in order to minimize the risk, along with the notations and assumptions that are used throughout the dissertation. We develop optimal algorithms for a special case of the problem, and a near-optimal algorithm and lower bounds based on that for the general problem. Our numerical study indicates that the heuristic algorithm is very effective for realistic problem sizes. We compare the test compositions generated by the heuristic algorithm for realistic data from sub-Saharan Africa, Ghana, Thailand, and the United States in the numerical study, which highlights the importance of generating region-specific test compositions for blood screening, explicitly taking into account the regional mono and co-infection prevalence rates, rather than following static guidelines, especially when these guidelines allow for a wide range of possible selections. In addition, our study of sub-Saharan Africa shows that an all-unit testing scheme, even with fewer tests per blood unit, outperforms a

partial testing scheme at the same budget level, and is certainly more equitable.

In Chapter 5, one of the extensions we incorporated is to introduce waste consideration (i.e., fraction of blood units that are falsely rejected) into the model as a constraint. This is an important extension as the supply of blood products is not sufficient to satisfy the demand worldwide, and this gap is increasing. We extend mathematical models of the decision problem studied in previous chapters, by considering the various objective functions (minimization of the TTI risk and minimization of the weighted TTI risk) and constraints (on budget and wasted blood) relevant in practice. Our work generates insights on the relationship among these different metrics, and on how they impact the test set. It also underscores the importance of considering these different metrics in decision-making through an optimization-based decision support system, as we find that the optimal test portfolio may have a complex structure, which we illustrate through examples. In the numerical study of this chapter, we further discuss the deviation between optimization-based approach and the current practice under different objective functions, and its implications on the policy making, especially when the prevalences of TTIs vary in regions.

In Chapter 6, we continue the blood testing study by considering a differential testing scheme for the problem of risk minimization, in which an optimal solution is allowed to contain multiple test sets, each applied to a fraction of the total blood units. We formulate the differential testing problem of risk minimization under budget constraint and propose the equivalent formulations of the problem. In addition, we discuss the structural properties of the formulated problem, based upon which we propose a simple greedy algorithm and prove that it is capable of finding the optimal solutions to the differential testing problem for a range of budget levels. We provide a numerical study on the effectiveness of the proposed algorithm and the results of both the optimization approach and current practice in sub-Saharan Africa. The numerical results show that flexibility in policy implementation by allowing a differential testing scheme further reduce risk over the "same-for-all" policy. The results also provide important policy implications on the implementation of blood screening schemes.

Finally, we studied the relationship between hospital and surgeon volume and outcomes following knee replacement in the context of joint replacement. In contrast to the robust literature examining outcomes after primary hip arthroplasty, this relationship has received little study. We successfully adjusted for relevant patient and hospital characteristics and took into account the surgeons' volumes for the establishment of association between volume and mortality. In our analysis, we also introduced a number of patient and hospital level factors as potential confounders.

We found some important relationships among independent variables including gender, race, age, region and charges for hip replacements and gender, age, and charges for knee replacements remained important. We captured, for the first time in the peer-reviewed literature, the threshold effect of the relationship between mortality and volume in our analysis by introducing the empirical thresholds on both hospital volume and surgeon volume for both hip and knee replacements. This empirical threshold effect and the method used in this work serve an insightful example and tool that can be useful for the study of the outcomes of other procedures. Our analysis focused on the elderly population demonstrates that neither hospital nor surgeon volume was found to be associated with patient outcome following knee replacement. We specifically attempted to capture the context of care, including anesthesia and nursing care, through the use of hospital bedsize and volume limits. Total joint replacement is frequently used to improve the mobility and quality of life for many patients. Elderly patients, in particular, may be at increased risk because of their comorbid conditions and potential for complications. By defining empiric surgeon and hospital volume thresholds for mortality using the method introduced in our work, these patients may be able to be served in a way that best meets their needs. In addition, analyses and methods in this work also provide a useful tool on other procedures in the context of volume-outcome analysis.

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Appendix A

Appendix for Chapter 3

A.1 ABO-incompatibility and Erroneous Blood Administration

The incidence of major blood groups in the United States and their ABO compatibility relationship are given in Table A.1 and A.2(American Red Cross, 2008).

Table A.1: Incidence of Major Blood Groups in the United States

	O Rh Positive	A Rh Positive	B Rh Positive	O Rh Negative	A Rh Negative	AB Rh Positive	B Rh Negative	AB Rh Negative
Percentage	40%	32%	11%	7%	5%	3%	1.5%	0.5%

Table A.2: The Relationship between Blood Groups in Terms of ABO Compatibility

		The patient can receive							
		$O-$	$O+$	$B-$	$B+$	$A-$	$A+$	$AB-$	$AB+$
If the patient's blood group is	$AB+$	O	O	O	O	O	O	O	O
	$AB-$	O	X	O	X	O	X	O	X
	$A+$	O	O	X	X	O	O	X	X
	$A-$	O	X	X	X	O	X	X	X
	$B+$	O	O	O	O	X	X	X	X
	$B-$	O	X	O	X	X	X	X	X
	$O+$	O	O	X	X	X	X	X	X
	$O-$	O	X	X	X	X	X	X	X

†O means the situation will not lead to ABO-incompatibility, X means it will.

We make two assumptions: (1) Erroneous blood administration rates are similar

among the different blood groups, and (2) the blood group distribution of blood donors and transfusion patients follow that of the general population given in Table A.1.

As defined in Chapter 3, I denotes the event of ABO incompatibility in case of an erroneous administration of blood. Also define events $RX+$ and $RX-$ as the events that the recipient is of blood group $X+$ and $X-$, respectively, for$X \in \{A, B, AB, O\}$. Then, we can derive the probability that a randomly selected unit will be compatible with a randomly selected recipient as follows:

$$\begin{aligned}
\Pr(I^c|E) &= \Pr(I^c|RAB+)\Pr(RAB+) + \Pr(I^c|RAB-)\Pr(RAB-) + \cdots + \Pr(I^c|RO-)\Pr(RO-) \\
&= (0.07 \times 0.03) + (0.4 \times 0.03) + \cdots + (0.07 \times 0.005) + \cdots + (0.005 \times 0.005) + \cdots + (0.07 \\
&= 0.5661
\end{aligned}$$

Thus, given error (i.e., units are randomly chosen), ABO-incompatibility happens with probability 0.4339, that is, $\Pr(I|E) = 0.4339$.

A.2 Frequency of Erroneous Administration

Table A.3: Frequency of Erroneous Administration of RBCs in the State of New York

	Number	Frequency
ABO-incompatible (I)	237	1/38,000
Reported ABO compatible	221	1/41,000
Adjusted ABO compatible	308	1/29,000
Total number of erroneous administration of RBC	462	1/19,000
Adjusted total number of erroneous administration of RBC	545	1/16,500

A.3 Risk Estimates in the PRA Models

Viral Infections

As mentioned above, when the only significant transfusion risk comes from window-period transmissions, mathematical models known as the incidence/window-period models (Glynn et al., 2002; Kleinman et al., 1997) become appropriate to estimate

Table A.4: Event Probabilities in the Acute Hemolytic Reaction Sub-tree

	Event description	Probability
$\Pr(E)$	Erroneous Administration of RBC	$1/16,500$
$\Pr(BE)$	Blood Bank Error Alone	1.758×10^{-5}
$\Pr(NE)$	Nonblood Bank Error Alone	3.394×10^{-5}
$\Pr(CE)$	Compound Error	9.9091×10^{-6}
$\Pr(A\|E)$	Acute Hemolytic Reaction given Erroneous Administration	0.214
$\Pr(A \cap I)$	Acute Hemolytic Reaction and ABO Incompatibility	1.298×10^{-5}
$\Pr(A \cap I^c)$	Acute Hemolytic Reaction and ABO Compatibility	4.257×10^{-5}
$\Pr(I\|E)$	ABO Incompatibility given Erroneous Administration	0.4339

the viral infection risks. These mathematical models typically take into account the window period, and incidence rate in repeat donors and first-time donors, together with their estimated weights in the population.

Retroviruses

Human Immunodeficiency Virus - HIV

Although transmission risks have been estimated at 80-90% for HIV and HCV even in the presence of the virus, most of these models assume a worst-case scenario of 100% transmission risk. In a 2007 publication, (Klein et al., 2007) estimated this risk to be 1 in 2,000,000 to 3,000,000 per unit transfused in the US. The research by Dodd et al. (2002)[1] provides a similar estimate, of 1 in 2,135,000. Dodd et al. (2002) also provide a similar conclusion about HIV risk, at 1 in 2,100,000, in their review. Thus, we will consider this risk to be in the interval, 1 in 2,000,000 to 3,000,000. All transfusion-transmitted HIV cases may suffer serious long-term complications based on the chronicity of HIV infection and the potential for the infected recipient to either develop disease or require long-term antiretroviral therapy. Thus, we will also consider the severe outcome risk related to HIV transmission as 1 in 2,000,000 to 3,000,000.

Human T-Lymphotropic Virus - HTLV

The HTLV virus group includes two retroviruses (HTLV-1 and HTLV-2) that can cause human disease. Schreiber et al. (1996) use the incidence/window-period model,

[1]Based on observed incidence (of 1 in 1,525,000 for HIV-1) calculated for repeat donors (80% of total donors) and an adjusted rate (of three times higher) for first-time donors (20% of total donors).

applied to US blood donor data between 1991 and 1993, and estimate the risk of HTLV transfusion to be 1 in 641,000. This is mainly due to the 51-day window period before the development of the HTLV antibody. This number is also adopted in the review paper by Klein et al. (2007). Since only 1/3 of cellular units transmit HTLV infection (Kleinman et al., 2003a), this translates into an approximate risk of 1 in 1,923,000.

Hepatitis Viruses

Hepatitis A Virus (HAV)

In a transfusion, HAV can only be transmitted during the brief several week period of asymptomatic HAV viremia (Brower et al., 2000). In Dodd (1994), the transfusion risk of HAV is estimated as 1 in 10,000,000 units. We will use this estimate in our study.

Hepatitis B virus HBV

The overall HBV risk from transfusion is the sum of the window-period transmission (i.e., before infected donors develop a positive HBsAg level) and transmission by chronic carriers who have undetectable levels of HBsAg. The first risk, from window-period transmission, is estimated to be 1 in 82,000 units in a Canadian study (Kleinman et al., 2003a)[2]. For the second risk (i.e., transmission from chronic carriers with undetectable HBsAg on blood donor screening assays), there are two US studies, both of which assume that HBV chronic carriers who are HBsAg negative, yet still capable of transmitting HBV, will test positive for anti-HBC and have HBV DNA that is detectable by very sensitive HBV NAT techniques (Kleinman and Busch, 2001; Kleinman et al., 2003a). The resulting estimate is 1 in 49,000 units. An American Red Cross study in 2003 suggests a similar rate of potentially infectious units in their donor population (Kleinman et al., 2003b). Therefore, the overall risk of HBV transmission can range from approximately 1 in 31,000 (if all chronic carriers transmit) to 1 in 82,000 (if no chronic carrier transmits). Klein et al. (2007) report this risk as 1 in 100,000 to 200,000 units. The corresponding estimate in Dodd et al. (2002)[3] is slightly lower, at 1 in 205,000 to 488,000. Because the estimates found in the literature lie within a wide range, in our study we will consider this risk to belong to the interval of 1 in 50,000 to 400,000. Data suggest that 1 in 40 transfusion-

[2]This estimate is obtained for a window period of 59 days and after adjusting for the fact that measuring HBsAg incidence will underestimate the true HBV incidence. This is because HBsAg is usually a transient marker, and disappears several months after infection.

[3]After the observed incidence of HBsAg is multiplied by a factor of 2.38, to adjust for the transient nature of the HBsAg marker, as noted above.

transmitted HBV infections will lead to the serious outcome of a chronic carrier state (with or without severe liver disease) (Kleinman et al., 2003b). Consequently, we will consider the severe outcome risk related to HBV transmission as 1 in 2,000,000 to 16,000,000.

Hepatitis C Virus (HCV)

The estimate for transfusion-transmitted HCV infection in the US is reported in Klein et al. (2007) as 1 in 1,000,000 to 2,000,000 units. Furthermore, Dodd et al. (2002) report a similar estimate, 1 in 1,935,000, using the incidence/window-period model[4]. Despotis et al. (2008) also report a similar estimate, of 1 in 1,800,000, in their review. Thus, it is reasonable to use the interval estimate in Klein et al. (2007) in our study.

It is estimated that 20% of HCV infected individuals resolve their infection, 60% develop chronic infection without severe liver disease, and 20% develop significant liver disease such as cirrhosis (e.g., Alter and Seeff, 2000; Busch, 2001; Kleinman et al., 2003a). Then, based on the transfusion-transmission risk of HCV of 1 in 1,000,000 to 2,000,000, the risk of a severe outcome is calculated as 1 in 5,000,000 to 10,000,000 units.

Non-A-E Hepatitis Virus

Studies indicate that approximately 20% of acute community-acquired hepatitis cases in the US cannot be attributed to A-E hepatitis viruses or other known causes; these transmission cases are likely due to a viral agent that is not yet discovered (Alter and Bradley, 1995). However, cases of chronic hepatitis are infrequently associated with this agent (Kleinman et al., 2003a). Based on these and other studies (including a retrospective evaluation of a 1970 US study, see Kleinman et al. (2003a), it is concluded that this risk is extremely low or nonexistent in the US. As a result, a very small probability, of 10^{-9}, is assigned to this event (and other such negligible events, as discussed below) in our study.

West Nile Virus (WNV)

The WNV epidemic in 2002 in the US saw over 3,300 reported human cases of WNV disease, with over 2,300 reported cases of WNV encephalitis and meningitis. The first documented cases of transfusion transmission of WNV through voluntary blood donation also occurred (Biggerstaff and Petersen, 2003). Since the risk was highly

[4]Based on observed incidence (of 1 in 390,000) calculated for repeat donors (80% of total donors) and an adjusted rate (of three times higher) for first-time donors (20% of total donors).

geographically and temporally variable, computation of geographically localized estimates has been recommended (Biggerstaff and Petersen, 2003). In response to these documented cases, routine blood screening of WNV (a combination of MP NAT during the "non-season" and a more sensitive ID NAT in epidemic locations during epidemic times) started in July 2003 in the US (Stramer, 2007). This testing scheme has been so effective that no transfusion-transmitted WNV has been observed in the US after that date (Stramer, 2007). Consequently, it is reasonable to treat this risk as extremely low to nonexistent in our study.

Cytomegalovirus - CMV

It is mostly in immunosuppressed patients that a Cytomegalovirus (CMV) transmission leads to important consequences, such as acute, severe clinical diseases manifested by pneumonia, hepatitis, and other symptoms that can even lead to death (Laupacis et al., 2001; Preiksaitis, 2000). Although the true risk of CMV transmission remains unknown, it is reasonable to infer, from the conclusion in Kleinman et al. (2003a), that the risk of significant CMV clinical disease from transfusion of cellular blood components in the United States is extremely low to nonexistent.

Bacterial Infection

Sepsis

The American Red Cross reports a risk from a septic transfusion reaction from a culture-negative apheresis unit (predominantly due to skin flora) at 1 in 75,100 (Stramer, 2007). In addition, in their review, Despotis et al. (2008) give a similar estimate of this risk, at 1 in 75,000. Thus, 1 in 75,100 would be an appropriate estimation of the transfusion risk of sepsis.

Treponema Pallidum (Syphilis)

The storage of RBCs at refrigerator temperature prevents the growth of many bacterial species. This, together with the routine testing of donated blood for serologic evidence of syphilis, has eliminated the syphilis cases. There have been only two cases of syphilis since 1950, and no incidence was reported since 1978 (Kleinman et al., 2003a). Thus, it is safe to conclude that the current risk of transfusion-transmitted syphilis in the United States is extremely low to nonexistent.

Protozoal Infection

Plasmodium (Malaria)

Although rare in North America, transfusion-transmitted malaria is common in some

parts of the world (Despotis et al., 2008). In the US, there has been 2-3 transfusion-transmitted malaria cases per year over the 40-year period from 1958 through 1998, resulting in an occurrence rate of 1 case per 4,000,000 red cells transfused during this period (Guerrero et al., 1983; Mungai et al., 2001). The same estimate is also given in Klein et al. (2007). Furthermore, the overall fatality rate of malaria is estimated as 11% (Kleinman et al., 2003a). Hence, for a transfusion risk of 1 in 4,000,000, its mortality rate is 1 in 36,363,636 units.

Babesiosis

After malaria, babesiosis is the second most commonly reported transfusion-transmitted parasitic infection in the US (Kleinman et al., 2003a). There have been slightly over 40 cases reported in the US in the last two decades (Leiby, 2001). Hence, the clinical case reporting data suggests an incidence of approximately 1 per 10,000,000 red cell units transfused in the US. The fatality rate of babesiosis is estimated to be very low; most transfusion-transmitted babesiosis infections will result in mild clinical disease (Kleinman et al., 2003a).

Chagas Disease

Chagas disease is caused by a protozoan parasite, Trypanosome cruzi, which establishes a chronic, asymptomatic carrier state in most infected persons (Kleinman et al., 2003a). Although large numbers of transfusion-transmitted cases have been documented in Mexico and Central and South America, only 6 cases of acute transfusion-transmitted Chagas disease have been reported in North America since the mid-1980s (Kleinman et al., 2003a). However, the numbers of infections are expected to be on the rise as a result of immigration from Mexico and Central and South America (American Red Cross, 2008). As such, the risk is higher in regions that face high immigration rates. Given these, we conclude that the risk of Chagas disease from transfusion of cellular blood components in the United States is extremely low to nonexistent for the time being, but this is likely to change in the future.

Toxoplasmosis

We were not able to find a clinical study that estimates the risk of transfusion-transmitted toxoplasmosis in the US. However, Despotis et al. (2008) state that toxoplasmosis is rarely transmitted via transfusion in the US. Therefore, we conclude that the risk is extremely low to nonexistent.

Transfusion Reactions

Hemolytic Reaction

The overall risk of a hemolytic reaction (acute or delayed) is estimated at 1 in 6,000 units (Klein et al., 2007). In what follows, we discuss the risk for each type of hemolytic reaction.

Acute Hemolytic Reaction

The frequency of acute hemolytic reactions is reported at 1 in 18,000, with a mortality rate between 1 in 600,000 and 1 in 1,800,000 per unit transfused (Klein et al., 2007; Linden et al., 2000; Mayer, 1982). Results of published studies and FDA adverse-event reporting suggest a similar mortality rate of hemolytic reactions, at around 0.8-1.2 per one million units transfused (Despotis et al., 2008).

Other Types of Incompatibility

Acute hemolytic reactions occur due to causes other than ABO incompatibility, and the nature of these causes is not well understood in the medical literature. In our model, we refer to these unknown causes of acute hemolytic reactions as "other types of incompatibility," and estimate the probability that an acute hemolytic reaction occurs due to other types of incompatibility, $\Pr(A \cap I^c)$, by deducting the risk of an acute hemolytic reaction due to ABO incompatibility from the total risk of an acute hemolytic reaction, as detailed in Chapter 3.

Delayed Hemolytic Reaction

Since the risk of a hemolytic reaction is 1 in 6,000 units of red blood cells transfused and the risk of acute hemolytic reaction is 1 in 18,000 units (Klein et al., 2007), the risk of delayed hemolytic reactions can be inferred as $1/6,000 - 1/18,000 = 1/9,000$, assuming that the two incidents are mutually exclusive, that is, the probability that a patient will have both acute hemolytic reaction and delayed hemolytic reaction is extremely low.

It is also stated, in Pineda et al. (1999), that delayed hemolytic reactions caused by RBC alloantibodies occur in 1 in 4,000 to 6,000 units. As a result, we will consider an interval of this risk, from 1 in 4,000 to 9,000 units.

Febrile Non-hemolytic Reaction

Klein et al. (2007) provide the estimated risk of febrile reaction as 1 in 300, which we will use in our study.

Allergic Reaction

Allergic reactions can occur in 0.1 to 0.3 percent of the transfused units (Brecher et al., 2003). This estimate is also consistent with that in Kleinman et al. (2003a).

More significant allergic reactions are analyzed below, as "anaphylaxis."

Anaphylaxis

The transfusion risk of anaphylaxis in the United States is reported as 1 in 20,000 to 50,000 in Klein et al. (2007). In addition, Despotis et al. (2008) provide the same estimate for this risk in their review. Hence we conclude that it is reasonable to use the estimate of 1 in 20,000 to 50,000 units. This interval is also consistent with that in Kleinman et al. (2003a).

Transfusion-associated Graft-versus-host Disease (TA-GvHD)

TA-GvHD leads to a combination of symptoms, including fever, skin rash, diarrhea, liver dysfunction, and bone marrow failure, typically occurring 7 to 10 days after transfusion (Williamson and Warwick, 1995). The risk in the United States is stated as uncommon in Klein et al. (2007), although 90% of the time it could be fatal. Thus, we consider this risk to be extremely low to nonexistent in our analysis.

RBC Alloimmunization

The risk of RBC alloimmunization in transfusion is stated at a rate of about 62.1 in 100,000 transfused red cell units (Kleinman et al., 2003a).

Transfusion-related Acute Lung Injury (TRALI)

TRALI is a serious blood transfusion complication, characterized by acute respiratory distress, noncardiogenic bilateral pulmonary edema, and hypoxemia that occur within 1 to 6 hours (more usually within 1-2 hours) after transfusion of plasma-containing blood components.

The incidence of TRALI is reported as 2 per 10,000 transfused units (or 16 per 10,000 transfused patients) in a study by Popovsky and Moore (1985); Popovsky et al. (1985). The study is conducted in hospitals associated with the Mayo Clinic from June 1982 to October 1984, and all cases of acute respiratory distress that occurred within 4 hours of transfusion are reported. Many reviews, including Klein et al. (2007), use this estimate. Kleinman et al. (2003a) state that the rate of TRALI from red cell transfusion has reduced since 1980. For example, the point estimate for TRALI risk in Canada, calculated from the data collected by Health Canada (1998), is 1.4 per 100,000 red cell units transfused. However, it is also stated that underrecognition and/or underreporting of TRALI could be a problem mainly because of the lack of a uniformly applied set of criteria for the diagnosis of TRALI. Many mild cases of TRALI may go unrecognized or may be misdiagnosed. Consequently, we will consider an interval for this risk, ranging from 1.4 to 20 in

100,000 units. Furthermore, a recent study estimates the fatality rate from TRALI as 0.4 per 1 million RBC units (Despotis et al., 2008).

Circulatory (Volume) Overload

The risk of circulatory (volume) overload results from the incapacity of the heart to adequately pump the additional blood volume (introduced by transfusion) through the circulation. As a result, congestive heart failure and acute pulmonary edema occur. The risk estimates in the literature vary from 141 (Popovsky and Taswell, 1985) to 6,220 (Bierbaum et al., 1999) per 100,000 recipients in different studies reviewed in Kleinman et al. (2003a). As stated above, this risk is expressed per recipient and it is difficult to convert this risk into per unit transfused. Hence, we will use this risk as is in our study. Furthermore, since the range reported in the literature is wide, we will consider an interval of this risk, from 1 in 200 to 10,000.

A.4 Importance Measures and Minimal Cut Sets in PRA Models

Table A.5: Importance Measures for the Overall Transfusion/Severe Outcome Risk

a. Importance Measures for the Overall Transfusion Risk - Base Case

Event	Importance measure	Event	Importance measure
Febrile nonhemolytic reaction	0.552557	Sepsis	0.002207
Allergic reaction	0.249274	Blood bank error alone	0.001264
RBC alloimmunisation	0.102941	HBV	0.000737
Circulatory overload	0.032503	Compound error	0.000654
Delayed hemolytic reaction	0.025503	HCV	0.000111
TRALI	0.017737	HTLV-1 & 2	0.000086
Acute hemolytic reaction and other types of incompatibility	0.007107	HIV-1 & 2	0.000066
Anaphylaxis	0.004736	Plasmodium	0.000041
Acute hemolytic reaction when error	0.004359	HAV	0.000017
Nonblood bank error alone	0.002441	Babesiosis	0.000017

b. Importance Measures for the Severe Outcome Risk - Base Case

Event	Importance measure	Event	Importance measure
Circulatory Overload	0.632592	TRALI	0.00129
Acute Hemolytic Reaction	0.179249	HIV	0.00129
Bacterial Infection	0.164537	HCV	0.00043
MISC	0.016938	Malaria	0.000089
HBV	0.003585		

Table A.6: Minimal Cut Sets for the Overall Transfusion/Severe Outcome Risk

a. Minimal Cut Sets for the Overall Transfusion Risk - Base Case		
Cut Sets	Events of the Cut Set	Risk
1	Febrile nonhemolytic reaction	3.330000E-03
2	Allergic reaction	1.503759E-03
3	RBC alloimmunization	6.210000E-04
4	Circulatory overload	1.960784E-04
5	Delayed hemolytic reaction	1.538462E-04
6	TRALI	1.070000E-04
7	Acute hemolytic reaction, other types of incompatibility	4.287400E-05
8	Anaphylaxis	2.857143E-05
9	Sepsis	1.331558E-05
10	Nonblood bank error alone, acute hemolytic reaction when error	1.472630E-05
11	Blood bank error alone, acute hemolytic reaction when error	7.626117E-06
12	Compound error, acute hemolytic reaction when error	9.090909E-06
13	HBV	4.444444E-06
14	HCV	3.9445454E-07
15	HTLV-1 &2	5.200000E-07
16	HIV-1 & 2	4.000000E-07
17	Plasmodium (malaria)	2.500000E-07
18	Babesiosis	1.000000E-07
19	HAV	1.000000E-07
b. Minimal Cut Sets for the Severe Outcome Risk - Base Case		
Cut Sets	Events of the Cut Set	Risk
1	Circulatory overload	1.96078E-04
2	Bacterial infection	5.10000E-05
3	MISC	5.25000E-06
4	Acute hemolytic reaction	1.00000E-06
5	TRALI	4.00000E-07
6	HIV	4.00000E-07
7	HBV	3.33333E-06
8	HCV	1.33333E-07
9	Malaria	2.75000E-08

Appendix B

Appendix for Chapter 4

B.1 Proof of Proposition 5

Risk

$$
\begin{aligned}
Risk(S) &\equiv \Pr\left(\bigcup_{i\in\Psi} A^i+ \,|\, \bigcap_{j\in S} T_j^{d(j)}-\right) \\
&= 1 - \frac{\Pr\left(\bigcap_{i\in\Psi} A^i-, \bigcap_{j\in S} T_j^{d(j)}-\right)}{\Pr\left(\bigcap_{i\in\Psi} A^i-, \bigcap_{j\in S} T_j^{d(j)}-\right) + \Pr\left(\bigcup_{i\in\Psi} A^i+, \bigcap_{j\in S} T_j^{d(j)}-\right)} \\
&= 1 - \frac{1}{1+\frac{\sum_{\overrightarrow{\lambda}\in\mathscr{S}\left(\overrightarrow{\Lambda}\right)\setminus\overrightarrow{0}} \Pr\left(\overrightarrow{\Lambda}=\overrightarrow{\lambda}\right)\Pr\left(\bigcap_{j\in S} T_j^{d(j)}-|\overrightarrow{\Lambda}=\overrightarrow{\lambda}\right)}{\Pr\left(\bigcap_{i\in\Psi} A^i-\right)\Pr\left(\bigcap_{j\in S} T_j^{d(j)}-|\bigcap_{i\in\Psi} A^i-\right)}}.
\end{aligned}
$$

By definition of Q_j and Assumption (A1), an equivalent representation of risk can be written as:

$$
Risk(S) = 1 - \frac{1}{1+\frac{1}{\Pr\left(\bigcap_{i\in\Psi} A^i-\right)}\sum_{\overrightarrow{\lambda}\in\mathscr{S}\left(\overrightarrow{\Lambda}\right)\setminus\overrightarrow{0}}\left\{\Pr\left(\overrightarrow{\Lambda}=\overrightarrow{\lambda}\right)\prod_{i\in\Psi:\lambda_i=1}\prod_{j\in S_i} Q_j\right\}}.
$$

Waste

$$\begin{aligned} Waste(S) &\equiv \Pr\left(\bigcup_{j\in S} T_j^{d(j)} + | \bigcap_{i\in\Psi} A^i - \right) \\ &= 1 - \Pr\left(\bigcap_{j\in S} T_j^{d(j)} - | \bigcap_{i\in\Psi} A^i - \right). \end{aligned}$$

By Assumption (A1), an equivalent representation of waste can be written as:

$$Waste(S) = 1 - \prod_{j\in S} \Pr\left(T_j^{d(j)} - | A^{d(j)} - \right).$$

TPF

$$\begin{aligned} TPF(S) &\equiv \Pr\left(\bigcup_{j\in S} T_j^{d(j)} + | \bigcup_{i\in\Psi} A^i + \right) \\ &= 1 - \frac{\sum_{\overrightarrow{\lambda}\in\mathscr{S}(\overrightarrow{\Lambda})\setminus\overrightarrow{0}} \Pr\left(\overrightarrow{\Lambda} = \overrightarrow{\lambda}, \bigcap_{j\in S} T_j^{d(j)} - \right)}{\Pr\left(\bigcup_{i\in\Psi} A^i + \right)}. \end{aligned}$$

By Assumption (A1), an equivalent representation of TPF can be written as:

$$TPF(S) = 1 - \frac{1}{\Pr\left(\bigcup_{i\in\Psi} A^i + \right)} \sum_{\overrightarrow{\lambda}\in\mathscr{S}(\overrightarrow{\Lambda})\setminus\overrightarrow{0}} \left\{ \Pr\left(\overrightarrow{\Lambda} = \overrightarrow{\lambda}\right) \prod_{j\in S} \Pr\left(T_j^{d(j)} - | \overrightarrow{\Lambda} = \overrightarrow{\lambda}\right) \right\}.$$

PPV

$$\begin{aligned} PPV(S) &\equiv 1 - \Pr\left(\bigcap_{i\in\Psi} A^i - | \bigcup_{j\in S} T_j^{d(j)} + \right) \\ &= 1 - \frac{\Pr\left(\bigcap_{i\in\Psi} A^i -\right) - \Pr\left(\bigcap_{i\in\Psi} A^i -, \bigcap_{j\in S} T_j^{d(j)} -\right)}{1 - \Pr\left(\bigcap_{j\in S} T_j^{d(j)} -\right)} \\ &= 1 - \frac{\Pr\left(\bigcap_{i\in\Psi} A^i -\right) - \prod_{j\in S} \Pr\left(T_j^{d(j)} - | A^{d(j)} -\right)}{1 - \Pr\left(\bigcap_{j\in S} T_j^{d(j)} -\right)} \end{aligned}$$

By Assumption (A1), an equivalent representation of PPV can be written as:

$$PPV(S) = 1 - \frac{\Pr\left(\bigcap_{i\in\Psi} A^i -\right) - \prod_{j\in S} \Pr\left(T_j^{d(j)} - | A^{d(j)} -\right)}{1 - \sum_{\overrightarrow{\lambda}\in\mathscr{S}\left(\overrightarrow{\Lambda}\right)} \left\{ \Pr\left(\overrightarrow{\Lambda} = \overrightarrow{\lambda}\right) \prod_{j\in S} \Pr\left(T_j^{d(j)} - | \overrightarrow{\Lambda} = \overrightarrow{\lambda}\right) \right\}}.$$

B.2 Proof of RMP NP-Hardness

The proof follows by the "restriction technique" (Garey and Johnson, 1979), that is, we show that a special case of our general problem given in (4.1) and (4.2), after considering Assumptions **(A1)** and **(A2)**, reduces to the *Series-parallel Redundancy Allocation Problem* (**RAP**), which is shown to be NP-hard (Chern, 1992). The **RAP** is given in the following:

$$\begin{aligned} \text{Maximize} \qquad & R' = \prod_{j=1}^{n} \left(1 - q_j^{x_j+1}\right) \\ \text{subject to} \qquad & \sum_{j=1}^{n} c_j x_j \leq b \end{aligned}$$

$$0 \leq x_j \leq u_j,\ x_j \text{ integer}, j = 1, \cdots, n,$$

where $n\ (>0)$ is the number of stages, $c_j\ (\geq 0)$ is the cost of component j, $0 \leq q_j \leq 1$ is the unreliability of each component in stage j, and $u_j \in Z^+$ is some positive integer upper bound, which equals 1 in our setting.

As our budget constraint is in the same functional form as the above constraint, we focus on equivalence of the objective functions of **RAP** and a special case of our general problem (**RMP**). The objective function of **RAP** can be written as

$$\begin{aligned} R' &= 1 - \sum_{j=1}^{n} q_j^{x_j+1} + \sum_{j=1}^{n}\sum_{k>j} q_j^{x_j+1} q_k^{x_k+1} - \cdots + (-1)^n \prod_{j=1}^{n} q_j^{x_j+1} \\ &= 1 - \sum_{j=1}^{n} q_j q_j^{x_j} + \sum_{j=1}^{n}\sum_{k>j} (q_j q_k)\, q_j^{x_j} q_k^{x_k} - \cdots + (-1)^n \left(\prod_{j=1}^{n} q_j\right) \prod_{j=1}^{n} q_j^{x_j}. \end{aligned}$$

The objective function of **RMP** in (4.1), considering **(A1)** and **(A2)**, is equivalent to the following (see Appendix B.4):

$$R = \frac{1}{\Pr\left\{\bigcap_{i\in\Psi} A^i-\right\}} \sum_{\overrightarrow{\lambda}\in\mathscr{S}\left(\overrightarrow{\Lambda}\right)\setminus\overrightarrow{0}} \left\{ \Pr\left\{\overrightarrow{\Lambda} = \overrightarrow{\lambda}\right\} \prod_{i\in\Psi:\lambda_i=1} \prod_{j\in S_i} Q_j \right\}.$$

Now consider a special case of **RMP**, with only one test available for each disease, i.e., $m_i = 1, i \in \Psi$. As defined in Chapter 4, n is the number of diseases the decision-maker is considering of testing for, and Q_j is the test efficacy parameter for each test $j \in \Omega$. To simplify the notation, refer to the single test that applies to disease j as test $j, j = 1, \cdots, n$. For this special case, the objective function of **RMP** reduces to the following:

$$\begin{aligned} R = &\sum_{\left\{\overrightarrow{\lambda}:\lambda_j=1,\lambda_k=0,\forall k\neq j\right\}} \frac{\Pr\left\{\overrightarrow{\Lambda} = \overrightarrow{\lambda}\right\}}{\Pr\left\{\bigcap_{i\in\Psi} A^i-\right\}} Q_j^{x_j} + \sum_{\left\{\overrightarrow{\lambda}:\lambda_j=1,\lambda_k=1,\lambda_l=0,\forall l\neq j,k\right\}} \frac{\Pr\left\{\overrightarrow{\Lambda} = \overrightarrow{\lambda}\right\}}{\Pr\left\{\bigcap_{i\in\Psi} A^i-\right\}} Q_j^{x_j} Q_k^{x_k} \\ &+ \cdots + \sum_{\left\{\overrightarrow{\lambda}:\lambda_j=1,\forall j\right\}} \frac{\Pr\left\{\overrightarrow{\Lambda} = \overrightarrow{\lambda}\right\}}{\Pr\left\{\bigcap_{i\in\Psi} A^i-\right\}} \prod_{j\in\Omega} Q_j^{x_j}. \end{aligned}$$

Functions $1 - R'$ and R are mathematically equivalent, and the result follows. $\square$

B.3 Proof of Property 1

For any $S = \bigcup_{i\in\Psi} S_i$ $(\subseteq \Omega)$, define $\overrightarrow{Y}(S\backslash\{k\})$ as the random vector of results of tests in $S\backslash\{k\}$, $\forall k \in S_i, i \in \Psi$. We first show that, $\forall k \in S$,

$$\Pr\left\{\bigcap_{i\in\Psi} A^i-, \left|\overrightarrow{Y}(S\backslash\{k\}), T_k^{d(k)}-\right.\right\} \geq \Pr\left\{\bigcap_{i\in\Psi} A^i-, \left|\overrightarrow{Y}(S\backslash\{k\}), T_k^{d(k)}+\right.\right\} \tag{B.1}$$

$$\Leftrightarrow \Pr\left\{\bigcap_{i\in\Psi} A^i-, \overrightarrow{Y}(S\backslash\{k\}), T_k^{d(k)}-\right\} \Pr\left\{\overrightarrow{Y}(S\backslash\{k\}), T_k^{d(k)}+\right\} \geq \Pr\left\{\bigcap_{i\in\Psi} A^i-, \overrightarrow{Y}(S\backslash\{k\}), T_k^{d(k)}+\right\} \Pr\left\{\overrightarrow{Y}(S\backslash\{k\}), T_k^{d(k)}-\right\}.$$

To simplify the notation, in what follows we drop the disease index of the tests. Since $\Pr\left\{\overrightarrow{Y}(S\backslash\{k\})\right\} = \Pr\left\{\overrightarrow{Y}(S\backslash\{k\}), T_k-\right\} + \Pr\left\{\overrightarrow{Y}(S\backslash\{k\}), T_k+\right\}$, an equivalent statement of (B.1) is given as

$$\Pr\left\{\bigcap_{i\in\Psi} \overline{A^i}, \overrightarrow{Y}(S\backslash\{k\}), T_k-\right\} \left(\Pr\left\{\overrightarrow{Y}(S\backslash\{k\})\right\} - \Pr\left\{\overrightarrow{Y}(S\backslash\{k\}), T_k-\right\}\right) \geq \Pr\left\{\bigcap_{i\in\Psi} A^i-, \overrightarrow{Y}(S\backslash\{k\}), T_k+\right\} \Pr\left\{\overrightarrow{Y}(S\backslash\{k\}), T_k-\right\}$$

$$\Leftrightarrow \Pr\left\{T_k - \left|\bigcap_{i\in\Psi} A^i-, \overrightarrow{Y}(S\backslash\{k\})\right.\right\} \geq \Pr\left\{T_k - \left|\overrightarrow{Y}(S\backslash\{k\})\right.\right\}$$

$$\Longleftrightarrow \Pr\left\{T_k - \left|\bigcap_{i\in\Psi} A^i-\right.\right\} \geq \Pr\left\{T_k - \left|\overrightarrow{Y}(S\backslash\{k\})\right.\right\}, \text{ by } \textbf{(A2)}. \tag{B.2}$$

$$\begin{aligned}
\Pr\left\{T_k-, \overrightarrow{Y}(S\backslash\{k\}), \bigcup_{i\in\Psi} A^i+\right\} &= \sum_{\overrightarrow{\lambda}\in\mathscr{S}\left(\overrightarrow{\Lambda}\right)\backslash\overrightarrow{0}} \Pr\left\{\overrightarrow{Y}(S\backslash\{k\}), \overrightarrow{\Lambda} = \overrightarrow{\lambda}\right\} \Pr\left\{\overline{T_k}\left|\overrightarrow{Y}(S\backslash\{k\}), \overrightarrow{\Lambda} = \overrightarrow{\lambda}\right.\right\} \\
&= \sum_{\overrightarrow{\lambda}\in\mathscr{S}\left(\overrightarrow{\Lambda}\right)\backslash\overrightarrow{0}} \Pr\left\{\overrightarrow{Y}(S\backslash\{k\}), \overrightarrow{\Lambda} = \overrightarrow{\lambda}\right\} \Pr\left\{T_k - \left|\overrightarrow{\Lambda} = \overrightarrow{\lambda}\right.\right\} (\text{by } \textbf{(A2)}) \\
&\leq \sum_{\overrightarrow{\lambda}\in\mathscr{S}\left(\overrightarrow{\Lambda}\right)\backslash\overrightarrow{0}} \Pr\left\{\overrightarrow{Y}(S\backslash\{k\}), \overrightarrow{\Lambda} = \overrightarrow{\lambda}\right\} \Pr\left\{T_k - \left|A^{d(k)}-\right.\right\} (Q_j \leq 1, \forall j \in \Omega, \text{ see Section 5.2}).
\end{aligned}$$

Then, reintroducing the disease index for the tests, we can write

$$\Pr\left\{T_k^{d(k)}-, \overrightarrow{Y}(S\backslash\{k\}), \bigcup_{i\in\Psi} A^i+\right\} \leq \Pr\left\{\overrightarrow{Y}(S\backslash\{k\}), \bigcup_{i\in\Psi} A^i+\right\} \Pr\left\{T_k^{d(k)} - \left|A^{d(k)}-\right.\right\}. \tag{B.3}$$

Therefore, the right hand side of Eq.(B.2) can be written as

$$\Pr\left\{T_k^{d(k)} - \left|\overrightarrow{Y}(S\backslash\{k\})\right.\right\} = \frac{\Pr\left\{T_k^{d(k)}-, \overrightarrow{Y}(S\backslash\{k\}), \bigcup_{i\in\Psi} A^i+\right\} + \Pr\left\{T_k^{d(k)}-, \overrightarrow{Y}(S\backslash\{k\}), \bigcap_{i\in\Psi} A^i-\right\}}{\Pr\left\{\overrightarrow{Y}(S\backslash\{k\})\right\}}$$

$$\leq \frac{\Pr\left\{\overrightarrow{Y}(S\backslash\{k\}), \bigcup_{i\in\Psi} A^i+\right\} \Pr\left\{T_k^{d(k)} - \left|A^{d(k)}-\right.\right\} + \Pr\left\{\overrightarrow{Y}(S\backslash\{k\}), \bigcap_{i\in\Psi} A^i-\right\} \Pr\left\{T_k^{d(k)} - \left|A^{d(k)}-\right.\right\}}{\Pr\left\{\overrightarrow{Y}(S\backslash\{k\})\right\}} \text{ by Eq. (B.3)}$$

$$= \Pr\left\{T_k^{d(k)} - \left|A^{d(k)}-\right.\right\} = \Pr\left\{T_k^{d(k)} - \left|\bigcap_{i\in\Psi} A^i-\right.\right\}, \qquad \text{by } \textbf{(A1)},$$

and Eq. (B.2) follows, which shows that the decision rule of classifying the blood unit as infection-free under test results $\left(\overrightarrow{Y}\left(S\backslash\{k\}\right), T_k^{d(k)}-\right)$ is better (in terms of risk) than a rule that classifies it as infection-free under test results $\left(\overrightarrow{Y}\left(S\backslash\{k\}\right), T_k^{d(k)}+\right)$. Then, applying this procedure iteratively for all tests in $S\backslash\{k\}$ with a "+" result in the decision rule will eventually achieve the lowest risk, and this corresponds to a decision rule that requires a "–" result for each test in set S for classifying the blood unit as infection-free, i.e., the BP rule. □

B.4 Proof of Proposition 1

From Property 1, under the BP rule, the objective function in Eq. (4.1) reduces to

$$R\left(S\right) = \Pr\left(\bigcup_{i\in\Psi} A^i+ \left|\bigcap_{j\in S} T_j^{d(j)}-\right.\right) = 1 - \frac{\Pr\left\{\bigcap_{i\in\Psi} A^i-, \bigcap_{j\in S} T_j^{d(j)}-\right\}}{\Pr\left\{\bigcap_{j\in S} T_j^{d(j)}-\right\}},$$

which is equivalent to maximizing

$$\frac{\Pr\left\{\bigcap_{i\in\Psi} A^i-, \bigcap_{j\in S} T_j^{d(j)}-\right\}}{\Pr\left\{\bigcap_{i\in\Psi} A^i-, \bigcap_{j\in S} T_j^{d(j)}-\right\}+\Pr\left\{\bigcup_{i\in\Psi} A^i+, \bigcap_{j\in S} T_j^{d(j)}-\right\}}=\frac{1}{1+\frac{\sum_{\vec{\lambda}\in\mathscr{S}\left(\vec{\Lambda}\right)\setminus\vec{0}}\Pr\left\{\vec{\Lambda}=\vec{\lambda}, \bigcap_{j\in S} T_j^{d(j)}-\right\}}{\Pr\left\{\bigcap_{i\in\Psi} A^i-, \bigcap_{j\in S} T_j^{d(j)}-\right\}}},$$

which then is equivalent to minimizing

$$\frac{\sum_{\vec{\lambda}\in\mathscr{S}\left(\vec{\Lambda}\right)\setminus\vec{0}}\Pr\left\{\vec{\Lambda}=\vec{\lambda}\right\}\Pr\left\{\bigcap_{j\in S} T_j^{d(j)}-\,\middle|\,\vec{\Lambda}=\vec{\lambda}\right\}}{\Pr\left\{\bigcap_{i\in\Psi} A^i-\right\}\Pr\left\{\bigcap_{j\in S} T_j^{d(j)}-\,\middle|\,\bigcap_{i\in\Psi} A^i-\right\}}.$$

By definition of Q_j and Assumptions **(A1)**,**(A2)**, the objective function reduces to

$$\frac{1}{\Pr\left\{\bigcap_{i\in\Psi} A^i-\right\}}\sum_{\vec{\lambda}\in\mathscr{S}\left(\vec{\Lambda}\right)\setminus\vec{0}}\left\{\Pr\left\{\vec{\Lambda}=\vec{\lambda}\right\}\prod_{i\in\Psi:\lambda_i=1}\prod_{j\in S_i} Q_j\right\}.$$

Introducing the binary decision variables $I_j \equiv \begin{cases} 1, & \text{if test } j \text{ is selected} \\ 0, & \text{otherwise} \end{cases}, \forall j \in \Omega,$ we have

$$\prod_{i\in\Psi:\lambda_i=1}\prod_{j\in S_i} Q_j = \prod_{i\in\Psi:\lambda_i=1}\prod_{j\in\Omega_i}\{1-(1-Q_j)\,I_j\},$$

and the result in Eq. (4.3) follows since $\overline{Q}_j = 1 - Q_j, j \in \Psi$. Then Eq. (4.3) follows by combining similar terms. □

B.5 Proof of Lemma 1

For $\mathbf{RMP}^0 - i$, $i \in \Psi$, the risk corresponding to any set $S_i \subseteq \Omega_i$ can be written as

$$\begin{aligned} R_i^0(S_i) &= \Pr\left\{ A^i + \left| \bigcap_{j \in S_i} T_j^{d(j)} - \right. \right\} \\ &= \frac{\Pr(A^i+) \prod\limits_{j \in S_i} \Pr\left(T_j^{d(j)} - |A^i+\right)}{\Pr(A^i+) \prod\limits_{j \in S_i} \Pr\left(T_j^{d(j)} - |A^i+\right) + \Pr(A^i-) \prod\limits_{j \in S_i} \Pr\left(T_j^{d(j)} - |A^i-\right)} \quad \text{(by } \mathbf{(A2)}\text{)} \\ &= \frac{1}{1 + \frac{\Pr(A^i-)}{\Pr(A^i+)} \prod\limits_{j \in S_i} \frac{\Pr\left(T_j^{d(j)} - |A^i-\right)}{\Pr\left(T_j^{d(j)} - |A^i+\right)}}. \end{aligned}$$

Thus, minimizing $R_i^0(S_i)$ over all $S_i \subseteq \Omega_i$ is equivalent to minimizing

$$\prod_{j \in S_i} \frac{\Pr\left(T_j^{d(j)} - |A^i+\right)}{\Pr\left(T_j^{d(j)} - |A^i-\right)} = \prod_{j \in S_i} Q_j, \quad \text{over} \quad S_i \subseteq \Omega_i,$$

which, after linearizing the objective function, becomes equivalent to minimizing $\sum\limits_{j \in S_i} \ln(Q_j)$, over $S_i \subseteq \Omega_i$, and the result follows. □

B.6 Proof of Proposition 4

Before we provide the proof for part (i), we introduce the following lemma.

Lemma 3 *For any $S \subseteq \Omega$,*

$$\Pr\left(\bigcap_{j \in S} T_j^{d(j)} - \right) \leq \prod_{j \in S} \Pr\left(T_j^{d(j)} - \left| A^{d(j)} - \right.\right).$$

Proof.

$$\Pr\left(\bigcap_{j \in S} T_j^{d(j)} - \right) = \Pr\left(\bigcap_{i \in \Psi} A^i - \right) \Pr\left(\bigcap_{j \in S} T_j^{d(j)} - \left| \bigcap_{i \in \Psi} A^i - \right. \right) + \Pr\left(\overline{\bigcap_{i \in \Psi} A^i -} \right) \Pr\left(\bigcap_{j \in S} T_j^{d(j)} - \left| \overline{\bigcap_{i \in \Psi} A^i -} \right. \right), \tag{B.4}$$

where

$$\Pr\left(\bigcap_{j\in S} T_j^{d(j)}-\left|\overline{\bigcap_{i\in\Psi} A^i-}\right.\right)=\frac{\sum_{\overrightarrow{\lambda}\in\mathscr{S}(\overrightarrow{\Lambda})\setminus\overrightarrow{0}}\Pr\left(\bigcap_{j\in S} T_j^{d(j)}-,\overrightarrow{\Lambda}=\overrightarrow{\lambda}\right)}{\Pr\left(\bigcup_{i\in\Psi} A^i+\right)}=\frac{\sum_{\overrightarrow{\lambda}\in\mathscr{S}(\overrightarrow{\Lambda})\setminus\overrightarrow{0}}\left\{\Pr\left(\overrightarrow{\Lambda}=\overrightarrow{\lambda}\right)\Pr\left(\bigcap_{j\in S} T_j^{d(j)}-\left|\overrightarrow{\Lambda}=\overrightarrow{\lambda}\right.\right)\right\}}{\Pr\left(\bigcup_{i\in\Psi} A^i+\right)}.$$

Observe that $\mathscr{S}(\overrightarrow{\Lambda})\setminus\overrightarrow{0}$ denotes the realizations of the random vector $\overrightarrow{\Lambda}$ in which the blood unit is infected by at least one disease. By Assumption **(A2)** and $Q_j \leq 1, \forall j \in \Omega$, we have, for $\overrightarrow{\lambda} \in \mathscr{S}\left(\overrightarrow{\Lambda}\right)\setminus\overrightarrow{0}$, $j \in \Omega$,

$$\begin{aligned}\Pr\left(T_j^{d(j)}-\left|\overrightarrow{\Lambda}=\overrightarrow{\lambda}\right.\right) &= \begin{cases}\Pr\left(T_j^{d(j)}-\left|A^{d(j)}-\right.\right), & if\ \Lambda_{d(j)}=0\\ \Pr\left(T_j^{d(j)}-\left|A^{d(j)}+\right.\right), & if\ \Lambda_{d(j)}=1\end{cases}\\ &\leq \Pr\left(T_j^{d(j)}-\left|A^{d(j)}-\right.\right).\end{aligned}$$

Then, for $\overrightarrow{\lambda} \in \mathscr{S}\left(\overrightarrow{\Lambda}\right)\setminus\overrightarrow{0}$, $\Pr\left(\bigcap_{j\in S} T_j^{d(j)}-\left|\overrightarrow{\Lambda}=\overrightarrow{\lambda}\right.\right) \leq \prod_{j\in S}\Pr\left(T_j^{d(j)}-\left|A^{d(j)}-\right.\right)$. Hence, it follows that,

$$\begin{aligned}\Pr\left(\bigcap_{j\in S} T_j^{d(j)}-\left|\overline{\bigcap_{i\in\Psi} A^i-}\right.\right) &\leq \frac{\prod_{j\in S}\Pr\left(T_j^{d(j)}-\left|A^{d(j)}-\right.\right)\sum_{\overrightarrow{\lambda}\in\mathscr{S}(\overrightarrow{\Lambda})\setminus\overrightarrow{0}}\Pr\left(\overrightarrow{\Lambda}=\overrightarrow{\lambda}\right)}{\Pr\left(\bigcup_{i\in\Psi} A^i+\right)}\\ &= \prod_{j\in S}\Pr\left(T_j^{d(j)}-\left|A^{d(j)}-\right.\right) \qquad \text{(B.5)}\\ &= \Pr\left(\bigcap_{j\in S} T_j^{d(j)}-\left|\bigcap_{i\in\Psi} A^i-\right.\right). \qquad \text{(B.6)}\end{aligned}$$

Then the result follows by first substituting (B.6) into (B.4), and then using the equivalence between (B.5) and (B.6). □

Proof of Proposition 4, part (i):
For any $S \subseteq \Omega$,

$$\Pr\left(\bigcup_{i\in\Psi} A^i+ \left| \bigcap_{j\in S} T_j^{d(j)}- \right.\right) = \frac{\Pr\left(\bigcup\limits_{i\in\Psi} A^i+, \bigcap\limits_{j\in S} T_j^{d(j)}-\right)}{\Pr\left(\bigcap\limits_{j\in S} T_j^{d(j)}-\right)} \geq \frac{\Pr\left(\bigcup\limits_{i\in\Psi} A^i+, \bigcap\limits_{j\in S} T_j^{d(j)}-\right)}{\prod\limits_{j\in S}\Pr\left(T_j^{d(j)} - |A^{d(j)}-\right)} \text{ (by Lemma 3)}$$

$$= \frac{\sum\limits_{\overrightarrow{\lambda}\in\mathscr{S}(\overrightarrow{\Lambda})\setminus\overrightarrow{0}} \left\{\Pr\left(\overrightarrow{\Lambda}=\overrightarrow{\lambda}\right)\Pr\left(\bigcap\limits_{j\in S} T_j^{d(j)} - \left|\overrightarrow{\Lambda}=\overrightarrow{\lambda}\right.\right)\right\}}{\prod\limits_{j\in S}\Pr\left(T_j^{d(j)} - |A^{d(j)}-\right)}.$$

Note that, for $\overrightarrow{\Lambda} \in \mathscr{S}(\overrightarrow{\Lambda})\setminus\overrightarrow{0}$,

$$\Pr\left(\bigcap_{j\in S} T_j^{d(j)} - \left|\overrightarrow{\Lambda}=\overrightarrow{\lambda}\right.\right) = \prod_{j\in S}\Pr\left(T_j^{d(j)} - |\Lambda_{d(j)}=\lambda_{d(j)}\right) \text{ (by } \textbf{(A1)} \text{ and } \textbf{(A2)}),$$

where, $Q_j \leq 1, \forall j \in \Omega$,

$$\Pr\left(T_j^{d(j)} - |\Lambda_{d(j)}=\lambda_{d(j)}\right) = \begin{cases} \Pr\left(T_j^{d(j)} - \left|A^{d(j)}-\right.\right), & if\ \Lambda_{d(j)}=0 \\ \Pr\left(T_j^{d(j)} - \left|A^{d(j)}+\right.\right), & if\ \Lambda_{d(j)}=1 \end{cases}$$
$$\geq \Pr\left(T_j^{d(j)} - \left|A^{d(j)}+\right.\right).$$

Then,

$$\Pr\left(\bigcup_{i\in\Psi} A^i+ \left| \bigcap_{j\in S} T_j^{d(j)}- \right.\right) \geq \frac{\prod\limits_{j\in S}\Pr\left(T_j^{d(j)} - |A^{d(j)}+\right)\sum\limits_{\overrightarrow{\lambda}\in\mathscr{S}(\overrightarrow{\Lambda})\setminus\overrightarrow{0}}\left\{\Pr\left(\overrightarrow{\Lambda}=\overrightarrow{\lambda}\right)\right\}}{\prod\limits_{j\in S}\Pr\left(T_j^{d(j)} - |A^{d(j)}-\right)} = \Pr\left(\bigcup_{i\in\Psi} A^i+\right)\prod_{j\in S} Q_j.$$

Note that Property 2 also applies to Problem **(LB)**, that is, the optimal solution to Problem LB must also belong to set Ω^D. Then, the result follows because for any $S \in \Omega^D$, $R(S) \geq LB(S) \geq LB^*$. This completes the proof. □

Proof of Proposition 4, part (ii)
Let $\mathscr{S}^1(\overrightarrow{\Lambda})$ denote the sample space of the random vector $\overrightarrow{\Lambda}$ with only a single

infection, i.e., $\mathscr{S}^1(\overrightarrow{\Lambda}) = \{\overrightarrow{\Lambda} \in \mathscr{S}(\overrightarrow{\Lambda}) : \sum_{i\in\Psi} \lambda_i = 1\}$. Recall that $I_j^*, j \in \Omega$, denotes the optimal solution to **RMP**. Then, from Proposition 1 Eq. (4.3), the objective function of **RMP** can be written as

$$
\begin{aligned}
& \sum_{\overrightarrow{\lambda}\in\mathscr{S}\left(\overrightarrow{\Lambda}\right)\setminus\overrightarrow{0}} \left\{ p_{\overrightarrow{\Lambda}}\left(\overrightarrow{\lambda}\right) \prod_{i\in\Psi:\lambda_i=1} \prod_{j\in\Omega_i} \{1-\overline{Q}_j I_j\} \right\} \\
= & \sum_{\overrightarrow{\lambda}\in\mathscr{S}^1(\overrightarrow{\Lambda})} \left\{ p_{\overrightarrow{\Lambda}}\left(\overrightarrow{\lambda}\right) \prod_{i\in\Psi:\lambda_i=1} \prod_{j\in\Omega_i} \{1-\overline{Q}_j I_j\} \right\} + \sum_{\overrightarrow{\lambda}\in\mathscr{S}\left(\overrightarrow{\Lambda}\right)\setminus\left\{\overrightarrow{0}\cup\mathscr{S}^1(\overrightarrow{\Lambda})\right\}} \left\{ p_{\overrightarrow{\Lambda}}\left(\overrightarrow{\lambda}\right) \prod_{i\in\Psi:\lambda_i=1} \prod_{j\in\Omega_i} \{1-\overline{Q}_j I_j\} \right\} \\
\geq & \sum_{\overrightarrow{\lambda}\in\mathscr{S}^1(\overrightarrow{\Lambda})} \left\{ p_{\overrightarrow{\Lambda}}\left(\overrightarrow{\lambda}\right) \prod_{i\in\Psi:\lambda_i=1} \prod_{j\in\Omega_i} \{1-\overline{Q}_j I_j\} \right\} \\
\geq & \text{ Minimize}_{I_j, j\in\Omega} \sum_{\overrightarrow{\lambda}\in\mathscr{S}^1(\overrightarrow{\Lambda})} \left\{ p_{\overrightarrow{\Lambda}}\left(\overrightarrow{\lambda}\right) \prod_{i\in\Psi:\lambda_i=1} \prod_{j\in\Omega_i} \{1-\overline{Q}_j I_j\} \right\}, (\overline{Q}_j = 1 - Q_j \leq 1, \forall j \in \Omega,) \qquad \text{(B.7)}
\end{aligned}
$$

where (B.7) is the objective function of $\mathbf{RMP}^0$; hence the result follows. □

Appendix C

Appendix for Chapter 5

C.1 TestSet-based Formulations of $\mathbf{RMP}^0$ and WT-$\mathbf{RMP}^0$

Proposition 3 (Bish et al., 2010) establishes the equivalence of $\mathbf{RMP}^0$ to the following integer programming problem:

TS-based formulation for $\mathbf{RMP}^0$:

$$\text{Minimize} \sum_{i\in\Psi} p_{\overrightarrow{\Lambda}}\left(\overrightarrow{\lambda} : \lambda_i = 1\right)\left(\begin{array}{l}\sum\limits_{j\in\Omega_i} Q_j x^i_j + \sum\limits_{j\in\Omega_i}\sum\limits_{k\in\Omega_i,k>j} Q_jQ_k x^i_{jk} + \\ \sum\limits_{j\in\Omega_i}\sum\limits_{k\in\Omega_i,k>i}\sum\limits_{l\in\Omega_i,l>k} Q_jQ_kQ_l x^i_{jkl} + \cdots + \prod\limits_{j\in\Omega_i} Q_j x^i_{\Omega_i} + x^i_{\emptyset}\end{array}\right)$$

$$\text{subject to} \quad \sum_{i\in\Psi}\left\{\begin{array}{l}\sum\limits_{j\in\Omega_i} c_j x^i_j + \sum\limits_{j\in\Omega_i}\sum\limits_{k\in\Omega_i,k>j} (c_j + c_k)\, x^i_{jk} + \\ \sum\limits_{j\in\Omega_i}\sum\limits_{k\in\Omega_i,k>j}\sum\limits_{l\in\Omega_i,l>k} (c_j + c_k + c_l)\, x^i_{jkl} + \cdots + \left(\sum\limits_{j\in\Omega_i} c_j\right) x^i_{\Omega_i}\end{array}\right\} \leq B \tag{C.1}$$

$$\sum_{i\in\Psi}\left\{\begin{array}{l}\sum\limits_{j\in\Omega_i} p_j x^i_j + \sum\limits_{j\in\Omega_i}\sum\limits_{k\in\Omega_i,k>j} (p_j + p_k)\, x^i_{jk} + \\ \sum\limits_{j\in\Omega_i}\sum\limits_{k\in\Omega_i,k>j}\sum\limits_{l\in\Omega_i,l>k} (p_j + p_k + p_l)\, x^i_{jkl} + \cdots + \left(\sum\limits_{j\in\Omega_i} p_j\right) x^i_{\Omega_i}\end{array}\right\} \geq \ln(1-\alpha) \tag{C.2}$$

$$\sum_{j\in\Omega_i} x^i_j + \sum_{j\in\Omega_i}\sum_{k\in\Omega_i,k>j} x^i_{jk} + \sum_{j\in\Omega_i}\sum_{k\in\Omega_i,k>j}\sum_{l\in\Omega_i,l>k} x^i_{jkl} + \cdots + x^i_{\Omega_i} + x^i_0 = 1, \forall i \in \Psi \tag{C.3}$$

$$x^i_{q_1,q_2,\ldots,q_k} \text{ binary}, \{q_1, q_2, \ldots, q_k\} \subseteq \Omega_i \setminus \emptyset, i \in \Psi \tag{C.4}$$

$$x^i_0 \text{ binary}, i \in \Psi, \tag{C.5}$$

where $p_j = \ln\left(\Pr\left(T_j^{d(j)} - |A^{d(j)}-\right)\right), \forall j \in \Omega$.

Similarly, we reformulate **WT-RMP**^{0} following the **TestSet-based** formulation.

TS-based formulation for **WT-RMP**^{0}:

$$\text{Minimize} \sum_{i\in\Psi} w\left(\overrightarrow{\lambda} : \lambda_i = 1\right) p_{\overrightarrow{\Lambda}}\left(\overrightarrow{\lambda} : \lambda_i = 1\right) \left(\begin{array}{l} \sum\limits_{j\in\Omega_i} \Pr\{T_j^{d(j)} - |\overrightarrow{\Lambda} = \overrightarrow{\lambda}\} x^i_j + \\ \sum\limits_{j\in\Omega_i} \sum\limits_{k\in\Omega, k>j} \Pr\{T_j^{d(j)} - |\overrightarrow{\Lambda} = \overrightarrow{\lambda}\} \Pr\{T_k^{d(k)} - |\overrightarrow{\Lambda} = \overrightarrow{\lambda}\} x^i_{jk} + \cdots \\ + \prod\limits_{j\in\Omega_i} \Pr\{T_j^{d(j)} - |\overrightarrow{\Lambda} = \overrightarrow{\lambda}\} x^i_{\Omega_i} + x^i_0 \end{array} \right)$$

$$\text{subject to} \quad (C.1), (C.2), (C.3), (C.4), (C.5).$$

Appendix D

Appendix for Chapter 6

D.1 Charnes & Cooper's Transformation of DF-RMP

Consider the LFP of **DF-RMP** in (6.1)-(6.3). In what follows, we convert it into a linear programming problem by applying the Charnes & Cooper's Transformation (Charnes and Cooper, 1962). Denote $t = \frac{1}{\sum_{k=0}^{f} p_k \Pr\left\{\bigcap_{j \in S_k} T_j^{d(j)}-\right\}}$. Then, an equivalent formulation of **DF-RMP** follows:

$$
\begin{aligned}
Maximize_{\vec{p},t}\,(1-R) \;=\; & t\sum_{k=0}^{f} p_k \Pr\left\{\bigcap_{i\in\Psi} A^i-, \bigcap_{j\in S_k} T_j^{d(j)}-\right\} \\
\text{subject to} \quad & \sum_{k=0}^{f} p_k \left(\sum_{j\in S_k} c_j\right) \le B \\
& \sum_{k=0}^{f} p_k = 1 \\
& t\sum_{k=0}^{f} p_k \Pr\left\{\bigcap_{j\in S_k} T_j^{d(j)}-\right\} = 1 \\
& t \ge 0 \\
& p_k \ge 0, k = 0, 1, \ldots, f.
\end{aligned}
$$

Multiplying all constraints by t and letting $x_k \equiv p_k t$, we obtain the following linear programming problem.

$$\begin{aligned} Maximize_{\vec{x},t}\,(1-R) \quad &= \quad \sum_{k=0}^{f} x_k \Pr\left\{ \bigcap_{i\in\Psi} A^i-, \bigcap_{j\in S_k} T_j^{d(j)}- \right\} \\ \text{subject to} \qquad & \sum_{k=0}^{f} x_k \left(\sum_{j\in S_k} c_j \right) - Bt \leq 0 \\ & \sum_{k=0}^{f} x_k = t \\ & \sum_{k=0}^{f} x_k \Pr\left\{ \bigcap_{j\in S_k} T_j^{d(j)}- \right\} = 1 \\ & t \geq 0 \\ & x_k \geq 0, k = 0, 1, \ldots, f. \end{aligned} \tag{D.1}$$

By replacing t with $\sum_{k=0}^{f} x_k$ using (D.1), this problem is then converted to the linear programming problem given in **DF-RMP2 Primal**.